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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Geographic Disparities in Referral Rates and Oncologic Outcomes of Intrahepatic Cholangiocarcinoma: A Population-Based Study

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ABSTRACT

Background. Intrahepatic cholangiocarcinoma (ICC) is a rare cancer. Patients in rural areas may face reduced access to advanced treatments often only available at referral centers. We evaluated the association of referral center treatment with treatment patterns, outcomes, and geography in patients with ICC.

Methods. We queried the Oregon State Cancer Registry for ICC between 1997 and 2016, collecting clinicopathologic, demographic, and oncologic data. Patients were classified by treatment at a referral center or non-referral center. 'Crowfly' distance to the nearest referral center (DRC) was calculated. Outcomes were evaluated using Kaplan–Meier, Cox proportional hazards modeling, and logistic regression.

Results. Over 20 years, 740 patients with ICC had a median age of 66 years. Slightly more than half ($n = 424$, 57%) were non-referral center treated and 316 (43%) were referral center treated. Referral center treatment increased over time (odds ratio [OR] 1.03/year, $p < 0.05$). Referral center-treated patients had improved overall survival in all patients (median 9 vs. 4 months, $p < 0.001$), in the non-metastatic group (median 13 vs. 6 months, $p < 0.001$), and in patients not receiving liver resection (median 6 vs. 3 months, $p < 0.05$). On multivariable analysis, referral center-treated patients more often underwent chemotherapy, resection, or radiation (all $p < 0.05$). Increasing DRC (OR 0.98/20 km, $p < 0.05$) was independently associated with non-referral center treatment.

Conclusion. Patients with ICC who are evaluated at a referral center are more likely to receive treatments associated with better oncologic outcomes, including patients who are not managed with hepatic resection. Increasing the DRC is associated with treatment at a non-referral center; interventions to facilitate referral, such as telemedicine, may lead to improved outcomes for patients with ICC in rural states.

Keywords Cholangiocarcinoma · Cancer registry · Telemedicine · Biliary tract cancer · Intrahepatic cholangiocarcinoma

Intrahepatic cholangiocarcinoma (ICC) is a deadly malignancy due to frequently advanced stages at presentation, leading to 5-year survivals of < 10%.[1–3] Long-term cure is possible in patients with surgically resectable disease; however, the majority of patients present with locally advanced or multifocal hepatic disease. For patients with unresectable or locally advanced disease, systemic chemotherapy with gemcitabine/platinum regimens is the current standard for first-line therapy;[3,4] however, treatment options now include mutation or genomically-targeted therapy such as the recently approved pemigatinib as second-line therapy for cancers with fibroblast growth

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factor receptor (FGFR) rearrangements or fusions.[5] Liver-directed therapies, including selective internal radiation therapy (SIRT),[6] external beam radiotherapy (RT),[7] and hepatic arterial infusion (HAI) pump therapy,[8] are also being actively investigated, with results being reported in recent phase II trials. Advanced interventions and modern therapies aimed at improving survival in ICC are not commonly available outside a multidisciplinary academic care setting, making patient access an essential aspect of delivering care for patients with this rare cancer.

Treatment at academic and high-volume referral centers has been cited as independently prognostic of overall survival (OS) in head and neck squamous cell carcinoma and metastatic pancreatic cancer.[9,10] Similar findings have been shown in ICC, where the academic status of the primary treatment facility is associated with higher R0 resection, completion of portal lymphadenectomy, and improved OS compared with non-academic centers.[11,12] This is hypothesized to be due to the benefits of centralized multidisciplinary care and cutting-edge treatments that may be unavailable in many community settings. Furthermore, such centers are often directly affiliated with a National Cancer Institute (NCI)-designated cancer center.

