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Editorial

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Surveillance, Diagnosis, and Treatment Outcomes of Hepatocellular Carcinoma in Japan: 2021 Update

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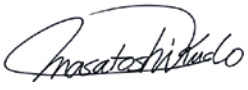

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Keywords
Hepatocellular carcinoma · Surveillance · Diagnosis · Treatment outcomes

Introduction

The Liver Cancer Study Group of Japan has recently published the results of its 21st Nationwide Follow-up Survey of Primary Liver Cancer in Japan [1]. The group's report covers a 2-year period from January 1, 2010, to December 31, 2011, and provides basic statistics on 22,134 prospectively enrolled patients from 546 institutions, and survival data on 41,956 previously enrolled patients, who were followed through this reporting period. The Liver Cancer Study Group of Japan was founded in 1965, and this year's follow-up survey report is the 21st in a series that started with the first such survey in 1969. The participating institutions in this survey register newly enrolled patients with primary liver cancer, and enter follow-up data on previously enrolled patients in the National Clinical Database once every 2 years, based on the General Rules for the Clinical and Pathological Study of Primary Liver Cancer [2–4]. This database is used for a range of analyses performed by the Liver Cancer Study Group of Japan, and the analysis results are published in Japanese in booklet form every 2 years. When each of the previous 20 survey reports was released, a concise version was published in Japanese in *Kanzo*, the journal of the Japan Society of Hepatology and in English in an international journal at the same time [5–49]. This editorial highlights the main results in the concise English version of the report and the longevity survey and analysis results for the patients registered in the 2-year period 2010–2011 and the previously registered patients (follow-up cases) [1]. In addition, surveillance, diagnosis, and treatment outcomes for hepatocellular carcinoma (HCC) in Japan are discussed.

Patient Characteristics at the Time of Initial Detection

The Japan Society of Hepatology's clinical practice guideline recommends that HCC surveillance cover the points outlined below. Patients at super-high risk for

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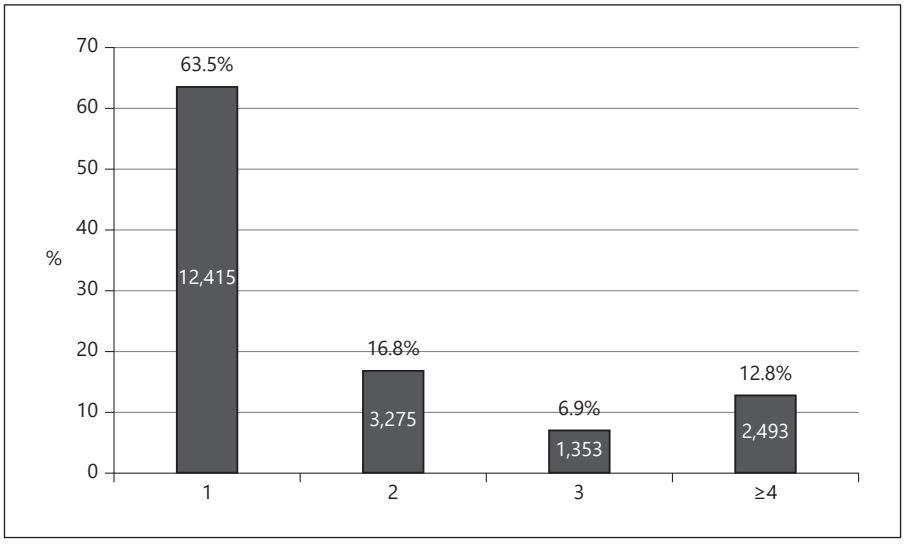

Fig. 1. Numbers of nodules at the time of initial detection in patients with HCC (n = 19,536) registered in the nationwide follow-up survey of the LCSGJ between January 1, 2010, to December 31, 2011, in 546 institutions throughout Japan. HCC, hepatocellular carcinoma; LCSGJ, Liver Cancer Study Group of Japan. Modified from Ref. [1] and [50] with permission.

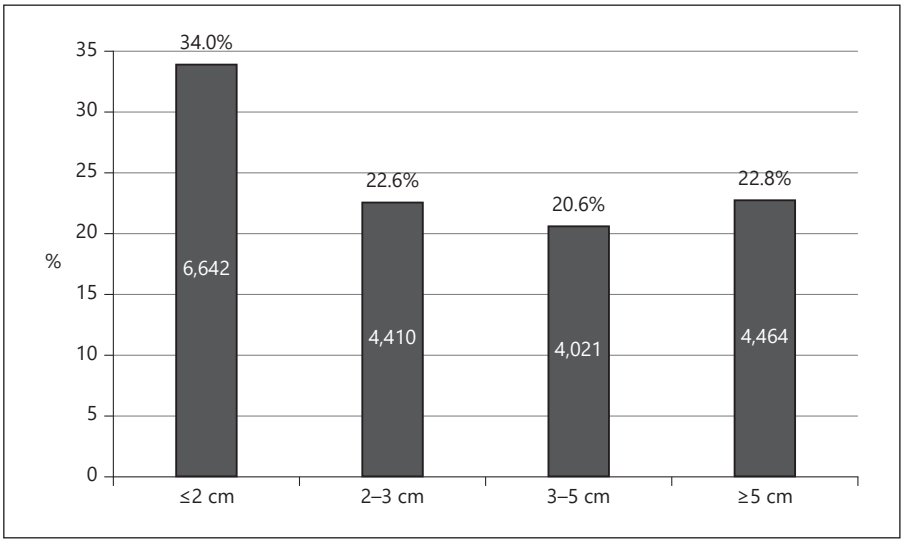

Fig. 2. Maximum tumor size at the time of initial detection in patients with HCC (n = 19,537) registered in the nationwide follow-up survey of the LCSGJ between January 1, 2010 to December 31, 2011 in 546 institutions throughout Japan. HCC, hepatocellular carcinoma; LCSGJ, Liver Cancer Study Group of Japan. Modified from Ref. [1] and [50] with permission.

HCC (those with hepatitis B or C cirrhosis or nonviral cirrhosis) are recommended to undergo ultrasonography and measurements of 3 tumor markers – namely, α-fetoprotein (AFP), protein induced by vitamin K absence or antagonist II (PIVKA-II), and *Lens culinaris* agglutinin-reactive AFP fraction (AFP-L3) – once every 3–4 months, with optional dynamic CT or Gd-EOB-DTPA-enhanced MRI once every 6–12 months.

High-risk patients (defined as those chronic hepatitis B or C are recommended to undergo surveillance by ultrasonography and measurements of the 3 tumor markers (AFP, PIVKA-II, and AFP-L3) once every 6 months. All imaging and tumor marker examinations are covered by national health insurance for super-high-risk and high-risk patients, and thus can be performed by almost all relevant institutions and private practitioners in Japan, thus contributing to the early detection of liver cancer.

