Research Article

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Estimation of lead-time bias and its impact on the outcome of surveillance for the early diagnosis of hepatocellular carcinoma

Alessandro Cucchetti[1,*], Franco Trevisani[1], Anna Pecorelli[1], Virginia Erroi[1], Fabio Farinati[2], Francesca Ciccarese[3], Gian Lodovico Rapaccini[4], Mariella Di Marco[5], Eugenio Caturelli[6], Edoardo G. Giannini[7], Marco Zoli[1], Franco Borzio[8], Giuseppe Cabibbo[9], Martina Felder[10], Antonio Gasbarrini[11], Rodolfo Sacco[12], Francesco Giuseppe Foschi[13], Gabriele Missale[14], Filomena Morisco[15], Gianluca Svegliati Baroni[16], Roberto Virdone[17], Mauro Bernardi[1], Antonio D. Pinna[1], for the Italian Liver Cancer (ITA.LI.CA) group

[1]*Dipartimento di Scienze Mediche e Chirurgiche, Policlinico S. Orsola-Malpighi, Alma Mater Studiorum – Università of Bologna, Italy;* [2]*Dipartimento di Scienze Chirurgiche e Gastroenterologiche, Unità di Gastroenterologia, Università di Padova, Padova, Italy;* [3]*Divisione di Chirurgia, Policlinico San Marco, Zingonia, Italy;* [4]*Unità di Medicina Interna e Gastroenterologia, Complesso Integrato Columbus, Università Cattolica di Roma, Roma, Italy;* [5]*Divisione di Medicina, Azienda Ospedaliera Bolognini, Seriate, Italy;* [6]*Unità Operativa di Gastroenterologia, Ospedale Belcolle, Viterbo, Italy;* [7]*Dipartimento di Medicina Interna, Unità di Gastroenterologia, Università di Genova, Genova, Italy;* [8]*Dipartimento di Medicina, Unità di Radiologia, Ospedale Fatebenefratelli, Milano, Italy;* [9]*Dipartimento Biomedico di Medicina Interna e Specialistica, Unità di Gastroenterologia, Università di Palermo, Palermo, Italy;* [10]*Ospedale Regionale di Bolzano, Unità di Gastroenterologia, Bolzano, Italy;* [11]*Unità di Medicina Interna e Gastroenterologia, Policlinico Gemelli, Università Cattolica di Roma, Roma, Italy;* [12]*Unità Operativa Gastroenterologia e Malattie del Ricambio, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy;* [13]*Unità di Medicina Interna, Presidio Ospedaliero di Faenza, Faenza, Italy;* [14]*Unità di Malattie Infettive ed Epatologia, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy;* [15]*Dipartimento di Medicina Clinica e Chirurgia, Unità di Gastroenterologia, Università di Napoli "Federico II", Napoli, Italy;* [16]*Clinica di Gastroenterologia, Università Politecnica delle Marche, Ancona, Italy;* [17]*Dipartimento Biomedico di Medicina Interna e Specialistica, Unità di Medicina Interna, Palermo, Italy*

Background & Aims: Lead-time is the time by which diagnosis is anticipated by screening/surveillance with respect to the symptomatic detection of a disease. Any screening program, including surveillance for hepatocellular carcinoma (HCC), is subject to lead-time bias. Data regarding lead-time for HCC are lacking. Aims of the present study were to calculate lead-time and to assess its impact on the benefit obtainable from the surveillance of cirrhotic patients.

Methods: One-thousand three-hundred and eighty Child–Pugh class A/B patients from the ITA.LI.CA database, in whom HCC was detected during semiannual surveillance (n = 850), annual surveillance (n = 234) or when patients came when symptomatic (n = 296), were selected. Lead-time was estimated by means of appropriate formulas and Monte Carlo simulation, including 1000 patients for each arm.

Results: The 5-year overall survival after HCC diagnosis was 32.7% in semiannually surveilled patients, 25.2% in annually surveilled patients, and 12.2% in symptomatic patients (p <0.001). In a 10-year follow-up perspective, the median lead-time calculated for all surveilled patients was 6.5 months (7.2 for semiannual and 4.1 for annual surveillance). Lead-time bias accounted for most of the surveillance benefit until the third year of follow-up after HCC diagnosis. However, even after lead-time adjustment, semiannual surveillance maintained a survival benefit over symptomatic diagnosis (number of patients needed to screen = 13), as did annual surveillance (18 patients).