In much of the Eastern US, access to such referral centers is relatively unrestricted geographically. There is great geographic breadth of the US, particularly in the Western US, where sparsely populated states may have one or no referral centers. Therefore, the potential exists for geographic disparity in patients' referral patterns in rural states, with a corresponding difference in care and outcomes. Based on our working hypothesis that treatment at referral centers may yield superior outcomes in care, we sought to investigate the proportion of patients with ICC treated at referral centers in Oregon, a large state with two such centers, one of which is an NCI Comprehensive Cancer Center. Furthermore, we sought to characterize risk factors for disparities in care.

METHODS

We queried the Oregon State Cancer Registry (OSCaR) for patients with biopsy-proven ICC between 1997 and 2016. The OSCaR is a statewide population-based cancer registry collecting cancer-related information from health care facilities, physicians, dentists, ambulatory care facilities, and clinical laboratories, as mandated by Oregon law. Data from these disparate sources are collated into single entries corresponding to first diagnosis of a particular malignancy and reporting data according to the Surveillance, Epidemiology, and End Results (SEER) format.[13] Patients were identified in the present study through International Classification of Diseases, Tenth Revision (ICD-10) or earlier codes for ICC, namely C221 and C220 when the primary tissue of origin was coded as 'bile duct' and location was 'intrahepatic'. Clinicopathologic, demographic, treatment-related, and oncologic outcomes data were obtained. The settings of individual treatments or procedures, such as hepatic resection, chemotherapy, and radiation were not coded in the OSCaR dataset.

While no standard definition for what constitutes a referral center exists, there are two high-volume hospitals in Oregon: Oregon Health and Science University (OHSU) and Providence Portland Medical Center, both located in Portland. Both hospitals engage in academic activity, including the training of hepato-pancreato-biliary (HPB) fellows, and prospective and retrospective research efforts, and have active clinical trials for patients with ICC at the time of data query (1 March 2020). OHSU is an NCI Comprehensive Cancer Center. In addition to academic activity, both hospitals are the only two in the state of Oregon that perform more than 80 liver resections yearly, and therefore meet previously proffered definitions of high-volume centers.[14] Both institutions utilize a multidisciplinary tumor board that includes surgical, medical, and radiation oncology, along with radiology and pathology, all of whom specialize in HPB malignancies. Patients were separated into three groups: those who received all first-course diagnosis/treatment at community centers, referral centers, and parts of first-course diagnosis/treatment at both community and referral centers. Patients treated at referral centers, regardless of additional community center treatment, were grouped in some analyses to compare patients with any treatment at referral centers with those with none.

Due to changes in American Joint Committee on Cancer (AJCC) staging for ICC throughout the study period, SEER staging was solely utilized to stratify patients into local, regional, and distant disease at diagnosis. Overall survival (OS) was measured from the date of diagnosis.

Geographic and Socioeconomic Variables

Patient county and zip code of origin were abstracted from the OSCaR database. The population-weighted geographic center of each zip code, as estimated by the 2010 census, was used to calculate the approximate distance in kilometers from the nearest referral center (DRC) for each patient. Patient socioeconomic status (SES) was approximated as proposed by Yost et al.,[15] using census tracts and zip code tabulation areas; 5-year averaged zip code census estimates from 2007 to 2011 were used to approximate median household income, educational attainment, and insurance status. Patients were assigned by zip code into socioeconomic quintiles for income, education, and healthcare based on median income, percentage of the population aged 45–65 years with a bachelor's degree or higher, and percentage of the population with health insurance, respectively. County of origin was designated as rural versus urban per Office of Management and Budget (OMB) definitions.

Statistical Analysis

We used Kaplan–Meier analysis with log-rank test and Cox proportional hazards modeling to evaluate associations with OS using hazard ratios (HR), with values > 1 indicating a higher risk of death. For these analyses, all patients not experiencing the endpoint of interest were censored at the date of last follow-up. Univariable and multivariable logistic regression was used and odds ratios (OR) were tabulated for the outcome metrics of treatment at a referral center, surgical resection, chemotherapy, and radiation, with values > 1 indicating higher odds of experiencing the outcome of interest. For multivariable regressions, final models for the outcome of interest were derived from single-backward elimination using the likelihood ratio test, including all variables with a p-value <0.2 on univariable analysis in the initial model iteration; in each iteration, the variable with the largest p-value was eliminated if doing so did not affect the model fit with a p-value <0.05. SPSS version 26 (IBM Corporation, Armonk, NY, USA) was used for all statistical operations.