The 21st follow-up survey presents a number of findings for patients newly diagnosed with HCC in the 2010–2011 period [50]. Among these patients (n = 19,536), 63.5% had a solitary nodule when they were diagnosed with HCC (Fig. 1). Measurements of maximum tumor size (irrespective of the number of nodules) revealed that small HCCs accounted for a large proportion of the newly diagnosed cases, with maximum tumor size measuring ≤3 cm in 56.6% of patients, and ≤2 cm in 34% of patients (Fig. 2). Thus, many of the HCCs in the Japanese population are detected as small and/or single tumors. Extrahe-

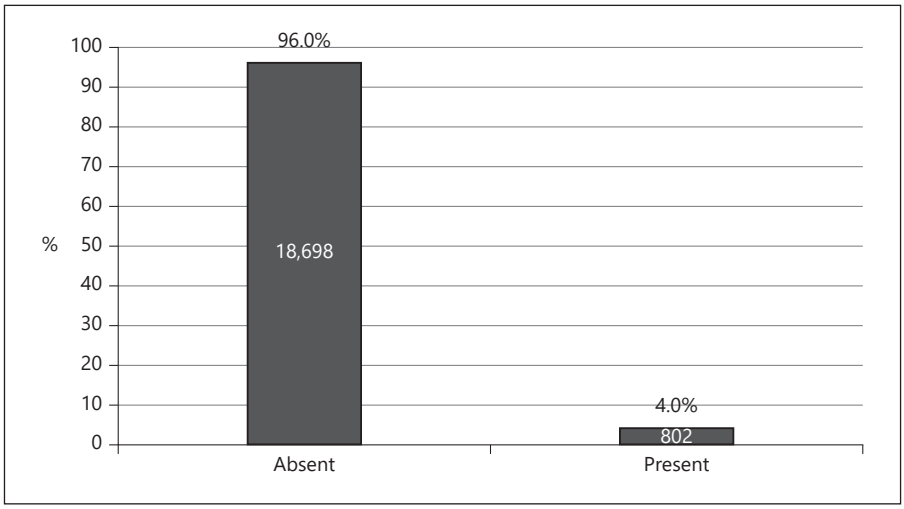

Fig. 3. Presence or absence of extrahepatic spread at the time of initial detection in patient with HCC (n = 19,887) registered in the nationwide follow-up survey of the LCSGJ between January 1, 2010, to December 31, 2011, in 546 institutions throughout Japan. HCC, hepatocellular carcinoma; LCSGJ, Liver Cancer Study Group of Japan. Modified from Ref. [1] and [50] with permission.

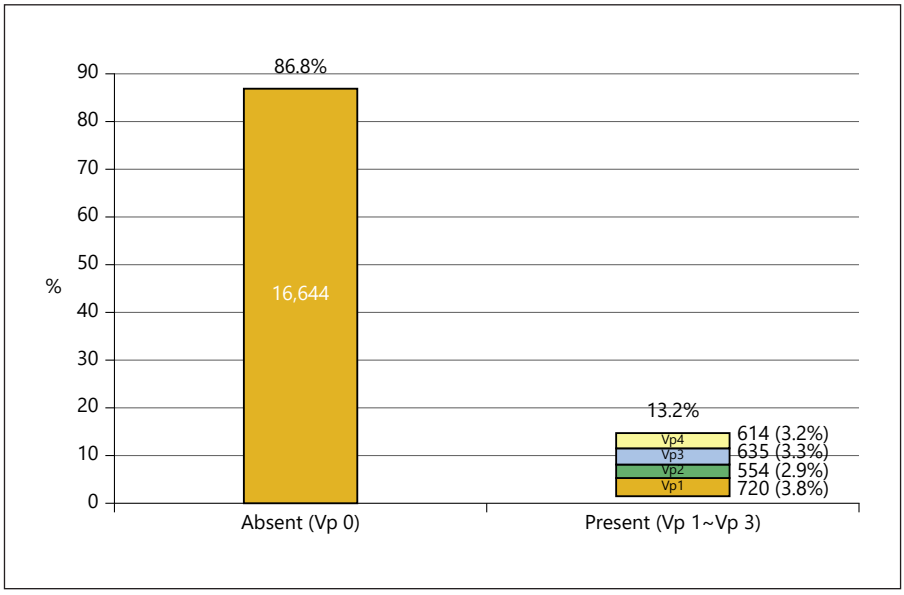

Fig. 4. Presence or absence of portal vein invasion at the time of initial detection in patients with HCC (n = 19,167) registered in the nationwide follow-up survey of the LCSGJ between January 1, 2010, to December 31, 2011, in 546 institutions throughout Japan. Portal vein invasion was observed in 13.2% of the patients. HCC, hepatocellular carcinoma; LCSGJ, Liver Cancer Study Group of Japan; Vp1, invasion (or tumor thrombus) distal to the second-order branches of the portal vein, but no invasion of the second-order branches; Vp2, invasion (or tumor thrombus) of the second-order branches of the portal vein; VP3, invasion (or tumor thrombus) of the first-order branches of the portal vein; Vp4, invasion (or tumor thrombus) of the main trunk of the portal vein and/or the portal vein branch contralateral to the primarily involved lobe. Modified from Ref. [1] and [50] with permission.

patic spread was found in 802 of 19,887 patients (4.0%) examined at the time of initial detection, showing that extrahepatic spread is considerably less common in Japan than in other countries (Fig. 3). Portal vein invasion was also less common in Japan than in other countries, but its incidence was higher than expected, occurring in 2,523 of 19,167 patients (13.2%) examined at the time of initial detection. This higher-than-expected incidence could be explained by recent advances in CT and MRI [51, 52] and abdominal contrast-enhanced ultrasound [53], which have made minor vascular invasion graded as Vp1 or Vp2 clinically discernable from the time of initial detection for small HCCs.

At initial detection, 22.8% of HCC patients had tumors measuring ≥5 cm, and 12.8% had multiple tumors with ≥4 nodules. Considering these findings, we can say that some cases had advanced HCC at the time of initial detection, and major vascular invasion graded as Vp3 or Vp4 occurred to some extent (Fig. 4). Hepatic vein invasion was found in 1,179 of 18,700 patients (6.2%) examined at the time of initial detection (Fig. 5). This result also demonstrates that, to a certain extent, HCC is detected in patients who do not regularly undergo the periodical surveillance. Up to now, the surveillance system has been designed to provide full coverage to patients with hepatitis B virus (HBV) or hepatitis C virus (HCV)-related

