

Trends in Survival after Surgery for Cholangiocarcinoma: A 30-Year Population-Based SEER Database Analysis

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Abstract The prognosis of patients with cholangiocarcinoma historically has been poor, even after surgical resection. Although data from some single-institution series indicate improvement over historical results, survival after surgical therapy for cholangiocarcinoma has not been investigated in a population-based study. We used the Surveillance, Epidemiology, and End Results database to identify patients who underwent surgery for cholangiocarcinoma from 1973 through 2002. Multivariate modeling of survival after surgery for intrahepatic cholangiocarcinoma showed an improvement in survival only within the last decade studied, resulting in a cumulative 34.4% improvement in survival from 1992 through 2002. In contrast, multivariate modeling of survival after surgery for extrahepatic cholangiocarcinoma revealed a 23.3% increase in adjusted survival per each decade studied, resulting in a cumulative 53.7% improvement from 1973 through 2002. We conclude that survival after surgery for extrahepatic cholangiocarcinoma has dramatically improved since 1973. Patients with intrahepatic cholangiocarcinoma, however, have achieved an improvement in survival largely confined to more recent years. We suggest that these trends are largely caused by developments in imaging technology, improvements in patient selection, and advances in surgical techniques.

Keywords Cholangiocarcinoma · Biliary tract neoplasms · SEER

Introduction

Cholangiocarcinoma is a malignancy arising from the ductal epithelium of the biliary tree. It is relatively uncommon, accounting for approximately 3% of all gastrointestinal cancers,¹ but historically it has carried a very poor prognosis. Cholangiocarcinomas are classified by location as either intrahepatic or extrahepatic, and extrahepatic

cholangiocarcinomas are often subclassified into those involving the hepatic duct bifurcation versus more distal lesions.² Temporal trends in the population-based survival of patients diagnosed with cholangiocarcinoma have been studied, but in limited detail. For intrahepatic cholangiocarcinoma (ICC), the 5-year survival has not changed significantly and has remained below 5% from 1975 to 1999.³ In contrast, the 5-year survival of patients with extrahepatic cholangiocarcinoma (ECC) increased from 11.7% in 1973–1977 to 15.1% in 1983–1987.⁴ These figures represent the aggregate prognosis of all patients with cholangiocarcinoma, most of whom are unresectable at presentation.⁵ Importantly, they may not accurately describe the outcomes of those patients who receive surgical therapy. Trends in survival after surgical therapy for cholangiocarcinoma have not been investigated in a population-based study.

Data on long-term survival of patients after surgical resection are limited to single-institution case series. Reported 5-year survival rates in recent surgical series (irrespective of margin status) vary widely, from 17 to 40% for ICC^{6–14} and from 9 to 41% for ECC.^{10,14–27} These

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single-institution data may not offer generalizable information and may not reflect outcomes in the general population. To determine whether there have been improvements in survival after surgery for cholangiocarcinoma on a population level, we investigated trends in the survival of patients undergoing cancer-directed surgery for both ECC and ICC over the last 30 years using the Surveillance, Epidemiology, and End Results (SEER) database.

Methods

This study was a retrospective analysis of prospectively collected data from the SEER database maintained by the National Cancer Institute.²⁸ The SEER database began in 1973 with data from seven cancer registries and today includes data from 17 cancer registries, representing 26.2% of the United States population. Compared to the general U.S. population, the SEER population is slightly more urban and has a slightly higher percentage of foreign-born individuals. Available data include patient demographics (e.g., age, gender, race), tumor data (histology, grade), SEER stage of disease, use of cancer-directed surgery, use of radiation therapy, and attributes of the patient's county of residence (e.g., urban-rural continuum code). Other data elements (e.g., American Joint Committee on Cancer staging, details of surgical therapy, tumor size, lymph node involvement) are consistently available only in more recent time periods.

Patients with cholangiocarcinoma were identified by the International Classification of Diseases for Oncology (ICD-O-3)²⁹ topography and histology codes that were chosen to minimize the possibility of inadvertently including metastatic lesions or non-cholangiocarcinoma hepatobiliary malignancies in the analysis (Table 1). Klatskin tumors that were coded as intrahepatic tumors were reclassified as extrahepatic, accounting for a known problem that erroneously cross-

references Klatskin tumors to the topography code for intrahepatic tumors.³⁰ The ICD-O-3 coding system does not allow perihilar tumors to be reliably distinguished from other tumors of the extrahepatic biliary tree, so all extrahepatic tumors were analyzed as one category. Only patients who were actively followed were included, and all patients diagnosed at autopsy or by death certificate were excluded. Those patients who underwent cancer-directed surgical procedures were identified using site-specific surgery codes 10–90 or surgery of primary site codes 10–90.