RESULTS

Clinicopathologic and Treatment Characteristics

Over the study period, 740 patients received a diagnosis of ICC in Oregon (Table 1). The median patient age was 67 years, with 351 males (47.4%). Overall, 424 patients (57.3%) underwent diagnosis and treatment only at community centers, 178 (24.1%) had diagnosis and treatment exclusively at referral centers, and 138 (18.6%) had diagnosis and treatment at both referral and community centers. Patients had significantly different demographic, clinicopathologic, and treatment-related characteristics by treatment groups (Table 1) and were only comparable in proportion with male sex and Hispanic ethnicity. The referral center and referral/community center groups were younger, more likely to have complete staging, and more likely to have received curative-intent surgery, chemotherapy, and radiation compared with the community center treatment group. Patients treated only at referral centers lived closer to such centers than patients with community center and combined community/referral center treatment. Overall, 89.9% ($n = 126$) of patients undergoing surgical intervention were treated at either referral centers only or in both settings.

Predictors of Oncologic Outcome

The median OS from diagnosis for all patients was 6 months, and 4, 6, and 13 months for patients treated at community centers, referral centers, and in both settings, respectively. On Kaplan–Meier analysis (Fig. 1), patients treated in both settings had increased OS compared with patients treated only at referral or community centers ($p < 0.001$ for both). Similarly, patients treated at referral centers had improved OS compared with patients treated at community centers ($p = 0.006$). These associations were preserved when adjusting for receipt of curative-intent surgery ($p < 0.001$ for all comparisons), except for the comparison of community center-only and referral center-only treatment ($p = 0.751$). The associations also remained when stratifying for SEER stage at diagnosis ($p < 0.001$ for community/referral center treatment comparisons, $p = 0.006$ for referral center vs. community center treatment). For patients with locoregional disease, median OS was 17 months for those treated at both referral and community centers, compared with 6 months for community center-only treatment ($p < 0.001$) and 12 months for referral center-only treatment ($p = 0.076$). For patients with distantly metastatic disease, median OS was 8 months for treatment in both settings, compared with 2 months for community center-only treatment ($p = 0.009$) and 4 months for patients treated only at referral centers ($p = 0.013$). For patients with incomplete staging information, median OS was 8 months for patients treated in both settings, compared with 5 months for referral centers ($p = 0.036$) and 3 months for community centers ($p < 0.001$).

On univariable analysis, increasing age, male sex, distantly metastatic disease and unstaged disease at diagnosis were associated with worse OS, while referral center treatment, combined treatment, and receipt of chemotherapy, surgery, and radiation were associated with improved OS (Table 2). On multivariable analysis, age (HR 1.01 per year, $p < 0.001$), male sex (HR 1.22, $p = 0.012$), and distantly metastatic disease at diagnosis (HR 1.60, $p < 0.001$) were independently associated with inferior OS, while receipt of curative-intent hepatic resection (HR 0.40, $p < 0.001$), chemotherapy (HR 0.59, $p < 0.001$), and combined referral/community center treatment (HR 0.79, $p = 0.041$) were independently associated with improved OS. Receipt of radiation was not significantly associated (HR 0.80, $p = 0.085$) with improved OS. Referral center-only treatment and incomplete staging were eliminated from the model on single-backward elimination and were therefore not independently associated with OS.

