

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

Clifton D. Fuller, M.D.¹⁻³, Samuel J. Wang, M.D., Ph.D.³, Mehee Choi, M.D.³, Brian G. Czito, M.D.⁴,
John Cornell, Ph.D.⁵, Tania M. Welzel, M.D., M.H.S.⁶, Katherine A. McGlynn, Ph.D., M.P.H.⁶,
Join Y. Luh, M.D.⁷, Charles R. Thomas, Jr., M.D.³

¹Department of Radiation Oncology and ²Graduate Division of Radiological Sciences/Department of Radiology,
The University of Texas Health Science Center at San Antonio, San Antonio, TX;

³Department of Radiation Medicine, Oregon Health Sciences University Cancer Institute, Portland, OR;

⁴Department of Radiation Oncology, Duke University, Durham, NC.

⁵Department of Epidemiology and Biostatistics, The University of Texas Health Science Center at San Antonio,
San Antonio, TX;

⁶ Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health,
Department of Health and Human Services, Bethesda, MD;

⁷St. Joseph Hospital, Eureka, CA;

Corresponding author: Clifton David Fuller, M.D.

Department of Radiation Oncology, and Graduate Division of Radiological Sciences/Department of Radiology,
The University of Texas Health Science Center at San Antonio,

7703 Floyd Curl Dr, MSC 7889,

San Antonio, TX, 78229

Office: 210-450-5699

Cell: 210-393-0625

Fax: 210-450-5085

Email: fullercd@uthscsa.edu

Running title: “Multimodality therapy for EHCC.”

Total number of: 1) text pages, including title page, references, and figure legends:16

2) tables: 2

3) illustrations:4

Funding/Acknowledgements: CDF received funding support from the National Institutes of Health/National
Institute of Biomedical Imaging and BioEngineering/ UTHSCSA Graduate Division of Radiological Sciences
Multidisciplinary Training Grant in Human Imaging (5T32EB000817-04).

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.

1 Introduction:

2 Primary cancers of the bile ducts, known as cholangiocarcinomas, are rare tumors, with an annual incidence of
3 0.6-1/100,000 persons in the United States^{1,2}. Despite their rarity, cholangiocarcinomas are highly lethal³.
4 Therapeutic interventions for cholangiocarcinomas are predicated on the distinction between intrahepatic and
5 extrahepatic cholangiocarcinomas^{1,4}, as well as the resectability of disease. At present, surgical resection is the
6 preferred therapy for extrahepatic disease⁵. Unfortunately, the vast majority of patients present with locally
7 advanced or metastatic disease which is not amenable to definitive resection, with reported 5-year overall
8 survival rates of 0-39%⁶. While definitive and adjuvant radiotherapy techniques have been investigated,
9 typically via retrospective data from single institutions, outcomes remain suboptimal⁷⁻¹⁵. At present, the utility
10 of incorporating radiotherapy, as well its impact on disease outcome, is an area of debate^{13,14}, owing in part to
11 the numerical rarity of these tumors¹⁶.

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

15

16 Specific aims of this study are:

- 17 1. Determination of observed mortality differentials, if any, for patients receiving combined
18 surgical/radiotherapy treatment compared with surgery only, radiotherapy only, or non-surgery/non-
19 radiotherapy cohorts.
- 20 2. Generation of potential population-based survival benchmarks and hypotheses for institutional and
21 cooperative group trials.

22

23 Methods:

24 Patient data from cases diagnosed from 1973-2005 was obtained from the April 2008 (based on the November
25 2007 submission) version of the Surveillance, Epidemiology, and End Results (SEER) limited-use dataset¹⁷.

26 Included cases of extrahepatic cholangiocarcinoma were identified by topography codes representing

1 extrahepatic bile ducts (C24.0) and histology codes representative of cholangiocarcinoma (histology codes
2 8010, 8020, 8041, 8070, 8140, 8144, 8160, 8162, 8260, 8310, 8490, and 8560). Perihilar
3 cholangiocarcinomas, or Klatskin's tumors, were specifically identified by topography codes C24.0 and specific
4 histology code 8162/3; since these tumors cannot be reliably differentiated from EHCC, in accordance with
5 previously described identification analysis of cases in SEER datasets¹, they therefore were included in this
6 analysis. Case data with malignant primary indicator status denoting second (or greater) primary tumor(s) and
7 those cases not specifically denoting local or regional disease (e.g. SEER Historic Stage A indicating
8 distant/unknown extent of disease) were excluded from analysis. Cases were included if a positive microscopic
9 confirmation, exfoliative cytology, or positive laboratory test/marker study was specified. SEER variable data
10 were derived from direct accession via SEER*Stat¹⁷, and extracted as tab-delimited data into commercial
11 statistical analysis software (StatView and JMP v6.0, SAS Institute, Cary, NC). The following variables were
12 extracted from SEER data: Age, Radiation, Surgery of Primary Site, Site Specific Surgery, Lymph Node
13 Surgery, Histologic Grade, Sex, Extent of disease, and Cause of Death. Specific nominal variables were created
14 using SEER data and software-scripted logic statements to create composite variables for analysis. As AJCC
15 staging was unavailable directly from SEER data for all patients, for those patients whom extent of
16 local/regional involvement and nodal status could be ascertained, AJCC stage (6th edition) was assigned by the
17 authors using custom scripting of logic statements to pool available case data. Cases without sufficient
18 information for AJCC grouping via custom scripting (e.g. TX, NX, MX, or "unknown" extent of disease values)
19 were excluded. Cases were coded by therapeutic modalities received as a logic statement using the Radiation
20 and Surgery of Primary Site/Site Specific Surgery variables derived from SEER*Stat, matching the therapeutic
21 data to the appropriate SEER documentation. Cases with denotation of either external beam radiotherapy, or no
22 radiotherapy in the Radiation variable of SEER*Stat were included; other radiation modalities (e.g.
23 brachytherapy) were excluded. Site Specific Surgery variables were utilized to exclude nontherapeutic intent
24 procedures (i.e. biopsy only, or exploratory surgical procedures). Those cases with Site Specific Surgery codes
25 indicating potential therapeutic intent resection were included. Cases with Site Specific Surgery variables

1 denoting “radical” or “total” resection were grouped; all other cases indicating “debulking” or “subtotal”
2 resection were pooled.