For descriptive analyses, crude survival statistics for ECC and ICC were generated using the Kaplan–Meier method³¹ and were then adjusted for expected death rates in SEER*Stat version 6.2.4 (Surveillance Research Program, National Cancer Institute, Silver Spring, MD). The resulting relative survival curves were compared using log-likelihood statistics.³² Differences in patient and tumor characteristics between decades were evaluated by Pearson's chi-squared test or Cuzick's nonparametric test for trend,³³ as appropriate. Trends in survival were then further explored using Cox proportional hazards models.³⁴ The SEER database codes cases with less than 1-month survival time as having zero survival time, an apparent truncation that would bias the survival analysis. To avoid this potential bias, we redefined survival times for these cases (81/2,107 for ECC and 15/591 for ICC), as 0.1 months. The variables considered in our analysis were age, gender, race, marital status at diagnosis, rural versus urban area of residence, SEER historic tumor stage, tumor grade, receipt of radiation therapy, SEER registry, and year of diagnosis.

Univariate and multivariate modeling of survival were performed using Cox proportional hazards models using the Efron method for ties. The appropriate functional forms of covariates were determined during exploratory data analysis using Martingale residuals. Entry of covariates into the multivariate models was generally determined by statistical significance in the univariate Cox models (using the likelihood ratio test). An exception was the variable for rural area of residence, which was force-entered in the model for ICC because of its significance in the multivariate model for ECC. Extensive sensitivity analyses of the final models were performed using likelihood ratio tests, Akaike information criteria, and stratified analyses to ensure that important variables or interaction terms had not been erroneously excluded. Adherence to the proportional hazards assumption was confirmed by Schoenfeld residuals and log–log plots.

The multivariate analyses were performed both by using complete records only and by including missing categories for covariates with missing data >5%. For ICC, these two approaches did not agree, so missing data were dealt with using multiple imputation.^{35–37} For ECC, these two approaches produced the same significant variables with

Table 1 ICD-O-3 Codes for Cholangiocarcinoma Identification

Site	Topography	Histology
Intrahepatic	220	8160, 8161
	221	8000, 8001, 8010, 8012, 8020, 8031, 8032, 8140, 8160, 8161, 8260, 8310, 8440, 8470, 8480, 8481, 8490, 8500, 8560
Extrahepatic	240	8000, 8001, 8010, 8012, 8020–8022, 8033, 8041, 8045, 8046, 8050, 8070, 8140, 8141, 8144, 8145, 8160, 8161, 8211, 8255, 8260, 8161, 8262, 8263, 8310, 8323, 8430, 8440, 8450, 8470, 8480, 8481, 8490, 8500, 8503, 8521, 8560, 8570, 8572
	241	8160
	Any	8162

<10% difference in the hazard ratios, so the results of the simpler model are reported. The final models included 591 of 591 ICC cases (with multiple imputation) and 1,529 of 2,107 ECC cases (using complete records only).

All tests of statistical significance were two-sided, and statistical significance was established at $\alpha=0.05$. Statistical analysis was performed using Stata/SE 9.2 for Windows (StataCorp, College Station, TX), and multiple imputation was performed using the ICE module for Stata.³⁸ This study was approved by the Johns Hopkins University School of Medicine Institutional Review Boards.

Results

Our selection criteria identified 591 patients with ICC and 2,107 patients with ECC who were diagnosed from 1973 through 2002 and underwent a cancer-directed surgical procedure. The range of follow-up times was 0–323 months for ICC and 0–321 months for ECC. Five-year relative survival (RS) over the entire period of study was 20.6% (crude survival 17.7%) for ICC and 20.5% (crude survival 17.1%) for ECC. There was no significant difference in overall relative survival (RS) between ECC and ICC ($P=0.221$) (Fig. 1).

Intrahepatic Cholangiocarcinoma

The only statistically significant trend in ICC patient and tumor characteristics (Table 2) was an increase in the

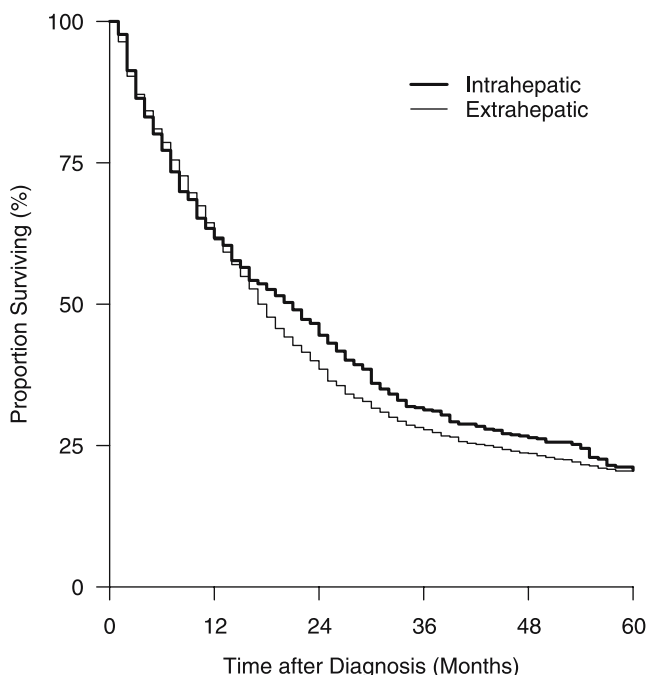


Figure 1 Relative Kaplan–Meier survival after surgery for cholangiocarcinoma, 1973–2002. ICC vs. ECC: $P=0.221$.

