Published in final edited form as:

J Gastrointest Surg. 2017 December ; 21(12): 2016–2024. doi:10.1007/s11605-017-3537-4.

The Effects of Travel Burden on Outcomes After Resection of Extrahepatic Biliary Malignancies: Results from the US Extrahepatic Biliary Consortium

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Abstract

Background—Surgical resection of extrahepatic biliary malignancies has been increasingly centralized at high-volume tertiary care centers. While this has improved outcomes overall, increased travel burden has been associated with worse survival for many other malignancies. We hypothesized that longer travel distances are associated with worse outcomes for these patients as well.

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Presented at the ACS Clinical Congress, Washington DC 2016, Podium presentation at Surgical Oncology Scientific Forum

Author Contributions: Study conception and design, drafting of manuscript, acquisition of data, critical revision: O'Connor, Mogal, Shen. Acquisition of data, interpretation of data, revision of manuscript, final approval of manuscript: Ethun, Fields, Jin, Hatzaras, Shenoy, Idrees, Isom, Martin, Scoggins, Pawlik, Schmidt, Poultsides, Tran, Weber, Salem, Maithel, Russell

Compliance with Ethical Standards: Ethics Statement: Institutional Review Board approval was obtained for the study.

Conflict of Interest: The authors declare that they have no conflicts of interest.

Study Design—Data was analyzed from the US Extrahepatic Biliary Consortium database, which retrospectively reviewed patients who received resection of extrahepatic biliary malignancies at 10 high-volume centers. Driving distance to the patient's treatment center was measured for 1025 patients. These were divided into four quartiles for analysis: < 24.5, 24.5–57.2, 57.2–117, and < 117 mi. Cox proportional hazard models were then used to measure differences in overall survival.

Results—No difference was found between the groups in severity of disease or post-operative complications. The median overall survival in each quartile was as follows: 1st = 1.91, 2nd = 1.60, 3rd = 1.30, and 4th = 1.39 years. Patients in the 3rd and 4th quartile had a significantly lower median household income ($p = 0.0001$) and a greater proportion Caucasian race ($p = 0.0001$). However, neither of these was independently associated with overall survival. The two furthest quartiles were found to have decreased overall survival (HR = 1.39, CI = 1.12–1.73 and HR = 1.3, CI = 1.04–1.62), with quartile 3 remaining significant after multivariate analysis (HR = 1.45, CI = 1.04–2.0, $p = 0.028$).

Conclusions—Longer travel distances were associated with decreased overall survival, especially in the 3rd quartile of our study. Patients traveling longer distances also had a lower household income, suggesting that these patients have significant barriers to care.

Keywords

Cholangiocarcinoma; Gallbladder cancer; Travel distance; Overall survival; Median household income

Introduction

Complex surgical cancer care has been increasingly centralized over the past decades in order to provide highly specialized care and make health care systems more efficient. This has been supported by evidence that treatment at a high-volume center results in improved overall survival when compared to that at low-volume centers.^{1–3} This centralization of care has led to an increase in the distance that many patients must travel to receive care. Stitenberg et al. have demonstrated a 70% increase in travel distance for surgery through the 1900s–2000s.⁴ The effect of travel distance on patient outcomes after surgery has been mixed and may be subject to both distance bias and referral bias.^{5,6} Wasif et al. investigated the 90-day mortality of patients with colon, esophageal, liver, and pancreatic cancers in four travel distance quartiles. In their study, the further quartiles were associated with improved 90-day mortality and 5-year survival. They postulated that patients traveling the furthest were likely very motivated to receive treatment and more health care literate which gave them a survival advantage over the closer groups.⁷ This “Distance bias” has also been well documented in the medical oncology literature, where patients motivated to travel further distances have better outcomes.^{6,8,9}

The disadvantage of travel distance documented in the literature has been an increase in complication rates. Etzioni et al. showed a worsening major complication rate in patients traveling further distances in their general surgery population.⁵ In a 2015 study by Stitenburg et al., travel distance was found to be an independent predictor of readmission for patients

after esophagectomy, pancreatectomy, or lung resection for cancer.¹⁰ This may be evidence of referral bias in surgical patients, where patients referred to high-volume centers are more complex and difficult and therefore more prone to complications post-operatively.