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

12 Evaluation of the main variable of interest, therapeutic regimen, was evaluated using univariate parametric
13 lognormal survival analysis¹⁸, after visual inspection revealed crossing of survival curves with graphic
14 representation of product-limit survival curves^{19, 20}. Since the proportional hazard assumption could not be met
15 for the variable of interest²¹, as determined by Schoenfeld residual calculation²², for multifactorial/multivariate
16 analysis, a parametric lognormal analysis was performed, obviating the need to hazard proportionality
17 throughout follow-up. A parametric lognormal¹⁸ full-factorial model, which included the following variables
18 (derived from literature review to impact survival with EHCC), was utilized: age (as a continuous measure),
19 year of diagnosis (as a continuous measure), therapy cohort (No treatment, EBRT alone, subtotal resection,
20 subtotal resection+RT, total resection, total resection+RT), grade (Well-differentiated/Grade I, moderately-
21 differentiated/Grade II, poorly-differentiated/Grade III, Undifferentiated/Grade IV, Unknown/Not specified),
22 and derived AJCC Sixth Edition Stage (IA, IB, IIA, IIB, III). Survival estimation was performed utilizing
23 lognormal parametric survival regression with a maximum likelihood approach to calculate β , the factor effect
24 of the aforementioned variables, as well as the 95% confidence interval of β , assuming an approximation of a
25 normal distribution. For categorical variables β values >0 indicate a positive association with regard to survival;
26 β <0 suggest an association with survival decrement. For continuous variables (age, year of diagnosis), positive

1 β values indicate increasing probability of survival with increasing numeric value of the variable in question.
2 Statistical significance for each variable was evaluated using a chi-square approximation set at a $\alpha=0.05$, with
3 $n-1$ degrees of freedom, where n is the number of subvariables within a categorical variable of interest, and was
4 uncorrected for multiple comparisons.

5 Results:

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

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

19 Discussion

20 With an estimated annual incidence of 3,000 cases annually in the United States, EHCC remains a rare but
21 aggressive neoplasm⁸. While complete surgical resection remains the foundation of curative intent therapy for
22 EHCC, owing to its anatomical location and natural history, the majority of patients present with locally
23 advanced disease at diagnosis. The rarity of EHCC has precluded mounting of large-scale randomized
24 controlled trials. Thus, at present, the role of adjuvant therapy for EHCC remains controversial, despite
25 promising institutional data²³⁻²⁵. Consequently, while imperfect, the utilization of large-scale population-based

1 datasets, such as SEER, represent a useful mechanism for mortality risk estimation. Such data may be especially
2 useful for tumors such as cholangiocarcinoma, where single institutions have difficulty accruing sufficient
3 numbers to afford appropriately statistically powered analyses.

4 The data presented herein suggest that the addition of radiotherapy to therapeutic intent surgical interventions
5 was associated with improved median survival compared to either surgery alone, radiotherapy alone or
6 nonsurgery/nonradiotherapy cohorts in a multifactorial model. However, it should be noted that, with sufficient
7 follow-up (i.e. >5 years), in univariate survival analysis, the mortality curves for the surgical and combined
8 modality cohorts converge, and, as shown in Figures 2 and 3, adjuvant radiotherapy may be associated with
9 long-term (>5 years) survival *decrement*. Long-term outcomes were uniformly dismal with 5-year survival rates
10 of 18% for surgery alone, 16% for surgery+RT, and under 3% for those receiving radiotherapy alone or no
11 recorded therapy. The majority of detected survival benefit from the addition of radiotherapy appears to be had
12 within the initial 1-2 years following therapy (Figures 2 and 3). Why this effect dissipates over time is unclear.
13 This observation may be due to delayed local recurrence in those patients receiving surgical resection and
14 radiotherapy; alternately, it may be attributable to treatment-related factors unaccounted for in SEER (e.g.
15 chemotherapeutic regimens not recorded in SEER, performance status differentials, variant radiotherapy
16 techniques and/or fractionation/dose schedules, post-therapy complication rates, delay in distant metastatic
17 progression due to improved local control²⁶). Alternatively, prognostic variables not recorded in SEER might
18 lead to negative selection bias for definitive or adjuvant radiotherapy (e.g. positive margins after resection,
19 advanced pathologic features). The surgical margin status issue is of special significance, and unfortunately, is
20 not a recorded variable within the SEER dataset. It is possible that the adjuvant radiotherapy cohort includes
21 many patients who received radiotherapy secondary to suboptimal resection. If true, radiotherapy might confer
22 some deferral of disease progression, but would be inadequate for eradicating bulk disease. If many
23 suboptimally resected cholangiocarcinomas are *de facto* unresectable tumors⁷, it becomes apparent, as Crane *et*
24 *al.* have noted previously, that conventional radiation-only regimens are insufficient to ensure local control¹⁰,
25 and may only be able to defer disease progression temporarily. However, such explanations are purely
26 conjecture in the absence of prospective clinical trial data.

1 Since SEER represents the largest domestic cholangiocarcinoma dataset, the observed phenomena whereby
2 early survival is improved by the addition of radiotherapy, while late survival is either unaltered or decreased,
3 may explain the relatively contradictory findings in smaller institutional series. Some posit minimal utility for
4 adjuvant therapy²⁷, while others suggest an appreciable survival benefit^{7, 12, 15, 16, 23, 28-33}. Consequently, our
5 findings may demonstrate both opinions to be correct, with early survival improvement noted despite minimal
6 benefit in the long-term (see Figures 2 and 3). Some authors have observed series where suboptimal resections
7 (R1) may derive minimal gain from the addition of surgery to radiotherapy⁷. While not directly answered in this
8 series, owing to the unavailability of margin status and other relevant pathologic (lymphovascular or perineural
9 invasion) and clinical (performance status, comorbid conditions) confounders in SEER, the significantly poorer
10 outcomes observed for the radiotherapy only cohort should at least give pause to implementation of radiation
11 monotherapy for patients with potentially difficult resections, and should spur aggressive surgery whenever
12 indicated clinically.