TABLE 1 Clinicopathologic characteristics of patients with intrahepatic cholangiocarcinoma

Variable	All patients [n = 740]	Community center treatment [n = 424]	Referral center treatment [n = 178]	Combined referral/community center treatment [n = 138]	p-Value
Age, years (median [IQR])	67 [60–76]	71 [62–78]	65 [56–74]	64 [56–70]	< 0.001
Race					< 0.01
Caucasian	671 (90.6)	397 (93.6)	146 (82.0)	128 (92.8)	
African American	11 (1.5)	6 (1.4)	3 (1.7)	2 (1.4)	
American Indian	15 (2.0)	9 (2.1)	4 (2.2)	2 (1.4)	
Asian	29 (3.9)	7 (1.7)	17 (9.6)	5 (3.6)	
Unknown	14 (1.9)	5 (1.2)	8 (4.5)	1 (0.7)	
Hispanic ethnicity	27 (3.6)	13 (3.1)	8 (4.5)	6 (4.3)	0.62
Male	351 (47.4)	206 (48.6)	87 (48.9)	58 (42.0)	0.37
Urban county of origin	534 (72.2)	299 (70.5)	137 (77.0)	98 (71.0)	0.26
SEER stage					< 0.001
Locoregional	281 (38.0)	127 (30.0)	81 (45.5)	73 (52.9)	
Distant	191 (25.8)	105 (24.8)	54 (30.3)	32 (23.2)	
Unstaged	268 (36.2)	192 (45.3)	43 (24.2)	33 (23.9)	
Distance to nearest referral center, km (median [IQR])	63 [14–191]	76 [14–191]	14 [8–113]	63 [14–240]	< 0.001
Received curative-intent surgery	169 (22.8)	43 (10.1)	60 (33.7)	66 (47.8)	< 0.001
Received radiation	101 (13.6)	37 (8.7)	30 (16.9)	34 (24.6)	< 0.001
Received chemotherapy	304 (41.1)	156 (36.8)	69 (38.7)	79 (57.2)	< 0.001

Data are expressed as n (%) unless otherwise specified

IQR interquartile range, *SEER* Surveillance, Epidemiology, and End Results

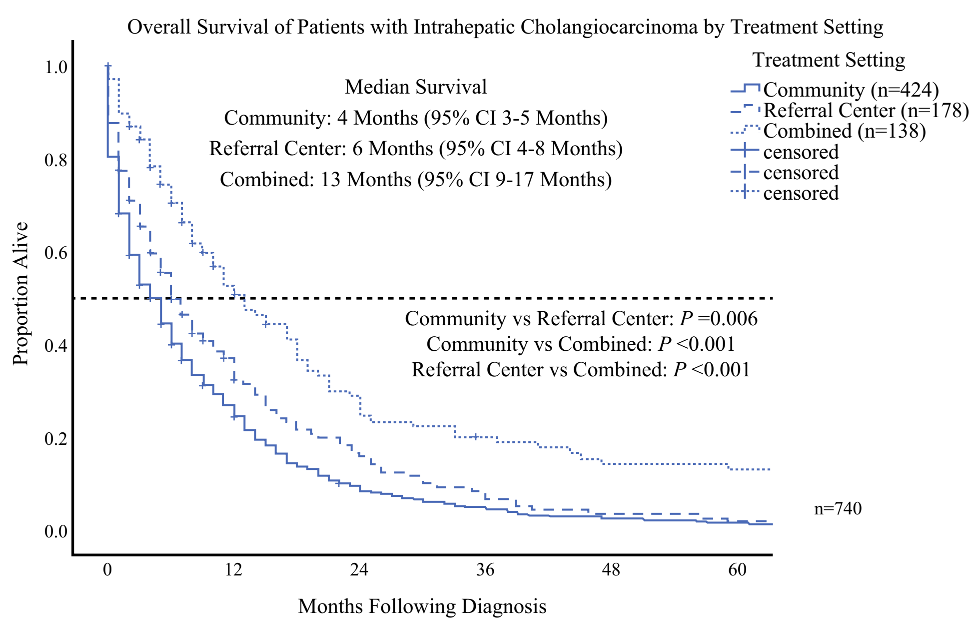

FIG. 1 Kaplan–Meier plot of overall survival in patients with intrahepatic cholangiocarcinoma by treatment setting: referral center, community center, or combined. Patients treated in a community center, referral center, and combined settings had a median overall survival of 4, 6, and 13 months, respectively. All intergroup log-rank comparisons are significant at $p < 0.01$. *CI* confidence interval