Table 2 ICC Patient and Tumor Characteristics

	1973– 1982	1983– 1992	1993– 2002	Total
Number of patients	42	129	420	591
Percent of total	7.1	21.8	71.1	100
Mean age at diagnosis (years)	62.5	62.5	63.2	63.0
Male (%)*	40.5	42.6	51.4	48.7
White (%)	81.0	81.4	84.7	83.7
Married (%)	60.6	64.5	67.1	66.1
Rural (%)	9.5	15.5	11.7	12.4
Stage (%)				
Localized	29.0	35.1	43.9	41.0
Regional	42.1	40.4	30.5	33.3
Distant	29.0	24.6	25.6	25.6
Grade (%)				
Well differentiated	35.3	16.4	18.4	18.8
Moderately differentiated	17.7	53.7	42.4	43.3
Poorly differentiated	47.1	26.9	36.8	35.6
Undifferentiated	0	3.0	2.3	2.3
Radiation therapy (%)	21.4	35.7	22.9	25.6
Survival <1 month (%)	2.4	4.7	1.9	2.5
Median survival (months)				
Crude	11	12	22	19
Relative	11	12	24	21
Five-year survival (%)				
Crude	11.9	15.0	19.7	17.7
Relative	14.0	17.2	22.9	20.6

Percentages exclude missing values.

*Significant test for trend ($P<0.05$). Tests for trend not performed for median and five-year survival.

proportion of male patients over this period ($P=0.046$). Because the type of cancer-directed surgery was not specified for a high proportion of patients (122 of 591), we were not able to analyze trends in the type of surgical procedure performed. Comparison of ICC survival between decades (Fig. 2) showed no significant difference between 1973–1982 and 1983–1992 ($P=0.547$), but survival improved between 1983–1992 and 1993–2002 ($P=0.015$). Because there was no difference in survival between the first two decades, and because there were only 42 patients in the first decade, we combined the first two decades in further analysis. Comparison of ICC survival in 1973–1992 compared against 1993–2002 showed a significant improvement ($P=0.003$), with 5-year RS rising from 16.5% to 22.9%. Comparisons of survival curves by stage at diagnosis (Fig. 3) were all highly significant ($P<0.001$). As expected, more advanced disease conferred a worse prognosis, with 5-year RS of 37.4% for localized disease, 14.7% for regional disease, and 5.3% for distant disease.

Although our exploratory univariate analysis revealed better survival for patients undergoing surgery for ICC in the last decade versus previous decades, this benefit did not persist in initial multivariate models that adjusted for

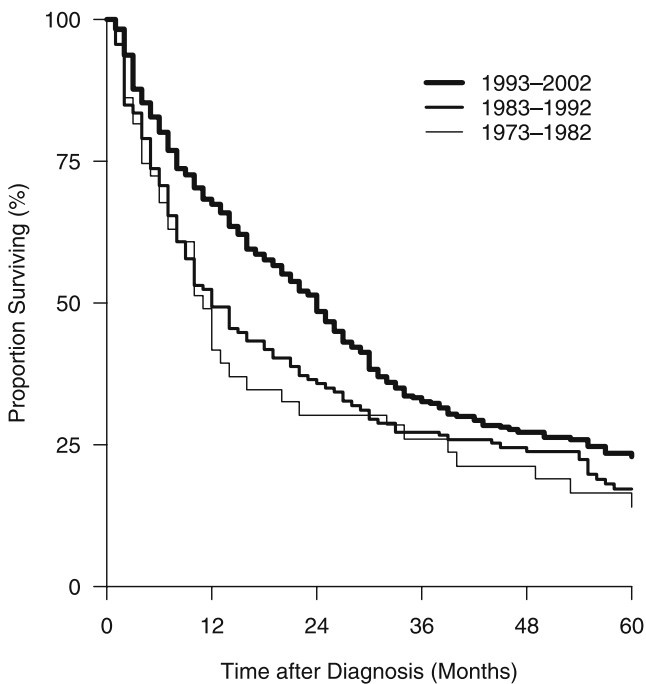


Figure 2 Relative Kaplan–Meier survival after surgery for ICC, by decade. 1973–1982 vs. 1983–1992: $P=0.547$. 1983–1992 vs. 1993–2002: $P=0.015$.