13 While SEER represents an exceedingly robust dataset, several limitations should be assiduously noted. SEER
14 data does not afford analysis of chemotherapy regimen utilization, and thus it is impossible to impute what role,
15 if any, the addition of chemotherapy to any treatment cohort may have on survival patterns. Furthermore,
16 relevant specific information regarding surgical and radiotherapy treatment techniques (e.g. margin status,
17 dose/fractionation, time between surgery and radiotherapy) are not captured within the SEER dataset. The
18 SEER Historic Staging system, while affording ready comparison between distinct eras, is inherently imprecise
19 in order to collapse patients based on extent of disease. Additionally, no EHCC patients diagnosed 1973-1998
20 received formal AJCC staging within SEER, making the logic-statement/scripting stage conversion by the
21 authors necessary, based on available extent of disease data. While some information regarding the anatomic
22 location may be gleaned from the SEER topography codes, insufficient information is available for rigorous
23 definition of tumor location³⁴ or resectability, major prognostic factors in many series^{5, 8, 13, 15, 29, 35, 36}. For
24 example, Welzel et al. demonstrated that discrimination of Klatskin's tumors from other extrahepatic
25 cholangiocarcinomas is unreliable using SEER¹; consequently, the inclusion of Klatskin's tumors within this
26 series should be noted, and might skew results. SEER, like most registry data, has multiple "catch-all"

1 identifiers (e.g. “Surgery NOS”, “Unknown Grade”) which may obfuscate careful definition of categorical
2 cohorts. SEER data is limited geographically, as not all U.S. cancer registries contribute to SEER, and
3 temporally limited, as not all registries have contributed data for the same span of time. Though we utilized year
4 of diagnosis as a surrogate for evolving radiotherapy, surgery, or chemotherapy practice, SEER variables does
5 not directly account for technological improvement or changes in either surgical^{35, 37} or radiation technique over
6 time¹¹. Finally, SEER data collection is dependent upon the quality of decentralized local registrars for
7 completeness and accuracy of data entry, with limited direct quality control.

8 Nonetheless, SEER provides the largest domestic population-based estimation of EHCC, with case numbers
9 several-fold greater than available in single-institutional series. The value of such numerical power should not
10 be underestimated. In addition, population-based datasets such as SEER may more accurately reflect the true
11 expected survival of EHCC patients in the community medical milieu, rather than only at specific academic
12 centers. These may explain why, in comparison to several retrospective series reported in the literature, survival
13 results from the present analysis show comparatively worse survival for adjuvant radiotherapy patients than the
14 markedly smaller, albeit more detailed, retrospective series available in extant literature^{7, 9, 10, 12, 13, 15, 16, 36, 38}.

15 Likewise, differentials in the clinical outcomes associated with tertiary centers (e.g. improved late survival at
16 high volume centers³⁹, or increased utilization of adjuvant radiotherapy in institutions with on-site radiotherapy
17 facilities⁴⁰) may be obscured in pooled registry data.

18 This dataset represents, to our knowledge, the first to characterize the effect of multimodality therapy as a using
19 parametric survival analysis in cholangiocarcinoma. The nonproportionality of the hazard functions observed in
20 this series with regard to therapeutic cohort necessitate a historically underutilized, but increasingly
21 implemented statistical comparison⁴¹⁻⁴³. Ahmed *et al.* have recently described several distinct methodologies for
22 accounting for nonproportionality in survival series¹⁹. We have chosen lognormal survival fitting, which has a
23 long history within cancer survival analysis⁴⁴, as it is robust^{45, 46}, applicable in cases of non-proportionality⁴⁷,
24 statistically succinct¹⁸, and broadly interpretable as a mechanism for defining survival event estimates⁴⁶. While
25 more elegant corrections for nonproportionality are available, none are widely implemented¹⁹. Additionally,
26 parametric analyses have the added benefit of the capacity to generate, given specific multivariate input

1 parameters, an estimation of the survival at any given time point in follow-up. We hope to eventually transform
2 this dataset into a risk-profiling tool, as has previously been performed using SEER data regarding gallbladder
3 carcinomas⁴⁸.

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

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

12 13 Conclusion

14 Baseline data from SEER indicate an improved early survival profile for patients receiving multimodality
15 therapy; however, long-term survival advantage was not demonstrated.

16
17
18
19
20
21
22
23
24
25
26

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28

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 (β), with 95% confidence interval.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58