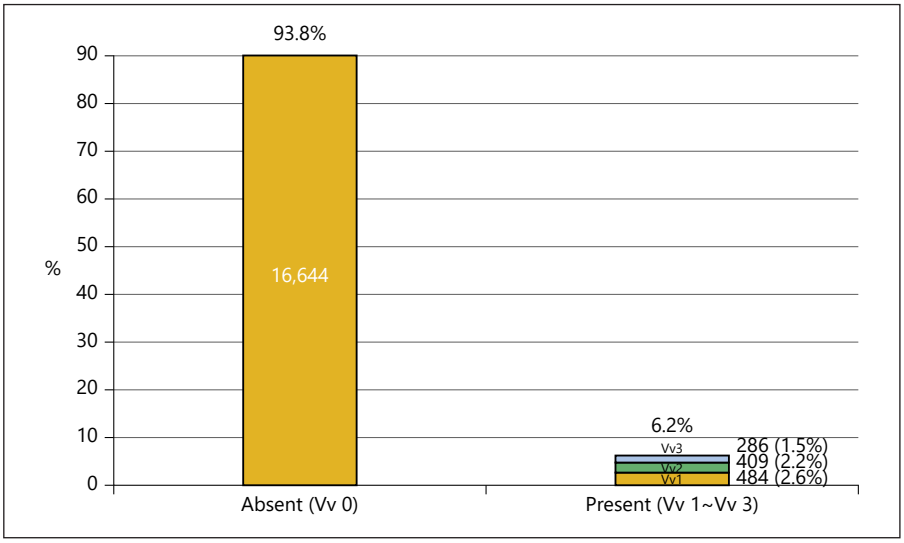

Fig. 5. Presence or absence of hepatic vein invasion at the time of initial detection in patients with HCC (n = 18,770) registered in the nationwide follow-up survey of the LCSGJ between January 1, 2010, to December 31, 2011, in 546 institutions throughout Japan. HCC, hepatocellular carcinoma; LCSGJ, Liver Cancer Study Group of Japan; Vv1, invasion (or tumor thrombus) of the peripheral branches of the hepatic vein; Vv2, invasion (or tumor thrombus) of the right, middle, or left hepatic vein, the inferior right hepatic vein, or the short hepatic vein; Vv3, invasion (or tumor thrombus) of the main hepatic vein or the inferior vena cava. Modified from Ref. [1] and [50] with permission.

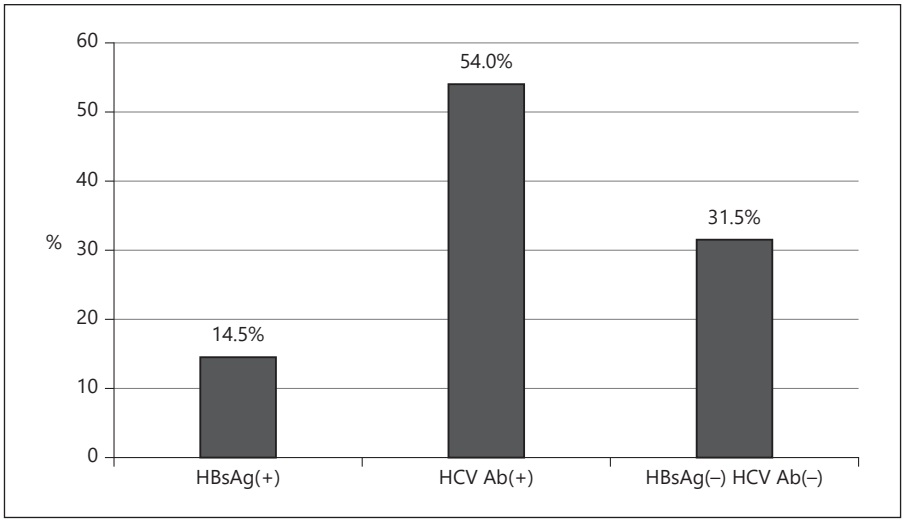

Fig. 6. Incidence rate of HCC according to etiology. HCC, hepatocellular carcinoma; HCV, hepatitis C virus. Modified from Ref. [1] and [50] with permission.

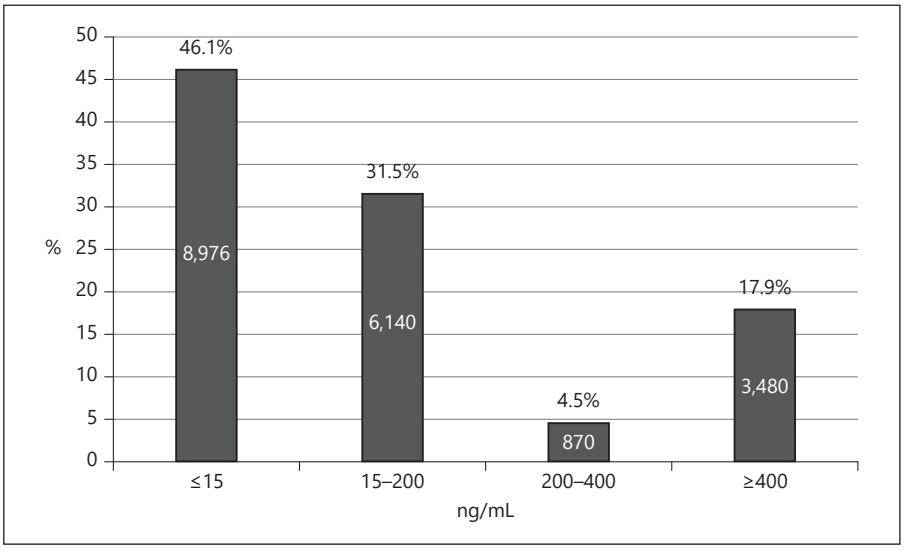

Fig. 7. AFP level (ng/mL) at the time of initial detection in patients with HCC (n = 19,466) registered in the nationwide follow-up survey of the LCSGJ between January 1, 2010, to December 31, 2011, in 546 institutions throughout Japan. HCC, hepatocellular carcinoma; LCSGJ, Liver Cancer Study Group of Japan; AFP, erum α-fetoprotein. Modified from Ref. [1] and [50] with permission.

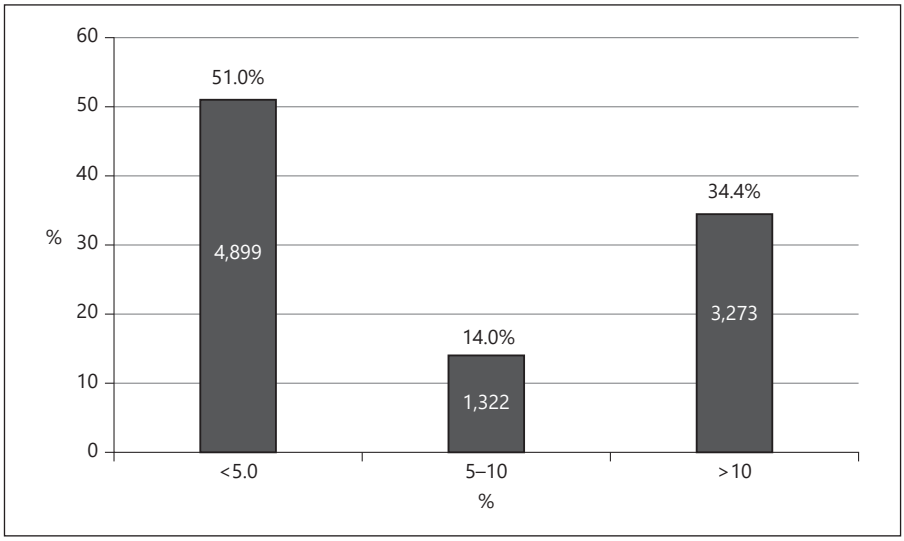

Fig. 8. AFP-L3 (*Lens culinaris* agglutinin-reactive AFP fraction; %) at the time of initial detection in patients with HCC (n = 9,504) registered in the nationwide follow-up survey of the LCSGJ between January 1, 2010 to December 31, 2011 in 546 institutions throughout Japan. HCC, hepatocellular carcinoma; LCSGJ, Liver Cancer Study Group of Japan; AFP, erum α-fetoprotein. Modified from Ref. [1] and [50] with permission.

