Research Article

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Marginal survival benefit in the treatment of early hepatocellular carcinoma

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Background & Aims: Early treatment has been recommended for hepatocellular carcinoma (HCC) due to its high cure rate. However, the reported survival benefits of treating early HCC may be affected by lead time.

Methods: Early HCC was defined as a well-differentiated cancer containing Glisson's triad (carcinoma *in situ*). We applied the concept of lead time to chronic liver disease, which is originally the length of time between screen-detected and symptom-detected disease. To evaluate prolongation of survival with treatment of early HCC, survivals of patients with early and overt HCCs smaller than 2.0 cm treated with liver resection were compared. To calculate lead time and survival benefit of liver resection, survivals of untreated early and overt HCC patients were compared.

Results: After liver resection, median overall survival of 46 patients with early HCC (8.8 years; 95% CI, 7.2–11.2) was significantly longer than that of the 202 with overt HCC (6.8 years; 95% CI, 6.2–8.3, $p = 0.0257$). The prolongation in survival time with liver resection for early HCC was 34.7 (95% CI, 22.1–46.5) months. On the other hand, comparing liver resection and natural history, the survival benefits of surgery for 12 patients with early and 16 with overt HCC were 74.7 (95% CI, 51.9–97.4) and 73.4 (95% CI, 57.9–88.9) months, respectively. Consequently, the lead time and survival benefit with resection for early HCC were estimated as 33.4 (95% CI, 18.9–47.8) and 1.3 (95% CI, –22.1–24.7) months, respectively.

Conclusions: Survival benefit of resection for early HCC is marginal because of a long lead time, and early HCC is therefore not a target lesion for surgery.

Keywords: Lead time; Liver resection; Natural history; Signaling lesion.
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Abbreviations: HCC, hepatocellular carcinoma; AUC, the area under the survival curve.

Introduction

A worldwide consensus on "early" hepatocellular carcinoma (HCC) (carcinoma *in situ*) has been established based on consistent terminology and histological criteria [1]. Histologically, the presence of stromal invasion is a reliable criterion for malignancy, and tumor is characterized by intratumoral portal tracts, increased cell density, and structural atypia [2].

Clinically, due to the high rate of surgical cure, we and others have advocated that patients with early HCC are good candidates for surgery [3–5]. This is because such lesions seldom spread to their surroundings, and resection would therefore result in complete tumor removal. In our previous report, both postoperative overall and recurrence-free survivals were significantly longer in patients with early HCC than in those with overt HCC [3]. Thereafter, the Barcelona-Clinic-Liver-Cancer (BCLC) treatment algorithm updated in 2011 recommends liver resection or ablation as the treatment of choice for early stage HCC [4].

However, the prolonged survival time in our previous study might have been affected by lead time bias [3]. Lead time is originally the length of time between detection of asymptomatic disease and diagnosis by its usual clinical presentation [6], and this concept is also applicable to some kinds of chronic disease [7]; that is, a transition period from early to overt HCCs could be considered "lead time". Therefore, potential survival benefit of diagnosis and treatment of earlier disease should be carefully evaluated [8–10].

Accordingly, small HCC, which is found during surveillance of cirrhotic patients, may be observed because it grows slowly and the patient is asymptomatic, any therapy may lapse disadvantage rather than benefit [11,12], and another second primary HCC may appear even after local control of early HCC [13,14]. Several studies examining the natural history of small HCC without antican-

cer treatment have suggested that long-term survival of patients with early HCC depends primarily on the status of the underlying liver disease [15,16].

To clarify whether such lesions need to be treated, we estimated lead time and survival benefit of resection for early HCC. The concept of lead time bias for cancer screening was applied to HCC surveillance [7,17], and the lead time from early to overt HCC was calculated using the survival curves of patients who underwent surgical treatment and those who received no treatments [18–20].

Patients and methods

Patients

Of 2768 patients with HCC between 1982 and 2011, 281 with a single HCC smaller than 2.0 cm underwent curative liver resection at Nihon University Itabashi Hospital or National Cancer Center Hospital, Tokyo. Thirty-one patients with other malignant diseases and two patients who died postoperatively (in-hospital death) were excluded, and the remaining 248 were studied (Table 1). There were 167 men and 81 women, with a median age of 63 years (range, 25–80 years).

Of 1912 patients with HCC between 1996 and 2009, 109 were placed under observation without cancer therapy because they chose not to be treated presenting with or without chronic disease at Kurume University Hospital or Kurume University Medical Center, Fukuoka. All patients were followed until they died of advanced HCC. Among these patients, 28 with a HCC smaller than 2.0 cm entered the study (Table 2).

All of the 276 patients in this series were diagnosed with HCC during the follow-up period for liver dysfunction without any symptoms due to HCC.

Diagnosis

According to the results of imaging modalities, including computed tomography or magnetic resonance, early HCC was determined to be hypovascular in the portal phase but non-enhancing in the arterial phase, all of which were diagnosed by following histological examination of resected specimens or fine needle biopsy [9]. Similarly, patients with enhancing tumor in the arterial phase and hypovascular in the portal phase were diagnosed with overt HCC.