Though other groups have studied the impact of travel distance on surgical procedures for colon, liver, lung, and pancreatic cancers, there has been no investigation into its effect on outcome for extrahepatic biliary malignancies. These tumors are rare and require very specialized care providers as well as close coordination between providers. As such, these are cases that are more likely to be treated at high-volume centers in larger cities, requiring patients to travel long distances for treatment and follow-up.

Previous studies have also postulated that patients traveling further distances may be of higher socioeconomic status which would improve their ability to travel for care and therefore improve their outcomes. The literature also suggests that patients from regions with lower median household incomes receive less aggressive treatment and have poorer overall survivals.¹¹ We hypothesized patients traveling longer distances for specialized hepaticobiliary surgery would experience worse outcomes. Therefore, using a large multi-institutional database, the primary aim of the present study was to assess the effect of travel distance on survival after resection of extrahepatic biliary malignancies. The secondary aim of this study was to determine the effects of median household income on survival.

Methods

Data Source

Retrospectively collected data from patients, undergoing surgical procedures for extrahepatic biliary malignancies between January 2000 and December 2014, in the US Extrahepatic Biliary Consortium was analyzed. The consortium comprises institutions from 10 states and from every region of the country with the exception of the Southwest (John Hopkins Hospital, Baltimore, MD; Emory University, Atlanta, GA; Stanford University, Palo Alto, CA; University of Wisconsin, Milwaukee, WI; The Ohio State University, Columbus, OH; Washington University, St. Louis, MO; Vanderbilt University, Nashville, TN; New York University, New York, NY; University of Louisville, Louisville, KY; Wake Forest University, Winston-Salem, NC). All are considered high-volume hepatobiliary surgery centers with greater than 25 liver and pancreatic resections per year.¹²

Inclusion/Exclusion Criteria and Variables

All patients who underwent resection of extrahepatic biliary tumors including hilar cholangiocarcinoma, distal cholangio-carcinoma, and gallbladder cancer were included in the study. Patients with intrahepatic cholangiocarcinoma were excluded and those with missing zip code information were excluded from analysis. Home zip codes were for calculation of each patient's shortest driving distance to their respective treatment centers using Google Maps™. Median household incomes from the 2015 US Census Bureau report were imported using the home zip codes and the Zip Who™ search engine.

The primary outcome measured was overall survival. The exposure variable was travel distance to their respective treatment facility. The quartiles were compared on 45

independent variables to ensure that demographic information, disease severity, stage, resection margin, and lymph vascular invasion as well as chemotherapy regimens were similar between the groups. Secondary outcomes were 30-day mortality, readmission rate, complication rate, and need for reoperation.

Statistical Analysis

Patients were categorized into four quartiles based on distance traveled to their respective institution. A Cox proportional hazard model was used to compare the overall survival of patients between the quartiles, using the first quartile (Q1) as the reference group. Demographic and clinicopathologic information was then compared between the groups to ensure that the groups had similar severity of illness and to identify demographic differences. These were analyzed using chi square test for categorical variables, *t* test for continuous variables, and analysis of variance for four group comparisons.

Both univariate and multivariate analyses were performed to identify variables effecting overall survival. Variables with a *p* value less than 0.2 were retained for multivariate analysis and included age, peak bilirubin, tumor size, margin status, and vascular involvement. A *p* value of < 0.05 and confidence interval (CI) of 95% were used as the threshold for statistical significance, and the analysis was performed using SAS 9.4 software (Carry, NC).

Results

Clinical and Pathologic Data

Seventy-one patients were excluded due to missing zip code information. One thousand twenty-five patients were included in the final analysis with an overall median travel distance of 58 mi, ranging from 0 to < 5000 mi. There were 30 patients who were considered outliers who traveled extremely far distances, which caused the mean travel distance to be 132 mi with a standard deviation of 333 mi. Patients were divided into four quartiles (Q1–4) with 252, 256, 257, and 260 patients, respectively. A significant difference in race was found between the quartiles, with more non-white patients in the closer quartiles ($p = > 0.0001$). Notably, there was a trend towards shorter follow-up times in the further quartiles: Q1 = 5.4 years, Q2 = 4.3 years, Q3 = 3.7 years, and Q4 = 4.0 years ($p = 0.77$). Though a significant difference was not found, this mirrored the survival trend with Q3 having the shortest length of follow-up. Otherwise, there was no difference between the groups on the other measured risk factors or treatment regimen (Table 1).