References

1. Welzel TM, McGlynn KA, Hsing AW, O'Brien TR, Pfeiffer RM. Impact of classification of hilar cholangiocarcinomas (Klatskin tumors) on the incidence of intra- and extrahepatic cholangiocarcinoma in the United States. *J Natl Cancer Inst* 2006;98(12):873-5. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16788161
2. Fuller C, Diehl A. Epidemiology of gallbladder and biliary tract cancer. In: Thomas CR, Fuller CD, eds. Biliary tract and gallbladder cancer : diagnosis & therapy New York, NY: Demos, 2008:p.
3. Vallis KA, Benjamin IS, Munro AJ, Adam A, Foster CS, Williamson RC, et al. External beam and intraluminal radiotherapy for locally advanced bile duct cancer: role and tolerability. *Radiother Oncol* 1996;41(1):61-6. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8961369
4. Curley SA. Diagnosis and management of intrahepatic and extrahepatic cholangiocarcinoma. *Cancer Treat Res* 2001;109:117-44. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11775432
5. Jarnagin WR, Shoup M. Surgical management of cholangiocarcinoma. *Semin Liver Dis* 2004;24(2):189-99. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15192791
6. Yalcin S. Diagnosis and management of cholangiocarcinomas: a comprehensive review. *Hepatogastroenterology* 2004;51(55):43-50. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15011829
7. Ben-David MA, Griffith KA, Abu-Isa E, Lawrence TS, Knol J, Zalupski M, et al. External-beam radiotherapy for localized extrahepatic cholangiocarcinoma. *Int J Radiat Oncol Biol Phys* 2006;66(3):772-9. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17011452
8. Jarnagin WR. Cholangiocarcinoma of the extrahepatic bile ducts. *Semin Surg Oncol* 2000;19(2):156-76. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11126380
9. McMasters KM, Tuttle TM, Leach SD, Rich T, Cleary KR, Evans DB, et al. Neoadjuvant chemoradiation for extrahepatic cholangiocarcinoma. *Am J Surg* 1997;174(6):605-8; discussion 08-9. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9409582
10. Crane CH, Macdonald KO, Vauthey JN, Yehuda P, Brown T, Curley S, et al. Limitations of conventional doses of chemoradiation for unresectable biliary cancer. *Int J Radiat Oncol Biol Phys* 2002;53(4):969-74. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12095564
11. Fuss M, Salter BJ, Cavanaugh SX, Fuss C, Sadeghi A, Fuller CD, et al. Daily ultrasound-based image-guided targeting for radiotherapy of upper abdominal malignancies. *Int J Radiat Oncol Biol Phys* 2004;59(4):1245-56. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15234062
12. Heron DE, Stein DE, Eschelmann DJ, Topham AK, Waterman FM, Rosato EL, et al. Cholangiocarcinoma: the impact of tumor location and treatment strategy on outcome. *Am J Clin Oncol* 2003;26(4):422-8. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12902899

13. Itoh H, Nishijima K, Kurosaka Y, Takegawa S, Kiriya M, Dohba S, et al. Magnitude of combination therapy of radical resection and external beam radiotherapy for patients with carcinomas of the extrahepatic bile duct and gallbladder. *Dig Dis Sci* 2005;50(12):2231-42. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16416167
14. Tsujino K, Landry JC, Smith RG, Keller JW, Williams WH, Davis LW. Definitive radiation therapy for extrahepatic bile duct carcinoma. *Radiology* 1995;196(1):275-80. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7784581
15. Kamada T, Saitou H, Takamura A, Nojima T, Okushiba SI. The role of radiotherapy in the management of extrahepatic bile duct cancer: an analysis of 145 consecutive patients treated with intraluminal and/or external beam radiotherapy. *Int J Radiat Oncol Biol Phys* 1996;34(4):767-74. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8598352
16. Fields JN, Emami B. Carcinoma of the extrahepatic biliary system--results of primary and adjuvant radiotherapy. *Int J Radiat Oncol Biol Phys* 1987;13(3):331-8. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=3104245
17. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 9 Regs Limited-Use, Nov 2007 Sub (1973-2005) <Katrina/Rita Population Adjustment> -Linked To County Attributes - Total U.S., 1969-2005 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2008, based on the November 2007 submission. 2008. Available from www.seer.cancer.gov.
18. Royston P. The lognormal distribution as a model for survival time in cancer, with an emphasis on prognostic factors. *Statistica Neerlandica* 2001;55(1):89-104. Available from <http://dx.doi.org/10.1111/1467-9574.t01-1-00177>
19. Ahmed FE, Vos PW, Holbert D. Modeling survival in colon cancer: a methodological review. *Mol Cancer* 2007;6:15. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17295918
20. Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. *Journal of the American Statistical Association*, 1958;53(282):457-81. Available from <http://links.jstor.org/sici?sici=0162-1459%28195806%2953%3A282%3C457%3ANEFIO%3E2.0.CO%3B2-Z>.
21. Cox DR. Regression and life tables (with discussion). *Journal of the Royal Statistical Society, Series B* 1972;34:187-200.
22. Grambsch PM, Therneau TM, Fleming TR. Diagnostic plots to reveal functional form for covariates in multiplicative intensity models. *Biometrics* 1995;51(4):1469-82. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8589234
23. Schoenthaler R, Phillips TL, Castro J, Efird JT, Better A, Way LW. Carcinoma of the extrahepatic bile ducts. The University of California at San Francisco experience. *Ann Surg* 1994;219(3):267-74. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8147607
24. Nakeeb A, Tran KQ, Black MJ, Erickson BA, Ritch PS, Quebbeman EJ, et al. Improved survival in resected biliary malignancies. *Surgery* 2002;132(4):555-63; discussion 63-4. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12407338.
25. Nelson JW, Ghafoori AP, Willett CG, Tyler DS, Pappas TN, Clary BM, et al. Concurrent Chemoradiotherapy in Resected Extrahepatic Cholangiocarcinoma. *Int J Radiat Oncol Biol Phys* 2008. Available from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18805651

