Conflict of interest

J-HL reports receiving lecture fee from GreenCross Cell (Yongin-si, Gyeonggi-do, Korea), Daewoong Pharmaceutical (Seoul, Korea), and Gilead Science Korea (Seoul, Korea). K-HK reports receiving research grant from Ildong Pharmaceutical (Seoul, Korea).

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

J-HL and K-HK wrote the manuscript and revised the text.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.08.030.

References

Author names in bold designate shared co-first authorship

[1] **Park ES**, **Lee AR**, **Kim DH**, **Lee JH**, Yoo JJ, Ahn SH, et al. Identification of a quadruple mutation that confers tenofovir resistance in chronic hepatitis B patients. J Hepatol 2019;70:1093–1102.
[2] Girones R, Miller RH. Mutation rate of the hepadnavirus genome. Virology 1989;170:595–597.
[3] Kitrinos KM, Corsa A, Liu Y, Flaherty J, Snow-Lampart A, Marcellin P, et al. No detectable resistance to tenofovir disoproxil fumarate after 6 years of therapy in patients with chronic hepatitis B. Hepatology 2014;59:434–442.
[4] Cathcart AL, Chan HL, Bhardwaj N, Liu Y, Marcellin P, Pan CQ, et al. No resistance to tenofovir alafenamide detected through 96 weeks of treatment in patients with chronic hepatitis B infection. Antimicrob Agents Chemother 2018;62.
[5] **Ahn SH**, **Kim DH**, **Lee AR**, Kim BK, Park YK, Park ES, et al. Substitution at rt269 in hepatitis B virus polymerase is a compensatory mutation associated with multi-drug resistance. PLoS ONE 2015;10 e0136728.

Jeong-Hoon Lee[1,*]
Kyun-Hwan Kim[1,2,3,4,*]
[1]*Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea*
[2]*Department of Pharmacology and Center for Cancer Research and Diagnostic Medicine, IBST, School of Medicine, Konkuk University, Seoul, Republic of Korea*
[3]*KU Open Innovation Center, Konkuk University, Seoul, Republic of Korea*
[4]*Research Institute of Medical Sciences, Konkuk University, Seoul, Republic of Korea*
*Corresponding authors. Address: Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, 103 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea. Tel.: +82 2 2072 2228; fax: +82 2 743 6701 (J.-H. Lee). Department of Pharmacology, School of Medicine, Konkuk University, 120 Neungdong-ro, Gwangjin-gu, Seoul 05029, Republic of Korea. Tel.: +82 2 2030 7833; fax: +82 2 2049 6192 (K.-H. Kim).
E-mail addresses: pindra@empal.com, khkim10@kku.ac.kr

Global trends in mortality from intrahepatic and extrahepatic cholangiocarcinoma

To the Editor:

We read with great interest the manuscript by Bertuccio and colleagues, which highlights an important but often neglected issue in liver cancer – rising rates of cholangiocarcinoma (CC), predominantly intrahepatic CC (ICC). However, there were some issues we feel need clarification.

The paper concludes that the decrease in extrahepatic cholangiocarcinoma (ECC)-related mortality most likely follows the increased use of cholecystectomy. This indicates the codes used for ECC include gall bladder cancer and hence increased use of cholecystectomy has reduced ECC overall. However, Gall bladder cancer specific (ICD-10 code C23) mortality rates were not studied. It would have been interesting to see if these mirrored those of declining rates of ECC C24.0.

There is an important issue about perihilar CC that requires comment. The terms "Klatskin", "hilar" and "perihilar" all fundamentally refer to the same entity. The authors state "Klatskin" tumours, a historic term referring to hilar CC, are relatively uncommon, accounting for 1–7% of CC. This is clearly not the case in real world practice. Any practicing clinician who sees CC cases can confirm perihilar CC make up a much larger proportion of CC than 1–7%. The perihilar area is a very common site of CC, accounting for around half of all cases.[1–7] How do we explain this disconnect between official data on the proportion of CC which are perihilar and the numbers we see in actual clinical practice? The likely answer is the decades-long systematic error in the recording of perihilar CC by the WHO's International Classification (ICD) system. This systematic error is the lack of a specific code for perihilar CC.

The main ICD lists all known medical diagnoses, cancer and non-cancer. The ICD system lists topography codes, which describe the anatomical site of origin, or organ, of a tumour. ICD-10 is currently in use and ICD-11 is due to come into effect in 2022. ICD versions have separate codes for ICC and ECC, but neither ICD-10 nor any previous version of ICD has had a separate code for perihilar CC. IARC (Lyon) is the specialized cancer agency of the WHO, and has a separate ICD for Oncology (ICD-O) which exists for cancers only. ICD-O consists of 2 coding systems, which together describe the tumour: the topographical code, which describes the anatomical site of origin of the tumour, and the morphological code, which describes the cell type (or histology) of the tumour, together with the behaviour (malignant or benign). Perihilar CC are extrahepatic but are not specifically differentiated in routine data. In all 3 versions of the ICD-O so far, "Klatskin" CC could have been cross-referenced to either ICC (C22.1) or ECC (C24.0). Furthermore, new versions of ICD and ICD-O are not adopted by all countries in the same year.