Predictors of Cancer-Directed Therapies

On univariable analysis, factors associated with receipt of curative-intent surgery, chemotherapy, and radiation were patient age, male sex, referral center treatment, combined referral/community treatment, and disease stage (all variables with $p < 0.05$ for all treatments). On multivariable analysis (Table 3), increased age (OR 0.98 per

TABLE 2 Univariable and multivariable analysis of 5-year overall survival in patients with intrahepatic cholangiocarcinoma

Variable	Univariable HR (95% CI)	*p*-Value	Multivariable HR (95% CI)	*p*-Value
Age	1.02 (1.02–1.03)	< 0.001	1.01 (1.01–1.02)	< 0.001
Male Sex	1.31 (1.12–1.53)	< 0.001	1.22 (1.05–1.43)	0.012
Well/moderate differentiation	Referent	–	–	–
Poorly differentiated	1.12 (0.77–2.14)	0.40	–	–
LVI present	1.09 (0.80–1.49)	0.59	–	–
Curative-intent surgery	0.35 (0.28–0.43)	< 0.001	0.40 (0.32–0.50)	< 0.001
Received radiation	0.60 (0.47–0.77)	< 0.001	0.80 (0.62–1.03)	0.09
Received chemotherapy	0.58 (0.50–0.69)	< 0.001	0.59 (0.50–0.71)	< 0.001
Community Center treatment	Referent	–	Referent	–
Referral Center treatment	0.79 (0.65–0.95)	0.012	E	–
Combined treatment	0.47 (0.37–0.58)	< 0.001	0.79 (0.62–0.99)	0.041
Locoregional disease	Referent		Referent	–
Distantly metastatic	1.86 (1.52–2.27)	< 0.001	1.60 (1.30–1.97)	< 0.001
Incompletely staged	1.61 (1.34–1.93)	< 0.001	E	–

LVI lymphovascular invasion, *HR* hazard ratio, *CI* confidence interval, *E* eliminated from the final model following single-backward elimination

TABLE 3 Multivariable models for receipt of curative-intent and palliative therapies in intrahepatic cholangiocarcinoma

Variable	Receipt of curative intent surgery[a]		Receipt of chemotherapy		Receipt of radiation	
	Multivariable OR (95% CI)	*p*-Value	Multivariable OR (95% CI)	*p*-Value	Multivariable OR (95% CI)	*p*-Value
Age	0.98 (0.95–0.98)	< 0.001	0.94 (0.92–0.95)	< 0.001	0.97 (0.95–0.98)	< 0.001
Male Sex	0.71 (0.50–1.00)	0.051	0.80 (0.59–1.07)	0.123	0.63 (0.41–0.97)	0.035
Community Center treatment	Referent	–	Referent	–	Referent	–
Referral Center treatment	4.51 (2.89–7.01)	< 0.001	1.09 (0.76–1.56)	0.648	2.12 (1.26–3.56)	0.004
Combined treatment	8.12 (5.13–12.86)	< 0.001	2.30 (1.56–3.40)	< 0.001	3.42 (2.05–5.71)	< 0.001
Locoregional disease	NA	–	Referent	–	Referent	–
Distantly metastatic	NA	–	1.18 (0.82–1.71)	0.368	0.79 (0.47–1.32)	0.359
Incompletely staged	NA	–	0.59 (0.42–0.84)	0.003	0.58 (0.35–0.96)	0.034

[a]For patients with locoregional disease only

NA not applicable, *OR* odds ratio, *CI* confidence interval

year, $p < 0.001$), referral center-only treatment (OR 4.10, $p < 0.001$), and combined referral/community center treatment (OR 7.17, $p < 0.001$) were independently associated with receipt of curative-intent surgery. Receipt of chemotherapy was associated with age (OR 0.94 per year, $p < 0.001$) and combined referral/community center treatment (OR 1.73, $p = 0.007$). Receipt of radiation was associated with age at diagnosis (OR 0.97, $p = 0.002$), referral center-only treatment (OR 1.84, $p = 0.025$), and combined referral/community center treatment (OR 2.76, $p < 0.001$).

