RESEARCH ARTICLE

The Effect of New Therapeutic and Diagnostic Agents on the Prognosis of Hepatocellular Carcinoma in Japan – An Analysis of Data from the Kanagawa Cancer Registry

Rena Kaneko*, Natsuko Nakazaki, Risa Omori, Yuichiro Yano, Masazumi Ogawa, Yuzuru Sato

Abstract

Objective: Notable advances in diagnostic imaging modalities and therapeutic agents have contributed to improvement in the prognosis of hepatocellular carcinoma (HCC) over the past decade. However, knowledge concerning their epidemiological contribution remains limited. The present study investigated the effect of emerging diagnostic and therapeutic agents on HCC prognosis, using the largest regional cancer registry in Japan. **Methods:** Using data from the Kanagawa Cancer Registry, the five-year survival rate of patients with liver cancer was estimated according to the International Statistical Classification of Diseases and Related Health Problems (10th Edition). **Result:** A total of 40,276 cases of HCC (from 1976 to 2013) were identified. The prognosis markedly improved after the introduction of new devices into the diagnosis and treatment of HCC ($p<0.01$). The trend of survival rate varied significantly between institutions with many registered patients (high-volume centers) ($p<0.01$). **Conclusion:** The five-year survival rate of patients with HCC in Kanagawa has markedly improved in recent years. This improvement in survival may be attributed to the advances in surveillance and intervention for the treatment of HCC.

Keywords: liver cancer- hepatocellular carcinoma- survival- epidemiology

Asian Pac J Cancer Prev, **18 (9)**, 2471-2476

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the fourth most common in Japan (Umemura et al., 2009; Zhu et al., 2016).

Treatment options are limited, with guidelines recommending resection, ablation, chemoembolization, radiotherapy or chemotherapy, depending on liver function and tumor burden (Makuuchi and Kokudo, 2006; Bruix and Sherman, 2011; Kudo et al., 2011). Detection of the tumor at an early stage of disease, coupled with effective systemic therapy, improves long-term survival in patients with HCC. (Forner et al., 2008)

In Japan, radiofrequency ablation (RFA) was approved in 2004 as a new curative treatment of HCC. In 2007, a new contrast-enhanced ultrasound agent known as perfluorobutane was approved. During the same year, gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) used in magnetic resonance imaging (MRI) was also approved. In 2009, sorafenib – an oral multikinase inhibitor – was introduced in the treatment of advanced HCC.

Although these new treatment and diagnosis options have become available, there is a lack of evidence from randomized controlled trials addressing their impact on HCC incidence and management. This may be due to the tailored treatment required to address the disease characteristics of HCC (Best et al., 2017).

The objective of this study was to examine the epidemiological effect of these new agents on the prognosis of HCC, using a large-scale cancer registry in Japan.

Materials and Methods

Kanagawa Cancer Registry

The Kanagawa Prefecture is the second largest in Japan, with a population of approximately nine million people. The Kanagawa Cancer Registry was founded in 1954, and is the largest regional cancer registry in Japan. By the end of 2013, the registry had accumulated and recorded approximately 990,000 cancer cases in the region. Details on the cancer registry system in Japan have been discussed elsewhere (Okamoto, 2008). Data were collected from neoplasm registration sheets produced by the diagnosing hospitals or from clinic and death certificates of patients residing in the Kanagawa Prefecture. The Kanagawa Cancer Center collected and

*Department of Gastroenterology, Japan Organization of Occupational Health and Safety Kanto Rosai Hospital, Japan. *For Correspondence: rena@kantoh.johas.go.jp*

consolidated the data into an anonymous format (to protect the identity of patients), making them available for research purposes.

The accumulated data include the following information: 1) personal identification code, 2) method of registry entry, 3) diagnosing institution, 4) sex, 5) date of birth, 6) date of diagnosis, 7) local government code for the patient's home address, 8) ICD-10 code for disease name, 9) ICD-O-3 code for pathology, 10) initial or recurrent tumor state, 11) therapeutic strategy (very brief), 12) operative procedure (if any), 13) date of death, 14) cause of death, 15) date of last follow-up and 16) tumor/node/metastasis (TNM) classification and pathological grade according to ICD-O-3 in diagnosed patients. The reporting of TNM classifications became mandatory in 2005.

