PROXIMITY TO SPECIALTY CARE AFFECTS OUTCOMES FOR BILIARY CANCERS

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ABSTRACT

Background: The management of biliary cancers is complex and requires a multidisciplinary approach. It is unknown how treatments are accessed by patients who live in areas that are remote from centers of expertise, and how access impacts resource use and survival. We conducted a population-based study of patients with biliary cancers to define the effects of proximity to specialists on survival outcomes, resource use and cost.

Methods: Clinical characteristics and outcomes of 1,610 patients with biliary cancers diagnosed in Alberta, Canada from 2001 to 2015 were determined. Driving time, physician billings, and types of medical services associated with 117,381 medical encounters were tracked throughout the entire clinical course. Proximity to specialty care was categorized according to driving time to the nearest specialist.

Results: Patients living ≥120 minutes from the nearest HPB surgeon and ≥120 minutes from the nearest cancer center had a significantly decreased survival ($P=0.0003$ and $P=0.001$, respectively). Location of residence was not associated with advanced stage, or probability of undergoing surgery or a biliary drainage procedure. Patients who lived ≥120 minutes from a cancer center were less likely to receive chemotherapy ($P=0.007$). Subgroup analysis demonstrated that the effect of travel time was especially pronounced in those who received only best supportive care, and in those who had biliary drains.

Interpretation: Geography and accessibility to specialty care impacts survival in biliary cancers. Further study is required to understand how patients with biliary drains and receiving best supportive care are affected by their residence. This will aid in the identification of strategies to provide improved care for that subgroup that is particularly affected by geography.

INTRODUCTION

Biliary cancers (intrahepatic and extrahepatic cholangiocarcinoma, gallbladder cancer, ampullary cancer) are rare tumors that are generally associated with a poor prognosis. Surgery is the only potentially curative option, although only a minority are candidates for resection.[1] Moreover, surgery can be technically difficult and is associated with very high morbidity and mortality rates.[2,3] In patients with advanced disease, palliative chemotherapy is advantageous if performance status is adequate.[4] However, the disease is often complicated by jaundice and sometimes sepsis, and performance status is often too poor to deliver chemotherapy. The mainstay of palliation consists of achieving stable biliary drainage, which generally requires repeated instrumentation of the biliary tract over the disease course.[5-7] In all, the management of biliary cancers is complex and requires the coordination of multiple specialties.

For the optimal management of biliary cancers, it is important that a patient has sufficient access to the appropriate facilities and specialists including hepatobiliary surgeons, oncologists, and interventional radiologists. This includes emergency access to experienced clinicians. In addition, ideally, it is important that there is some degree of continuity of care, so that a management plan can be followed. For patients living far from major population centers, these features of care are difficult to deliver, even in a developed country with universal insurance. Our objective was to understand what disparities of care exist as a function of driving time to tertiary and quaternary care facilities, and how these disparities affect outcomes, including survival and cost.

Few data are available that provide a comprehensive picture of the needs of biliary cancer patients, from diagnosis to death. Moreover, little is known about the adequacy of care delivery for patients who live at a distance from specialists in the care of biliary cancers in a universal health system. We postulated that individuals who lived more remotely would have worse survival due to difficulty accessing highly expert care. We conducted this population-based study to understand the needs of biliary cancer patients as they navigate the health care system, and to understand the relationship of geography with care delivery and clinical outcomes.

METHODS

Data and Study Population

This study was approved by the Health Research Ethics Board of Alberta – Cancer Committee (ID: HREBA.CC-17-0110). The Alberta Cancer Registry (ACR), provincial physician claims, hospital discharge abstract, ambulatory care, provincial population registry, and 2011 census data were used. Physician claims data were used to track all medical encounters. Data from these diverse sources could be linked by a unique provincial health number. Charlson comorbidity index (CCI) for each patient was calculated by well-defined algorithms using discharge abstracts and ambulatory care data within a year prior to diagnosis. The neighborhood socioeconomic status (SES) including average income and proportion with a post-high school education were derived from 2011 census data. Patient postal code was derived from provincial population registry data. Postal code was used to link to census data, as well as to calculate the driving times to the nearest facility with a hepatopancreaticobiliary (HPB) surgeon and to the nearest cancer centers. Travel times for each medical visit were calculated using Google map application programming interfaces (APIs)[8], based on driving times at noon on a weekday.

The study included all cases of biliary cancers diagnosed in Alberta from September 1, 2001 to December 31, 2015. This included intrahepatic cholangiocarcinoma (IHCC), extrahepatic cholangiocarcinoma (EHCC), gallbladder cancer (GBC) and ampullary cancer (AmpC). All cases were adenocarcinoma histology. 107 (6.2%) patients with invalid provincial health numbers (non-residents of Alberta) or without follow-up after diagnosis or primary treatment were excluded.

Study outcomes

The primary outcome was overall survival, beginning from the date of tissue diagnosis or first biliary intervention (whichever was first). Median follow-up was 6.8 months (interquartile range (IQR): 2.5 – 16.8 months) with 1,299 patients (82.9%) followed until date of death. The median follow-up for the remainder was 49.9 months (IQR: 23.1 – 92.9 months). Secondary outcomes included proportion with delayed diagnosis; treatments delivered; treatment costs; and patient costs.

Statistical analysis

Statistics were analyzed with SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC), and data visualization was performed using Tableau version 10.3 (Seattle, US). Descriptive statistics were used to characterize the study cohort. Continuous data were compared using t-test. Chi-squared test was used for comparison of categorical variables. Cox proportional hazard regression was conducted to evaluate the effects of driving time on overall survival, adjusting for related risk factors including age, sex, neighbourhood SES, resection, chemotherapy, tumor type (IHCC, EHCC, GBC or AmpC), presence of stage IV disease, year of diagnosis (from 2001 to 2015), and CCI. Multivariate logistic regression was conducted to evaluate the effect of driving times on treatment types and on stage at diagnosis. Two sided p-value ≤0.05 was considered statistically significant.

In assessing treatment types, medical visits and physician billings, we considered three intervals during each patient's disease trajectory. The pre-diagnosis interval included the 3 months prior to date of diagnosis; the post-diagnosis interval included all activity from date of diagnosis to the ensuing 24 months; and the end-of-life interval included the final 8 weeks of life. For patients whose life span (after diagnosis) was ≤8 weeks, only activity in the final interval could be described.