Survival

The median of overall survival for each quartile was as follows: Q1 = 1.91, Q2 = 1.60, Q3 = 1.30, and Q4 = 1.39 years. Q3 (HR = 1.39, CI = 1.12–1.73) and Q4 (HR = 1.3, CI = 1.04–1.62) were found to have significantly decreased overall survival on univariate analysis, with quartile 3 remaining significant after multi-variate analysis (HR = 1.45, CI = 1.04–2.0, $p = 0.028$) (Figs. 1 and 2).

Since quartile 4 included patients traveling extreme distances, we independently analyzed the distance outliers, which was composed of 30 patients who traveled greater than 2

standard deviations above the mean (< 850 mi). These patients were found to have a decreased median overall survival at 0.95 years; however, this did not reach statistical significance (HR = 1.51, $p = 0.12$). Other factors found to be associated with decreased survival on multivariate analysis included age (HR = 1.024, CI = 1.013–1.036, $p < 0.0001$), tumor size (HR = 1.11, CI = 1.05–1.18, $p = 0.0006$), margin status in both R1 (HR = 1.55, CI = 1.19–2.02, $p = 0.0012$) and R2 (HR = 2.94, CI = 1.85–4.67, $p < 0.001$), vascular involvement (HR = 1.56, CI = 1.06–2.31, $p = 0.023$), positive lymph nodes (HR = 1.54, CI = 1.22–1.93, $p = 0.0002$), and institution ($p = 0.036$) (Table 2). Of note, no differences were found between the quartiles in secondary outcomes including 30-day mortality ($p = 0.275$), readmission rate ($p = 0.148$), complication rate ($p = 0.914$), or need for reoperation ($p = 0.410$). Though there was no statistical difference found between the groups in follow-up time ($p = 0.77$) or in disease-free survival (DFS) ($p = 0.58$), the trend between the quartiles followed the same pattern as with overall survival, with Q1 having the longest, Q3 having the shortest, and Q4 being slightly improved over Q3.

Income

Median annual household income data was available for 960 of the patients included in the original data set. The overall median household income was found to be \$48,432/year with a standard deviation of \$21,320. Notably, this is slightly lower than the overall US median household income at \$56,516/year in 2015.¹³ The average median household incomes for each quartile were as follows: Q1 = \$55,084, Q2 = \$55,566, Q3 = \$43,475, and Q4 = \$38,462; with a significant trend towards lower household incomes in the furthest quartiles ($p = 0.0001$). Median household income (per 10,000 dollar increase) was independently analyzed and was not found to be associated with overall survival (HR = 0.989, CI = 0.947–1.306) (Table 2). Outlier patients who traveled greater than 850 mi (> 2 standard deviations above the mean) were independently analyzed and were found to have a median household income of \$53,060/year, similar to those in the closest quartile. In spite of their higher median income, overall survival tended to be lower in the outlier group at 0.95 years (HR = 1.51, $p = 0.12$).

Discussion

Since the trend towards centralization of care has continued over the past decades, the distances that patients must travel for care has been an ongoing issue of discussion. This is a particularly important topic for cancer patients in that they often require close coordination of care with many subspecialists and frequent follow-up. The effects of travel distance on overall survival and complication rates have been studied for esophageal cancer, colon cancer, pancreatic cancer, lung cancer, and breast cancer, but it has not been well studied in patients with biliary cancer.^{1,2,7,14} The present study investigates travel distance's effect on outcomes after surgery for extrahepatic biliary tumors.

The study demonstrates a trend towards worse overall survival in patients traveling further distances, with patients traveling “intermediate” distances being particularly vulnerable. This aligns with studies suggesting worse outcomes in patients who travel further for cancer treatment. Amborggi et al. performed an extensive review of the literature on the effects of

travel burden in patients receiving both medical and surgical treatments for cancer. They found that patients traveling further distances had more advanced disease at diagnosis, worse overall survival, and worse quality of life.¹⁵ Still, others have shown worse complication rates, readmission rates, and later stage at diagnosis for patients who have an increased travel burden.^{5,10,16} This contradicts data suggesting that distance bias can improve outcomes for cancer patients undergoing resection.⁷