All information was collected by trained healthcare professionals in Japan according to the Surveillance, Epidemiology, and End Results (SEER) program. Information was updated every year from vital statistics and death certificates. Previous versions of pathological codes were updated to the latest versions through standardized regulations consistent with changes in coding practices for cholangiocarcinoma. The proportion of death-certificate-only (DCO) cases in the entire database was 18.2% by the end of 2013 (Goverment, 2016).

Subjects and classification method

Clinical data relating to gastrointestinal cancers between June 15, 1954 and December 30, 2013 were obtained from the Kanagawa Cancer Center. From these records, data pertaining to liver cancer (C220), according to the International Statistical Classification of Diseases and Related Health Problems (ICD), 10th Revision (ICD-10), were extracted and included for analysis in the present study.

In order to estimate the five-year survival rate of patients, the analysis period was divided into four parts: (1) from 1954 to 1999 (4 years prior to the introduction of RFA), (2) from 2000 to 2003 (4 years prior to RFA approval), (3) from 2004 to 2007 (from RFA administration until Gd-EOB-DTPA and perfluorobutane approval) and (4) from 2008 to 2013 (following the approval of Gd-EOB-DTPA, perfluorobutane and sorafenib). Due to the one-year difference in the approvals of Gd-EOB-DTPA, perfluorobutane and sorafenib, the last period was analyzed collectively.

The two-year survival rate of patients every two years was calculated, to determine the trend in patient survival rate throughout the entire analysis period.

The analysis was limited to high-volume centers (facilities registering >400 cases) and cases with available TNM classification. The differences in the survival rates between these facilities were also estimated. Each high-volume center was assigned a letter (from A to O), according to the five-year survival rate ranking.

Statistical analysis

The five-year survival rate was estimated using the Kaplan–Meier method. P values <0.05*or <0.01** were considered to be statistically significant. Analyses were performed using the STATA/MP14.0 software (Stata-Corp LP, College Station, TX).

This study was approved by the ethics committee of the Japan Organization of Occupational Health and Safety Kanto Rosai Hospital (No.2014-34).

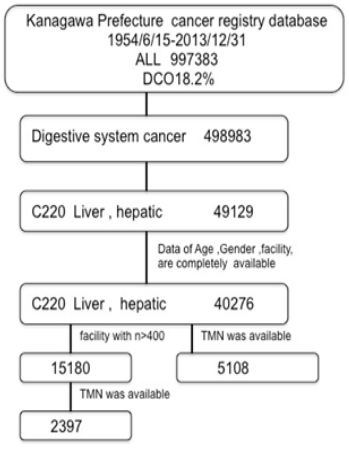

Figure 1. Flow Diagram of Patient Selection Out of a Total of 997,383 Patients (from 1954 to 2013) Identified in the Database of the Kanagawa Cancer Registry, to Reach the Final Number of Eligible Patients Included in This Survival Analysis.

Results

The total number of patients with gastrointestinal cancer registered in the Kanagawa Cancer Registry from 1954 to 2013 was 498,983. Among them, patients with HCC comprised 49,129 cases registered between 1976 and 2013. Of those, 40,276 cases with complete data were enrolled in the present study. Of note, the records of 15,180 cases were derived from the top 15 high-volume centers. The number of cases with available TNM classification was 5,108 (Figure 1).