- 1 26. Punglia RS, Morrow M, Winer EP, Harris JR. Local therapy and survival in breast
2 cancer. *N Engl J Med* 2007;356(23):2399-405. Available from
3 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u
4 [ids=17554121](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u)
- 5 27. Pitt HA, Nakeeb A, Abrams RA, Coleman J, Piantadosi S, Yeo CJ, et al. Perihilar
6 cholangiocarcinoma. Postoperative radiotherapy does not improve survival. *Ann Surg*
7 1995;221(6):788-97; discussion 97-8. Available from
8 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u
9 [ids=7794082](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u)
- 10 28. Stein DE, Heron DE, Rosato EL, Anne PR, Topham AK. Positive microscopic margins
11 alter outcome in lymph node-negative cholangiocarcinoma when resection is combined with
12 adjuvant radiotherapy. *Am J Clin Oncol* 2005;28(1):21-3. Available from
13 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u
14 [ids=15685030](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u)
- 15 29. Todoroki T. Radiotherapy as a component of multidisciplinary treatment of bile
16 duct cancer: a surgeon's perspective. *J Hepatobiliary Pancreat Surg* 2001;8(2):130-6.
17 Available from
18 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u
19 [ids=11455468](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u)
- 20 30. Todoroki T, Ohara K, Kawamoto T, Koike N, Yoshida S, Kashiwagi H, et al.
21 Benefits of adjuvant radiotherapy after radical resection of locally advanced main
22 hepatic duct carcinoma. *Int J Radiat Oncol Biol Phys* 2000;46(3):581-7. Available from
23 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u
24 [ids=10701737](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u)
- 25 31. Zlotecki RA, Jung LA, Vauthey JN, Vogel SB, Mendenhall WM. Carcinoma of the
26 extrahepatic biliary tract: surgery and radiotherapy for curative and palliative intent.
27 *Radiat Oncol Investig* 1998;6(5):240-7. Available from
28 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u
29 [ids=9822171](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u)
- 30 32. Schoenthaler R, Castro JR, Halberg FE, Phillips TL. Definitive postoperative
31 irradiation of bile duct carcinoma with charged particles and/or photons. *Int J Radiat*
32 *Oncol Biol Phys* 1993;27(1):75-82. Available from
33 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u
34 [ids=8365945](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u)
- 35 33. Veeze-Kuijpers B, Meerwaldt JH, Lameris JS, van Blankenstein M, van Putten WL,
36 Terpstra OT. The role of radiotherapy in the treatment of bile duct carcinoma. *Int J*
37 *Radiat Oncol Biol Phys* 1990;18(1):63-7. Available from
38 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u
39 [ids=2153649](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u)
- 40 34. Alden ME, Waterman FM, Topham AK, Barbot DJ, Shapiro MJ, Mohiuddin M.
41 Cholangiocarcinoma: clinical significance of tumor location along the extrahepatic bile
42 duct. *Radiology* 1995;197(2):511-6. Available from
43 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u
44 [ids=7480704](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u)
- 45 35. DeOliveira ML, Cunningham SC, Cameron JL, Kamangar F, Winter JM, Lillemoe KD,
46 et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single
47 institution. *Ann Surg* 2007;245(5):755-62. Available from
48 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u
49 [ids=17457168](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u)
- 50 36. Nakeeb A, Pitt HA, Sohn TA, Coleman J, Abrams RA, Piantadosi S, et al.
51 Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. *Ann Surg*
52 1996;224(4):463-73; discussion 73-5. Available from
53 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u
54 [ids=8857851](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u)
- 55 37. Nathan H, Pawlik TM, Wolfgang CL, Choti MA, Cameron JL, Schulick RD. Trends in
56 survival after surgery for cholangiocarcinoma: a 30-year population-based SEER database
57 analysis. *J Gastrointest Surg* 2007;11(11):1488-96; discussion 96-7. Available from
58 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u
59 [ids=17805937](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u)
- 60 38. Kaido T, Imamura M. Unresectable hilar cholangiocarcinoma completely reduced by
61 external radiation therapy. *Hepatogastroenterology* 2005;52(63):725-7. Available from

- 1 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u
2 [ids=15966192](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u)
- 3 39. Birkmeyer JD, Sun Y, Wong SL, Stukel TA. Hospital volume and late survival
4 after cancer surgery. *Ann Surg* 2007;245(5):777-83. Available from
5 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u
6 [ids=17457171](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u)
- 7 40. Wong SL, Wei Y, Birkmeyer JD. Use of adjuvant radiotherapy at hospitals with
8 and without on-site radiation services. *Cancer* 2007;109(4):796-801. Available from
9 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u
10 [ids=17211840](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u)
- 11 41. Chapman JW, Hanna W, Kahn HJ, Lickley HL, Wall J, Fish EB, et al. Alternative
12 multivariate modelling for time to local recurrence for breast cancer patients receiving
13 a lumpectomy alone. *Surg Oncol* 1996;5(5-6):265-71. Available from
14 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u
15 [ids=9129140](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u)
- 16 42. McCreedy DR, Chapman JA, Hanna WM, Kahn HJ, Murray D, Fish EB, et al. Factors
17 affecting distant disease-free survival for primary invasive breast cancer: use of a log-
18 normal survival model. *Ann Surg Oncol* 2000;7(6):416-26. Available from
19 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u
20 [ids=10894137](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u)
- 21 43. Tai P, Chapman JA, Yu E, Jones D, Yu C, Yuan F, et al. Disease-specific
22 survival for limited-stage small-cell lung cancer affected by statistical method of
23 assessment. *BMC Cancer* 2007;7:31. Available from
24 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u
25 [ids=17311683](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u)
- 26 44. Boag J. Maximum likelihood estimates of the proportion of patients cured by
27 cancer therapy. *J R Stat Soc B* 1949(11):15-44.
- 28 45. Gamel JW, Vogel RL. Comparison of parametric and non-parametric survival
29 methods using simulated clinical data. *Stat Med* 1997;16(14):1629-43. Available from
30 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u
31 [ids=9257417](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u)
- 32 46. Mould RF, Boag JW. A test of several parametric statistical models for
33 estimating success rate in the treatment of carcinoma cervix uteri. *Br J Cancer*
34 1975;32(5):529-50. Available from
35 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u
36 [ids=1212415](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u)
- 37 47. Gore SM, Pocock SJ, Kerr GR. Regression Models and Non-Proportional Hazards in
38 the Analysis of Breast Cancer Survival. *Applied Statistics* 1984;33(2):176-95. Available
39 from <http://www.jstor.org/stable/2347444>
- 40 48. Wang SJ, Fuller CD, Kim JS, Sittig DF, Thomas CR, Jr., Ravdin PM. Prediction
41 model for estimating the survival benefit of adjuvant radiotherapy for gallbladder
42 cancer. *J Clin Oncol* 2008;26(13):2112-7. Available from
43 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u
44 [ids=18378567](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u)
- 45 49. Shinohara ET, Mitra N, Guo M, Metz JM. Radiation Therapy is Associated with
46 Improved Survival in the Adjuvant and Definitive Treatment of Intrahepatic
47 Cholangiocarcinoma. *Int J Radiat Oncol Biol Phys* 2008. Available from
48 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u
49 [ids=18472359](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u)
- 50 50. Jarnagin WR, Ruo L, Little SA, Klimstra D, D'Angelica M, DeMatteo RP, et al.
51 Patterns of initial disease recurrence after resection of gallbladder carcinoma and hilar
52 cholangiocarcinoma: implications for adjuvant therapeutic strategies. *Cancer*
53 2003;98(8):1689-700. Available from
54 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u
55 [ids=14534886](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u)
- 56 51. Park SW, Park YS, Chung JB, Kang JK, Kim KS, Choi JS, et al. Patterns and
57 relevant factors of tumor recurrence for extrahepatic bile duct carcinoma after radical
58 resection. *Hepatogastroenterology* 2004;51(60):1612-8. Available from
59 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u
60 [ids=15532789](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u)
- 61 52. de Castro SM, Kuhlmann KF, van Heek NT, Busch OR, Offerhaus GJ, van Gulik TM,
62 et al. Recurrent disease after microscopically radical (R0) resection of periampullary