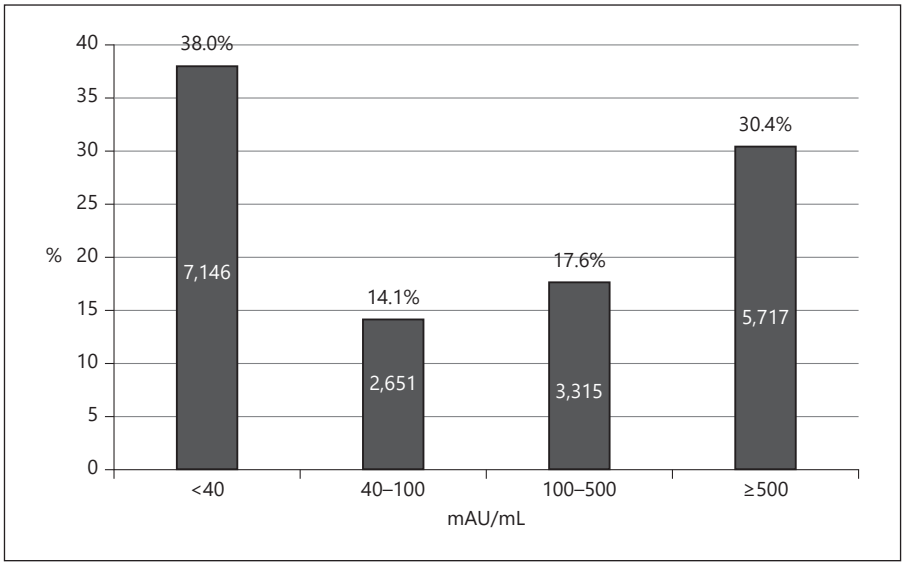

Fig. 9. PIVKA-II level at the time of initial detection in patients with HCC (n = 18,824) registered in the nationwide follow-up survey of the LCSGJ between January 1, 2010, to December 31, 2011, in 546 institutions throughout Japan. HCC, hepatocellular carcinoma; LCSGJ, Liver Cancer Study Group of Japan; PIVKA-II, protein induced by vitamin K absence or antagonist II. Modified from Ref. [1] and [50] with permission.

chronic liver disease; however, non-HBV/non-HCV-related HCC, including HCC related to nonalcoholic steatohepatitis, has become relatively common in Japan [54]. This phenomenon may explain why cases of advanced disease have recently continued to be detected at the same rates as previously in Japan. Indeed, non-HBV/non-HCV-related HCCs account for a high proportion of patients (31.5%) in the report of the 21st Nationwide Follow-up Survey of Primary Liver Cancer in Japan (Fig. 6). We consider it necessary to further promote awareness-raising among the general public and private practitioners in Japan.

Serum AFP level was below the normal range (≤15 ng/mL) in 46.1% of patients and ≤200 ng/mL in 77.6% of patients; overall, AFP levels were low in many cases at diagnosis (Fig. 7). Abnormal levels of the AFP-L3 fraction (≥10%) were noted in 3,273 of 9,504 patients (34.4%) (Fig. 8), and screening with this tumor marker had high specificity but not sensitivity [55–59]. The 3 tumor markers AFP, PIVKA-II, and AFP-L3 are known not to be correlated; therefore, measuring all 3 markers at the same time enables complimentarily greater detection of HCCs [58]. The proportion of patients with normal levels of PIVKA-II, which is also called DCP (des-gamma-carboxy prothrombin), was 38.0% (Fig. 9).

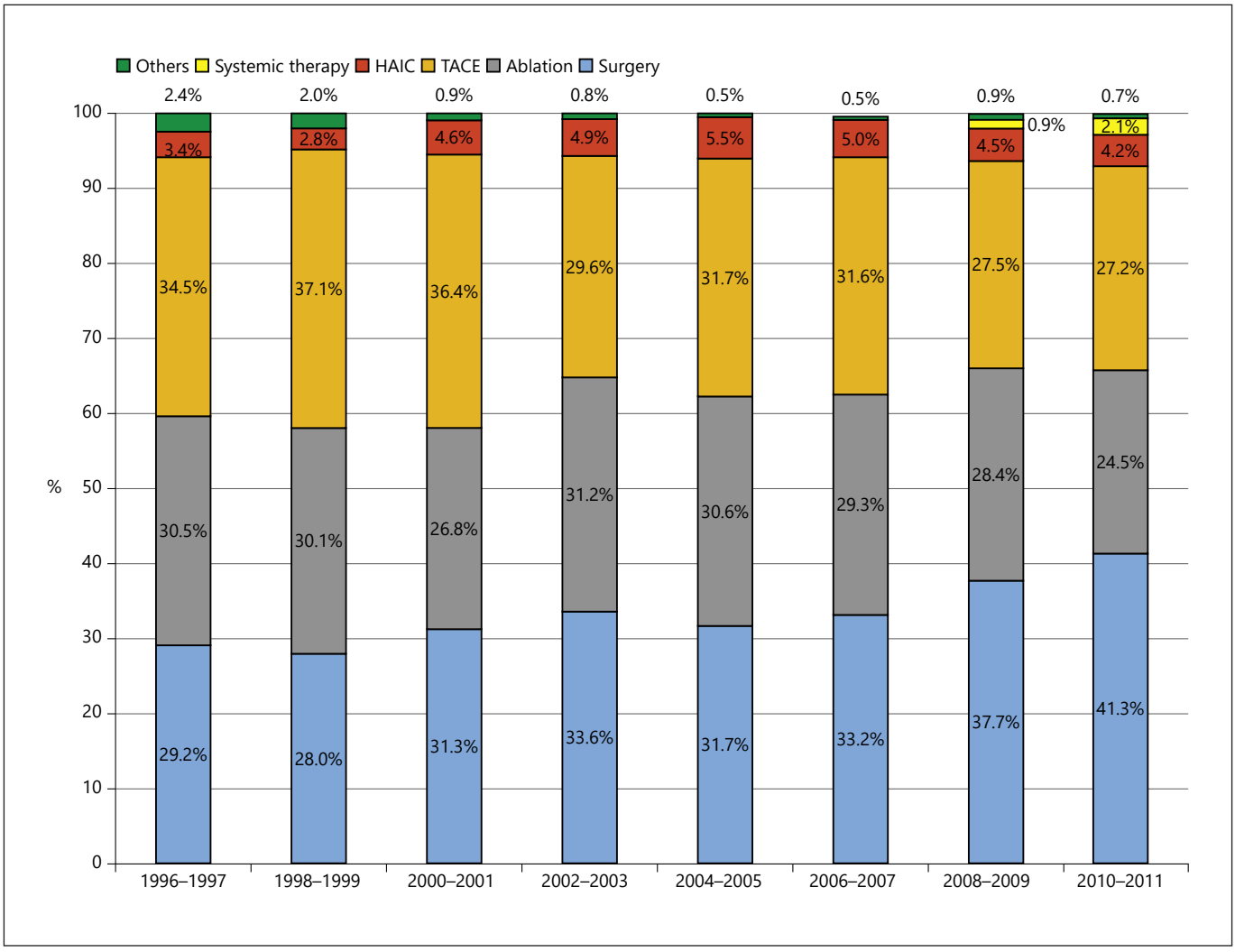

Fig. 10. Initial treatment modality selected after diagnosis of HCC over time. Curative treatments (resection 41.3%, ablation 24.5%) were performed in 65.8% of HCC patients registered in the nationwide follow-up survey of the LCSGJ between January 1, 2010, to December 31, 2011, in 546 institutions throughout Japan. The rate of resection is gradually increasing over time. Systemic therapy was used in only 2.1% of HCC patients. HCC, hepatocellular carcinoma; LCSGJ, Liver Cancer Study Group of Japan; HAIC, hepatic arterial infusion chemotherapy; TACE, transcatheter arterial chemoembolization. Modified from Ref. [1] and [50] with permission.