RESULTS

Incidence and Geographic Distribution of Biliary Cancers

During the 15 year study period, there were 1,610 cases, including 386 IHCC, 396 EHC, 531 GBC, and 243 AmpC. The provincial annual incidence of the 4 types of tumors were 0.9, 1.0, 1.3, and 0.6 per 100,000 population, respectively. The geographic distribution of cases throughout the province is depicted in Figure 1. Patient characteristics are summarized in Table 1 and Supplementary Table 1. There were 114 patients who lived at least 120 minutes' driving time from the nearest cancer center and 245 patients who had to drive 120 minutes or more to the nearest HPB surgeon. Among the study cohort, 1067 (62.1%) patients received best supportive care (BSC); 270 (15.7%) patients received chemotherapy alone; 274 (16.0%) patients received surgery alone; and 107 (6.2 %) patients received surgery and chemotherapy. Biliary drains were inserted in 182 patients; 777 biliary drains in total were inserted.

Survival as a Function of Residence

As expected, median survival was best for patients who underwent resection (35.6 months, confidence interval [CI]: 26.2–49.6 months), followed by patients who had palliative chemotherapy (12.0 months, 95% CI: 10.6–13.4); it was worst for patients who received only best supportive care (4.6 months, 95% CI: 4.1–5.1 months). Survival associated with AmpC (24.5 months, 95% CI: 18.9–27.2 months) was considerably better than survivals for IHCC (5.7 months, 95% CI: 4.7–7.0 months); EHCC (10.2 months, 95% CI: 9.1–12.5 months); and GBC (8.0 months, 95% CI: 6.7–9.6 months).

Without adjusting for other factors, overall survivals were not significantly different according to driving time to the nearest HPB surgeon, cancer center or interventional radiologist (categorized in 5 groups, Table 1 and Supplementary Table 1). However, after adjusting for age, sex, comorbidities, income and education levels, treatment (surgery or chemotherapy), stage and tumor type, longer driving time to the nearest HPB surgeon and driving time to the nearest cancer center were significantly associated with decreased survival ($P=0.0003$ and $P=0.001$, respectively). The association was particularly pronounced for driving time ≥120 minutes. Living ≥120 minutes from the nearest HPB surgeon was significantly impactful ($P= 0.002$; Table 2), and residence ≥ 120 minutes from the nearest cancer center was also associated with a decreased survival ($P=0.029$; Supplementary Table 2). Survival outcomes were better in cancers diagnosed from 2010 onwards ($P=0.004$; Table 2) in the multivariate model, and the number of biliary drains was also a significant factor associated with survival ($P=0.025$; Table 2). Further analyses focused on outcomes as a function of driving time to the nearest HPB surgeon (≥120 versus <120 minutes), since that had the greatest impact on survival.

A subgroup analysis was performed (Figure 2). The effect of driving time to the nearest HPB surgeon was pronounced for subgroups of older age, lower CCI, and those who did not receive chemotherapy or surgery. The effect was also significant for patients who had biliary drainage. Interestingly, in the tumor type subgroups the effect of driving time was greatest for ampullary cancer and, to a lesser degree, IHCC.

Disease Stage and Treatment as a Function of Residence

Treatments strategies changed during the fifteen year study period. While the proportion of patients with EHCC, GBC and AmpC who had surgery remained stable, the proportion of patients with IHCC who underwent resection increased from 18.8% prior to 2010 to 36.6% from 2010 onwards (P = 0.001). In the same time periods, chemotherapy was administered to more patients with EHCC (16.0% to 39.7%; P=0.0003), GBC (13.2% to 35.7%; P<0.0001) and AmpC (8.0% to 18.4%), but did not change significantly for IHCC (24.8% to 25.0%).

A number of secondary outcomes were evaluated as a function of driving time from tertiary and quaternary care centers (Supplementary Table 3). Disease stage at diagnosis (a surrogate for delayed diagnosis) was not affected by driving time to HPB surgeon as estimated by the proportion of cases with stage IV disease (P=0.89). Treatment strategies were affected by proximity to specialty care. Driving time to the nearest HPB surgeon did not affect the likelihood of receiving chemotherapy (P= 0.17), except for patients with EHCC diagnosed from 2010 onwards (42.1% vs. 23.3%; P= 0.05). On the other hand, patients living ≥120 minutes from the nearest cancer center were less likely to receive chemotherapy (P=0.007). The likelihood of having surgery and receiving only best supportive care was unrelated to residence.

It was considered that survival could be impacted by timely access to gastroenterology or interventional radiology if a complication such as biliary sepsis occurred. The number of biliary drainage procedures was tracked. A total of 2,027 drains was inserted in 861 patients. The average number of biliary drainage procedures per person was the same in patients who lived near and far (1.3 vs. 1.2 drains per person; P=0.632). Of patients who had drains, the proportion who had 2 or more drainage procedures was the same in patients who lived far and near (56.0% vs 55.8%, respectively; P=0.72). Unexpectedly, in the final 8 weeks of life, the probability of having a biliary drainage procedure was slightly higher in patients who lived > 120 minutes away (19.8% vs. 15.7%, P=0.080, adjusted).

Resource Utilization and Patterns of Care as a Function of Residence

In the entire cohort, there were 117,381 physician encounters. The type and number of physician encounters were evaluated during the disease trajectory. The highest concentration of visits occurred in the final 8 weeks of life (Figure 3A). The number of visits to physicians was not significantly different during any of the time intervals, when comparing patients who lived near and far from the nearest HPB surgeon. However, in patients who lived ≥120 minutes from the nearest HPB surgeon, in the period following diagnosis, there was a higher frequency of emergency room visits (P<0.0001). This was particularly prominent in individuals treated with chemotherapy or who received BSC (Figure 3B). In the final 8 weeks of life, surgeons appeared to be more frequently involved in the care of patients who lived close, but this was not statistically significant (P= 0.237).

Travel Behavior as a Function of Residence: Costs to the Patient

Patient travel time to attend medical visits were considered a surrogate for patient costs. Two-way driving time was calculated for every medical visit (Figure 3C). The time taken to drive to medical appointments is a reflection of costs to the patient. As expected, total driving time was related to distance from HPB surgeon (P<0.0001). Total driving times were greatest for patients who had surgery and, to a lesser extent, chemotherapy. The documented driving times in the final weeks of life were striking. In the final 8 weeks of life, total driving times were 773 minutes (0.5 days) per person in patients living close to an HPB surgeon, and 2,388 minutes (1.6 days) per person in patients living farther away (P<0.0001).