Pathology

Early HCC was diagnosed as described previously [1,3,21]. Briefly, the tumor macroscopically contained Glisson's triad and was a distinctive nodule from the surrounding lobules on the basis of size or color, but did not substantially destroy the pre-existing hepatic framework (Supplementary Fig. 1). It microscopically showed hypercellularity (>2.0) with cellular or nuclear atypia, as well as definite structural atypia, as indicated by acinar formation, thin trabeculae, or remodeling of the cord architecture.

Estimation of survival time

The area under the survival curve (AUC) from zero to infinity represents the mean survival time after treatment. This total area was estimated as the sum of the measured AUC plus that of the extrapolated right tail [19]. The Gompertz function as a mathematical function from zero to infinity is applied to determine the right tail after a follow-up period (Fig. 1A) [18–20].

$$R(t) = \exp\left[-\frac{e^{\lambda}}{\gamma}(e^{\gamma t} - 1)\right] \quad (1)$$

The most likely estimates of λ and γ were calculated with the observed survival time. Then, the difference between the two AUCs represents the increase in survival due to treatment [19].

In cancer screening, if survival curves of both screened and unscreened groups start from the onset of the disease, the difference in AUCs represents the survival benefit for the screened group. On the other hand, if the survival curve of the unscreened group migrates horizontally during the time lag between onset and therapy, the difference in AUCs includes lead time in addition to survival benefit (Fig. 1B) [17], and was calculated as follows;

$$B + L = \left\{\int_0^{T_1} S_e(t)dt + \int_{T_1}^{\infty} R_e(t)dt\right\} - \left\{\int_0^{T_2} S_o(t)dt + \int_{T_2}^{\infty} R_o(t)dt\right\} \quad (2)$$

(B, survival benefit; L, lead time; S_e and S_o, survival curve for early and overt HCCs after liver resection; R_e and R_o, Gompertz function for early and overt HCCs according to formula (1); T_1 and T_2, the last time of the follow-up of S_e and S_o)

Because the start time for liver resection and the natural history for early HCC (diagnosis 1) or overt HCC groups (diagnosis 2) are the same, the lead time between liver resection and the natural history in each group could be considered 0 months (Fig. 2). Then, the differences in the AUCs for the groups were the survival benefit for liver resection for the early (B_1) and overt (B_2) HCC groups, and were calculated as follows;

$$B_1 = \left\{\int_0^{T_1} S_e(t)dt + \int_{T_1}^{\infty} R_e(t)dt\right\} - \left\{\int_0^{T_3} K_e(t)dt\right\} \quad (3)$$

$$B_2 = \left\{\int_0^{T_2} S_o(t)dt + \int_{T_2}^{\infty} R_o(t)dt\right\} - \left\{\int_0^{T_4} K_o(t)dt\right\} \quad (4)$$

(K_e and K_o, survival curve for untreated early and overt HCCs; T_3 and T_4, the last time of the follow-up of K_e and K_o from diagnosis 1 and 2, respectively).

To estimate the survival benefit (B) offered by liver resection, the natural history of patients with HCC was followed, and their survival was compared to that of patients who underwent surgery (B_1 and B_2). As shown in Fig. 2, the survival benefit (B) was calculated as $B = B_1 - B_2$.

Statistical analysis

The statistical analysis of parameters collected from early and overt HCC groups was determined by the Fisher's exact test and the Wilcoxon rank sum test. Survival curves were generated using the Kaplan–Meier method and compared by the log-rank test. Prognostic factors on the 14 parameters listed in Table 1 for overall survival were identified with the Cox proportional hazards regression model. Statistical significance was taken as p <0.05.

Results

Pathological outcome

On the basis of the histological examination of the resected specimens, 46 patients were diagnosed with early HCC, and 202 with overt HCC (Table 1). Tumor size in the early HCC group (14.6 ± 3.7 mm) was significantly smaller than that in the overt HCC group (16.4 ± 3.1 mm) (95% confidence interval [CI], 0.63–3.03; p = 0.002). The incidence of vascular invasion in the early HCC group (4%) was significantly lower than that in the overt HCC group (25%, odds ratio [OR], 0.14, 95% CI, 0.02–0.55; p = 0.001). Intrahepatic metastatic lesions did not co-exist in early HCC specimens, and were present in 22% of overt HCC specimens (OR 0, 95% CI, 0–0.31; p <0.001).

Patients' survival

After a median follow-up of 4.1 years (range, 0.8–18.3 years), a total of 171 patients (68%) had recurrence; 166 patients (67%) in the remnant liver and seven patients (3%) in distant sites (two patients with both intra and extrahepatic recurrences) (Table 3). The patients with early HCC had neither local recurrence nor distant metastasis.

In the 46 patients with early HCC and the 202 patients with overt HCC, the median overall survivals were 8.8 years (95% CI, 7.2–11.2) and 6.8 years (95% CI, 6.2–8.3; p = 0.025), respectively, and recurrence-free survivals were 4.1 years (95% CI, 3.4–5.8) and 2.0 years (95% CI, 1.8–2.2; p = 0.001), respectively (Fig. 3A and B). The 5-year rates of overall survivals were 86.8% (95% CI, 76.6–98.3) and 65.8% (95% CI, 58.2–74.2), and those of recurrence-free survival were 38.4% (95% CI, 25.4–58.2) and 19.3% (95% CI, 13.7–27.2) in the two groups, respectively.