The above findings show that, with the establishment of the Japanese nationwide surveillance program [1, 60], detected HCCs tended to be solitary, small tumors and the levels of tumor markers tended to be low [61].

Treatment options selected by patients initially diagnosed with HCC in 2010–2011 were surgical resection in 41.3% of patients, ablation therapy in 24.5%, and transcatheter arterial chemoembolization (TACE) in 27.2%. Only 2.1% of patients opted for systemic therapy as initial treatment (Fig. 10). The proportion of patients opting for surgical resection has gradually increased in recent years, and probably this may be related to the increase in non-HBV/non-HCV-related HCCs.

Overall Survival by Treatment Modality and Other Factors

Overall survival (OS) is presented by Child-Pugh grade for 27,903 patients who underwent liver resection between 2002 and 2013 in Figure 11. Of these patients, 25,492 had preserved liver function (Child-Pugh grade

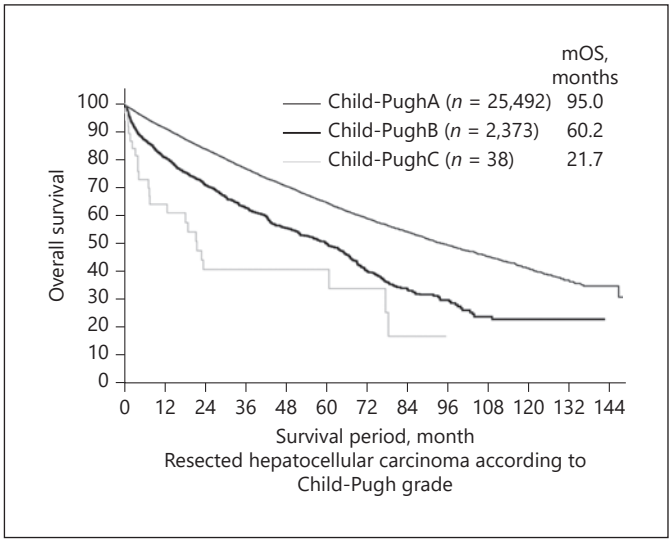

Fig. 11. OS in HCC patients (registered in the follow-up survey from 2002 to 2013) who were treated with resection according to the Child-Pugh grade (n = 27,903). Median OS for Child-Pugh A patients treated with resection was 95.0 months, and 5- and 10-year survival rates were 64.9 and 41.3%, respectively. HCC, hepatocellular carcinoma; LCSGJ, Liver Cancer Study Group of Japan; OS, overall survival. Modified from Ref. [1] and [50] with permission.

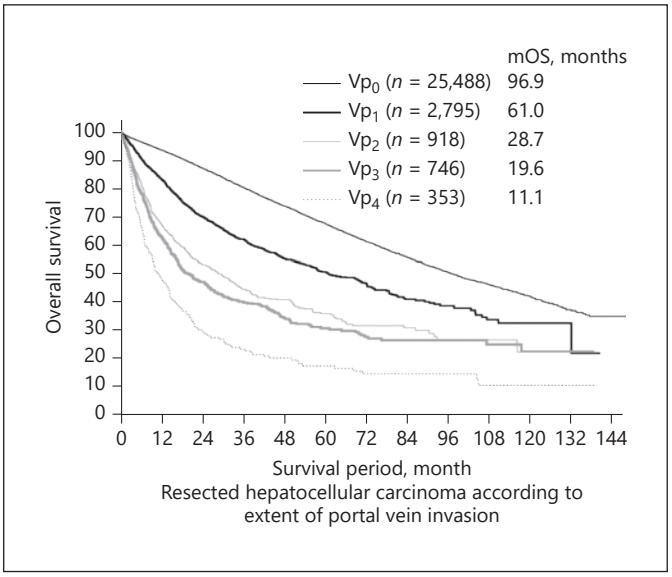

Fig. 12. OS in HCC patients (registered in the follow-up survey from 2002 to 2013) who treated with resection according to extent of portal vein invasion. HCC, hepatocellular carcinoma; LCSGJ, Liver Cancer Study Group of Japan; OS, overall survival; Vp0, absence of portal vein invasion; Vp1, invasion (or tumor thrombus) distal to the second-order branches of the portal vein, but no invasion of the second-order branches; Vp2, invasion (or tumor thrombus) of second-order branches of the portal vein; Vp3, invasion (or tumor thrombus) of the first-order branches of the portal vein; Vp4, invasion (or tumor thrombus) of the main trunk of the portal vein and/or the portal vein branch contralateral to the primarily involved lobe. Modified from Ref. [1] and [50] with permission.

A), Their median OS was 95.0 months (approximately 7.9 years), and their 5- and 10-years survival rates were 65 and 41%, respectively (Fig. 11). Portal vein invasion was associated with survival, and patients with portal vein invasion graded as Vp4 who underwent surgical resection had a median OS of 11.1 months (Fig. 12). Serum AFP level was correlated with OS in patients with resected HCC (Fig. 13). This is highly consistent with the fact that AFP is a strong prognostic factor [62].

OS is presented by Child-Pugh grade for patients who underwent local ablation therapy in Figure 14. Median OS for patients with Child-Pugh grade A liver function was 79.9 months (approximately 6.7 years), and their 5- and 10-years survival rates were 64.1 and 28.3%, respectively (Fig. 14). Numerically, local ablation therapy showed OS inferior to that of surgical resection: 6.7 versus 7.9 years. However, survival rates did not differ between radiofrequency ablation and surgery in a multicenter, randomized control study (the SURF Trial, recently conducted in Japan) of 300 HCC patients with ≤3 tumors measuring ≤3 cm [63]. Accordingly, the difference in survival between surgical resection and ablation was attributable to patients with a more favorable condition, among those with Child-Pugh grade A liver function, opting for surgical resection.

OS is presented by Child-Pugh grade for patients who underwent TACE in Figure 15. Median OS for patients with Child-Pugh grade A liver function was 45.3 months, and the 5- and 10-years survival rates for these patients were 38.3 and 14.7%, respectively (Fig. 15). This 45.3-month OS represents a markedly prolonged survival period. Given that the longest OS shown in 6 randomized control trials of TACE monotherapy (post TACE [64], TACE-2 [65], SPACE [66], ORIENTAL [67], BRISK-TA [68], and TACTICS [69]) was 30 months in the TACTICS study [70], we consider that many of the patients in Japan may have corresponded to Stage A in the Barcelona Clinic Liver Cancer system (a single tumor of any size or ≤3 tumors measuring ≤3 cm).

