Research Article

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

Semiannual surveillance is superior to annual surveillance for the detection of early hepatocellular carcinoma and patient survival

Valentina Santi[1], Franco Trevisani[1,*], Annagiulia Gramenzi[1], Alice Grignaschi[1], Federica Mirici-Cappa[1], Paolo Del Poggio[2], Maria Anna Di Nolfo[3], Luisa Benvegnù[4], Fabio Farinati[5], Marco Zoli[6], Edoardo Giovanni Giannini[7], Franco Borzio[8], Eugenio Caturelli[9], Maria Chiaramonte[10], Mauro Bernardi[1], for the Italian Liver Cancer (ITA.LI.CA) Group [†]

[1]*Dipartimento di Medicina Clinica, Unità di Semeiotica Medica, Alma Mater Studiorum – Università di Bologna, Italy;* [2]*Divisione di Medicina, Ospedale Treviglio-Caravaggio, Treviglio, Italy;* [3]*Divisione di Medicina, Azienda Ospedaliera Bolognini, Seriate, Italy;* [4]*Dipartimento di Medicina Clinica e Sperimentale, Unità di Medicina, Università di Padova, Italy;* [5]*Dipartimento di Scienze Chirurgiche e Gastroenterologiche, Unità di Gastroenterologia, Università di Padova, Italy;* [6]*Dipartimento di Medicina Clinica, Unità di Medicina, Alma Mater Studiorum – Università di Bologna, Italy;* [7]*Dipartimento di Medicina Interna, Unità di Gastroenterologia, Università di Genova, Italy;* [8]*Dipartimento di Medicina, Unità di Medicina Interna ed Epatologia, Ospedale Fatebenefratelli, Milano, Italy;* [9]*Unità di Gastroenterologia, Ospedale Belcolle, Viterbo, Italy;* [10]*Unità di Gastroenterologia, Ospedale Sacro Cuore Don Calabria, Negrar, Italy*

Background & Aims: The current guidelines recommend the surveillance of cirrhotic patients for early diagnosis of hepatocellular carcinoma (HCC), based on liver ultrasonography repetition at either 6 or 12 month intervals, since there is no compelling evidence of superiority of the more stringent program. This study aimed at comparing cancer stage, treatment applicability, and survival between patients on semiannual or annual surveillance.
Methods: We analyzed the clinical records of 649 HCC patients in Child-Pugh class A or B, observed in ITA.LI.CA centers. HCC was detected in 510 patients submitted to semiannual surveillance (Group 1) and in 139 submitted to annual surveillance (Group 2). In Group 1 the survival was presented as *observed* and *corrected for the lead time*.
Results: The cancer stage was less severe in Group 1 than in Group 2 ($p < 0.001$), with more single tiny ($\leqslant$2 cm) and less advanced tumors. Treatment applicability was improved by the semiannual program ($p = 0.020$). The median *observed* survival was 45 months (95% CI 40.0–50.0) in Group 1 and 30 months (95% CI 24.0–36.0) in Group 2 ($p = 0.001$). The median *corrected* survival of Group 1 was 40.3 months (95% CI 34.9–45.7) ($p = 0.028$ with respect to the observed survival of Group 2). Age, platelet count, α-fetoprotein, Child-Pugh class, cancer stage, and hepatocellular carcinoma treatment were independent prognostic factors.
Conclusions: Semiannual surveillance increases the detection rate of very early hepatocellular carcinomas and reduces the number of advanced tumors as compared to the annual program. This translates into a greater applicability of effective treatments and into a better prognosis.