Conclusions: Lead-time bias is the main determinant of the short-term benefit provided by surveillance for HCC, but this benefit becomes factual in a long-term perspective, confirming the clinical utility of an anticipated diagnosis of HCC.

Keywords: Hepatocellular carcinoma; Cirrhosis; Surveillance; Lead-time bias.
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* Corresponding author. Address: General and Transplant Unit, Department of Medical and Surgical Sciences, S. Orsola-Malpighi Hospital, Alma Mater Studiorum – University of Bologna, Via Massarenti n°9, Bologna, Italy.
E-mail address: aleqko@libero.it (A. Cucchetti).

Introduction

The global incidence of hepatocellular carcinoma (HCC) is increasing worldwide and the only chance for cure depends on an early diagnosis by means of surveillance of patients at risk [1,2]. The rationale of surveillance is that it can identify HCC at early stages, allowing the use of treatment capable of prolonging survival. In the assessment of the benefit provided by screening or surveillance of any curable disease, lead time represents a potential source of bias [3–5]. Lead time is the time by which

the diagnosis is anticipated by screening or surveillance with respect to the clinical presentation of a disease [6]. It represents an artificial addition of time to survival of cases detected during screening, leading to a specious improvement in prognosis. Only randomized controlled trials (RCTs) can completely eliminate this bias by comparing mortality rates from the time of patient enrollment in the study, instead of from the time of HCC diagnosis. In the field of surveillance of patients at risk for HCC development, the few available RCTs report conflicting results regarding the benefit of surveillance [7,8], and additional trials are unlikely to be conducted if patients are correctly informed about the risks and benefits of surveillance [9]. Therefore, the actual benefit of surveillance for this type of cancer remains to be defined. Several cohort studies have shown a benefit of surveillance on HCC prognosis, but their results are biased by lead time [10–14]. To limit this bias, some authors have roughly adjusted the survival of patients under surveillance for lead time, but none computed a precise estimation of lead–time bias; therefore, their findings can be substantially affected by different baseline assumptions.

This study aimed at accurately estimating the lead time affecting semiannual and annual surveillance for HCC through a rigorous mathematical model already proposed in other cancer screening programs [15,16]. The impact of lead-time bias on the results achieved by such surveillance programs in a "real world" clinical setting was also explored. Finally, the *number-needed-to screen* (NNS) was calculated to estimate the effect size which should be expected by surveillance.

Patients and methods

Study population

Data were derived from the ITA.LI.CA database. This database currently includes 5136 HCC patients, consecutively seen from January 1987 to December 2012 at 18 medical institutions. Patients having the following inclusion criteria were selected for this study: (a) Child–Pugh class A or B, as surveillance is useless and not recommended by international guidelines in advanced cirrhosis [2,3,12]; (b) treatment description and complete clinical data, and (c) HCC diagnosis reached during surveillance based on liver ultrasonography (US) with or without serum alpha-fetoprotein (AFP) determination, performed every 6 (±1 month; semi-annual surveillance) or 12 months (±1 month; annual surveillance), or at the time of cancer symptom occurrence (outside any surveillance schedule/no-surveillance). Hepatocellular carcinomas incidentally diagnosed as a result of clinical evaluation for other diseases were excluded from the analysis. Patient surveillance was classified as semiannual or annual on the basis of the schedule adopted in the two years preceding HCC diagnosis. In addition, patients under surveillance in whom diagnostic procedures were performed earlier with respect to the scheduled interval, due to the development of signs or symptoms of cancer, were kept in their original surveillance group and computed accordingly. The interval of surveillance was established by the referring physician of each patient. Patients were excluded from the study due to: incomplete clinical data (1195 patients), Child–Pugh class C (278 patients), inconsistent (interval >13 months) surveillance or 3 month-surveillance (total: 808 patients), incidental tumor diagnosis (1475 patients). Accordingly, 1380 patients were enrolled. The time that elapsed between diagnosis and treatment was approximately 40 days for the majority of patients (maximum 2 months) except for candidates for liver transplantation. Cirrhosis was histologically confirmed in 364 patients; in the remaining patients, diagnosis was made unequivocally by clinical and radiological evaluations together with laboratory findings. All patients provided informed consent for the anonymous recording of their data in the ITA.LI.CA database. The study was approved by the Institutional Review Board of each participating center.