Predictors of Referral Center Treatment

Given the association of treatment at a referral center with curative-intent and palliative therapies, we sought to evaluate factors associated with treatment at a referral center (Table 4). On univariable analysis, increasing age (OR 0.95 per year, $p < 0.001$), distance to the nearest referral center (OR 0.97 per 20 km, $p = 0.003$), and distantly metastatic (OR 0.68, $p = 0.037$) or unstaged disease (OR 0.33, $p < 0.001$) were associated with lower odds of treatment at a referral center, while later year of diagnosis (OR 1.04 per year, $p = 0.013$) was associated with higher

TABLE 4 Factors associated with treatment at a referral center for intrahepatic cholangiocarcinoma

Variable	Univariable OR (95% CI)	*p*-Value	Multivariable OR (95% CI)	*p*-Value
Age	0.96 (0.95–0.97)	< 0.001	0.96 (0.95–0.98)	< 0.001
Male sex	0.90 (0.67–1.20)	0.467	–	–
Distance to nearest referral center (per 20 km)	0.97 (0.94–0.99)	0.003	0.98 (0.95-0.99)	0.046
Urban county of origin	1.21 (0.87–1.68)	0.248	–	–
Income SES quintile	1.08 (0.96–1.21)	0.230	–	–
Insurance SES quintile	1.05 (0.90–1.23)	0.50	–	–
Education SES quintile	1.01 (0.89–1.15)	0.889	–	–
Year of diagnosis	1.04 (1.01–1.07)	0.013	1.03 (1.00–1.06)	0.09
Locoregional disease	Referent	–	Referent	–
Distantly metastatic	0.68 (0.47–0.98)	0.037	0.61 (0.42–0.90)	0.012
Incompletely staged	0.33 (0.23–0.47)	< 0.001	0.39 (0.28–0.57)	< 0.001

OR odds ratio, *CI* confidence interval, *SES* socioeconomic status

odds of treatment at a referral center. These factors remained independently predictive of treatment at a referral center on multivariable analysis, with the exception of year of diagnosis, which remained in the model, reflecting an increase in the treatment at referral centers over time ($p = 0.091$). Sex, rural designation of originating county, and education/income/insurance SES quintiles were not associated with treatment at referral centers. Single-backward elimination did not result in the removal of any variables that were initially significant.

DISCUSSION

In our study of the population-based delivery of care to patients with ICC, oncologic outcomes are stratified by treatment at referral centers, even with adjustment for patient stage at diagnosis and other relevant clinicopathologic factors. Improved OS is strongly associated with receipt of curative-intent and palliative therapies, which were more likely in patients treated at referral centers in our study, regardless of stage. While just over half of patients with apparent locoregional disease were evaluated or treated at referral centers, such patients accounted for approximately 90% of all curative-intent operations. Indeed, referral center treatment was independently associated with receipt of chemotherapy, radiation, and hepatic resection, which were each associated with improved OS, although referral center treatment itself was not independently associated with improved OS. We therefore conclude that outcomes in ICC are primarily tied to the receipt of curative-intent and palliative therapies and that patients managed at least in part by referral centers are significantly more likely to receive these therapies. We expect this trend to become increasingly apparent, with recent advances in next-generation sequencing and data supporting the efficacy of novel targeted therapeutics for actionable mutations in ICC, such as FGFR and isocitrate dehydrogenase (IDH) inhibitors, which have an estimated frequency of >25% in this patient population.[16,17]