The average age of patients with HCC was 66.6 years (±10.7), and their average age at death was 68.3 years (±10.8). Approximately three-quarters of patients were males (29,646; 73.6%), whereas 10,630 (26.4%) were

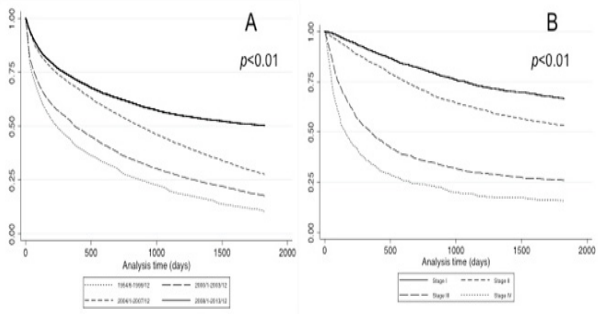

Figure 2. Kaplan–Meier Survival Curves for Overall Survival in Each Period (A) and TNM Stage (B) for Patients with Hepatocellular Carcinoma. Survival was estimated using the Kaplan–Meier method in 31,921 patients with complete information on sex, age and observation period, and with right censoring at the 5-year mark. The p values were calculated using a log-rank test. TNM, tumor/node/metastasis classification

Table 1. Baseline Characteristics

Period	N (%)[2]	Age of diagnosis (mean±SD)	Age of death (mean±SD)	Gender	
				Male (%)	Female (%)
Overall[1]	4,0276 (100)	66.6±10.7	68.31±10.79	29,646 (73.6)	10,630 (26.39)
1954-1999	22,968 (57.0)	64.2±10.5	66.0±10.6	17,435 (75.9)	5,523 (24.1)
2000-2003	6,161 (15.3)	68.8±9.8	71.0±9.8	4,442 (72.1)	1,790 (27.9)
2004-2007[3]	4,546 (11.3)	69.5±9.6	72.5±9.5	3,191 (70.2)	1,355 (29.8)
2008-2013[4]	6,611 (16.3)	71.3±10.4	73.8±10.1	4,578 (69.3)	2,033 (30.8)

[1]Data for 40,276 patients with complete information on sex, age and period; [2]Because of rounding, percentages may not total 100; [3]Period after radiofrequency ablation was approved for the treatment; [4]Period after Gd-EOB, Perflubutane and Sorafenib was approved for the treatment.

Table 2. Distribution of TMN Stage in Each Period

Period	N (%)[1]	TMN[5] stage at initial daignosis			
		1	2	3	4
Overall[1]	5108	1,849 (36.2)	1,635 (32.0)	1,111 (21.8)	513 (10.4)
1954-1999	25	6 (24.0)	11 (44.0)	7 (28.0)	1 (4.0)
2000-2003	91	25 (27.5)	31 (34.1)	21 (23.1)	14 (15.4)
2004-2007[3]	820	246 (30.0)	269 (32.8)	201 (24.5)	104 (12.7)
2008-2013[4]	4172	1,572 (37.7)	1,324 (31.8)	882 (21.1)	394 (9.4)

[1]Data for 5108 patients with complete information on sex, age, period and TMN stage; [2]Because of rounding, percentages may not total 100; [3]Period after radiofrequency ablation was approved for the treatment; [4]Period after Gd-EOB, Perflubutane and Sorafenib was approved for the treatment; [5]TNM, tumor/node/metastasis classification.

females. Cases of HCC, classified according to study period were: 22,968 (57.0%), 6,161 (15.3%), 4,546 (11.3%) and 6,611 (16.3%), for the study parts 1954-1999, 2000-2003, 2004-2007 and 2008-2013, respectively (Table 1).

The distribution of disease stage at initial registration for the 5,108 cases with available TNM classification is demonstrated in Table 2. The proportion of stage I disease gradually increased over time: 24% (1954-1999), 27.5% (2000-2003), 30% (2004-2007) and 37.7% (2008-2013).

Five-year survival rate

Figure 2 shows five-year survival rates prior to and after the introduction of new diagnostic and therapeutic modalities (A) and by TNM classification (B). Based on the data, the five-year survival rate was prolonged over time: 10.4% (1954-1999), 17.5% (2000-2003), 27.6% (2004-2007) and 50.2% (2008-2013) ($p<0.01$). TNM classification demonstrated the following: 66.7% (stage I), 55.3% (stage II), 25.9% (stage III) and 15.7% (stage IV) respectively ($p<0.01$).

