Research Article

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The changing scenario of hepatocellular carcinoma over the last two decades in Italy

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Background & Aims: This study investigates whether the aetiologic changes in liver disease and the improved management of hepatocellular carcinoma (HCC) have modified the clinical scenario of this tumour over the last 20 years in Italy.

Methods: Retrospective study based on the analysis of the ITA.LI.CA (Italian Liver Cancer) database including 3027 HCC patients managed in 11 centres. Patients were divided into 3 groups according to the period of HCC diagnosis: 1987–1996 (year of the "Milano criteria" publication), 1997–2001 (year of release of the EASL guidelines for HCC), and 2002–2008.

Results: The significant changes were: (1) progressive patient ageing; (2) increasing prevalence of HCV infection until 2001, with a subsequent decrease, when the alcoholic aetiology increased; (3) liver function improvement, until 2001; (4) increasing "incidental" at the expense of "symptomatic" diagnoses, until 2001; (5) unchanged prevalence of tumours diagnosed during surveillance (around 50%), with an increasing use of the 6-month schedule; (6) favourable HCC "stage migration", until 2001; (7) increasing use of percutaneous ablation; (8) improving survival, until 2001.

Conclusions: Over the last 20 years, several aetiologic and clinical features regarding HCC have changed. The survival improvement observed until 2001 was due to an increasing number of tumours diagnosed in early stages and in a background of compensated cirrhosis, and a growing and better use of locoregional treatments. However, the prevalence of early cancers and survival did not increase further in the last years, a result inciting national policies aimed at implementing surveillance programmes for at risk patients.

Keywords: Hepatocellular carcinoma; Cirrhosis; Epidemiology; Surveillance; Treatment; Survival.

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Abbreviations: HCC, Hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen; ITA.LI.CA, Italian Liver Cancer; C–P, Child–Pugh; AFP, α-fetoprotein; EASL, European Association of the Study of the Liver; US, ultrasound; CT, computed tomography; MRI, magnetic resonance imaging; CEUS, contrast enhanced–US; V_0, without macrovascular invasion; L_0, without lymph node invasion; M_0, without distant metastases; CLIP, Cancer of the Liver Italian Program; BCLC, Barcelona Clinic Liver Cancer; OLT, orthotopic liver transplantation; PEI, percutaneous ethanol injection; RF, radiofrequency thermoablation; TACE, transcatheter arterial chemoembolization; HBcAb, hepatitis B core antibody; SD, standard deviation; HDV, hepatitis D virus; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steato-hepatitis.

Introduction

Hepatocellular carcinoma (HCC) is the third cause of cancer death and the leading cause of mortality among cirrhotic patients [1]. Most HCCs arise in a cirrhotic liver [2] and, worldwide, 75–80% of them are related to hepatitis B virus (HBV) or hepatitis C virus (HCV) chronic infections [3]. HBV still represents the leading risk factor worldwide, although its impact is declining in several endemic countries due to vaccination campaigns [4]. Conversely, the role of HCV infection is growing in geographic areas with a low HCC incidence, such as the US and Northern Europe, mainly due to increasing rates of intravenous drug abuse and contaminated blood supply [5]. Moreover, a rising proportion of HCCs is ascribed to alcohol abuse and metabolic disorders in developed countries [2].

Cancer

The only chance to achieve long-term survival in HCC patients is to detect the tumour at an early stage, suitable for curative or effective therapies, as demonstrated in hepatitis B surface antigen (HBsAg) carriers by a randomized trial [6] and suggested in cirrhotic patients by several cohort studies [7–10]. This becomes realistic for most patients diagnosed with HCC if a regular surveillance, recommended for subjects at risk [11–13], is widely implemented in clinical practice. Lastly, the huge effort made in recent years to standardize and refine HCC treatments is expected to produce beneficial effects on the prognosis of treatable patients [14].

Therefore, the clinical scenario of HCC may have changed over time in most developed areas of the world, including Southern Europe. Our study aimed at evaluating whether and how risk factors, modality of diagnosis, clinical characteristics, treatment approach and survival of HCC patients have evolved over the last two decades in Italy.

Patients and methods

Patients

We analyzed the data of the Italian Liver Cancer (ITA.LI.CA) database, currently including 3027 HCC patients seen consecutively from January 1987 to December 2008 at 11 medical institutions. The data were collected prospectively and were updated every 2 years.