OS is presented by the Child-Pugh grade for patients who underwent reservoir-based continuous hepatic arterial infusion chemotherapy (HAIC) in Figure 16. Median OS for patients with Child-Pugh grade A liver function was 12.9 months, and the 5- and 10-years survival

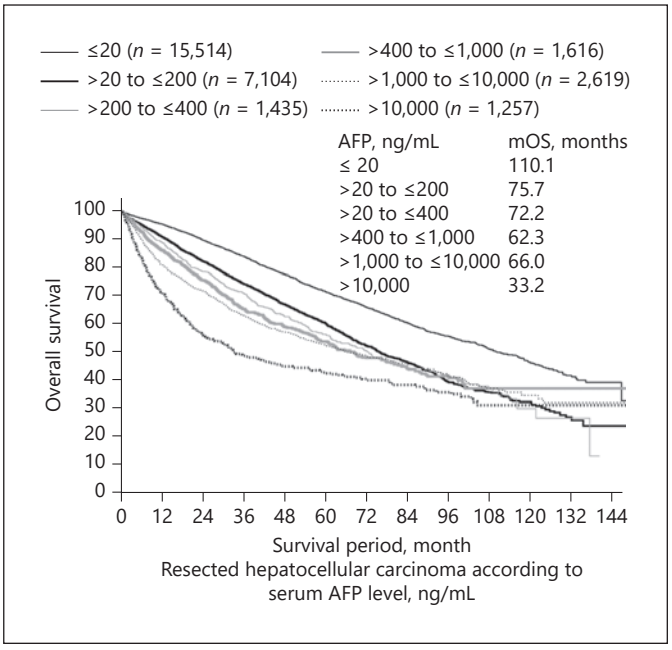

Fig. 13. OS in HCC patients (registered in the follow-up survey from 2002 to 2013) who were treated with resection according to serum AFP level (ng/mL). HCC, hepatocellular carcinoma; OS, overall survival; AFP, erum α-fetoprotein. Modified from Ref. [1] and [50] with permission.

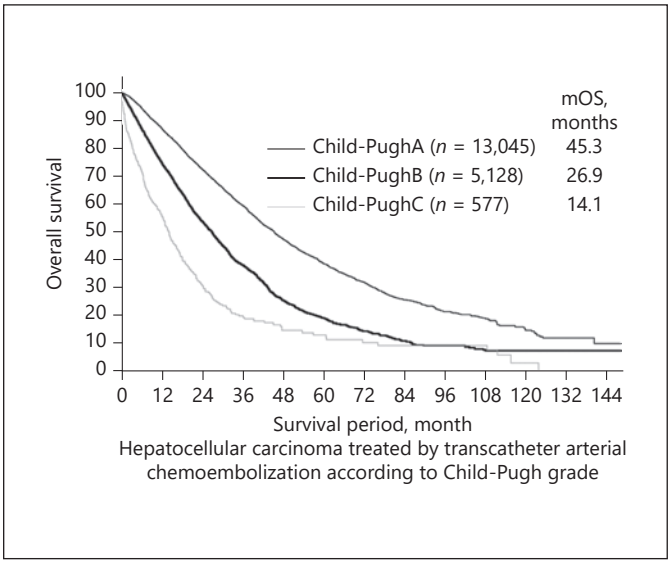

Fig. 15. OS in HCC patients (registered in the follow-up survey from 2002 to 2013) who were treated with TACE according to Child-Pugh grade (*n* = 18,750). Median OS for Child-Pugh A patients treated with TACE was 45.3 months, and 5- and 10-year survival rates were 38.3 and 14.7%, respectively. HCC, hepatocellular carcinoma; OS, overall survival; TACE, transcatheter arterial chemoembolization. Modified from Ref. [1] and [50] with permission.

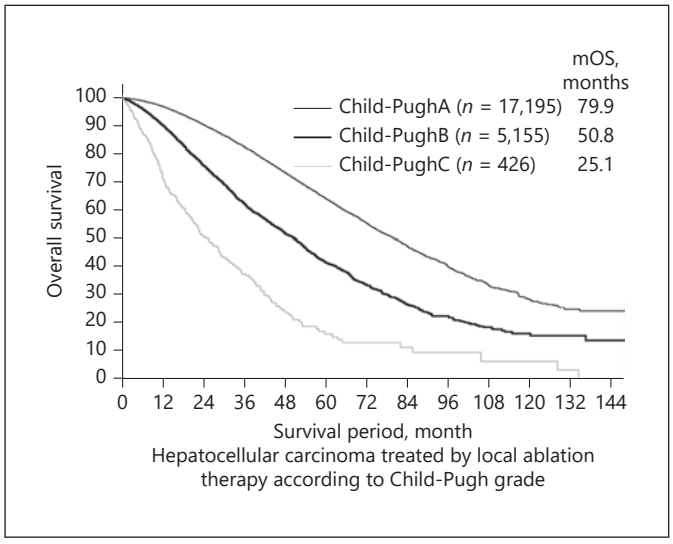

Fig. 14. OS in HCC patients (registered in the follow-up survey from 2002 to 2013) treated with local ablation therapy according to Child-Pugh grade (*n* = 22,776). Median OS for Child-Pugh A patients (registered in the follow-up survey from 2002 to 2013) who were treated with local ablation therapy was 79.9 months, and 5- and 10-year survival rates were 64.1 and 28.3%, respectively. HCC, hepatocellular carcinoma; OS, overall survival. Modified from Ref. [1] and [50] with permission.

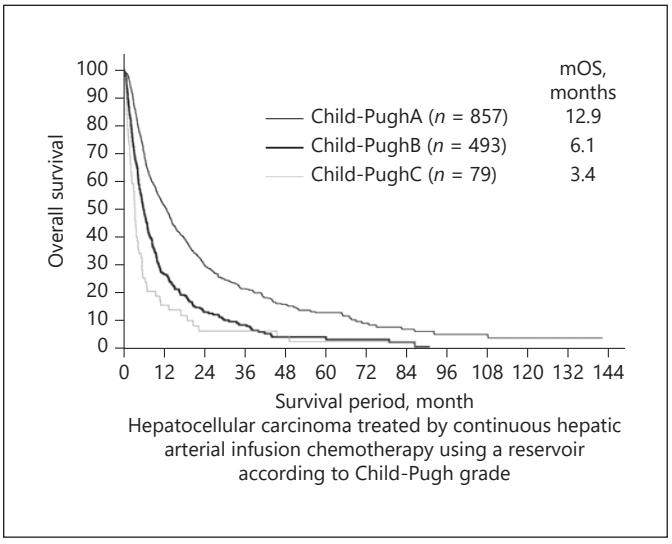

Fig. 16. OS in HCC patients (registered in the follow-up survey from 2002 to 2013) treated with continuous HAIC using a reservoir (implanted port system) according to Child-Pugh grade (*n* = 1,429). Median OS for Child-Pugh A patients treated with HAIC was 12.9 months, and 5- and 10-year survival rates were 14.0 and 5.0%, respectively. HCC, hepatocellular carcinoma; OS, overall survival; HIAC, hepatic arterial infusion chemotherapy. Modified from Ref. [1] and [50] with permission.