demographics, tumor characteristics, and receipt of radiation therapy. Having found no improvement in the aggregate survival of patients diagnosed in 1993–2002 versus 1973–1992, we explored the possibility that there has nevertheless been more recent incremental improvement by focusing on the year-to-year changes after 1992. Univariate Cox proportional hazards analysis for ICC (Table 3) showed the following variables to be significantly associated with decreased survival (P value for likelihood ratio test, percent of data missing): age per year over 80 years ($P=0.001$, 0%), tumor stage ($P<0.001$, 7.6%), tumor grade ($P=0.017$, 34.4%), and year of diagnosis per year after 1992 ($P<0.001$, 0%). These variables, together with rural area of residence (0.2% missing), were entered into the multivariate model for ICC. This approach revealed a year-to-year improvement in ICC survival over the years 1992–2002 that remained significant in multivariate analysis. In the final model of ICC survival (Table 3), age per year over 80 years and stage at diagnosis were strong predictors of worse survival, but the effect of tumor grade was not statistically significant. This analysis demonstrated a significant year-to-year improvement in ICC survival after 1992, corresponding to a cumulative 34.4% increase in adjusted survival from 1992 through 2002.

Extrahepatic Cholangiocarcinoma

Several ECC patient and tumor characteristics changed significantly over the period of this study (Table 4). On

average, patients in later decades tended to be older ($P=0.021$), and fewer came from rural areas ($P<0.001$). They also had higher stages of disease ($P=0.008$) and more aggressive tumor histology ($P<0.001$). There was no significant association between stage of disease and rural area of residence. The proportion of patients surviving less than 1 month after diagnosis (a surrogate marker of perioperative mortality) decreased over the three decades studied from 6.7% to 2.7% ($P<0.001$). Because the type of cancer-directed surgery was not specified for a high proportion of patients (771 of 2,107), we were not able to analyze trends in the type of surgical procedure performed.

Higher proportions of patients in later decades received radiation therapy ($P<0.001$). Receipt of radiation therapy was not significantly associated with tumor grade, but it was associated with tumor stage. Overall, 31.1% of patients with regional disease received radiation therapy, significantly more than those with localized (21.8%) or distant (22.0%) disease ($P<0.001$). Stratification by decade consistently demonstrated that patients with regional disease had the highest rate of radiation therapy, but this difference was statistically significant only in 1993–2002, when 39.2% of patients with regional disease received radiation therapy versus 23.6% of those with localized and 27.9% of those with distant disease ($P<0.001$). Stratification by stage showed that patients with every stage of disease were more likely to receive radiation therapy in later decades.

Comparison of ECC survival between decades (Fig. 4) showed significant improvements between 1973–1982 and

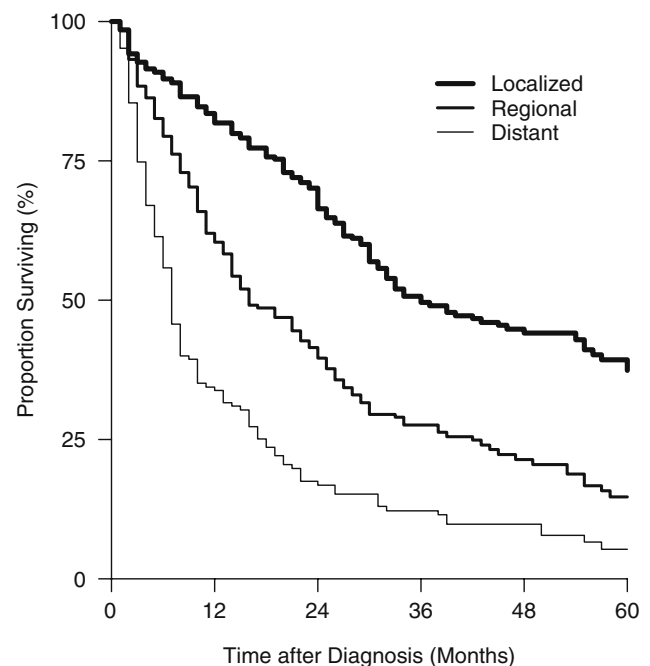


Figure 3 Relative Kaplan–Meier survival after surgery for ICC, by stage. All comparisons: $P<0.001$.

Table 3 Predictors of Survival after Surgery for ICC

Variable	Univariate			Multivariate		
	HR	95% CI	<i>P</i> Value*	HR	95% CI	<i>P</i> Value
Age at diagnosis [†]	1.80	1.33–2.45	<0.001	2.19	1.56–3.10	<0.001
Male	1.09	0.91–1.31	0.354	NE	–	
White	1.06	0.82–1.37	0.676	NE	–	
Married	0.85	0.70–1.04	0.112	NE	–	
Rural area of residence	0.82	0.62–1.08	0.163	0.76	0.56–1.02	0.067
Stage						
Localized	1.00	–	Ref.	1.00	–	Ref.
Regional	1.77	1.42–2.20	<0.001	1.71	1.36–2.15	<0.001
Distant	3.05	2.40–3.88	<0.001	2.98	2.31–3.85	<0.001
Grade						
Well differentiated	1.00	–	Ref.	1.00	–	Ref.
Moderately differentiated	1.07	0.80–1.43	0.641	1.07	0.79–1.44	0.679
Poorly differentiated	1.34	0.97–1.83	0.073	1.18	0.86–1.61	0.305
Undifferentiated	1.58	0.78–3.21	0.204	1.61	0.73–3.52	0.236
Radiation therapy	1.06	0.86–1.30	0.592	NE	–	
Year of diagnosis [‡]	0.58	0.45–0.76	<0.001	0.66	0.50–0.86	0.003

Results for SEER registry site are omitted for brevity but were not statistically significant.