Figure 3 shows the temporal change in the two-year survival rate (every two years from 1975 to 2013). According to the data, prognosis was improved with the introduction of new diagnostic and therapeutic agents.

Five-year survival rate in high-volume centers

Fifteen institutions were identified as high-volume centers. The five-year survival rate was estimated for each facility. Figures 4A and 4B show survival rates for all cases and for those who underwent surgical resection, respectively. The performance ranking among facilities remained unchanged regardless of surgical treatment. The survival rate of facility A was 49.8% in all cases and 47.6% in those who underwent surgery. In contrast, the

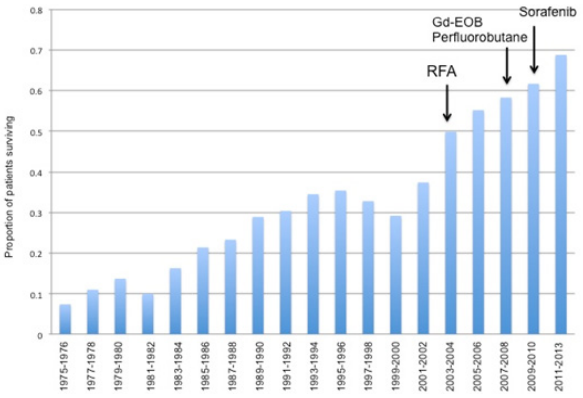

Figure 3. Two-Year Survival Rate Every Two Years from 1975 to 2013. Arrows show the time of radiofrequency ablation, Gd-EOB-DTPA, perfluorobutane and sorafenib introduction. RFA, radiofrequency ablation; Gd-EOB-DTPA, gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid

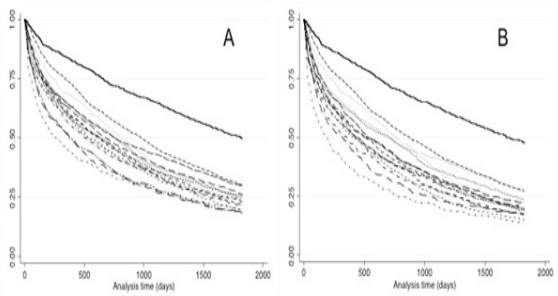

Figure 4. Five-Year Survival Estimated for All High-Volume Centers. Kaplan–Meier survival curves for the overall survival of patients with hepatocellular carcinoma in all cases (A) and those who underwent surgery (B).

Table 3. Distribution of TMN Staging in Each Hospital Over 400 Registered Cases

Rank	Hospital	N (%)		TMN[1] staging at initial daignosis			
		Overall	Stage available	1	2	3	4
1	A	615	235	55 (25.4)	107 (45.5)	46 (19.6)	27 (11.5)
2	B	1,624	100	22 (22.0)	49 (49.0)	20 (20)	9 (9)
3	C	890	6	2 (33.3)	2 (33.3)	1 (16.7)	1 (16.7)
4	D	1,467	338	160 (47)	107 (31.7)	55 (16.3)	16 (4.7)
5	E	639	154	58 (37.7)	36 (23.4)	20 (13.0)	40 (26.0)
6	F	1132	185	47 (25.4)	64 (34.6)	48 (26.0)	26 (14.1)
7	G	566	9	2 (22.2)	2 (22.2)	4 (44.4)	1 (11.1)
8	H	707	215	97 (45.1)	61 (28.4)	46 (21.4)	11 (5.1)
9	I	1,074	460	189 (41.1)	127 (27.6)	121 (26.3)	23 (5)
10	J	616	78	37 (47.4)	23 (29.5)	11 (14.1)	7 (9.0)
11	K	1,033	312	116 (37.2)	116 (37.2)	57 (18.3)	23 (7.4)
12	L	676	128	45 (35.2)	43 (33.6)	31 (24.2)	9 (7.0)
13	M	509	25	4 (16.0)	9 (36.0)	8 (32.0)	4 (16.0)
14	N	400	95	25 (26.3)	20 (21.1)	29 (30.5)	21 (22.1)
15	O	489	57	12 (21.1)	23 (40.4)	19 (33.3)	3 (5.3)

