Ann Surg Oncol (2019) 26:1979–1980
https://doi.org/10.1245/s10434-019-07176-3

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

EDITORIAL – HEPATOBILIARY TUMORS

Intrahepatic Cholangiocarcinoma: Rising Burden and Glaring Disparities

Ujwal Yanala, MD, Gautam Malhotra, MD, Chandrakanth Are, MD, and James Padussis, MD

Department of Surgery, Fred and Pamela Buffett Cancer Center, University of Nebraska Medical Center, Omaha, NE

Cholangiocarcinoma is the second most common primary hepatic malignancy worldwide, next to hepatocellular carcinoma. In the US alone, cholangiocarcinoma accounts for approximately 5000 new cases every year. Of the different types of cholangiocarcinoma (extrahepatic, intrahepatic, and hilar), intrahepatic cholangiocarcinoma (ICC) is the least common but accounts for high mortality. In the last two to three decades, ICC has become the leading cause of primary hepatic malignancy-related deaths in England and Wales.[1] Although ICC is more common in East Asian countries such as China and Thailand, it has been reported that the incidence and mortality of ICC have been increasing in developed Western countries, including the US and the UK.[1] Studies with data gathered from the Surveillance, Epidemiology, and End Results (SEER) program database have shown some interesting findings with respect to changes in the incidence and mortality based on ethnic and racial variations in the US. One study based on SEER data from the years 1990 to 2001 showed that the age-adjusted prevalence in Hispanics was 1.22/100,000 (highest) and 0.3/100,000 in African Americans (lowest). American Indian/Alaska Natives and Asian/Pacific Islanders were noted to have higher mortality rates compared with other groups.[2] The same research group, in their most recent epidemiological study based on the SEER database from 1995 to 2014, found that the incidence has increased significantly. The incidence rate increased threefold from 0.49/100,000 in 1995 to 1.49/100,000 in 2014, with an average annual rate of increase of 5.49%. The incidence rate was higher among males versus females (0.97 vs. 0.88 per 100,000) and among Hispanics versus non-Hispanics (1.8 vs. 0.89 per 100,000). Hispanics had poorer 5-year all-cause and ICC-specific mortality (hazard ratio [HR] 1.11, 95% confidence interval [CI] 1.05–1.19; HR 1.15, 95% CI 1.07–1.24, respectively). This study also found that while African Americans had a lower incidence, they had shorter survival compared with Caucasians, likely due to the presentation at late stages. Asian/Pacific Islanders had a higher ICC incidence rate than any other racial group in the US.[3] Survival rates were also poor for individuals over the age of 45 years, men, African Americans, and American Indians/Alaska Natives who are more prone to be uninsured.[3] In summary, this study demonstrated substantial ethnic-, racial-, sex-, and age-related variations in ICC incidence and survival.

The substantial evidence from the SEER database showing variations in incidence and mortality underscores the importance of identifying the modifiable risk factors that contribute to these variations. One such important factor is socioeconomic status, as well as access to healthcare. Considering that Hispanics and African Americans are the fastest growing and largest minority ethnic groups in the US, respectively, and because of the poor outcomes, it is imperative to develop strategies aimed at eliminating health disparities in access to cancer care.

The authors of the article by Uhlig et al. have identified similar variations in the treatment patients received depending on socioeconomic status, demographic variables, and, interestingly, geographic region.[4] This study is one of the first to identify the variations in the treatment patterns for ICC based on geographic location. Certain regions within the US had significantly higher resection rates and overall survival rates compared with others. Although the factors contributing to this variability have not been analyzed, they could be secondary to variations in regional treatment strategies, inequitable access to tertiary care cancer centers, risk factor exposures, and socioeconomic status. Further research is warranted in identifying

First Received: 14 December 2018;
Published Online: 28 February 2019

C. Are, MD
e-mail: care@unmc.edu

the reasons for such geographic variations in the treatment patterns of ICCs, which could potentially improve survival in ICC.

It is universally accepted and recommended that treatment for all types of cancers are to be approached in a multidisciplinary fashion, with recommendations from medical, surgical, and radiation oncology. The availability of such multidisciplinary platforms may be limited in different regions of the country, particularly in underserved areas. The regional variations in survival rate for ICC demonstrated by Uhlig et al. could be due to inequitable penetration of multidisciplinary platforms, which are particularly important when treating a disease with such a low incidence.

Although R0 surgical resection is the only definitive cure for ICC, a majority of patients (>80%) present with unresectable diseasex.[4] A single tumor without nodal or extrahepatic metastatic disease in a patient with good performance status is ideally treated by surgical resection. Surgery for patients with multifocal disease should only be considered in unusual situations, and preferably within a study protocol. Whether there is a difference between satellites and multifocal disease remains to be determined.[5] With the advent of improved chemotherapy regimens, not only is there a survival benefit for advanced ICCs but neoadjuvant chemotherapy can also potentially downsize tumors, allowing for resection.[6] While there are several retrospective studies showing improved survival in patients undergoing interventional oncologic treatments for unresectable ICCs, the published literature on its benefits is inconclusive. A meta-analysis conducted to compare the effectiveness of hepatic arterial-based therapies for unresectable ICC demonstrated improved tumor response and survival for hepatic arterial infusion therapy, but expressed concerns regarding toxicity.[7] There is a need for prospective, randomized controlled trials in this regard, and the ClinicalTrials.gov website (www.clinicaltrials.gov) currently has 10 ongoing trials in the US involving interventional oncologic procedures for unresectable ICCs.

We commend the authors for tackling this topic via a large database study and believe the results of this article will add to the literature of a greatly understudied disease, in a meaningful way.

REFERENCES

1. Bridgewater J, Galle PR, Khan SA, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *J Hepatol*. 2014;60(6):1268–1289.
2. McLean L, Patel T. Racial and ethnic variations in the epidemiology of intrahepatic cholangiocarcinoma in the United States. *Liver Int*. 2006;26(9):1047–1053.
3. Antwi SO, Mousa OY, Patel T. Racial, Ethnic, and Age Disparities in Incidence and Survival of Intrahepatic Cholangiocarcinoma in the United States; 1995–2014. *Ann Hepatol*. 2018;17(4):604–614.
4. Uhlig J, Sellers CM, Cha C, et al. Intrahepatic cholangiocarcinoma: socioeconomic discrepancies, contemporary treatment approaches and survival trends from the National Cancer Database. *Ann Surg Oncol*. 2019. https://doi.org/10.1245/s10434-019-07175-4.
5. Abou-Alfa GK, Geschwind JF, Choti M, et al. Consensus conference on intrahepatic cholangiocarcinoma. *HPB (Oxford)*. 2015;17(8):661–3.
6. Le Roy B, Gelli M, Pittau G, et al. Neoadjuvant chemotherapy for initially unresectable intrahepatic cholangiocarcinoma. *Br J Surg*. 2018;105(7):839–847.
7. Boehm LM, et al. Comparative effectiveness of hepatic artery based therapies for unresectable intrahepatic cholangiocarcinoma. *J Surg Oncol*. 2015;111(2):213–220.