*See text for *P* values for likelihood ratio tests, used to determine entry into multivariate model.

[†] Modeled continuously per year over 80 years; HR shown is per 5-year increment over 80 years.

[‡] Modeled continuously per year after 1992; HR shown is for the decade 1992–2002.

HR = hazard ratio, CI = confidence interval, Ref. = reference, NE = not entered into final model

1983–1992 ($P=0.004$) and again between 1983–1992 and 1993–2002 ($P=0.001$). These improvements corresponded to 5-year RS of 14.4%, 19.1%, and 24.5% in the three decades studied. Comparisons of survival curves by stage at diagnosis (Fig. 5) were all highly significant ($P<0.001$). As with ICC, more advanced disease conferred a worse prognosis, with 5-year RS of 33.7% for localized disease, 17.7% for regional disease, and 16.6% for distant disease.

Univariate Cox proportional hazards analysis for ECC (Table 5) showed the following variables to be significantly associated with decreased survival (*P* value for likelihood ratio test, percent of data missing): age per year over 60 years ($P<0.001$, 0%), male gender ($P=0.007$, 0%), marital status ($P=0.006$, 5.7%), rural area of residence ($P<0.001$, 1.4%), tumor stage ($P<0.001$, 3.2%), tumor grade ($P<0.001$, 22.7%), radiation therapy ($P=0.003$, 0%), and year of diagnosis per year after 1973 ($P<0.001$, 0%). These variables were entered into the multivariate model for ECC. In the final model of ECC survival (Table 5), age over 60 years and rural area of residence were strong predictors of worse survival. Advanced stage of disease and histological de-differentiation also conferred a worse prognosis. Gender, marital status, and radiation therapy did not show statistically significant effects on survival in the multivariate model. In sharp contrast to ICC, there was a dramatic improvement in adjusted ECC survival over the entire 30-year period studied, corresponding to a 23.3% increase in adjusted survival per decade and a cumulative 53.7%

improvement from 1973 through 2002. A sensitivity analysis that restricted the cohort to those patients surviving at least 1 month did not yield qualitatively different conclusions, suggesting that the observed improvement was not solely a result of decreasing perioperative mortality.

Discussion

Historically, analyses of patient survival after surgery for cholangiocarcinoma have been restricted to single-institution series. Although such institutional data may offer great depth of clinical information, they may be limited by poor generalizability and potential selection bias. In this population-based study, we analyzed long-term survival after cancer-directed surgery for cholangiocarcinoma using data derived from a national cancer registry. We found 5-year crude survival rates of 17.7% for ICC and 17.1% for ECC over the period 1973–2002. For ICC, recent single-institution surgical series have reported 5-year crude survival rates of 17–40%.^{6–14} Even the highest 5-year crude survival rate for ICC in our analysis, 19.7% in the decade 1993–2002, falls below all except one of these single-institution rates.⁶ For ECC (including perihilar tumors), recent single-institution surgical series have reported 5-year crude survival rates of 9–41%.^{10,14–27} Again, our analysis found 5-year crude survival rates for ECC that were at the lower end of this spectrum. These results are not surprising, as the results we

Table 4 ECC Patient and Tumor Characteristics

	1973– 1982	1983– 1992	1993– 2002	Total
Number of patients	434	623	1,050	2,107
Percent of total	20.6	29.6	49.8	100
Mean age at diagnosis (years)*	67.4	66.7	65.6	66.3
Male (%)	55.5	55.4	58.1	56.8
White (%)	85.5	81.1	81.2	82.1
Married (%)	62.7	66.6	67.9	66.6
Rural (%)*	16.8	14.5	8.7	12.1
Stage (%)*				
Localized	31.4	30.2	22.1	26.4
Regional	60.4	57.4	71.3	65.0
Distant	8.2	12.4	6.7	8.7
Grade (%)*				
Well differentiated	37.9	30.7	18.4	24.9
Moderately differentiated	37.9	42.8	49.6	45.9
Poorly differentiated	22.6	24.3	30.7	27.6
Undifferentiated	1.7	2.3	1.3	1.7
Radiation therapy (%)*	10.8	27.6	34.7	27.7
Survival <1 month (%)*	6.7	3.9	2.7	3.8
Median survival (months)				
Crude	12	16	19	17
Relative	14	16	20	18
Five-year survival (%)				
Crude	11.8	15.9	20.8	17.1
Relative	14.4	19.1	24.5	20.5

Percentages exclude missing values.