In this study, patients traveling further distances had significantly lower median household incomes, which could amplify the effects of their already heavy travel burden. Not only are these patients required to travel further for care, but they are also likely less able to take time off from work for long hospital stays and frequent follow-up visits. Though income was not independently associated with overall survival in our study, it can certainly make the travel burden more difficult to bear and could be a confounding variable when analyzing outcomes of rural patients. Multiple trials have shown that patients with lower socioeconomic status are less likely to undergo indicated cancer screenings, are less likely to participate in clinical trials, and suffer poorer outcomes.¹⁷

Race was also found to be significantly different between the quartiles, with a decreased number of non-white patients in the furthest quartiles. These findings could be due to more diverse populations being present in the large city centers where most of the institutions are located. In 2015, Al-Rafaie et al. studied the demographics associated with travel patterns for patients undergoing resection of lung, esophageal, pancreatic, and colorectal cancers. They found that African-American patients in particular were less likely to travel further distances for treatment when compared to white, Asian, and Hispanic patients.¹⁸ In contrast, the present study found a significant decrease in all non-white races including Black, Hispanic, and Asian patients in the furthest quartiles. However, this did not appear to affect survival since race was not independently associated with overall survival.

While both of the furthest groups had lower overall survival, Q4 patients had a small survival advantage over patients in Q3. Outlier patients in Q4 had higher median household incomes, were likely well motivated, highly health care literate, and put substantial time and research into selecting their treatment center. Many of these patients were likely able to fly to their treatment center and stay for a period of time prior to going home to ensure appropriate perioperative care and long-term follow-up. Given these perceived advantages, we hypothesized that the outlier patients for travel distance could have improved the overall survival of Q4 over Q3. However, we found that the overall survival of the outliers was worse than that of the remainder of Q4. In this study cohort, higher income did not translate into a survival advantage. Patients in the “intermediate” travel group were most vulnerable to the effects of travel distance though the exact reason for this remains unknown. It is likely a combination of multiple factors including motivation, socioeconomic status, health care literacy, travel distance, and travel modality that ultimately accounts for the particular vulnerability of the intermediate group.

We found no difference in 30-day mortality, complications, readmission, or reoperation rates in the further quartiles, indicating that patients performed similarly in the immediate postoperative recovery period regardless of their travel distance. This suggests that the

disparity occurs after patients have recovered from surgery and are being followed longitudinally. This is confirmed by the declining trend in follow-up time and DFS seen in the furthest quartiles, particularly in Q3. Though these did not reach statistical significance, follow-up times and DFS followed the same pattern as overall survival with Q1 having the longest times, Q3 having the shortest, and Q4 slightly improved over Q3 (Table 1). The lack of follow-up may have led to inadequate surveillance and treatment of recurrences, thus negatively affecting the overall survival of the furthest groups. Lack of follow-up may also have affected the ability to detect and subsequently treat complications in the furthest groups affecting their survival. Extra vigilance should be applied when coordinating long-term care of patients living far from their treatment center in order to bridge this disparity. Many surgeons recommend that patients stay in affiliated local hospitality houses until their first follow-up visit if there is no appropriate health care facility near their home. Institutions are attempting to close the gap by setting up satellite facilities in rural referring areas; this allows patients to have more access to follow-up without sacrificing continuity of care. Also, patient navigation programs have shown improved results in coordination of care and can be used to target patients traveling great distances in order to improve follow-up and adherence to therapy.^{19,20}

The retrospective nature of this study is a weakness in that the individual decision-making between providers and patients was not controlled for and outcomes are subject to bias. Also, the quartiles were created to divide patients into four equal groups and therefore would be different if the study were repeated with a different population. The distance cutoffs should not be seen as lines in the sand, but rather suggesting a trend towards worse outcomes at further distances. Only readmissions and complications that presented to the primary institution were captured, leaving the possibility of uncaptured data from outlying hospitals. Lastly, we recognize that gallbladder cancer and hilar and distal cholangiocarcinomas are resected by a broad range of procedures that can have differing types and severity of complications, as well as differing mortality rates. Procedures performed in this cohort included bile duct resection, cholecystectomy, radical cholecystectomy and portal lymph node dissection, right and extended right hepatectomy, left and extended left hepatectomy, right and left trisectorectomy, classic and pylorus preserving whipple, and whipple with right hepatectomy. Although hilar cholangiocarcinoma, gallbladder carcinoma, and distal cholangiocarcinoma represent a diverse range of malignancies of the extrahepatic biliary system, the proportions of these subgroups of tumors were similar between the quartiles, thereby negating any bias that could potentially arise from variations in tumor biology within the different quartiles.