In our study, we identified three groups of patients according to their treatment at referral centers. Patients listed as undergoing diagnosis and treatment at both community and referral centers had far better outcomes, owing to increased receipt of surgery, chemotherapy, and radiation compared with patients treated solely at referral or community centers. This population may represent those who transferred care from a community practitioner to a referral center, or those co-managed by surgeons, radiation oncologists, or medical oncologists at referral centers with a counterpart in the community. It is possible that patients with a combined treatment setting may have more favorable disease characteristics, however that is not reflected in the staging data as the proportion of patients with distant disease was similar in patients treated only at community centers compared with those receiving combined community/referral center treatment. This may suggest that patients with even metastatic disease benefit from evaluation and treatment at a referral center. Their improved survival may suggest the advantage that robust systems for referral or remote consultation can bring to patients with rare hepatobiliary malignancies, particularly in rural states with long travel distances. The rise of widespread telehealth use in the wake of the coronavirus disease 2019 (COVID-19) pandemic may lead to improved oncologic care through improved access to evaluation at referral centers. This may encourage patients to travel longer distances for higher quality care, enroll in clinical trials, or to utilize treatment plans developed at referral centers but delivered by local providers.

We additionally evaluated factors associated with receipt of treatment at a referral center. Socioeconomic status measures, including zip code income, educational attainment, and insurance status, were not associated with receipt of care at a referral center. Distance from the nearest referral center was an independent predictor of treatment at a referral center. For many disease processes, this might be an acceptable and expected outcome; however, for ICC, advanced oncologic therapies and improved outcomes are associated with treatment at referral centers, and the observed association of distance with outcomes represents a significant geographic disparity in Oregon, which is a state with a predominately rural population.

This study is limited by its reliance on a prospectively maintained statewide dataset that is part of the SEER program and under the regulation of the North American Association of Central Cancer Registries. Additionally, three iterations of the AJCC staging guidelines (5th–7th) are represented in the current patient cohort. While disease site was updated to ensure all patients had ICC, specific AJCC TNM staging was not uniform across the population. Therefore, patients were grouped into the SEER-designated locoregional, distant, and unstaged disease groups. This lack of granularity may conceal substage-specific differences in treatment and survival outcomes. It is also possible that disease-specific factors not coded in the database led to patients receiving treatment at referral centers versus community centers. This may be particularly true for the cohort of patients evaluated and/or treated in both community and referral center settings, who experienced improved outcomes relative to other groups, possibly due to referral bias of patients with resectable or otherwise more treatable disease burdens; unfortunately, without more granular data, this question cannot be definitively answered. In our cohort, patients treated at referral centers were more likely to have locoregional disease, therefore a referral bias may exist that was not fully accounted for by stratifying by SEER stage. Notably, in other disease sites such as pancreatic cancer, high-volume academic centers are known to see a population of patients with more advanced disease, yet these patients still experience improved oncologic outcomes than patients treated in the community.[18] Finally, distance from the patient's home zip code to the nearest referral center ("Crow-fly distance"), as well as SES measures, were limited by estimations based on zip code of origin; exact values for these measures were not available on the individual patient level and may have influenced the results of the analysis. However, given the large population size and uniform unbiased approach that was applied to all patients, patient-specific inaccuracies for these measures are not likely to have significantly influenced the results.

CONCLUSION

Given the association between referral center evaluation for patients with ICC and improved oncologic outcomes, we encourage outreach and partnership with community oncologists by referral centers within states with a predominately rural population, as well as consideration for institution-sponsored and insurance-reimbursed travel expenses or telehealth evaluations for specialized care for ICC and other rare hepatobiliary malignancies. This is becoming increasingly important as next-generation sequencing technologies become more widely available and targeted therapies for biliary tract cancers are now approved in the second-line setting, along with a host of liver-directed therapy options, including HAI, external beam RT, and SIRT. Finally, the importance of telemedicine needs to be considered as a means toward offering patients with ICC an evaluation by a specialist to discuss the available advanced treatment options, including evaluation for and potential participation in clinical trials.

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