*Significant test for trend ($P<0.05$). Tests for trend not performed for median and five-year survival.

report are not restricted to specialized centers, and single-institution series are susceptible to publication bias.

Our analysis offers a more generalizable assessment of the progress made in the surgical therapy of cholangiocarcinoma. In particular, we defined cancer-directed surgery as it is defined in the SEER database, including a range of procedures from cryoablation and enucleation to hepatectomy and pancreaticoduodenectomy. Some of these less aggressive practices might not be considered oncologically adequate at specialized centers, which may also explain the poorer survival seen in this analysis as compared to single-institution series. Importantly, however, our analysis reflects the full range of practice patterns in the treatment of cholangiocarcinoma in the United States, not just the results of specialized centers employing more aggressive surgical approaches.

We did not find an improvement in ICC survival until the last decade studied. During the period from 1992 through 2002, there was a cumulative 34.4% increase in adjusted survival after surgery. Unfortunately, the SEER data do not allow us to specifically identify the factors responsible for this improvement, but based on the

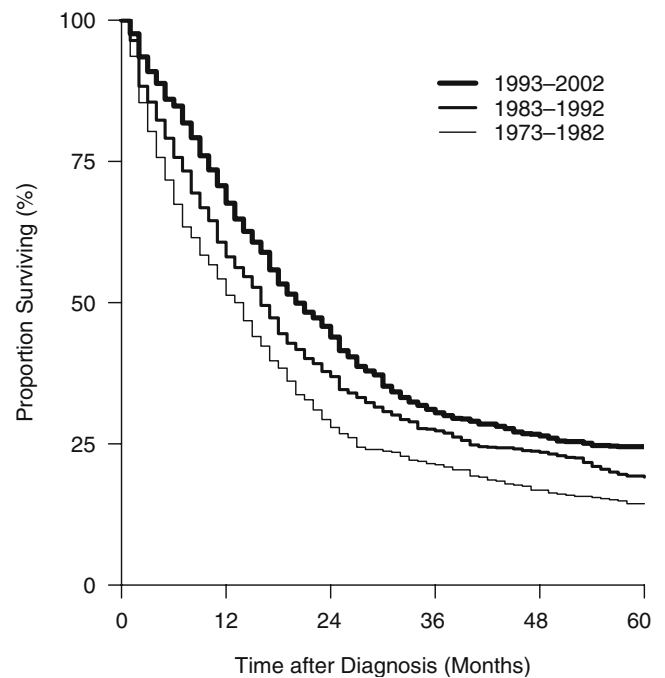


Figure 4 Relative Kaplan–Meier survival after surgery for ECC, by decade. 1973–1982 vs. 1983–1992: $P=0.004$. 1983–1992 vs. 1993–2002: $P=0.001$.

substantial collective experience with cholangiocarcinoma at our institution there are several factors that we believe have likely played an important role. The improvement in ICC survival may reflect improving patient selection over time, likely as the result of improvements in imaging technology, such as multidetector computed tomography,

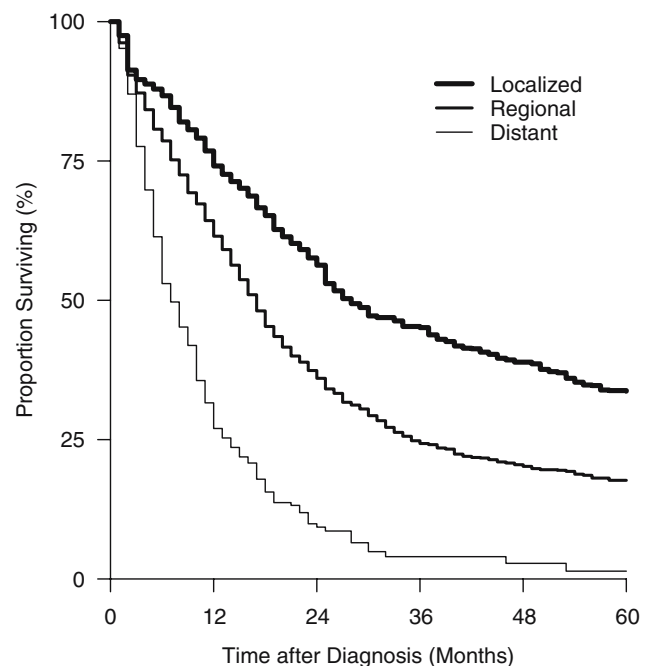


Figure 5 Relative Kaplan–Meier survival after surgery for ECC, by stage. All comparisons: $P<0.001$.