Keywords: Hepatocellular carcinoma; Cirrhosis; Diagnosis; Surveillance interval; Cancer stage; Survival.
Received 21 December 2009; received in revised form 12 March 2010; accepted 16 March 2010; available online 27 April 2010
*Corresponding author. Address: Dipartimento di Medicina Clinica, Semeiotica Medica, via Albertoni, 15, 40138 Bologna, Italy. Tel.: +39 051 6362923; fax: +39 051 6362930.
E-mail address: franco.trevisani@unibo.it (F. Trevisani).
[†]Other members of the ITA.LI.CA group: *Dipartimento di Medicina Clinica, Alma Mater Studiorum – Università di Bologna, Italia*: Pietro Andreone, Paolo Caraceni, Antonio Di Micoli, Marco Domenicali, Gianluca Fatti, Donatella Magalotti, Andrea Zambruni; *Divisione di Medicina, Azienda Ospedaliera Bolognini, Seriate, Italia*: Claudia Balsamo, Maria Di Marco, Elena Vavassori; *Divisione di Medicina, Ospedale Treviglio-Caravaggio, Treviglio, Italia*: Lodovico Gilardoni, Mario Mattiello; *Dipartimento di Medicina Clinica e Sperimentale, Università di Padova, Italia*: Alfredo Alberti, Angelo Gatta, Maurizio Gios; *Dipartimento di Scienze Chirurgiche e Gastroenterologiche, Università di Padova, Italia*: Massimo De Giorgio, Anna Giacomin, Simona Gianni, Michela Rinaldi, Adriana Sergio, Veronica Vanin; *Dipartimento di Discipline Chirurgiche, Rianimatorie e dei Trapianti, Alma Mater Studiorum – Università di Bologna, Italia*: Gian Luca Grazi, Antonio Daniele Pinna, Matteo Ravaioli; *Dipartimento di Malattie Apparato Digerente e Medicina Interna, Azienda ospedaliero-universitaria di Bologna, Italia*: Emanuela Giampalma, Rita Golfieri; *Unità di Gastroenterologia, Ospedale Belcolle, Viterbo, Italia*: Giorgia Ghittoni, Paola Roselli; *Dipartimento di Medicina Interna, Unità di Gastroenterologia, Italia, Università di Genova*: Giorgia Bodini, Marina Corbo, Vincenzo Savarino.
Abbreviations: HCC, hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; US, ultrasonographies; AASLD, American Association of the Study of the Liver Disease; C-P, Child-Pugh; ITA.LI.CA, Italian Liver Cancer; AFP, α-fetoprotein; HCV, hepatitis C virus; HBV, hepatitis B virus; CT, computed tomography; MRI, magnetic resonance imaging; CEUS, contrast enhanced–US; V0, without macrovascular invasion; L0, without lymph-node invasion; M0, without distant metastases; PEI, percutaneous ethanol injection; RF, radiofrequency thermoablation; TACE, transarterial chemoembolization; ALT, alanine aminotranspherase; CI, confidence interval; DT, doubling time; OLT, orthotopic liver transplantation.

Introduction

Hepatocellular carcinoma (HCC) is a major health problem, being the sixth most common cancer, the third cause of cancer death worldwide, and the leading cause of mortality among cirrhotic patients [1,2]. Liver cirrhosis is in fact the main risk factor for HCC [3], and the annual incidence of HCC in cirrhotic patients is 3–7% [4–6].

Cancer

The sole approach to achieve long-term survival is to detect the tumor at an early stage, suitable for curative or effective therapies, as suggested by a randomized controlled study performed in hepatitis B surface antigen (HBsAg) carriers [7] and several observational studies [2,8–10]. International guidelines for HCC management therefore recommend surveying patients at risk of HCC development with serial ultrasonographies (US) of the liver [11,12].

The ideal goal of surveillance is the detection of single tiny HCCs, which have the highest chance of being cured since the rate of microvascular invasion and satellite nodules – predictors of recurrence after radical therapy [3,13] – significantly increase when the tumor exceeds 2 cm [14]. Indeed, a size $\leqslant$2 cm predicts a lower recurrence and better survival after surgical [15,16] and percutaneous ablative procedures [17]. Other studies raise the threshold to 3 cm for an excellent outcome after curative treatments [18,19].

Both semiannual and annual surveillance are recommended by the American Association of the Study of the Liver Disease (AASLD) guidelines [12] since there is no clear evidence of superiority of the more stringent program concerning either cancer features [2,20] or patient survival [10,21]. However, in the studies describing survival the potential advantage offered by the semiannual program could have been marred by the presence of Child-Pugh (C-P) class C patients, in whom the surveillance becomes useless [22,23]. Lastly, a Korean study, presented as abstract, showed that the semiannual schedule improves patient survival compared with the annual one [24]. Therefore, what is the ideal interval of surveillance is still a matter of debate. This study aimed at comparing the efficiency of semiannual and annual surveillance in terms of early diagnosis of HCC and survival in C-P class A and B cirrhotic patients.

Patients and methods

Patients

We analyzed the data of the Italian Liver Cancer (ITA.LI.CA) database, currently including 2193 HCC patients seen consecutively from January 1987 to December 2006 at 10 medical institutions. The data were collected prospectively and were updated every 2 years. Antecedent versions of this database, updated at 1998 and 2004, were utilized in our previous studies describing the impact of interval surveillance on patient survival [10,21].