In conclusion, though there are clearly benefits to having surgery at a high-volume center for rare cancers, traveling far distances to these centers can place patients at a survival disadvantage. Patients may want to pursue treatment at a high-volume center closest to their home rather than traveling across the country to undergo surgery at a particular institution. However, the ultimate responsibility lies on the institution to arrange adequate follow-up and long-term care for patients traveling great distances for resection. This could be done through collaborating with local oncologists, improving patient navigation programs, or by setting up satellite clinics in strategic areas to ensure continuity of care for the most vulnerable patients.

Acknowledgments

Supported by: Wake Forest University Biostatistics shared resource NCI CCSG P30CA012197.

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Fig. 1. Kaplan Meier curve of survival analysis based on quartiles ($p = 0.006$)

Fig. 2. Hazard ratio for overall survival amongst the quartiles

Table 1
Clinicopathologic and demographic information compared between quartiles

	Overall	Demographic data of travel quartiles									
		Q1 24.5 mi (n = 252)	Q2 24.5 mi < 57.2 (n = 256)	Q3 57.2 mi < 117 (n = 257)	Q4 117 mi (n = 260)	p value					
	Mean / N	SD									
Age	65.49	11.15	65.34	12.20	65.38	10.67	65.43	11.18	65.80	10.54	0.96
BMI	27.32	6.26	27.16	6.78	26.65	5.72	28.27	6.20	27.31	6.23	0.08
Peak bilirubin (mg/dL)	6.02	7.50	6.61	7.83	5.41	7.30	6.64	7.58	5.40	7.22	0.10
CA19-9	1269.85	10,495.77	2363.19	19,722.92	577.31	1649.54	1215.44	4451.78	855.68	3977.96	0.45
EBL (mL)	565.54	1038.87	514.22	550.00	503.61	618.40	558.87	922.81	684.33	1665.11	0.28
Tumor size (mm)	29.53	20.90	27.45	16.12	29.79	22.43	31.20	20.89	29.79	23.63	0.38
Vascular involvement	54	5.27	14	5.56	12	4.69	13	5.06	15	5.77	0.95
Race	97	9.91	43	17.02	23	9.5	11	4.56	20	7.94	
Black	743	75.89	143	58.61	181	74.79	209	86.72	210	83.33	
White	47	4.8	17	6.97	10	4.13	10	4.15	10	3.97	< 0.00001
Latino	62	6.33	30	12.3	19	7.85	6	2.49	7	2.78	
Asian	16	1.63	5	2.05	7	2.89			4	1.59	
Other	14	1.43	6	2.46		0.83	5	2.07	1	0.4	
Na	48,432	21,320	55,084	27,407	55,566	20,140	43,475	16,059	38,462	12,738	< 0.00001
Median household income	200	21.93	50	21.37	43	18.78	45	21.13	62	26.27	0.26
Smoking history	861	94.82	210	92.11	218	95.2	203	94.42	230	97.46	
Functional status	43	4.74	16	7.02	10	4.37	11	5.12	6	2.54	0.28
Independent	4	0.44	2	0.88	1	0.44	1	0.47	0	0	
Partially dependent	490	53.61	120	51.06	131	57.21	116	54.46	123	51.9	0.54
Totally dependent	132	14.44	31	13.08	38	16.67	39	18.4	24	10.13	
Oral medication	63	6.89	23	9.7	16	7.02	11	5.19	13	5.49	0.06
Insulin-dependent	39	4.27	11	4.66	9	3.93	12	5.66	7	2.95	0.54
Severe COPD	23	2.51	7	2.97	3	1.31	5	2.33	8	3.38	0.51
CHF	12	1.31	4	1.69	4	1.74	2	0.94	2	0.84	0.75
Acute renal failure	545	56.01	141	57.32	131	53.91	135	57.94	138	54.98	0.79
Clinical jaundice											