For the purpose of this study, we included all but 37 (1.2%) patients for whom the year of HCC diagnosis was not reported. The following variables were available in at least 80% of cases and were included in our analysis:

- Age.
- Gender.
- Aetiology of liver disease.
- Child–Pugh (C–P) class.
- Modality of HCC diagnosis.
- Surveillance intervals.
- Histological confirmation of HCC diagnosis.
- α-Fetoprotein (AFP) level.
- Gross pathological features and stage of cancer.
- Main treatment.
- Survival.

Based on the year of tumour diagnosis, patients were allocated to 3 groups: Group 1 (G1) including 760 (25.1%) patients observed between 1987 and 1996; Group 2 (G2) encompassing 856 (28.3%) seen between 1997 and 2001; Group 3 (G3) including 1374 (45.4%) enrolled between 2002 and 2008. These periods were delimited by the dates of two milestones of HCC management, i.e. the publication of the "Milano criteria" [15] – which re-opened the doors of liver transplantation to HCC patients – and the availability of the evidence-based guidelines released by the European Association of the Study of the Liver (EASL) [12].

Aetiology and diagnosis of liver disease

The cause of liver disease was classified as:

- HBV, if patients were HBsAg + carriers;
- HCV, if patients were positive for serum anti-HCV antibody;
- alcoholic, if the daily ethanol intake was more than 60 g for women and 80 g for men for more than 10 years, in the absence of any other known causes of liver disease;
- multi-viral aetiology, if patients were carriers of al least two hepatitis viruses;
- combined aetiology, if hepatitis virus infection/s was/were associated with alcohol abuse;
- other.

In 2893 cases (96.1%), HCC was associated with cirrhosis (histologically confirmed in 813 patients and by laparotomy or laparoscopy in 55). In the remaining patients, this diagnosis was made unequivocal by clinical and ultrasound (US) evaluations, endoscopic findings suggesting the presence of portal hypertension, and laboratory features. Among the non-cirrhotic patients, 116 had a chronic liver disease (hepatitis, fibrosis or fatty liver), while the features of extra-tumoural liver were not specified in 18 cases.

Modality of HCC diagnosis

HCC diagnosis was classified as:

- Under surveillance (regular US surveillance ± AFP determination).
- Incidental (investigations for other diseases or for a general check-up).
- Symptomatic (work-up prompted by tumour symptom occurrence).

The cases diagnosed during surveillance were further sub-grouped according to the surveillance interval:

- 3–7 months (accepted delay for the semi-annual programme: 1 month).
- 8–13 months (idem for the annual programme).
- >13 months.

Two-hundred and nine patients (13.3% of surveyed cases) were excluded from this sub-analysis since the interval was not specified.

Diagnosis and staging of HCC

The diagnosis was based on histology and/or cytology in 1195 (39.5%) patients. In the remainder, diagnosis was confirmed by combining a diagnostic value (>200 ng/ml) of AFP [12,14] with typical features in one imaging technique (dynamic computed tomography [CT] scan or magnetic resonance imaging [MRI] or contrast enhanced US [CEUS]) or, in the absence of diagnostic AFP elevation, in at least two techniques.

Cancer was staged by CT scan or MRI. All patients had a chest X-ray, whereas additional investigations to detect metastases were performed when extra-hepatic involvement was suspected.

HCC gross pathology was staged as:

- Solitary nodule $\leqslant$2 cm without macrovascular invasion (V_0), lymph-node invasion (L_0) or distant metastases (M_0) ("very early" HCC);
- solitary nodule of 2.1–3 cm, V_0, L_0, M_0;
- solitary nodule of 3.1–5 cm, V_0, L_0, M_0;
- 2–3 nodules, each $\leqslant$3 cm (paucifocal), V_0, L_0, M_0;
- advanced tumour (beyond the Milano criteria) [15].

HCC was staged according to the Cancer of the Liver Italian Program (CLIP) system proposed in 1998 [16]. For cases recruited prior to this year, the CLIP score was calculated retrospectively. The Barcelona Clinic Liver Cancer (BCLC) staging system [17] was not utilized due to the high risk of inaccuracy in defining the performance status retrospectively.

Treatments

Patients were classified in 5 groups according to the main treatment received:

- Orthotopic liver transplantation (OLT).
- Hepatic resection.
- Percutaneous ablation with ethanol injection (PEI) or radiofrequency (RF).
- Trans-catheter arterial chemoembolization (TACE).
- Others (systemic chemotherapy, anti-estrogens or palliation).

Sorafenib was not included among treatments since the drug only became available for clinical practice in Italy at the end of 2008.

Statistical analysis

Continuous data are expressed as mean value ± standard deviation (SD), and discrete variables as absolute and relative frequencies. To compare continuous variables among the 3 periods, the ANOVA or the Kruskal–Wallis tests were used, as