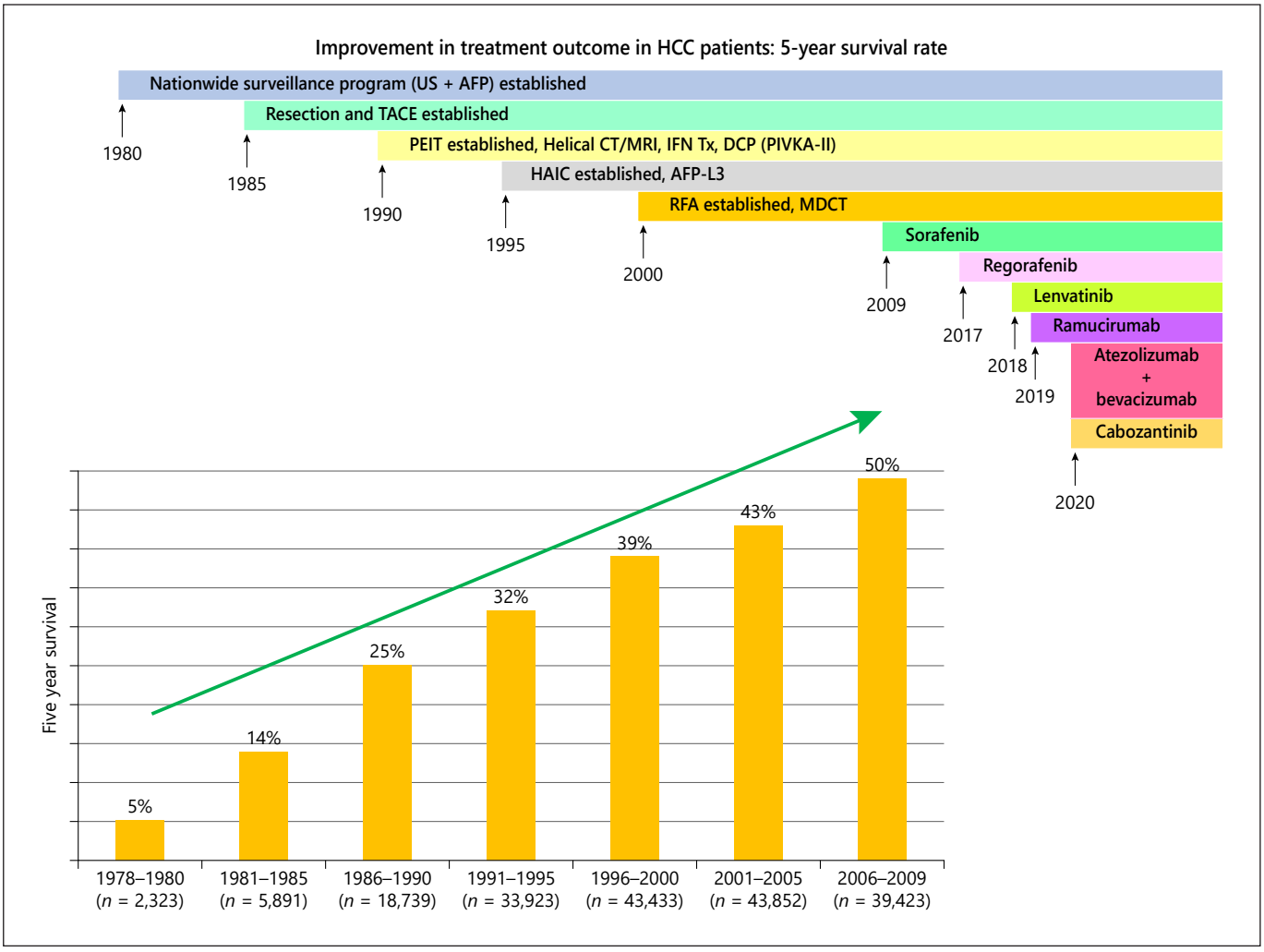

Fig. 17. Improvement of 5-year survival rates in all patients with BCLC Stage 0, A, B, C, and D registered in the follow-up survey during the 7 periods listed below. The 5-year survival rates for HCC patients registered in the nationwide follow-up survey in the periods 1978–1980, 1981–1985, 1986–1990, 1991–1995, 1996–2000, 2001–2005, and 2006–2009 were 5, 14, 25, 32, 39, 43, and 50%, respectively. HCC, hepatocellular carcinoma; HAIC, hepatic arterial infusion chemotherapy; PIVKA-II, protein induced by vitamin K absence or antagonist II; BCLC, Barcelona Clinic Liver Cancer. Modified from Ref. [1] and [50] with permission.

rates for these patients were 14.0 and 5.0%, respectively (Fig. 16). Reservoir-based arterial infusion achieved similar outcomes to molecularly targeted therapy with sorafenib, which is restricted to patients with Child-Pugh grade A liver function. The SILIUS study [71] compared OS between sorafenib plus arterial infusion chemotherapy and sorafenib alone and demonstrated that addition of HAIC to sorafenib was not effective; however, sorafenib plus arterial infusion chemotherapy demonstrated clear superiority among patients with tumors showing Vp4 portal vein tumor thrombus, with a median OS of 11.4 versus 6.5 months for sorafenib alone (hazard ratio: 0.493; 95% confidence interval: 0.240–1.014) [71]. According to this 21st nationwide follow-up survey in Japan, OS for patients with Vp4 portal vein invasion receiving HAIC monotherapy was 5.7 months [1]. A large proportion of these patients were classified as Child-Pugh grade B rather than Child-Pugh grade A, and this raises the possibility that HAIC is at least equivalent or slightly superior to sorafenib. Nationwide data on arterial infusion chemotherapy versus sorafenib were evaluated retrospectively by propensity score matching, and the results showed that HAIC was significantly superior to sorafenib in patients with Vp3/Vp4 vascular