Physician Costs as a Function of Residence

Physician billings were considered a surrogate for treatment costs. Costs related to physician billings summarized by treatment type and proximity to the nearest HPB surgeon are depicted in Figure 3D. The greatest costs were incurred during the post-diagnosis interval, which is proportional to the number of visits to physicians. Surgery was associated with highest costs, and chemotherapy was similarly associated with high costs. Costs were compared between patients who lived <120 minutes from the nearest HPB surgeon and those who lived ≥120 minutes away. There was no difference in total cost, nor was there a difference in cost during any of the time intervals.

DISCUSSION

Few data are available that accurately describe the experience for patients with biliary cancers during their entire disease trajectory. To the best of our knowledge, this is the first study that has comprehensively explored the association of proximity to specialty care and survival, treatment, and health utilization for patients with biliary cancers. We have derived a population-based, rich and highly granular database that provides some insight on patient experiences, and we have provided an understanding of the effects on accessibility to care. Patients living far from HPB surgical centers and cancer centers generally have worse survival outcomes. Given the complexity of caring for patients with biliary malignancies, this is not unexpected. What was not anticipated was which subgroups were most affected. While the proportion of patients who underwent resection was not affected by geographic constraints, chemotherapy was administered less frequently in patients living remotely. Moreover, the deleterious effects of living remotely were particularly pronounced in patients who required biliary drainage and who received best supportive care.

Patients living remotely have a smaller likelihood of receiving palliative chemotherapy. We speculate that another major contributory factor was related to achieving and maintaining biliary drainage and controlling biliary sepsis. The number and frequency of biliary drainage procedures was not significantly different in patients who lived remotely. However, patients living remotely who received only best supportive care had more frequent emergency visits, which might indicate a higher rate of biliary sepsis. Alternatively, it may reflect the lack of availability of definitive expertise. That is, in centers where HPB surgeons work, HPB surgeons are immediately available to manage the often subtle signs of biliary sepsis that can lead to a precipitous clinical deterioration in the absence of timely management.

One surprising finding is that the effects of driving time on survival are so pronounced in patients with ampullary cancers. Our *a priori* hypothesis was that any effects on driving time would be less apparent in patients in whom decisions related to chemotherapy were less complicated and who did not frequently require complicated biliary interventions. Further study will be required to understand the factors responsible for this observation.

The effects of proximity to specialist care are complex and probably influenced by health care system, socioeconomic factors, as well as by disease process. For example, in the U.S., some studies have shown that patients traveling to high volume cancer centers had improved survival compared to those who chose lower volume, closer care facilities.[9-12] In these studies, where there is heterogeneity in access due to differences in health care insurance, improved survivals may have been subjected “travel bias”[13] or “referral bias”[14]. That is, patients traveling farther to seek care were more motivated or capable of receiving intense or complex treatments. Indeed, Wasif et al. reported that older patients, patients on Medicaid, and African Americans were less likely to travel far.[12] In contrast, a U.K study demonstrated worse survival outcomes in cancer patients who had to contend with greater travel burden.[15] Patients who underwent surgery for extrahepatic biliary cancers at one of 10 high volume U.S. institutions had worse outcomes when large distances were travelled.[16] Our results derived from a publicly funded health system would be expected to remove the effects of disparities in health insurance[17,18] on treatment choices; the effects of socioeconomic factors (education and income levels)[19,20] may also be smoothed out, albeit not completely eliminated.

While this study provided a comprehensive evaluation of factors that comprise the delivery of care to patients who live remotely or close to high level medical resources, there were some limitations. First, biliary cancers are rare, and therefore the study population is small despite the fact that it is population-based over a long period of observation. Second, Alberta has a relatively low population-area ratio relative to other provinces in Canada, and therefore the absolute number of patients who live remotely is small. The effects that we have observed may be exacerbated in larger provinces where the distances to advanced care centers are greater. Third, the findings stem from a constituency where universal health care is instituted, and the effects of geography may vary in constituencies where there is variability in health care insurance. Finally, we have not explored the effects of ethnicity on the studied outcomes, which would be more feasible with a larger study cohort.

Centralization of surgical management of cancer patients who require advanced and sophisticated treatments is a trend in recent years.[21,22] This is perhaps most apparent in patients who require continuous management of complications of malignancy such as biliary cancer patients. Similarly, administration of chemotherapy to patients with biliary cancers requires a high level of expertise and support from other disciplines with experience in managing hepatobiliary complications. With centralization comes the challenge of delivering timely and appropriate care for rural patients. For patients with biliary cancers, this will require urgent access to optimize biliary drainage and to treat biliary sepsis.

REFERENCES

1. de Groen PC, Gores GJ, LaRusso NF, et al: Biliary tract cancers. N Engl J Med 341:1368-78, 1999

2. Wiggers JK, Groot Koerkamp B, Cieslak KP, et al: Postoperative Mortality after Liver Resection for Perihilar Cholangiocarcinoma: Development of a Risk Score and Importance of Biliary Drainage of the Future Liver Remnant. J Am Coll Surg 223:321-331 e1, 2016

3. Jarnagin WR, Fong Y, DeMatteo RP, et al: Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg 234:507-17; discussion 517-9, 2001

4. Valle J, Wasan H, Palmer DH, et al: Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 362:1273-81, 2010

5. Lai EC, Chu KM, Lo CY, et al: Choice of palliation for malignant hilar biliary obstruction. Am J Surg 163:208-12, 1992

6. Targarona EM, Ayuso RM, Bordas JM, et al: Randomised trial of endoscopic sphincterotomy with gallbladder left in situ versus open surgery for common bileduct calculi in high-risk patients. Lancet 347:926-9, 1996

7. Chopra KB, Peters RA, O'Toole PA, et al: Randomised study of endoscopic biliary endoprosthesis versus duct clearance for bileduct stones in high-risk patients. Lancet 348:791-3, 1996

8. Google Maps APIs: https://developers.google.com/maps/documentation/javascript/. Accessed on Jan 8th:

9. Lamont EB, Hayreh D, Pickett KE, et al: Is patient travel distance associated with survival on phase II clinical trials in oncology? J Natl Cancer Inst 95:1370-5, 2003

10. Speicher PJ, Englum BR, Ganapathi AM, et al: Traveling to a High-volume Center is Associated With Improved Survival for Patients With Esophageal Cancer. Ann Surg 265:743-749, 2017

11. Lidsky ME, Sun Z, Nussbaum DP, et al: Going the Extra Mile: Improved Survival for Pancreatic Cancer Patients Traveling to High-volume Centers. Ann Surg 266:333-338, 2017

12. Wasif N, Chang YH, Pockaj BA, et al: Association of Distance Traveled for Surgery with Short- and Long-Term Cancer Outcomes. Ann Surg Oncol 23:3444-3452, 2016

