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Low use of surveillance and early diagnosis of hepatocellular carcinoma in Norway—A population-based cohort study

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ABSTRACT

Background and aims: Curative treatment of hepatocellular carcinoma (HCC) is dependent on early diagnosis. Surveillance of patients at high risk for HCC is a key determinant to achieve this goal, but may be an underutilized tool. The aim of this study was to determine the rate of pre-diagnosis surveillance in patients with HCC in a large population-based cohort and to assess to what extent cirrhosis was known prior to the diagnosis of HCC.

Methods: All patients diagnosed with HCC during 2000–2009 in The South-Eastern Regional Health Authority, representing 56% of the Norwegian population, were identified from The National Cancer Registry and the medical records were reviewed.

Results: Fifteen out of 486 patients (3%) were diagnosed by surveillance. Potential curative treatment was offered to 58% of the patients who underwent surveillance as opposed to 15% in the non-surveillance group. Only age ≤65 years was an independent predictor of screening in a multivariate model. Almost two thirds of the patients with cirrhosis were unrecognized prior to the HCC diagnosis. Two hundred and fourteen patients (44%) were non-cirrhotics.

Conclusion: Regular HCC surveillance in at-risk populations is virtually not applied in Norway and this may contribute to inferior overall survival. Failure to recognize cirrhosis and a high rate of HCC in non-cirrhotic patients will be limiting factors for the overall effectiveness of a potential surveillance program.

1. Introduction

Hepatocellular carcinoma (HCC) is the 5th most common cancer in men and the 7th in women with over half a million new cases diagnosed worldwide each year [1]. There is a considerable geographical variation in incidence rates that is mainly determined by differences in underlying risk factors [2]. Patients from Eastern Asia and sub-Saharan Africa, where chronic hepatitis B (CHB) is endemic, account for around 85% of all cases [2]. Norway has a low incidence of primary liver cancer (PLC) although the age-adjusted annual incidence rates per 100,000 have increased from 2.3 in men and 1.0 in women in 2002 to 3.0 and 1.4 respectively in 2011 [3].

The prognosis for HCC without treatment is dismal with a median survival of only a few months from the onset of symptoms [4]. Curative treatment modalities are hepatic resection (HR), liver transplantation (LT) or ablation if the tumor is diagnosed at an early and asymptomatic state [2]. Therefore semiannual surveillance with ultrasound (US) in patients with high risk for HCC, that is patients with cirrhosis and certain groups of patients with hepatitis B, is recommended by both the European Association for the Study of the Liver-the European Organization for Research and Treatment of Cancer (EASL-EORTC) and the American Association for the Study of Liver Diseases (AASLD) [2,5]. This recommendation

Abbreviations: HCC, hepatocellular carcinoma; CHB, chronic hepatitis B; PLC, primary liver cancer; HR, hepatic resection; LT, liver transplantation; US, ultrasound; EASL, European Association for the Study of the Liver; EORTC, European Organization for Research and Treatmen of Cancer; AASLD, the American Association for the Study of Liver Diseases; CHC, chronic hepatitis C; ICD-10, international classification of diseases 10th edition; AFP, alpha fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CT, computed tomography; MRI, magnetic resonance imaging.

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relies on one placebo-controlled trial from China which included nearly 19,000 patients with CHB and led to a 37% reduction in HCC-related mortality [6] and several observational and case-control studies [7–13]. Randomized controlled trials in other high-risk groups than CHB would strengthen the evidence for the clinical benefit of surveillance programs, but due to ethical considerations, it is unlikely that such studies will ever be undertaken [14].

The primary aim of this study was to determine the rate of prediagnosis surveillance in patients with HCC in a large population-based cohort that comprises more than half of the Norwegian population and to identify possible determinants of surveillance. The secondary aim was to determine to which extent cirrhosis and hepatitis B was diagnosed prior to HCC and hence estimate the potential for surveillance at a population level in a low-incidence country.

2. Patients and methods

2.1. Study population

The Norwegian specialist health care system is organized in four geographical health care regions.

The South-Eastern Regional Health Authority encompasses 10 of the country's 19 counties, covers an area of 111,000 km^2 and serves 2.8 million people representing 56% of the entire Norwegian population. Reporting of all cancer cases to the National Cancer Registry is statutory for clinicians and pathologists. These reports include a personal identification number coupled to age, gender, the municipality where the patient lived and when and at which hospital the cancer was diagnosed. The National Cancer Registry is coupled to the Norwegian Death Registry enabling calculation of overall mortality from a specific cancer. In the 10th version of the International Classification of Diseases (ICD-10) PLC are coded C22 and HCC is coded C22.0.