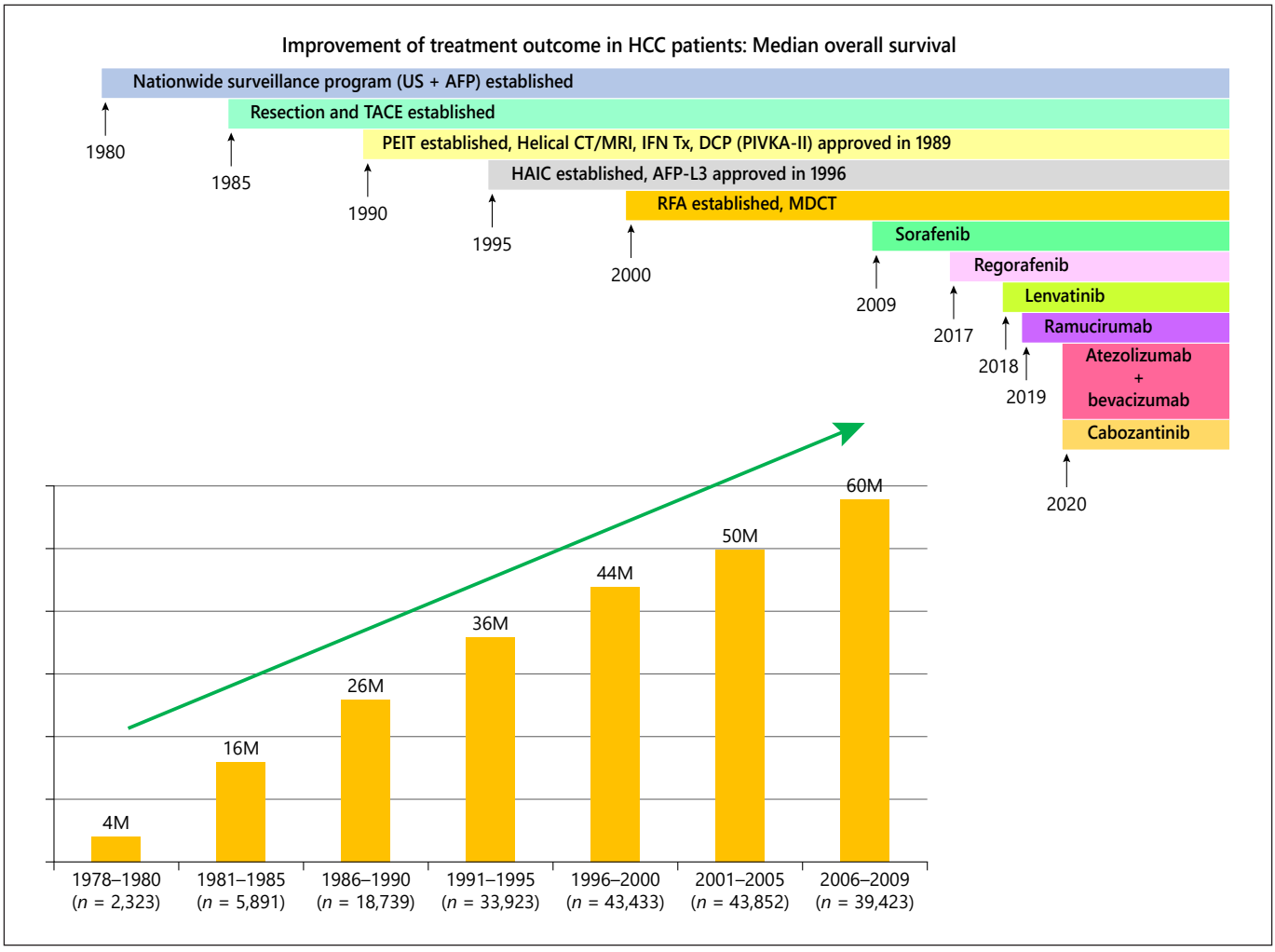

Fig. 18. Improvement of OS in all patients with BCLC Stage 0, A, B, C, and D registered in the follow-up survey during the 7 periods listed below. Median OS for patients with HCC registered in the nationwide follow-up survey in the periods 1978–1980, 1981–1985, 1986–1990, 1991–1995, 1996–2000, 2001–2005, and 2006–2009 was 4, 16, 26, 36, 44, 50, and 60 months, respectively. HCC, hepatocellular carcinoma; OS, overall survival; BCLC, Barcelona Clinic Liver Cancer. Modified from Ref. [1] and [50] with permission.

invasion, with a median OS of 10.6 months versus 9.1 for sorafenib [72].

HAIC with a FOLFOX regimen plus sorafenib was reported to be significantly superior to sorafenib alone in cases of advanced HCC with portal vein invasion in a study in China [73]. Accordingly, among the treatment options, HAIC will probably be used as the first-line therapy for patients with major vascular invasion (Vp3 or Vp4) in Asia [74, 75]. Meanwhile, a groundbreaking therapy, atezolizumab plus bevacizumab combination immunotherapy, was approved in 2020 [76]. As a result, with the accumulation of cases given this therapy, consideration is now being given to atezolizumab plus bevacizumab combination immunotherapy becoming the treatment of choice for patients with major vascular invasion (Vp3 or Vp4). This is because of the high efficacy shown in a subset of patients in IMbrave150 trial – the so-called REFLECT out patients set (101 cases, comprising 19% of the original study population) – who were excluded from the REFLECT study in patients with Vp4 vascular invasion, tumors occupying >50% and invasion to the bile duct [77]. "REFLECT out" patents with Vp4 vascular invasion (48 cases, 14%) had OS of 7.6 months, progression-free survival of 5.4 months, and an objective response rate of 25% [78].

Improvement of Treatment Outcomes in Patients with HCC

Between 1978 and 1980, the 5-year survival rate for the 2,323 HCC patients registered was 5%; however, this rate has gradually improved for subsequently registered patients. The 5-years survival rate for the 39,423 patients registered between 2006 and 2009 was 50%. This includes survival for all patients at all Barcelona Clinic Liver Cancer stages, from the early stage of 0 to stage D (Fig. 17). Median OS for patients registered between 1978 and 1980 was 4 months but has gradually improved since then, with median OS of 60 months for patients registered between 2006 and 2009 (Fig. 18). The major reasons for this improvement were as follows: AFP tests and ultrasound were first introduced into the Japanese nationwide surveillance program in the 1980s, surgical resection was established and TACE started being adopted as a treatment option across Japan around 1985, and percutaneous ethanol injection therapy was developed in Japan in the 1990s. All these factors are considered to have contributed to improved outcomes for HCC. Other contributing factors have been proposed: the growing use of helical CT and abdominal MRI across Japan since the 1990s, and the approval of interferon therapy for HCV and PIVKA-II testing approved by insurance in 1989. These developments have further enabled early detection of HCC.

Furthermore, HAIC has been implemented in many hospitals in Japan since around 1995, improving survival for HCC patients with vascular invasion. Insurance coverage was extended to AFP-L3 testing in 1996, and methods were developed for analysis of the 3 tumor markers AFP, AFP-L3, and DCP (PIVKA-II). These developments have further advanced the potential for early HCC detection.

The years just after 2000 saw rapidly increasing use of radiofrequency ablation as well as an increase in the use of multi-detector row CT scanners, which were also factors in improving early HCC detection. Since that time, sorafenib was approved in Japan in 2009 [79]. Accordingly, some of the patients registered in the 2001–2005 or 2006–2009 period received sorafenib or other molecular targeted agents after undergoing surgical resection or locoregional therapy, and this is also considered to be a factor in the improved survival outcomes. With the approval of regorafenib in 2017 [80], lenvatinib in 2018 [77], ramucirumab in 2019 [81], and atezolizumab plus bevacizumab combination immunotherapy [76] and cabozantinib 2020 [82], further improvements in survival for HCC patients are expected [83, 84].

The survival of intermediate-stage HCC patients is also being markedly improved through the evolution of therapeutic strategies, with a gradual change to a strategy of selective TACE after initial introduction of systemic therapy [85–87]. Clinical trials now in progress are evaluating combination immunotherapies (anti-PD-1/PD-L1 antibody plus anti-CTL4 antibody [88] and anti-PD-1/anti-PD-L1 antibody plus anti-VEGF antibody [89]) applied after surgical resection or ablation as adjuvant therapy, and in combination with TACE [90]. With the application of these therapies in actual clinical settings, we can anticipate further improvements in survival for Japanese patients with HCC who previously would be out of treatment options.

Statement of Ethics

Not applicable.

Conflict of Interest Statement

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Author Contributions

M. Kudo conceived, wrote, and approved the final manuscript.

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