For the purpose of this study, we selected patients fulfilling the following inclusion criteria: (1) C-P class A or B; (2) HCC diagnosis made during a regular surveillance based on liver US, with or without α-fetoprotein (AFP) determination, performed every 6 (±1 month) or 12 month (±1 month); (3) description of presenting cancer stage available. Accordingly, 649 patients were selected. The causes of exclusion were: C-P class C or unspecified in 472 cases, diagnosis of HCC made outside any surveillance in 816, unspecified modality of HCC diagnosis in 10, unspecified interval of surveillance in 109, and interval outside the above mentioned ranges in 137.

Patients were divided into:

- *Group 1*, consisting of 510 (78.6 %) patients with HCC detected during semiannual surveillance.
- *Group 2*, consisting of 139 (21.4 %) cases with HCC detected during yearly surveillance.

The interval was established by the referring physician of each patient, who was not necessarily one of the ITA.LI.CA clinicians since a number of patients were referred to our centers for diagnosis and/or treatment.

Etiology and diagnosis of cirrhosis

The cause of liver disease was classified as:

- hepatitis C virus (*HCV*), if patients were positive for serum anti-HCV antibody;
- hepatitis B virus *(HBV)*, if patients were HBsAg + carriers;
- *alcoholic*, if the daily ethanol intake was more than 60 g for women and 80 g for men for more than 10 yrs, in the absence of any other known causes of liver disease;
- *multifactorial*, if the disease had two or more causative factors;
- *other* (22 cryptogenic liver diseases, 1 hereditary hemochromatosis, and 2 primary biliary cirrhosis).

Cirrhosis was histologically confirmed in 271 patients and by laparotomy or laparoscopy in 11. In the remaining patients, the diagnosis was made unequivocal by clinical evaluation, presence of nodular liver margins at US examination, endoscopic and/or US findings suggesting the presence of portal hypertension, and laboratory features.

Diagnosis and staging of HCC

The diagnosis was based on histology or cytology in 96 patients. Otherwise, diagnosis was confirmed by combining an increase (>200 ng/ml) of AFP [12,25] with typical features of the lesion 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, while additional investigations to detect metastases were performed when extrahepatic involvement was suspected.

For the purpose of this study, HCC was staged as:

- solitary nodule $\leqslant$2 cm without macrovascular invasion (V0), lymph-node invasion (L0) or distant metastases (M0);
- solitary nodule of 2.1–3 cm, V0, L0, M0;
- solitary nodule of 3.1–5 cm, V0, L0, M0;
- 2–3 nodules, each $\leqslant$3 cm (paucifocal), V0, L0, M0;
- advanced tumor (outside the Milano criteria [26]).

Therapeutic decision

The eligibility criteria for hepatic resection, percutaneous ethanol injection (PEI), radiofrequency thermoablation (RF) or transarterial chemoembolization (TACE) have been reported in detail elsewhere [10].

Serologic testing

Liver tests, serum virological markers and AFP were determined by conventional methods, using commercial kits.

Statistical analysis

Continuous data are expressed as median ± range, and discrete variables as absolute and relative frequencies. The Mann–Whitney *U* test was used to compare continuous data, and χ^2 test or Fisher's exact test to compare discrete variables.

To identify factors significantly associated with the cancer stage, logistic regression analysis was used, only including variables available in more than 90% of patients. We tested: age, sex, etiology (HCV vs. other causes), decade of diagnosis (1987–1996 and 1997–2006), C-P class, esophageal varices (present/absent), comorbidities (cardiovascular, pulmonary, renal, gastrointestinal and hematological diseases, obesity and diabetes) (present/absent), alanine aminotranspherase (ALT), platelet count, AFP ($\leqslant$20 ng/ml, 21–200 ng/ml, >200 ng/ml) and surveillance interval. Continuous variables, if not otherwise specified, were dichotomized according to the median value. Variables associated ($p \leqslant 0.10$) with the cancer stage at the univariate analysis were included in a stepwise multivariate analysis to identify those providing independent information.

Survival was calculated from the time of cancer diagnosis to death, with values censored at the date of the last follow-up, and was expressed as median and 95% Confidence Interval (CI). Life table estimates were calculated according to the Kaplan–Meier method, and compared by the log-rank test. To minimize the *lead time bias* [27], we calculated the "lead time" for semiannual surveyed patients using Schwartz's formula [28], originally proposed for calculating tumor growth:

$$t = \mathrm{DT} \times 3 \times \log(d1/d0)/\log(2)$$

where t is the lead time (days), DT is the median value of the tumor volume doubling time proposed by Scheu et al. [29], $d0$ is the median tumor diameter