1 adenocarcinoma in patients without adjuvant therapy. *J Gastrointest Surg* 2004;8(7):775-
2 84; discussion 84. Available from
3 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u
4 [ids=15531230](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u)

5 53. Hughes MA, Frassica DA, Yeo CJ, Riall TS, Lillemoe KD, Cameron JL, et al.
6 Adjuvant concurrent chemoradiation for adenocarcinoma of the distal common bile duct. *Int*
7 *J Radiat Oncol Biol Phys* 2007;68(1):178-82. Available from
8 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u
9 [ids=17276614](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u)

10 54. Cameron JL, Pitt HA, Zinner MJ, Kaufman SL, Coleman J. Management of proximal
11 cholangiocarcinomas by surgical resection and radiotherapy. *Am J Surg* 1990;159(1):91-7;
12 discussion 97-8. Available from
13 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u
14 [ids=1688486](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u)

15 55. Gerhards MF, van Gulik TM, Gonzalez Gonzalez D, Rauws EA, Gouma DJ. Results of
16 postoperative radiotherapy for resectable hilar cholangiocarcinoma. *World J Surg*
17 2003;27(2):173-9. Available from
18 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u
19 [ids=12616432](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_u)

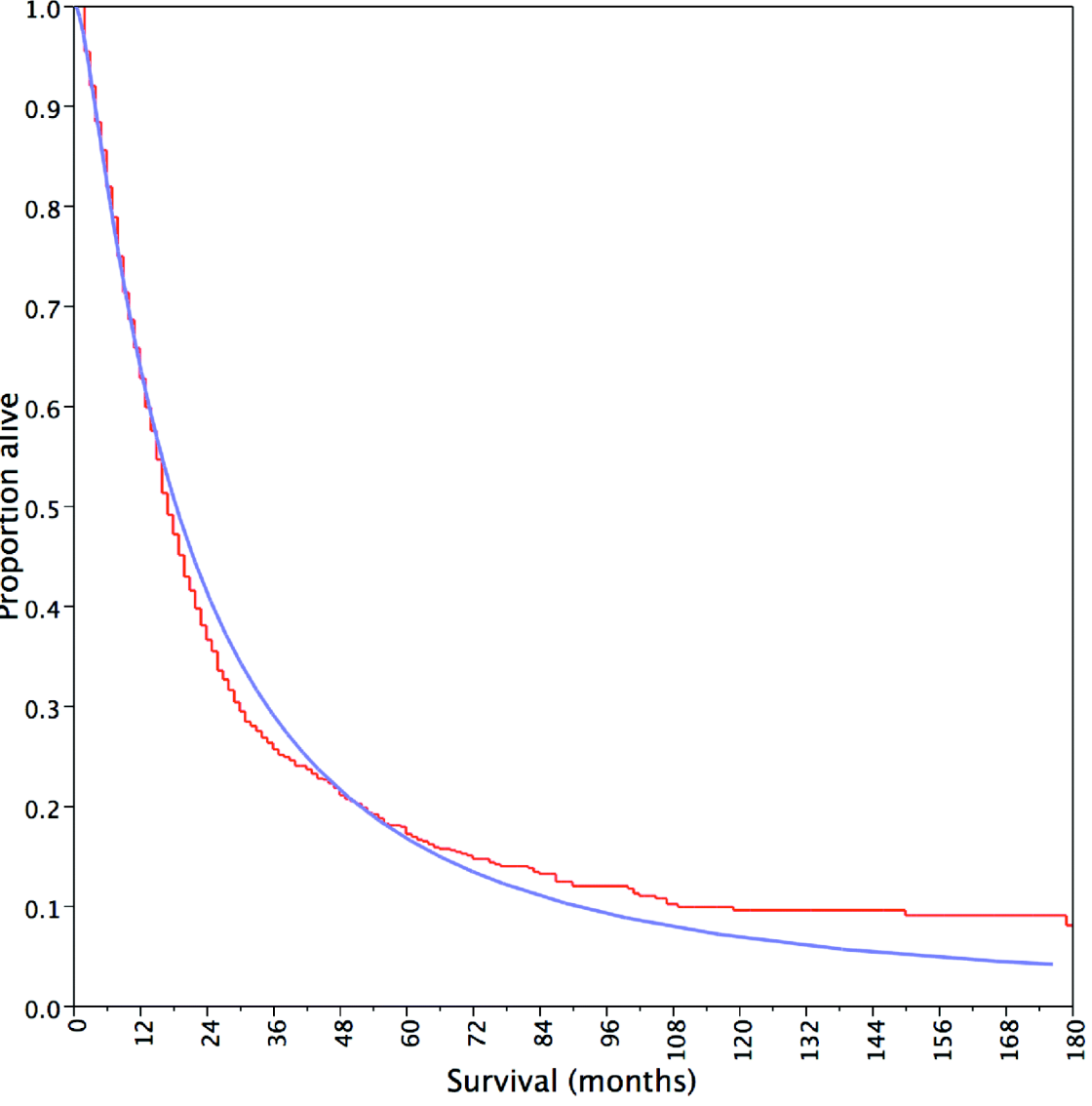
20 56. Czito BG, Fuller CD. Radiation therapy. In: Thomas CR, Fuller CD, eds. Biliary
21 tract and gallbladder cancer : diagnosis & therapy New York, NY: Demos, 2008:p.217-35.
22
23