13. Etzioni DA, Fowl RJ, Wasif N, et al: Distance bias and surgical outcomes. Med Care 51:238-44, 2013

14. Paltiel O, Ronen I, Polliack A, et al: Two-way referral bias: evidence from a clinical audit of lymphoma in a teaching hospital. J Clin Epidemiol 51:93-8, 1998

15. Turner M, Fielding S, Ong Y, et al: A cancer geography paradox? Poorer cancer outcomes with longer travelling times to healthcare facilities despite prompter diagnosis and treatment: a data-linkage study. Br J Cancer 117:439-449, 2017

16. O'Connor SC, Mogal H, Russell G, et al: The Effects of Travel Burden on Outcomes After Resection of Extrahepatic Biliary Malignancies: Results from the US Extrahepatic Biliary Consortium. J Gastrointest Surg, 2017

17. Niu X, Roche LM, Pawlish KS, et al: Cancer survival disparities by health insurance status. Cancer Med 2:403-11, 2013

18. Robbins AS, Chen AY, Stewart AK, et al: Insurance status and survival disparities among nonelderly rectal cancer patients in the National Cancer Data Base. Cancer 116:4178-86, 2010

19. Gorey KM, Luginaah IN, Bartfay E, et al: Effects of socioeconomic status on colon cancer treatment accessibility and survival in Toronto, Ontario, and San Francisco, California, 1996-2006. Am J Public Health 101:112-9, 2011

20. Gorey KM: Breast cancer survival in Canada and the USA: meta-analytic evidence of a Canadian advantage in low-income areas. Int J Epidemiol 38:1543-51, 2009

21. Aquina CT, Probst CP, Becerra AZ, et al: High volume improves outcomes: The argument for centralization of rectal cancer surgery. Surgery 159:736-48, 2016

22. Stitzenberg KB, Sigurdson ER, Egleston BL, et al: Centralization of cancer surgery: implications for patient access to optimal care. J Clin Oncol 27:4671-8, 2009

FIGURE LEGEND

Figure 1. Geographic distribution of cases of biliary cancers in the province of Alberta between 2001 and 2015. Main population centers, cancer centers and sites where HPB surgeons exist are marked.

Figure 2. Forest plot depicting the effect of driving time to the nearest HPB surgical center on survivals in various subgroups.

Figure 3. Resource utilization and costs related to residence location at three intervals: within the 3 months prior to tissue diagnosis, in the 24 months after diagnosis; and in the last 8 weeks of life. A. Number of visits per four weeks. B. Number of visits per four weeks categorized by specialty. C. Average total travel time spent going to and from physician visits. D. Average total physician billings.

TABLES

Table 1. Patient characteristics as a function of driving time to the nearest HPB surgical center (frequency and column %)

Variables	**Driving time to nearest HBP surgeon (minute)**						**P-value**
	≤30	**>30, ≤60**	**>60, ≤120**	**>120, ≤180**	**>180**	**Total**	
Sex							0.45

Female	524(53.8)	115(48.5)	73(47.4)	67(52.3)	61(52.1)	840(52.2)	
Male	450(46.2)	122(51.5)	81(52.6)	61(47.7)	56(47.9)	770(47.8)	
Age (year), mean (SD)	67.6(13.0)	65.4(12.8)	67.5 (11.5)	67.7(12.7)	64.8(13.5)	67.1 (12.9)	0.05
CCI score							
≤2	391(40.1)	95(40.1)	64(41.6)	46(35.9)	52(44.4)	648(40.3)	0.94
3–4	251(25.8)	59(24.9)	37(24.0)	36(28.1)	24(20.5)	407(25.3)	
≥5	332(34.1)	83(35.0)	53(34.4)	46(35.9)	41(35.0)	555(34.5)	
Tumor Type							
IHCC	241(25.7)	57(24. 9)	35(23.0)	22(17.6)	31(27.4)	386(24.0)	
EHCC	332(35.4)	76(33.2)	53(34.9)	43(34.4)	27(23.9)	396(24.6)	0.26
GBC	232(24.8)	56(24.5)	42(27.6)	36(28.8)	30(26.6)	531(33.0)	
AmpC	132(14.1)	40(17.5)	22(14.5)	24(19.2)	25(22.1)	243(15.1)	
Stage							
I, II, III	590(60.6)	137(57.8)	93(60.4)	86(67.2)	72(61.5)	978(60.8)	0.54
IV	384(39.4)	100(42.2)	61(39.6)	42(32.8)	45(38.5)	632(39.3)	
Treatment							
Surgery	156(16.0)	37(15.6)	29(18.8)	22(17.2)	26(22.2)	270(16.8)	
Chemotherapy	169(17.4)	48(20.3)	14(9.1)	13(10.2)	18(15.4)	26216.3)	0.08
Chemotherapy + Surgery	56(5.8)	20(8.4)	9(5.8)	9(7.0)	9(7.7)	103(6.4)	
BSC	593(60.9)	132(55.7)	102(66.2)	84(65.6)	64(54.7)	975(60.6)	
Number of Biliary drain							
0	450(46.2)	105(44.3)	75(49.0)	48(37.5)	49(41.9)	727(45.2)	
1	230(23.6)	56(23.6)	36(23.5)	31(24.2)	34(29.1)	387(24.0)	0.29
≥2	295(30.3)	76(32.1)	42(27.5)	49(38.3)	34(29.1)	496(30.8)	
Year of diagnosis							
Before 2010	493(50.6)	99(41.8)	92(60.1)	62(48.4)	63(53.9)	809(50.6)	0.01