[1]TNM, tumor/node/metastasis classification

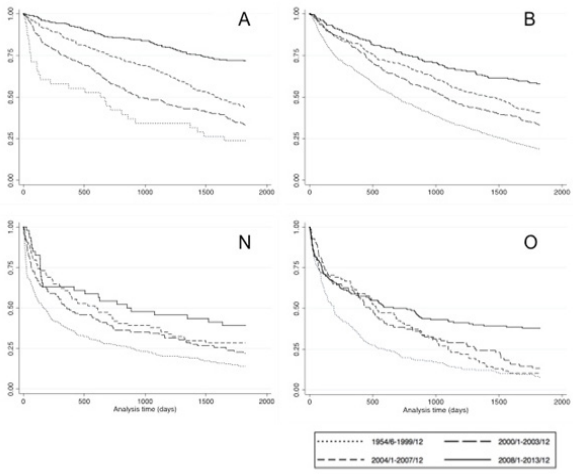

Figure 5. Temporal Change in Five-Year Survival in the Facilities with the Highest Prognosis (A and B), and in Those Two with the Lowest prognosis (N and O). A consistent improvement was obtained in facilities A and B, unlike facilities N and O in which improvement was inconsistent.

rate of facility O was 18.6% and 13.7%, respectively.

Figure 5 demonstrates temporal changes in the five-year survival rate observed in the two facilities with the highest rates (A and B) and the two facilities with the lowest rates (N and O). During the four analysis periods, prognosis improved in facility A (23.7%, 33.4%, 43.4% and 71.8%) and facility B (18.7%, 32.9%, 40.6% and 58.1%, respectively). In contrast, improvement was low in facility N (14.0%, 22.9%, 28.4% and 39.1%) and facility O (7.7%, 10.3%, 13.3% and 37.9%, respectively).

Table 3 shows HCC staging at initial registration. Facilities A, D, F, H and I were university hospitals and cancer center hospitals. Facilities E and N with the proportion of stage IV cases >20%, and facility M (stage IV >15%) were located in the port and harbor of the prefecture.

Discussion

This study demonstrated that the prognosis of HCC improved over the past four decades, as a result of the introduction of new diagnostic and therapeutic agents. The rate of improvement was significantly different between facilities.

According to the data from a large-scale cancer registry, the five-year survival rate of HCC patients improved consistently over time. The prognosis of HCC was good for all stages of disease (I-IV). These results secure the external validity of this data source.

The Kaplan–Meier curve for the period 2008-2013 reached "plateau" after 1,000 days of analysis time as shown in Figure 2. A reason for this may be that the surviving patients at the end of this analysis were censored. However, the most important reason may be the early diagnosis of cancer enabled by the introduction of new diagnostic modalities and effective treatment options. Detection of the tumor at an early stage, when effective therapy may be applied, is important for achieving long-term survival (Forner et al., 2008). Gd-EOB-DTPA and perfluorobutane permitted the evaluation of early-stage HCC and prolonged survival (Matsuda et al., 2014;Kim et al., 2015). Imaging with Gd-EOB-DTPA presented higher diagnostic accuracy and sensitivity compared with 64-section multidetector computed tomography (CT) (Di Martino et al., 2010;Akai et al., 2011). Perfluorobutane enabled the detection of small HCC visible only through dynamic CT in continuous view, unlike the B-mode (Kan et al., 2010;Mandai et al., 2011). These agents contributed to the detection of early-stage HCC and may be responsible for the observed increase in the proportion of stage I cases (Table 2). Consequently, the two-year survival rate was markedly improved with

the introduction of new diagnostic and therapeutic agents (Figure 3).