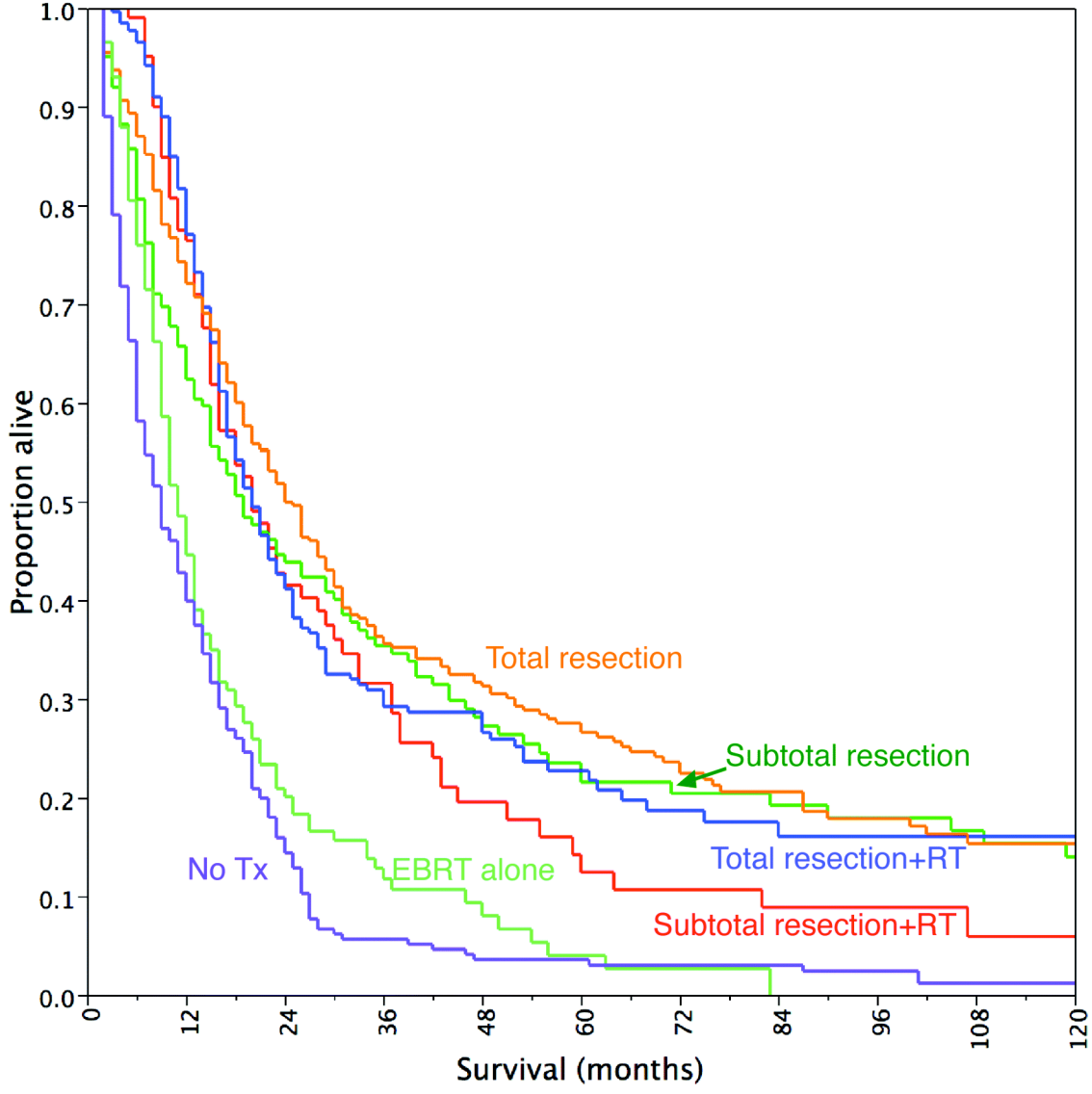
	Sex		Age		AJCC Stage					Pathologic Grade					Ethnicity			
	Female	Male	<65	>65	IA	IB	IIA	IIB	III	Grade I	Grade II	Grade III	Grade IV	Unknown	Black	Other (American Indian/Asian/Pacific Islander)	Unknown	White
Subtotal resection + RT	33	71	46	58	12	24	30	36	2	17	43	31	1	12	4	21	0	79
	2.10	4.53	2.93	3.70	0.76	1.53	1.91	2.29	0.13	1.08	2.74	1.98	0.06	0.76	0.25	1.34	0.00	5.04
Subtotal resection alone	73	114	84	103	45	29	59	51	3	29	67	59	2	30	14	24	1	148
	4.65	7.27	5.35	6.56	2.87	1.85	3.76	3.25	0.19	1.85	4.27	3.76	0.13	1.91	0.89	1.53	0.06	9.43
Total resection + RT	102	173	170	105	15	46	73	132	9	37	135	78	5	20	15	42	0	218
	6.50	11.03	10.83	6.69	0.96	2.93	4.65	8.41	0.57	2.36	8.60	4.97	0.32	1.27	0.96	2.68	0.00	13.89
Total resection alone	191	273	185	279	79	56	161	156	12	84	206	118	2	54	33	67	1	363
	12.17	17.40	11.79	17.78	5.04	3.57	10.26	9.94	0.76	5.35	13.13	7.52	0.13	3.44	2.10	4.27	0.06	23.14
EBRT alone	67	79	51	95	24	11	70	32	9	19	26	19	1	81	9	23	0	114
	4.27	5.04	3.25	6.05	1.53	0.70	4.46	2.04	0.57	1.21	1.66	1.21	0.06	5.16	0.57	1.47	0.00	7.27
No Tx	194	199	109	284	127	20	161	67	18	32	66	56	2	237	34	61	0	298
	12.36	12.68	6.95	18.10	8.09	1.27	10.26	4.27	1.15	2.04	4.21	3.57	0.13	15.11	2.17	3.89	0.00	18.99
All patients	660	909	645	924	302	186	554	474	53	218	543	361	13	434	109	238	2	1220
	42.07	57.93	41.11	58.89	19.25	11.85	35.31	30.21	3.38	13.89	34.61	23.01	0.83	27.66	6.95	15.17	0.13	77.76