We requested data from The National Cancer Registry from all patients diagnosed with PLC, that is C22, in South-Eastern Regional Health Authority in the 10-year period 2000–2009. By choosing C22 with subgroups we intended to minimize consequences of possible coding errors. The present study cohort was established as depicted in Fig. 1. Although the individual patient reports from the National Cancer Registry contain some tumor specific information like mode of diagnosis and treatment they were not detailed enough to provide sufficient information for this study. As a consequence, we performed manual chart reviews of all the patient records.

2.2. Data collection

The following demographic and tumor specific data were collected: Age, gender, country of origin, HCC risk factors including cirrhosis, parameters for viral hepatitis, alcohol consumption and diabetes. Mode of diagnosis, histology, alpha fetoprotein (AFP) tumor size and number, Barcelona Clinic Liver Cancer (BCLC) staging and treatment modality was registered, and survival data were obtained from the National Cancer Registry.

2.3. Definitions

Diagnosis of HCC was based on the Barcelona-2000 EASL Conference criteria for 2000–2005 and on the AASLD-2005 criteria for the period 2006–2009 [5,15]. Barelona-2000 EASL Conference criteria: (1) histology or (2) non-invasive criteria (restricted to cirrhotic patients with a focal lesion >2 cm): (a) two coincident imaging techniques with arterial hypervascularization or (b) one imaging technique with arterial hypervascularization associated with AFP levels >400 ng/ml. AASLD-2005 criteria: (1) histology or (2) non-invasive criteria (restricted to cirrhotic patients with a focal lesion >2 cm: (a) one dynamic imaging technique demonstrating arterial hypervascularity and venous/late phase washout or (b) one dynamic imaging technique with arterial hypervascularization and AFP > 200 ng/ml. For nodules between 1 and 2 cm two imaging techniques demonstrating typical vascular pattern were diagnostic. Cases not fulfilling these definitions were considered to have inadequate data and excluded from the study.

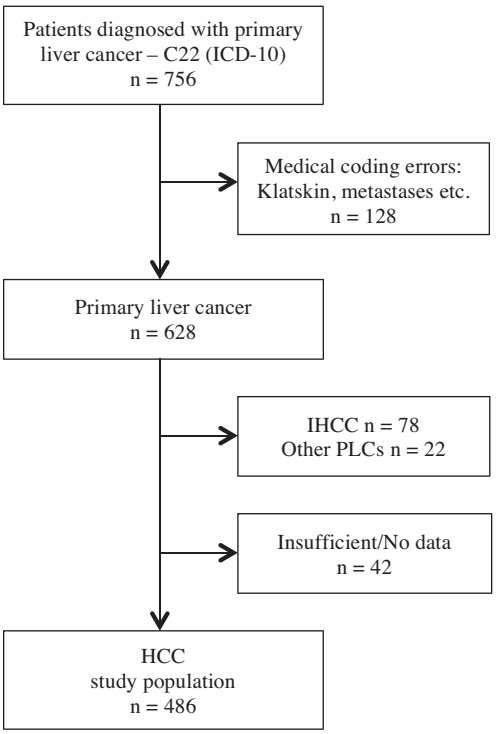

Fig. 1. Flow diagram to illustrate how the HCC study cohort was selected. ICD-10, International classification of diseases, 10th edition PLC, Primary Liver Cancer; IHCC, Intrahepatic cholangiocarcinoma.

Mode of diagnosis was divided into the following five categories: surveillance, symptomatic, incidental, that is during diagnostic work-up for other reasons, before LT for another indication and explant liver or autopsy.

Surveillance for HCC was defined as US of the liver with the intention of screening at least once annually with or without AFP assessment. A negative US at least 6 months prior to HCC diagnosis had to have been performed. Although now considered substandard, AFP alone measured at least once annually was also accepted as surveillance since patients were included from year 2000 and in the earlier part of the study period the documentation of the limited value of AFP as a single test, was not unequivocal.

Indications for surveillance followed the EASL-EORTC guideline that is in essence, cirrhosis of any etiology, non-cirrhotic HBV carriers with active hepatitis or a family history of HCC and non-cirrhotic hepatitis C patients with advanced fibrosis [2]. Patients with porphyria were added to the list since they carry a very high risk of developing HCC and the benefit of surveillance has been demonstrated [16].

Cirrhosis was defined either by histological evaluation or from obvious clinical signs such as ascites and esophageal varices or from typical radiological patterns like irregular surface, general atrophy and hypertrophy of caudate lobe.

Non-cirrhosis was defined either from histology or from the combination of no clinical signs and no radiological features of cirrhosis.