A further important issue to highlight is the potential misclassification between hepatocellular carcinoma (HCC) and iCCA

which may be confounding the reported data. There is also a well-established overlap between these two primary liver cancers and an estimated 5–15% of primary liver cancers could be combined iCCA/HCC (Cholangiocellular Ca).[3] A historical lack of biopsy data has not helped with diagnostic certainty and classification. There may also be issues with misdiagnosis as carcinoma of unknown primary.

In summary, bile duct cancers should be clearly sub-classified as intrahepatic, perihilar or distal (extrahepatic (ECC)). These three types of CC are anatomically distinct, have differing epidemiology, pathobiology, clinical presentations and management.[2] The term "Klatskin" is historic, unclear and should be abandoned in subsequent versions of the ICD and ICD-O classification systems.

Diagnostic data needs to be recorded uniformly and accurately. The responsibility to do so lies with both clinicians and cancer registries. ICD-11 and subsequent iterations of ICD-O should have clearly separate topography and morphology codes for iCCA, pCCA and dCCA. Until then, epidemiological trends in cholangiocarcinoma/biliary tract cancer need to be interpreted with caution. Nonetheless, however CC is classified, its overall incidence seems to be rising and urgent studies into its causes and effective therapies are needed.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.07.024.

References

[1] Rizvi S, Khan SA, Hallemeier CL, Kelley RK, Gores GJ. Cholangiocarcinoma – evolving concepts and therapeutic strategies. Nat Rev Clin Oncol 2017. https://doi.org/10.1038/nrclinonc.2017.157.

[2] Connell LC, Harding JJ, Shia J, Abou-Alfa GK. Combined intrahepatic cholangiocarcinoma and hepatocellular carcinoma. Chin Clin Oncol 2016;5:66. https://doi.org/10.21037/cco.2016.10.02.

[3] Khan AS, Dageforde LA. Cholangiocarcinoma. Surg Clin North Am 2019;99:315–335. https://doi.org/10.1016/j.suc.2018.12.004.

[4] Razumilava N, Gores GJ. Cholangiocarcinoma. Lancet 2014;383:2168–2179. https://doi.org/10.1016/S0140-6736(13)61903-0.

[5] DeOliveira ML, Cunningham SC, Cameron JL, Kamangar F, Winter JM, Lillemoe KD, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. Ann Surg 2007;245:755–762.

[6] Primrose JN, Fox RP, Palmer DH, Malik HZ, Prasad R, Mirza D, et al. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. Lancet Oncol 2019;20:663–673. https://doi.org/10.1016/S1470-2045(18)30915-X.

[7] Nakeeb A, Pitt HA, Sohn TA, Coleman J, Abrams RA, Piantadosi S, et al. Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. Ann Surg 1996;224:463–473.

Shahid A. Khan[1,*]
Tracey Genus[2,3]
Helen Morement[2]
Andrew Murphy[3]
Brian Rous[3]
Daniela Tataru[3]

[1]*Department of Hepatology and Gastroenterology, Imperial College London, UK*
[2]*AMMF – The Cholangiocarcinoma Charity, Stansted, UK*
[3]*Public Health England, London, UK*

*Corresponding author. Address: Liver Unit, 10th Floor, QEQM Building, St Mary's Hospital Campus, South Wharf Road, London W2 1NY, England, UK.
Tel.: +44 (0)203 312 6454/6254, fax: +44 (0)207 724 9369.
E-mail address: shahid.khan@imperial.ac.uk

Reply to: "Global trends in mortality from intrahepatic and extrahepatic cholangiocarcinoma"

To the Editor:

We thank Dr. Khan *et al.* for their interest in our work.[1] They are right in pointing out that trends in extrahepatic cholangiocarcinoma (ECC) mirror the long-term declines in gallbladder cancer,[2,3] due to the increase in cholecystectomy. Gallbladder cancer mortality rates in the European Union, in fact, have been declining in women from 2.52/100,000 (world standard) in 1990 to 1.24 in 2015 (−51%). Comparable figures in men were 1.65 in 1990 and 1.24 in 2015 (−25%).[4]

We agree that misclassification in cancer registration, death coding and certification may have affected the incidence and mortality rates of intrahepatic cholangiocarcinoma (ICC), ECC and, mainly, their subsites. The WHO dataset did not enable the subsites of ECC to be distinguished, and the complex of hilar and perihilar CC is a larger proportion than the "historic Klatskin's tumors".[5] However, due to the small overall proportion of Klatskin's tumors reported using current methodology, this misclassification is not likely to materially affect the overall ICC/ECC trends.[6]

We also agree with the plea by Dr. Khan *et al.* that further attention should be given to the diagnosis, classification and registration of ICC and ECC, and their subsites, by hepatologists, pathologists, cancer registration and death certification systems.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.08.033.

References

[1] Bertuccio P, Malvezzi M, Carioli G, Hashim D, Boffetta P, El-Serag HB, et al. Global trends in mortality from intrahepatic and extrahepatic cholangiocarcinoma. J Hepatol 2019;71:104–114.