Guidelines

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma

John Bridgewater[1], Peter R. Galle[2], Shahid A. Khan[3], Josep M. Llovet[4,5], Joong-Won Park[6], Tushar Patel[7], Timothy M. Pawlik[8], Gregory J. Gores[9,*]

[1]*University College, London Cancer Institute, 72 Huntley St., London WC1E 6AA, UK;* [2]*Department of Internal Medicine I, University Medical Center, Johannes Gutenberg University, Mainz, Germany;* [3]*Hepatology and Gastroenterology Section, Department of Medicine, Imperial College London, UK;* [4]*HCC Translational Research Laboratory, Barcelona-Clínic Liver Cancer Group, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Hospital Clinic Barcelona, Catalonia, Spain;* [5]*Mount Sinai Liver Cancer Program, Division of Liver Diseases, Icahn School of Medicine at Mount Sinai, New York, USA;* [6]*Center for Liver Cancer, National Cancer Center, Goyang, Republic of Korea;* [7]*Department of Transplantation, Mayo College of Medicine, Mayo Clinic, 4500 San Pablo Boulevard, Jacksonville, FL 32224, USA;* [8]*Department of Surgery, Sidney Kimmel Cancer Center, Johns Hopkins University School of Medicine, Harvey 611, 600 N Wolfe Street, Baltimore, MD 21287, USA;* [9]*Division of Gastroenterology and Hepatology, Mayo College of Medicine, Mayo Clinic, Rochester, MN, USA*

Introduction

Cholangiocarcinoma (CCA) comprises a heterogeneous group of cancers with pathologic features of biliary tract differentiation, and is presumed to arise from the intra- or extrahepatic biliary tract. Two recent papers suggest these cancers may also arise directly from transdifferentiation of hepatocytes [1,2]. Gallbladder cancer is distinct from cholangiocarcinoma in epidemiology, pathobiology, clinical presentation and management, and should be considered a different form of biliary tract cancer [3]. On the basis of its anatomical origin, CCA is best classified anatomically as intrahepatic (iCCA), perihilar (pCCA), or distal (dCCA) CCA [4]. The incidence of iCCA appears to be increasing and may be as high as 2.1 per 100,000 person years in Western Countries [5]. iCCA may occur in patients with normal liver or with underlying liver disease, and in either clinical context usually is classified pathologically as an adenocarcinoma, although mixed hepatocellular – cholangiocarcinomas also occur, especially in chronic liver disease [6].

Given the increasing incidence of this complex and fatal disease, the growing recognition of iCCA as a distinct cancer, and the large number of recent publications on this disease, the International Liver Cancer Association (ILCA) governing board noted it was both timely and topical to develop practice guidelines on iCCA. These guidelines are largely based on a consensus of a multidisciplinary, geographically diverse writing committee using a data-supported approach, and subsequently reviewed by a separate Practice Guidelines committee of ILCA. The ILCA guidelines committee employed an extensive PubMed search to broadly canvas the existing literature. Each author then wrote different sections of the manuscript relative to their expertise. All authors then reviewed and edited the manuscript to ensure objectivity and evidence-based recommendations. Finally an ILCA oversight committee reviewed the document, provided recommendations, and then additional edits were made to the document. Thus, a two-tiered integrated and interactive process was employed to generate the guidelines. These recommendations suggest preferred approaches to the diagnostic and therapeutic aspects of care, and are intended to be flexible, in contrast to standards of care, which should be supported by robust evidence-based data. Thus, the guidelines have two principal goals: (1) to provide physicians with pragmatic clinical recommendations; and (2) to identify areas of interest for future research, including suggestions for conducting clinical trials. The evidence and recommendations in these guidelines have been graded according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) system, Table 1 [7]. The GRADE system classifies the evidence as high, moderate, low or very low quality. The strength of recommendation is either strong or weak based on the quality of underlying evidence, outcomes, and cost.

Epidemiology & risk factors

The incidence of cholangiocarcinoma varies substantially worldwide with the highest known rates in Northeast Thailand (>80 per 100,000 population) and much lower rates in the Western world, for example Canada (0.3 per 100,000) (Fig. 1) [8]. iCCA is the second most common primary liver cancer in humans, after hepatocellular carcinoma (HCC). Although the frequency of iCCA worldwide is considerably less than HCC, of note, several recent studies from around the world have reported rapidly rising rates of iCCA over the last few decades [9–11].

Keywords: Intrahepatic cholangiocarcinoma; Practice guidelines; Diagnosis and management.
Received 12 July 2013; received in revised form 22 January 2014; accepted 29 January 2014

* Corresponding author. Address: Mayo College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. Tel.: +1 507 284 0686; fax: +1 507 284 0762.
E-mail address: gores.gregory@mayo.edu (G.J. Gores).

ELSEVIER

Table 1. Grading of evidence and recommendations (adapted from GRADE system) [7].