Table 5 Predictors of Survival after Surgery for ECC

Variable	Univariate			Multivariate		
	HR	95% CI	<i>P</i> value*	HR	95% CI	<i>P</i> value
Age at diagnosis [†]	1.16	1.12–1.19	<0.001	1.14	1.10–1.19	<0.001
Male	0.88	0.80–0.97	0.007	0.98	0.87–1.10	0.724
White	0.99	0.88–1.12	0.884	NE	–	
Married	0.87	0.78–0.96	0.005	0.93	0.82–1.05	0.257
Rural area of residence	1.31	1.14–1.51	<0.001	1.43	1.21–1.69	<0.001
Stage						
Localized	1.00	–	Ref.	1.00	–	Ref.
Regional	1.50	1.34–1.68	<0.001	1.61	1.40–1.84	<0.001
Distant	3.34	2.78–4.00	<0.001	3.57	2.84–4.49	<0.001
Grade						
Well differentiated	1.00	–	Ref.	1.00	–	Ref.
Moderately differentiated	1.17	1.02–1.34	0.024	1.19	1.04–1.38	0.015
Poorly differentiated	1.57	1.36–1.82	<0.001	1.67	1.43–1.95	<0.001
Undifferentiated	1.66	1.11–2.48	0.013	1.38	0.91–2.09	0.124
Radiation therapy	0.85	0.77–0.95	0.003	0.93	0.82–1.05	0.258
Year of diagnosis [‡]	0.82	0.78–0.87	<0.001	0.77	0.71–0.83	<0.001

Results for SEER registry site are omitted for brevity but were not statistically significant.

*See text for *P* values for likelihood ratio tests, used to determine entry into multivariate model.

[†] Modeled continuously per year over 60 years; HR shown is per each 5-year increment over 60 years.

[‡] Modeled continuously per year after 1973; HR shown is per each decade after 1973

HR = hazard ratio, CI = confidence interval, Ref. = reference, NE = not entered into final model

that allow better preoperative assessments of resectability. Also, improvements in the safety of hepatic resection³⁹ have likely led to the increased utilization of aggressive hepatic resection for ICC, contributing to improved oncologic results and increased long-term survival. Unfortunately, details of the type of surgical resection in the SEER database are inconsistently available, and margin status information is absent, preventing us from further investigating these hypotheses.

We noted improvements in ECC survival over the entire 30-year time period studied, corresponding to a 23.3% increase in adjusted survival per decade and a cumulative 53.7% improvement from 1973 through 2002. As with ICC, the improvement in ECC survival may reflect improvements in preoperative imaging and patient selection, as well advances in surgical techniques. Decreases in the morbidity and mortality of complex hepatobiliary procedures may have expanded the use of such operations in ECC patients. For example, advances in the safety of pancreaticoduodenectomy are well documented.⁴⁰ Technical advances may also have resulted in a higher proportion of margin-negative resections, resulting in fewer patients undergoing inadequate resections. For example, concomitant hepatic resection for hilar cholangiocarcinoma has recently gained popularity as a strategy to achieve adequate margins.^{14,19,22,27} It is possible that the increased use of hepatic resection in hilar cholangiocarcinoma has resulted in better oncologic results. Again, the SEER data do not

permit the identification of such specific reasons for the observed trends.

The proportion of surgical patients surviving less than 1 month after diagnosis of ECC has decreased from 6.7% in the first decade to 2.7% in the last. Although these figures are not, strictly speaking, measures of 30-day surgical mortality, this decrease in 1-month survival likely indicates decreasing perioperative mortality. This interpretation assumes that the interval from diagnosis to surgery has not lengthened over the last three decades. More likely, this interval has either not changed or has shortened, which would underestimate perioperative mortality in the early years and overestimate it in the later years, resulting in a bias toward the null. Furthermore, our analysis demonstrates that an improvement in long-term ECC survival persists even when the effect of decreasing perioperative mortality is removed.

Despite these overall improvements, patients from rural areas who undergo surgery for ECC experience a 43% decrease in adjusted survival compared with those who live in more metropolitan areas. Rural patients did not, in fact, present with more advanced disease, suggesting that differences in survival were not related to delayed diagnosis. Instead, such differences may be related to discrepancies in access to specialized care or adequate follow-up, although we note that a rural area of residence does not necessarily imply treatment at a rural hospital. Another possible explanation is that the effect of rural area of residence

was confounded by socioeconomic status. Socioeconomic data are only available in later years of the SEER database, so we were unable to test this hypothesis.

The use of radiation therapy in ECC patients increased from 10.8% in the first decade to 34.7% in the last. Patients with regional disease were especially likely to receive radiation therapy. Most prior studies show that adjuvant radiation does not confer a survival benefit in cholangiocarcinoma,^{41–43} although some evidence suggests that higher doses of radiation and concurrent chemotherapy may be of benefit.^{44,45} In the present study, the increasing use of adjuvant radiation therapy demonstrated no independent survival benefit, underscoring the need for rigorous prospective evaluation of its efficacy in resected patients.

This study is limited primarily by the depth of surgical data in the SEER database. In addition to the lack of margin status data, the level of detail and completeness of data on tumor size, lymph node involvement, and details of resection have varied since 1973, such that comparisons that account for these factors over all 30 years are not possible. Although we did have some data on radiation therapy, we did not have any information on the use of chemotherapy. Finally, the ICD-O-3 coding scheme used in the SEER database did not allow us to separate perihilar tumors from other ECC, limiting comparisons with other studies.