Mathematical estimation of lead time

Algebraic details of the mathematical model for lead-time calculation are provided in the Supplementary materials and methods. Briefly, we assumed an *exponential* tumor growth during the *sojourn time* since it best reflects the tumor growth kinetics over the range of sizes at which the majority of HCCs are detected in screening programs (equation 1) [17]. The mean size (together with relevant 95% confidence intervals [95% CI]) of tumors detected during 6-month or 12-month surveillance programs, and the mean size of symptomatic tumors were used for sojourn time calculation (equation 2) [18,19]. Calculation of the sojourn time requires the tumor growth rate to be known, and this variable was derived from the tumor volume doubling time (DT) (equation 3). Thus, the basis of lead-time estimation relies on the doubling time. Hence, a systematic review of the literature was carried out to obtain the most suitable DT values. Details of the literature review are reported in the Supplementary materials and methods. Four studies fulfilled the requirements for the present analysis, involving a total of 155 HCCs, in which the DT was calculated using the formula proposed by Schwartz [20–23]. The distribution of HCC DT was fitted with a log-normal function having $\mu = 4.5253$ and $\sigma = 0.7313$ (Fig. 1). This distribution was used to calculate the *transition rate* to symptomatic disease and lead time, using the appropriate formula (equation 4) [15,16,19].

Simulation methodology

A probabilistic analysis (Monte-Carlo simulation) was initially applied to estimate lead-time and lead-time bias; in this analysis, a theoretical cohort of 1000 patients undergoing semiannual or annual surveillance was considered, and a theoretical cohort of 1000 patients with a symptomatic diagnosis (who did not suffer from lead-time bias) was used as a control group. As previously described, a log-normal distribution was used for doubling time whereas tumor sizes at diagnosis and survival rates varied within a triangular distribution, where interquartile ranges and confidence limits determine the minimum and the maximum values assumed. Base-case time horizon was set at 10 years of follow-up, and a sensitivity analysis was carried out at times varying from 1 year up to 10 years in order to assess the impact of lead time at varying follow-up periods. Survival rates in relationship with surveillance programs were properly calculated and reported in 10-years life-expectancy before and after adjustment for lead-time bias, subtracting the lead time from life-expectancy. Since the whole study population encompasses a large time-period, all the analyses were repeated for patients diagnosed with HCC in more recent years (between 2005 and 2012), on the basis of the premise that advancements in surveillance tools could further anticipate HCC diagnosis [3,4–8,12].

Statistical analysis

Categorical variables are reported in a number of cases and proportions, and comparisons between the subgroups were carried out using the Fisher's exact test. The distribution of continuous variables was checked for normality using the Kolmogorov-Smirnov test, and comparisons between the subgroups were carried out using appropriate tests. Continuous variables are reported as means and 95% CI of the means or as median and interquartile ranges (IQR: 25th and 75th percentiles). Survival rates after HCC diagnosis were computed from the day of diagnosis until death or the last follow-up visit using the Kaplan–Meier method. Survival rates were transformed into monthly probabilities of death, applying the *declining exponential approximation of life expectancy* (DEALE) approach [24].

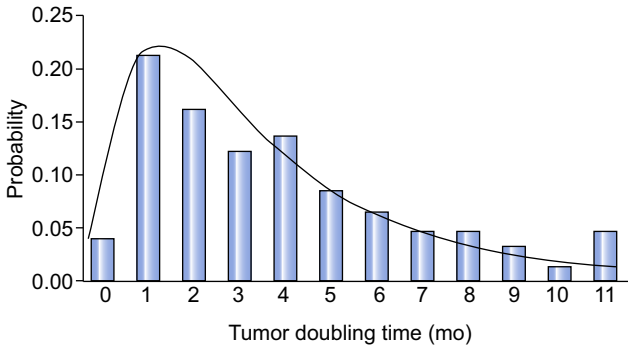

Fig. 1. Distribution of HCC volume doubling time (DT) obtained from the literature review of 155 tumors. The distribution was positively skewed and was fitted with a lognormal function having $\mu = 4.5253$ and $\sigma = 0.7313$ (Median value = 105 days; 25th percentile = 45 days; 75th percentile = 165 days; mode = 45 days). In 53.5% of cases (no = 83), DT value did not exceed 3 months.