Evidence quality	Notes	Grading
High	Further research is very unlikely to change our confidence in the estimate of effect	A
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	B
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any change of estimate is uncertain	C
Recommendation	**Notes**	**Grading**
Strong recommendation warranted	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost	1
Weak	Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted. Recommendation is made with less certainty, higher cost or resource consumption	2

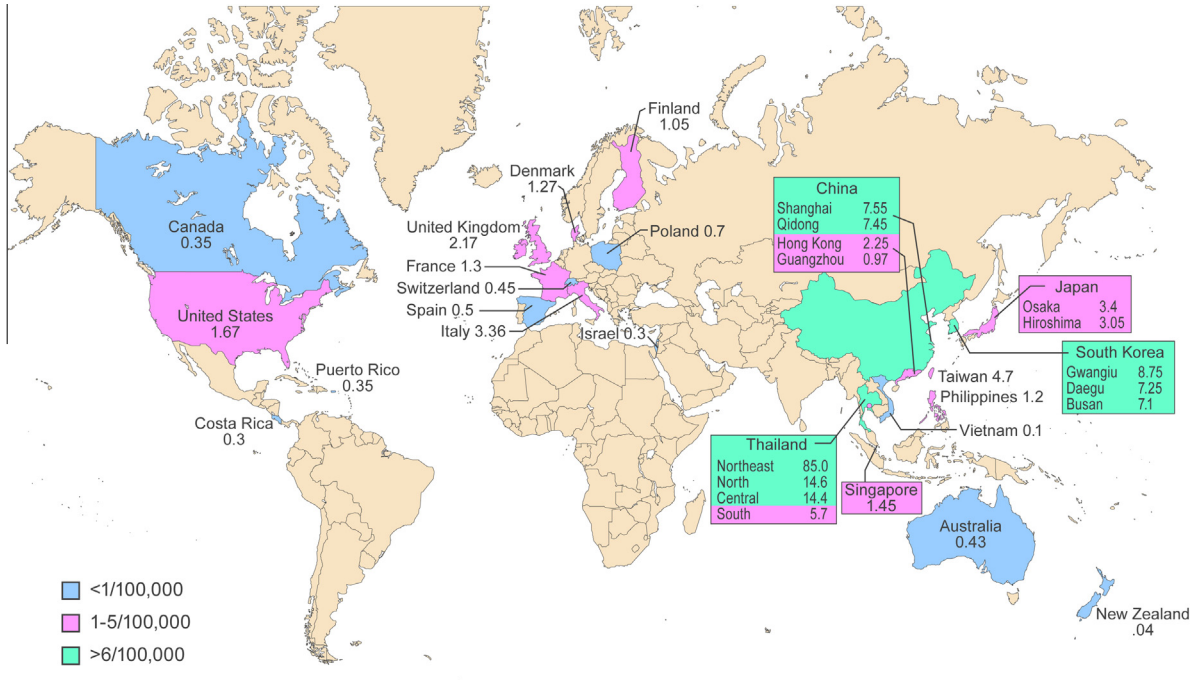

Fig. 1. Incidence of cholangiocarcinoma worldwide where reported.

Trends in iCCA rates worldwide

An increase in mortality rates from iCCA was concomitantly reported in studies from the US and the UK [12,13]. The study from the UK analyzed age standardized mortality rates (ASMR) per 100,000 population for hepatopancreatobiliary (HPB) tumors [12]. Between 1968 and 1996, there was a 15-fold increase in age specific mortality rates (ASpMR) from 0.1 to 1.5 per 100,000 population in ages 45 and above in both sexes. Since the mid-1990s, iCCA has become the most common cause of death from a primary liver tumor in England and Wales, overtaking HCC. Similar trends were found in incidence rates of this cancer in England and Wales [14]. A study from the US also reported a marked rise in both incidence and mortality rates from iCCA between 1973 and 1997, with an estimated annual percent change (EAPC) of 9.1% and 9.4% respectively [13]. Age-adjusted incidence rates of iCCA in the US increased by 165% from 0.3 per 100,000 in 1975–1979 to 0.9 per 100,000 in 1995–1999 [10,11]. More recent studies from Italy and Germany also reported rises in iCCA. In Italy iCCA mortality rates increased from 0.2 to 5.9 per million between 1980 and 2003 [15] and in Germany iCCA mortality more than tripled between 1998 and 2008 [16]. Incidence rates of iCCA have also recently increased in Korea, with an annual percent change (APC) of 8% in males and 11% in females, between 1999 and 2005 [17].

Two studies examining international time trends in mortality rates using the World Health Organization's (WHO) database found that ASMR for iCCA had risen in almost all countries across all continents, albeit at different rates [18,19]. The average global estimated annual percent change (EAPC) in ASMR for males was 6.9 ± 1.5, and for females 5.1 ± 1.0 [19]. In contrast to the aforementioned data, in Denmark between 1978 and 2002, incidence