From 2010 onwards	482(49.4)	138(58.2)	61(39.9)	66(51.6)	54(46.2)	801(49.4)	
Overall Survival Length (month), mean (SD)							
IHCC	12.7 (19.4)	10.7 (18.9)	11.1 (12.2)	11.6 (17.4)	10.3(13.4)	12.0 (18.2)	0.66
EHCC	23.0(33.3)	20.4(29.8)	22.7(38.6)	21.0(30.2)	20.6(31.8)	22.2(32.9)	
GBC	25.6(41.6)	18.6(33.3)	22.2(31.6)	14.0(22.8)	26.5(45.4)	23.3(38.6)	
AmpC	35.5(36.3)	33.5(39.3)	40.0(47.4)	44.9(53.3)	22.2(22.5)	35.1(38.8)	
Neighborhood education level (% with high school and above)							
<75%	386(39.6)	82(34.6)	53(34.6)	52(40.6)	51(43.6)	624(38.8)	
75-85%	262(26.9)	78(32.9)	48(31.4)	40(31.3)	40(34.2)	468(29.1)	0.15
>85%	327(33.5)	77(32.5)	52(34.0)	36(28.1)	26(22.2)	518(32.2)	
Neighborhood income level (average annual income, $)							
<35,000	342(35.1)	69(29.1)	48(31.4)	51(39.8)	48(41.0)	558(36.5)	
35,000-50,000	360(36.9)	98(41.4)	57(37.3)	49(38.3)	46(39.3)	610(37.9)	0.18
>50,000	273(28.0)	70(29.5)	48(31.4)	28(21.9)	23(19.7)	442(27.5)	
Average annual incidence (per 100,000), (95%CI)							
IHCC	0.58 (0.30-0.89)	0.14 (0-0.30)	0.09 (0-0.18)	0.05 (0-0.11)	0.07 (0-0.18)	0.93 (0.56-1.30)	
EHCC	0.58 (0.30-0.89)	0.14 (0-0.30)	0.1 (0-0.24)	0.09 (0-0.24)	0.08 (0-0.18)	1.27 (0.84-1.70)	<0.001^
GBC	0.79 (0.45-1.12)	0.17 (0.02-0.35)	0.14 (0-0.30)	0.1 (0-0.24)	0.07 (0-0.18)	0.98 (0.61-1.35)	

AmpC	0.32	0.09	0.05	0.06	0.06	0.58
	(0.09-0.51)	(0-0.24)	(0-0.11)	(0-0.18)	(0-0.18)	(0.29-0.87)

HPB: hepatopancreatobiliary; SD: standard deviation; CCI: Charlson comorbidity index; IHCC: Intrahepatic cancer; EHCC : Extrahepatic cancer; GBC: Gallbladder cancer; AmpC: Ampullary cancer; BSC: best supportive care; CI: confidence interval.

^the p-value is for comparison of incidence among the driving time categories after adjusting for the tumor type.

Table 2. Univariate and multivariate analyses of factors associated with overall survival in patients with biliary cancers, including driving time to the nearest HPB surgical center as a covariate

Risk Factors	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P-Value	HR (95% CI)	P-Value
Sex (male vs. female)	1.03 (0.97-1.08)	0.637	1.10 (1.04-1.17)	0.090
Age (per 1 year increase)	1.01 (1.01-1.02)	<.0001	1.01 (1.01-1.01)	<.0001
Chemotherapy (yes vs. no)	0.75 (0.70-0.80)	<.0001	0.65 (0.60-0.70)	<.0001
Surgery (yes vs. no)	0.34 (0.31-0.36)	<.0001	0.40 (0.37-0.44)	<.0001
Tumor Type				
Amp Ca (reference)	1.0 -	-	1.0 -	-
IHCC	2.61 (2.38-2.87)	<.0001	2.06 (1.86-2.28)	<.0001
EHCC	1.67 (1.52-1.84)	<.0001	1.71 (1.55-1.89)	<.0001
GBC	1.72 (1.57-1.88)	<.0001	1.45 (1.32-1.59)	<.0001
Number of biliary drainage (per 1 drainage increase)	1.0 (0.99-1.02)	0.77	0.97 (0.95-0.98)	0.025
Stage IV (vs. stages I-III)	3.32 (3.13-3.53)	<.0001	2.47 (2.30-2.66)	<.0001
CCI (per 1 point increase)	1.10 (1.09-1.11)	<.0001	1.09 (1.08-1.10)	<.0001
Diagnosed from 2010 onwards (vs. before 2010)	1.02 (0.96-1.07)	0.769	0.84 (0.79-0.89)	0.004
Driving time to nearest HPB surgeon ≥ 120 minutes (vs. <120 minutes)	1.06 (0.99-1.15)	0.416	1.27 (1.17-1.37)	0.002
Neighborhood education level (% with				

high school and above)				
<75% (reference)	1.0 -	-	1.0 -	-
75-85%	0.92 (0.87-0.99)	0.228	0.93 (0.86-1.00)	0.317
>85%	0.97 (0.91-1.04)	0.704	0.96 (0.88-1.05)	0.644
Neighborhood income level (average annual income, $)				
<35,000 (reference)	1.0 -	-	1.0 -	-
35,000-50,000	0.96 (0.90-1.03)	0.576	1.03 (0.96-1.10)	0.716
>50,000	1.02 (0.95-1.09)	0.806	1.09 (0.99-1.19)	0.364

HR: hazard ratio; IHCC: intrahepatic cholangiocarcinoma; EHCC: extrahepatic cholangiocarcinoma; GBC: gallbladder cancer; AmpC: ampullary cancer; CCI: Charlson comorbidity index; HPB: hepatopancreatobiliary.

Table 3. Multivariate analysis of association between driving time to the nearest HPB surgical center and secondary outcomes: stage IV, chemo, surgery, biliary drainage (odds ratio, 95% CI)

Risk Factors	Stage IV	Chemotherapy	Surgery	Biliary drainage^
Sex (male vs. female)	0.76(0.61-0.96)*	1.19(0.91-1.55)	1.16(0.88-1.52)	0.81(0.62-1.05)
Age (per 1 year increase)	0.99(0.99-1.01)	0.95(0.94-0.96)**	0.98(0.97-0.99)**	1.02(1.01-1.03)**
Tumor Type				
AmpC (reference)	1.0	1.0	1.0	1.0
IHCC	0.23(0.14-0.36)**	2.22(1.45-3.40)**	0.99(0.674-1.44)	0.35(0.24-0.52)**
EHCC	3.28(2.47-4.36)**	2.47(1.71-3.56)**	1.14(0.76-1.71)	0.91(0.64-1.30)
GBC	1.01(0.76-1.34)	2.51(1.73-3.62)**	3.26(2.32-4.57) **	0.16(0.11-0.23)**
Stage IV (vs. stages I-III)	-	1.11(0.84-1.48)	0.04(0.03-0.07)**	0.86(0.65-1.15)
CCI (per 1 point increase)	1.09(1.05-1.13)**	0.96(0.92-1.01)	1.0(0.95-1.05)	0.89(0.85-0.93)
Diagnosed from 2010 onwards (vs. before 2010)	1.68(1.34-2.11)**	2.66(2.03-3.49)**	1.66(1.26-2.18)**	1.13(0.87-1.45)
Driving Time to nearest HPB surgeon ≥ 120 minutes (vs. <120 minutes)	0.86(0.63-1.19)	0.75(0.52-1.09)	1.07(0.97-1.19)	0.84(0.60-1.20)
Neighborhood education level (% with high school and above)				
<75% (reference)	1.0	1.0	1.0	1.0
75-85%	1.17(0.83-1.65)	1.28(0.90-1.82)	1.01(0.75-1.36)	0.80(0.57-1.14)
>85%	1.10(0.72-1.68)	1.32(0.86-2.05)	1.06(0.73-1.52)	0.82(0.55-1.22)
Neighborhood income level (average				

annual income, $)				
<35,000 (reference)	1.0	1.0	1.0	1.0
35,000-50,000	0.87(0.61-1.23)	0.89(0.62-1.28)	1.10(0.81-1.49)	1.12(0.80-1.57)
>50,000	0.80(0.54-1.19)	0.92(0.62-1.38)	1.13(0.81-1.60)	1.31(0.85-2.01)
Model diagnostics	N=1610, C-statistic = 0.736	N=1610, C-statistic = 0.754	N=1610, C-statistic = 0.809	N=975, C-statistic = 0.714