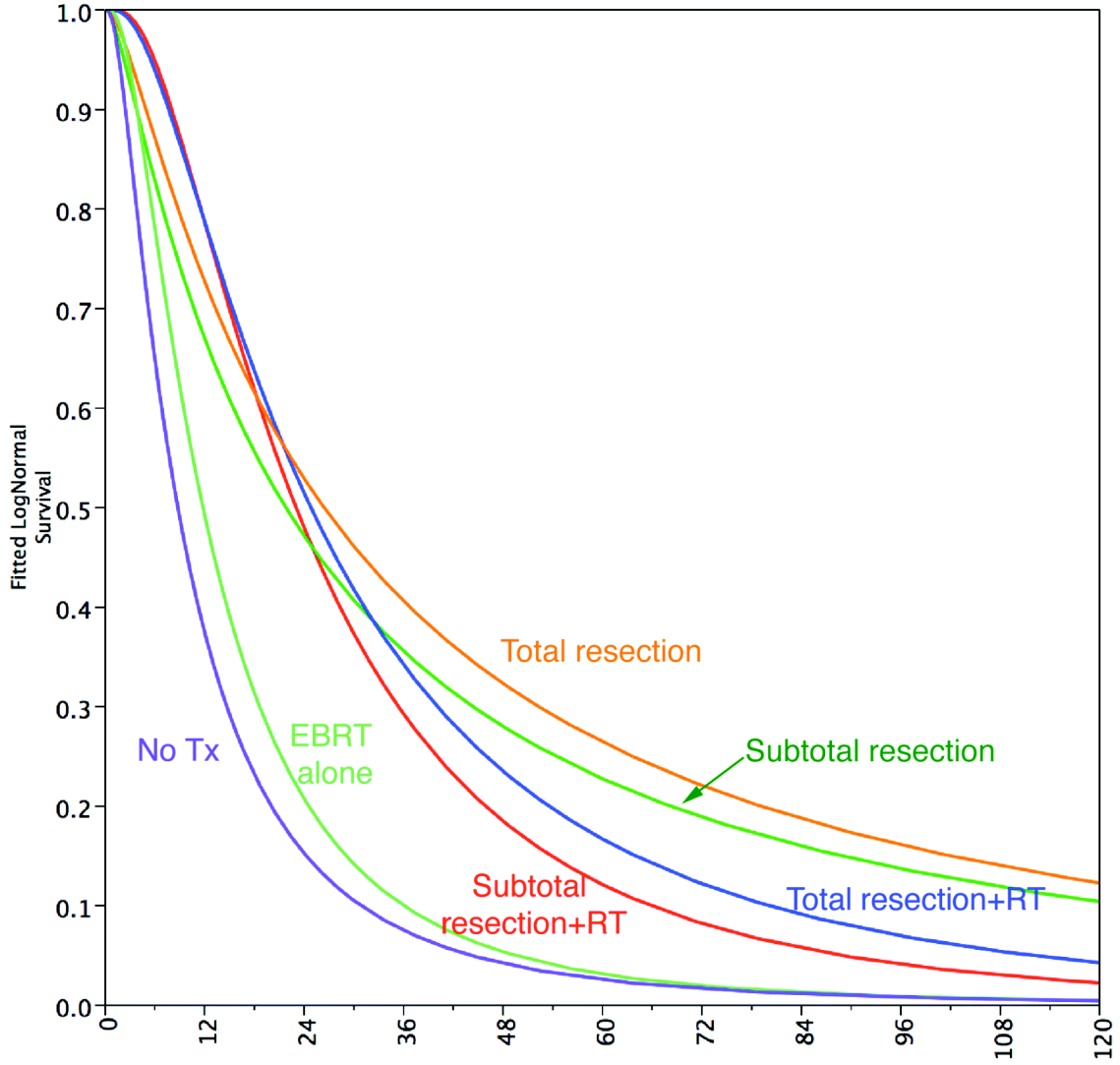
Table 1: Demographic features of included cases, stratified by treatment cohort (number above, percent of total cases, below).

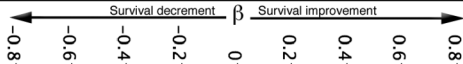
Table 2: Lognormal parametric survival regression results by therapeutic cohort.

Cohort	N Events	N Censored	β	SE	95% CI	Estimated median survival (months)	95% CI (months)	Whole Model Effect Likelihood
Subtotal resection + RT	75	28	0.30	0.10	0.10-0.49	24.46	19.56-30.57	<0.001
Subtotal resection alone	120	42	0.13	0.08	-0.03-0.29	20.70	17.38-24.66	
Total resection + RT	173	95	0.36	0.07	0.23-0.50	26.12	22.66-30.09	
Total resection alone	267	132	0.32	0.06	0.20-0.43	24.96	22.26-27.99	
EBRT alone	121	23	-0.40	0.08	-0.56- -0.24	12.18	10.13-14.64	
No treatment	245	46	0.00	-	-	8.97	7.88-10.20	









Grade [Grade I]

Grade [Grade II]

Grade [Grade III]

Grade [Grade IV]

Grade [Unknown]

Age at diagnosis

AJCC Stage [IA]

AJCC Stage [IB]

AJCC Stage [IIA]

AJCC Stage [IIB]

AJCC Stage [III]

Treatment [Subtotal resection + RT]

Treatment [Subtotal resection alone]

Treatment [Total resection + RT]

Treatment [Total resection alone]

Treatment [EBRT alone]

Treatment [No surgery/no RT]

Year of diagnosis