Alternative explanations for the improvements we describe include the possibilities of lead time bias and stage migration. Even today, just as 30 years ago, patients with cholangiocarcinoma are typically diagnosed only after they develop symptoms of obstructive jaundice. Lead time bias is therefore unlikely to play a role in explaining these findings. Stage migration may have also played a role, but because we focused on a surgical population we would expect that patients would be appropriately upstaged at the time of surgery, even if their preoperative workups did not reveal the full extent of their disease. This would have resulted in more uniform coding of stage than in a nonsurgical population, for whom stage migration would be a more important issue.

In conclusion, this population-based analysis demonstrates that survival after surgery for extrahepatic cholangiocarcinoma has dramatically improved since 1973. Patients with intrahepatic cholangiocarcinoma, however, have achieved an improvement in survival largely confined to more recent years. We suggest that improvements in imaging technology, patient selection, and surgical techniques are largely responsible for these improvements. The discrepancies between the survival rates we report and those reported in single-institution series deserve further investigation to determine whether they are the result of publication bias, patient selection, disease characteristics, or disparities in access to adequate care. Finally, these

population-based survival statistics demonstrate that extrahepatic and intrahepatic cholangiocarcinoma continue to carry very poor prognoses. Despite incremental advances in the surgical therapy of these biliary tract malignancies over the last three decades, there remains much opportunity for improvement.

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DISCUSSION

Bryan M. Clary, M.D. (Durham, NC): This is another very nice paper. I must admit when I read reports of this nature, I am not always sure what to do with them. Number one, I would like to commend you on your manuscript. This type of a study is all about the statistics, and in your manuscript's methods section you very eloquently state the methods that you use, and you also include a number of very relevant references to help guide individuals such as myself as to what the statistics mean.

Again, the problem is what you gain from this. You in general get a look at how we are doing in certain eras, and trying to come up with the explanations as to why that is, is really pure speculation. One of the main concerns I have with the intrahepatic cholangio population is just the definition as to what is an intrahepatic cholangiocarcinoma during different eras. In eras past, including the '70s and '80s, this was essentially adenocarcinoma of unknown primary in the liver, and really it was a diagnosis of exclusion for cytokeratin staining was not as sophisticated as it is now. And so I would venture to guess that one of the problems that you have in this series is that a large proportion of your intrahepatic cholangiocarcinomas were adenocarcinomas metastatic from other sites such as occult pancreatic cancers which were very common with poor imaging back then, and possibly even gastric cancers and lung cancers, et cetera. I wonder if you might make some comment to that specific issue.

The thing that clearly isn't brought out in this, which you already mentioned, is that of chemotherapy and the issue about rural populations not doing as well. Again, that explanation may not be a surgical issue but it instead that in their follow-up they don't have

medical oncologists who were offering chemotherapy, et cetera. But again, those types of things are pure speculation.

Hari Nathan, M.D. (Baltimore, MD): Dr. Clary, thank you very much for your review of our manuscript and your insightful questions. Your first question was whether the intrahepatic cholangiocarcinomas are truly cholangiocarcinomas. We specifically designed our selection criteria with that issue in mind. The SEER data allow the identification of tumors based on two codes: one is a topography code indicating the location of the tumor and the other is a histology code indicating the pathological diagnosis. For tumors that were located in the liver, the intrahepatic cholangiocarcinomas, we specifically excluded adenocarcinomas that were not otherwise specified and other lesions that we could not specifically identify as being cholangiocarcinomas. We were less stringent, for example, in the extrahepatic biliary tree, where we might accept a histological diagnosis of adenocarcinoma, not otherwise specified. But in the liver or at the ampulla we were much more strict about requiring a specific histological diagnosis of cholangiocarcinoma. So we feel very comfortable that we have excluded metastatic malignancies and other adenocarcinomas not arising from the bile ducts.

With regard to chemotherapy and rural patients, you are correct in

pointing out that one of the weaknesses of the study is that we just don't have the depth of data in this database that would be required to specifically identify what the reasons for the improvements are. But I think this study provides two important pieces of information.

One, it gives us a sense as to the generalizability of the results that we see reported from single institutions. In terms of prognostication for patients and to get a general sense of how we are doing in the country as a whole, it is important to have that reality check of not exclusively relying on reports from specialized centers to guide our impression of how we are doing across the entire country.

And the other contribution is that it points to a direction for future research. There are other data that are available that may help us to identify why exactly, for example, rural patients with ECC have worse survival. The SEER-Medicare data, for example, which we are currently trying to acquire, do include information on chemotherapy receipt. So as we investigate further why these disparities do exist in patient outcomes, not just with cholangiocarcinoma but with a variety of malignancies, I think that this study and others like it give us a starting point. In future work, we hope to move from describing the differences to identifying the reasons for these disparities and actually trying to do something about them.

Thanks again for your comments and questions.