CI: confidence interval; IHCC: intrahepatic cholangiocarcinoma; EHCC: extrahepatic cholangiocarcinoma; GBC: gallbladder cancer; AmpC: ampullary cancer; CCI: Charlson comorbidity index; HPB: hepatopancreatobiliary.

Note: ^ modeling likelihood of biliary drainage among patients who received best supportive care; * the P-value is less than 0.05; ** the P-value is less than 0.01.

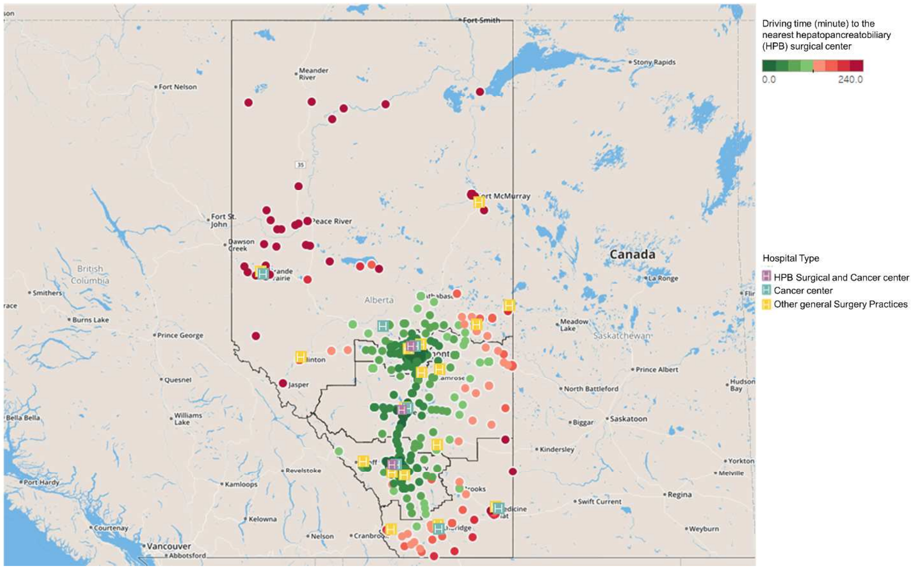

Figure 1. Geographic distribution of cases of biliary cancers in the province of Alberta between 2001 and 2015. Main population centers, cancer centers and sites where HPB surgeons exist are marked.

451x254mm (300 x 300 DPI)

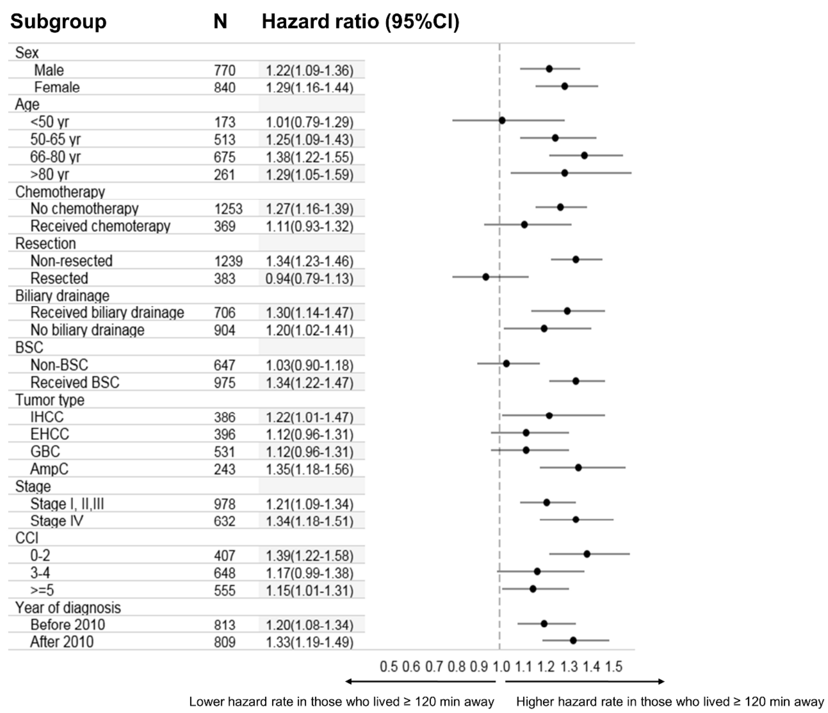

Figure 2. Forest plot depicting the effect of driving time to the nearest HPB surgical center on survivals in various subgroups.

338x254mm (300 x 300 DPI)