	Overall	Demographic data of travel quartiles					p value
		Q1 24.5 mi (n = 252)	Q2 24.5 mi < 57.2 (n = 256)	Q3 57.2 mi < 117 (n = 257)	Q4 117 mi (n = 260)		
Preop biliary drainage/stent							
	442	43.68	46.15	44.88	43.58	40.16	
	368	36.36	36.03	34.65	36.19	38.58	
2	117	11.56	10.12	13.78	9.34	12.99	
3	85	8.4	7.69	6.69	10.89	8.27	
Gallbladder	436		111		114	109	
Hilar cholangio	272		72		64	73	
Distal cholangio	316		73		79	78	
Open	912	95	91.6	95.08	227	235	
Laparoscopic	26	2.71	4.2	2.87	4	5	
Laparoscopic hand-assisted	2	0.21	2	0.82	0	0	
Robotic	3	0.31	2		1		
Lap converted open	17	1.77	3	1.23	3	3	
Common bile duct (CBD) resection							
Final margin status	115	32.12	25	31.58	28	35	
R0 = 0	609	59.19	57.37	62.5	155	150	
R1 = 1	185	18.1	21.51	18.75	46	37	
R2 = 2	228	22.31	21.12	18.75	54	73	
Lymphovascular invasion (LVI)	317	48.55	45.34	50.58	76	81	
Lymph node positive	373	47.64	44.79	45.63	96	97	
Highest Clavien-Dindo grade							
Minor	264	51.87	51.61	43.85	68	75	
Major	205	40.28	41.94	43.08	52	45	
Death	40	7.86	6.45	13.08	5	10	
Palliative	109	12	11.84	11.86	22	32	
Curative	799	88	88.16	88.14	203	187	
Neoadjuvant chemotherapy	36	3.54	2.81	1.95	9	15	
Neoadjuvant radiotherapy	15	1.49	1.27	0.78	5	5	
Adjuvant chemotherapy	465	53.23	56.74	53.64	104	121	
Adjuvant radiotherapy	289	353	34	32.73	73	76	
Length of follow-up	4.3		4.3	3.7	4		
Disease-free survival	1.40		1.63	1.34	1.47		

Not applicable

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Table 2
Cox proportional hazard models for overall survival. Variables with univariate *p* values less than 0.2 were retained in the final multivariate model unless there was high missing data

	Univariate models				Multivariate models			
	HR	95% CI	<i>p</i> value	Overall <i>p</i> value	HR	95% CI	<i>p</i> value	Overall <i>p</i> value
Age	1.015	1.008	1.023	<0.0001	1.024	1.013	1.036	<0.0001
Male sex	1.02	0.87	1.19	0.81				<0.0001
Non-white race	0.91	0.75	1.010	0.32				
2 or more comorbidities	1.11	0.95	1.31	0.20				
Median household income (per \$10,000 increments)	0.99	0.95	1.03	0.6321				
Functional status								
Independent	Ref							
Partially dependent/totally dependent	1.45	1.02	2.08	0.041	1.25	0.76	2.05	0.38
Ca-19, per 100-unit increase	1.001	1	1.001	0.081	High missing data			
Peak bilirubin, per 10-unit increase	1.29	1.17	1.43	<0.0001	1.13	0.95	1.33	0.16
PSC	0.84	0.48	1.45	0.84				
Tumor size, per 10-unit increase	1.10	1.05	1.16	<0.0001	1.11	1.05	1.18	0.0006
Distance to the closest margin	0.70	0.53	0.92	0.0097	High missing data			
Margin status								
R2	1.75	1.43	2.15	<0.0001	2.94	1.85	4.67	<0.0001
R1	3.46	2.88	4.15	<0.0001	1.55	1.19	2.02	0.0012
R0	Ref							
Vascular involvement	1.26	0.91	1.75	0.16	1.57	1.06	2.31	0.023
Positive lymph nodes	1.66	1.38	1.99	<0.0001	1.54	1.22	1.93	0.0002
Lymphovascular invasion	1.64	1.34	2.01	<0.0001	High missing data			
Perineural invasion	1.49	1.19	1.87	0.0005	High missing data			
Major complication	1.07	0.86	1.33	0.54				
Institution				0.045			0.036	0.036
Distance to CC								
Q1 = < 24.5 mi	Ref							
Q2 = 24.5 mi < 57.2	1.06	0.85	1.32	0.61	1.11	0.81	1.53	0.53
				0.0063				0.12

		Univariate models				Multivariate models			
		HR	95% CI	p value	Overall p value	HR	95% CI	p value	Overall p value
Q3 = 57.2	mi < 117	1.39	1.12	1.73	0.003	1.45	1.04	2.00	0.028
Q4 = 117	mi	1.30	1.04	1.62	0.018	1.31	0.94	1.83	0.11