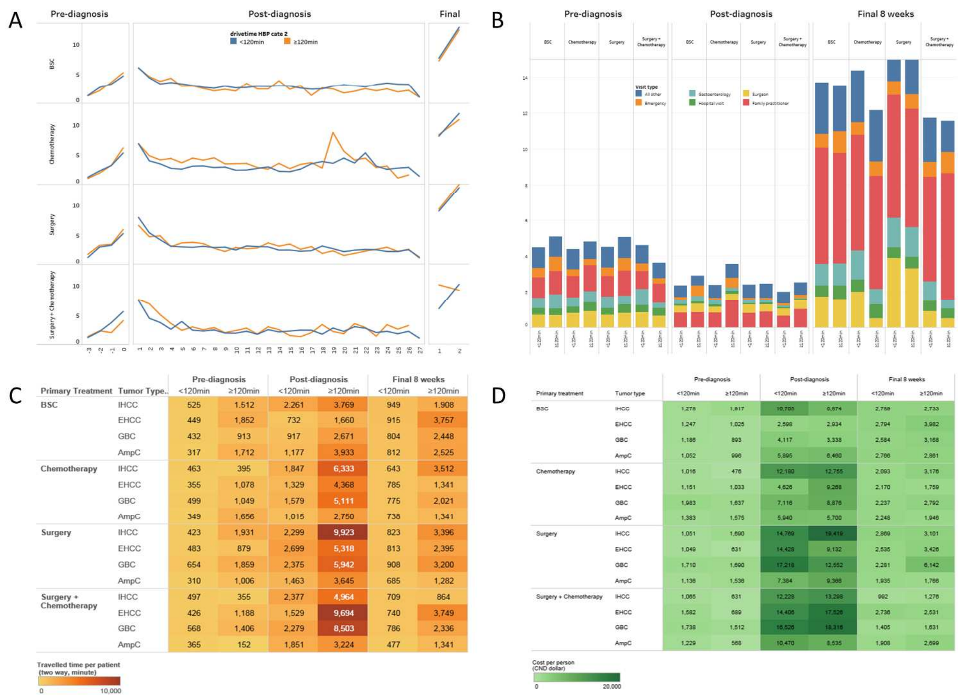

Figure 3. Resource utilization and costs related to residence location at three intervals: within the 3 months prior to tissue diagnosis, in the 24 months after diagnosis; and in the last 8 weeks of life. A. Number of visits per four weeks. B. Number of visits per four weeks categorized by specialty. C. Average total travel time spent going to and from physician visits. D. Average total physician billings.

254x190mm (300 x 300 DPI)

Supplementary Table 1. Description of patient characteristics as a function of driving time to the nearest cancer center (frequency and column %)

Variables	Driving time to nearest cancer center (minute)						P-value
	≤30	>30, ≤60	>60, ≤120	>120, <180	>180	Total	
Sex							
Female	560(53.6)	137(49.1)	82(47.7)	44(51.2)	17(60.7)	840(52.2)	0.39
Male	485(46.4)	142(50.9)	90(52.3)	42(48.8)	11(39.3)	770(47.8)	
Age (year) mean, SD	67.8(13.1)	65.4(12.6)	67.2(11.1)	66.3(12.6)	58.0(14.4)	67.1(12.9)	<0.001
CCI score							
=< 2	415(39.7)	113(40.5)	76(44.2)	34(39.5)	10(35.7)	648(40.3)	0.13
3–4	279(26.7)	71(25.5)	38(22.1)	17(19.8)	2(7.1)	407(25.3)	
>=5	351(33.6)	95(34.1)	58(33.7)	35(40.7)	16(57.1)	555(34.5)	
Tumor Type							
IHCC	255(25.4)	63(23.5)	38(22.5)	18(21.2)	12(42.9)	386(24.0)	
EHCC	253(25.2)	66(24.6)	51(30.2)	20(23.5)	6(21.4)	396(24.6)	0.40
GBC	351(34.9)	93(34.7)	53(31.4)	29(34.1)	5(17.9)	53133.0)	
AmpC	147(14.6)	46(17.2)	27(16.0)	18(21.2)	5(17.9)	243(15.1)	
Stage							
I, II, III	647(61.9)	162(58.1)	103(59.9)	52(60.5)	14(50.0)	978(60.8)	0.58
IV	398(38.1)	117(41.9)	69(40.1)	34(39.5)	14(50.0)	632(39.3)	
Treatment							
Surgery	170(16.3)	48(17.2)	29(16.9)	18(20.9)	5(17.9)	270(16.8)	
Chemotherapy	176(16.8)	56(20.1)	18(10.5)	8(9.3)	4(14.3)	262(16.3)	0.28
Chemotherapy + Surgery	64(6.1)	22(7.9)	10(5.8)	6(7.0)	1(3.6)	103(6.4)	
BSC	635(60.8)	153(54.8)	115(66.9)	54(62.8)	18(64.3)	975(60.6)	
Number of Biliary drain							

0	475(45.4)	119(42.7)	77(45)	39(45.4)	17(60.7)	727(45.2)	
1	252(24.1)	64(22.9)	41(24)	24(27.9)	6(21.4)	387(24)	0.66
≥2	319(30.5)	96(34.4)	53(31)	23(26.7)	5(17.9)	496(30.8)	
Year of diagnosis							
Before 2010	531(50.8)	117(41.9)	108(63.2)	40(46.5)	13(46.4)	809(50.3)	<0.001
From 2010 onwards	482(49.4)	138(58.2)	61(39.9)	66(51.6)	54(46.2)	801(49.4)	
Overall Survival Length (month), mean, SD							
IHCC	12.9(19.5)	10.2(18.0)	10.2(10.8)	12.6(16.6)	6.2(7.2)	12.0(18.2)	
EHCC	23.0(33.6)	21.7(31.6)	19.4(35.6)	21.4(23.6)	21.7(25.5)	22.2(32.9)	<0.001
GBC	26.0(42.1)	19.7(33.7)	22.0(31.8)	7.4(8.7)	12.5(16.4)	23.3(38.6)	
AmpC	36.4(37.8)	30.3(35.4)	37.5(45.6)	36.8(49.5)	24.2(19.3)	35.1(38.8)	
Neighborhood education level (% with high school and above)							
<75%	411(39.3)	102(36.6)	66(38.6)	34(39.5)	11(39.3)	624(38.8)	
75-85%	284(27.2)	88(31.5)	54(31.6)	28(32.6)	14(50.0)	468(29.1)	0.12
>85%	351(33.6)	89(31.9)	51(29.8)	24(27.9)	3(10.7)	518(32.2)	
Neighborhood income level (average annual income, $)							
<35,000	369(35.3)	86(30.8)	62(36.3)	31(36.1)	10(35.7)	558(35.7)	
35,000-50,000	397(38.0)	109(39.1)	58(33.9)	36(41.9)	10(35.7)	610(37.9)	0.77
>50,000	280(26.8)	84(30.1)	51(29.8)	19(22.1)	8(28.6)	442(27.5)	
Average annual incidence (per 100,000), (95%CI)							
IHCC	0.61	0.15	0.1	0.04	0.02	0.93	<0.001
	(0.33-0.94)	(0-0.30)	(0-0.24)	(0-0.11)	(0-0.11)	(0.56-1.30)	^

EHCC	0.63	0.17	0.12	0.05	0.01	0.98
	(0.33-0.94)	(0.02-0.35)	(0-0.24)	(0-0.11)	(0-0.06)	(0.61-1.35)
GBC	0.84	0.21	0.14	0.07	0.01	1.27
	(0.48-1.16)	(0.04-0.40)	(0-0.30)	(0-0.18)	(0-0.06)	(0.84-1.70)
AmpC	0.35	0.1	0.06	0.05	0.01	0.58
	(0.12-0.56)	(0-0.24)	(0-0.18)	(0-0.11)	(0-0.06)	(0.29-0.87)

SD: standard deviation; CCI: Charlson comorbidity index; IHCC: intrahepatic cancer; EHCC: extrahepatic cancer; GBC:gallbladder cancer; AmpC: ampullar cancer; BSC: best supportive care; CI: confidence interval.

^the p-value is for comparison of incidence among the driving time categories after adjusting for the tumor type.

Supplementary Table 2. Univariate and multivariate analyses of factors associated with overall survival in patients with biliary cancers, using driving time to the nearest cancer center (CC) as a factor

Risk Factors	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P-Value	HR (95% CI)	P-Value
Sex (male vs. female)	1.03 (0.97-1.08)	0.6371	1.10 (1.04-1.16)	0.097
Age (per 1 year increase)	1.01 (1.01-1.02)	<.0001	1.01 (1.01-1.01)	<.0001
Chemotherapy(yes vs. no)	0.75 (0.70-0.80)	<.0001	0.65 (0.60-0.70)	<.0001
Surgery(yes vs. no)	0.34 (0.31-0.36)	<.0001	0.41 (0.38-0.44)	<.0001
Tumor Type				
AmpC (reference)	1.0 -	-	- -	-
IHCC	2.61 (2.38-2.87)	<.0001	2.04 (1.84-2.25)	<.0001
EHCC	1.67 (1.52-1.84)	<.0001	1.70 (1.54-1.88)	<.0001
GBC	1.72 (1.57-1.88)	<.0001	1.43 (1.30-1.57)	<.0001
Number of biliary drainage (per 1 drainage increase)	1.0 (0.99-1.02)	0.77	0.97 (0.95-0.98)	0.024
Stage IV (vs. stages I-III)	3.32 (3.13-3.53)	<.0001	2.45 (2.28-2.63)	<.0001
CCI (per 1 point increase)	1.10 (1.09-1.11)	<.0001	1.09 (1.08-1.10)	<.0001
Diagnosed from 2010 onwards (vs. before 2010)	1.02 (0.96-1.07)	0.769	0.84 (0.79-0.89)	0.003
Driving time to nearest CC ≥ 120 minutes (vs. <120 minutes)	1.14 (1.03-1.27)	0.214	1.27 (1.14-1.41)	0.029
Neighborhood education level (% with				

high school and above)				
<75% (reference)	1.0 -	-	1.0 -	-
75-85%	0.92 (0.87-0.99)	0.228	1.02 (0.95-1.10)	0.779
>85%	0.97 (0.91-1.04)	0.704	1.07 (0.98-1.17)	0.443
Neighborhood income level (average annual income, $)				
<35,000 (reference)	1.0 -	-	1.0 -	-
35,000-50,000	0.96 (0.90-1.03)	0.576	0.94 (0.87-1.01)	0.401
>50,000	1.02 (0.95-1.09)	0.806	0.97 (0.89-1.05)	0.713

HR: hazard ratio; IHCC: intrahepatic cholangiocarcinoma; EHCC: extrahepatic cholangiocarcinoma; GBC: gallbladder cancer; AmpC: ampullary cancer; CCI: Charlson comorbidity index.

Supplementary Table 3. Multivariate analysis of association between driving time to nearest cancer center (CC) and secondary outcomes: stage IV, chemo, surgery, biliary drainage (odds ratio, 95% CI)

Risk Factors	Stage IV	Chemotherapy	Surgery	Biliary drainage^
Sex (male vs. female)	0.77(0.61-0.97)*	1.19(0.91-1.55)	1.17(0.89-1.54)	0.80(0.62-1.05)
Age (per 1 year increase)	0.99(0.99-1.00)	0.95(0.94-0.96)**	0.98(0.97-0.99)**	1.02(1.01-1.03)**
Tumor Type				
AmpC (reference)	1.0	1.0	1.0	1.0
IHCC	3.24(2.43-4.32)**	2.28(1.49-3.50)**	0.99(0.67-1.45)	0.34(0.23-0.51)**
EHCC	0.99(0.74-1.32)**	2.57(1.78-3.73)**	1.15(0.77-1.74)	0.90(0.64-1.14)
GBC	0.22(0.14-0.35)	2.60(1.79-3.78)**	3.30(2.34-4.65)**	0.15(0.111-0.22)
Stage IV (vs. stages I-III)	-	1.13(0.85-1.50)	0.04(0.03-0.07)**	0.86(0.52-1.26)**
CCI (per 1 point increase)	1.09(1.05-1.13)**	0.96(0.92-1.01)	1.00(0.95-1.05)	0.89(0.85-0.92)
Diagnosed from 2010 onwards (vs. before 2010)	1.69(1.35-2.12)**	2.66(2.03-3.50)**	1.66(1.26-2.18)**	1.23(0.77-2.04)
Driving time to nearest CC > 120 minutes (vs. <120 minutes)	1.16(0.75-1.79)	0.51(0.29-0.88)*	1.21(0.73-2.03)	1.16(0.53-2.54)
Neighborhood education level (% with high school and above)				
<75% (reference)	1.0	1.0	1.0	1.0
75-85%	1.01(0.75-1.36)	1.18(0.83-1.66)	1.27(0.90-1.81)	0.80(0.46-1.41)
>85%	1.07(0.74-1.54)	1.10(0.72-1.68)	1.31(0.85-2.03)	1.76(0.91-3.41)
Neighborhood income level (average				

annual income, $)				
<35,000 (reference)	1.0	1.0	1.0	1.0
35,000-50,000	1.09(0.81-1.48)	0.87(0.61-1.24)	0.90(0.63-1.30)	0.85(0.48-1.50)
>50,000	1.14(0.81-1.61)	0.80(0.54-1.19	0.93(0.62-1.39)	0.73(0.38-1.39)
Model diagnostics	N=1610, C-statistic = 0.736	N=1610, C-statistic = 0.754	N=1610, C-statistic = 0.809	N=975, C-statistic = 0.714

CI: confidence interval; IHCC: intrahepatic cholangiocarcinoma; EHCC: extrahepatic cholangiocarcinoma; GBC: gallbladder cancer; AmpC: ampullary cancer; CCI: Charlson comorbidity index;

Note: ^ modeling likelihood of biliary drainage among the patients who received best supportive care; * the P-value is less than 0.05; ** the P-value is less than 0.01.