Approximately, 70% of HCC cases in Japan are attributable to hepatitis C virus (HCV) infection (Lavanchy, 2011;Zhu et al.,, 2016). The overall reduction in HCC mortality observed since the late 1990s in Japan may be associated with the decreased incidence and improved management of HCV infection compared with the period between 1940 and 1970. During this time, the widespread use of unsterile needles and blood transfusions resulted in an epidemic of HCV infection. (Nishiguchi et al., 1995; Tanaka et al., 2008; Umemura et al., 2009; Goh et al., 2015; Bertuccio et al., 2017). In addition, protease inhibitors such as simeprevir or telaprevir resulting in highly sustained virologic response (SVR) in HCV were introduced in 2013 (Kumada et al., 2012; Hayashi et al., 2014; Izumi et al., 2014). More recently, direct-acting antiviral agents inhibiting key viral functions have become the mainstay of anti-HCV treatment (Pawlotsky, 2013; Suzuki et al., 2013; Mizokami et al., 2015). Prior to the introduction of these therapeutic agents, interferon (IFN)-based treatment was recognized as the standard therapy against HCV infection (Izumi, 2010), despite the suboptimal SVR induced by this treatment (40%-50%). However, patients responding to IFN therapy and sustaining loss of HCV RNA are generally regarded as being at low risk of developing liver cirrhosis or HCC (Nishiguchi et al., 1995). Furthermore, IFN decreased the rate of carcinogenesis in those with normal or persistent low alanine aminotransferase levels (Ikeda et al., 1999). These continuous efforts and advances in anti-HCV therapy may have influenced the improvement in the long-term outcome of patients with HCV.

Sorafenib, an oral multikinase inhibitor with antiproliferative and antiangiogenic effects, was an epoch-making drug for HCC. This agent has been shown to improve overall survival in patients with advanced HCC (Llovet et al., 2008; Cheng et al., 2009). In the past 30 years, the use of anticancer agents for the treatment of HCC has not shown consistent survival benefits (Llovet and Bruix, 2003; Lopez et al., 2006). Sorafenib successfully addressed this unmet medical need, prolonging patient survival. This effect may have contributed to the prolonged five-year survival rate observed after 2009 in this study.

Survival rates varied considerably between the high-volume centers investigated in this study. Prognosis was shown to improve over time in all facilities. However, institutions linked to good prognosis tended to improve more aggressively than those associated with poor prognosis. The reason for this tendency may be "lead-time bias" (Huo et al., 2007; Singal et al., 2014). The detection of early-stage HCC and the appropriate administration of curative treatment leads to prolonged survival (Huo et al., 2007; Oeda et al., 2016; Singal et al., 2017).

It has been shown that the proportion of patients with small-size HCC and curative therapy was higher in the surveillance group than in the non-surveillance group (Tanaka et al., 2006).

Morphological differentiation between early-stage, well-differentiated HCC and dysplastic nodules is often challenging (Kojiro and Roskams, 2005). The approach toward initiating treatment of a small nodule as an early cancer differs among facilities. To address this point, the distribution of cases according to the TNM classification of disease stage was evaluated in this study (Table 3). The results showed that the distribution of staging was affected by locality and did not relate to the ranking based on survival rate. However, the cases with TNM stage were very few and the lead-time bias remained the main reason for this difference.

In addition, the preferred treatment against HCC differs among facilities. The use of methods such as transarterial chemoembolization (TACE) was heterogeneous between facilities, and the timing of administration of a multikinase inhibitor may be critical to the outcome of HCC (Lencioni et al., 2016).

This is the first study to examine the prognosis of HCC over approximately 40 years using a large-scale database. However, the available data did not include information regarding the etiological factors affecting HCC such as liver function, viral infection and treatment course. Therefore, it was not possible to determine the cause of these changes in survival rate.

In conclusion, this study revealed that five-year survival of HCC improved over the past decades. This may be explained by the development of surveillance and follow-up screening for high-risk groups among HCC patients. This allowed the early detection of HCC and appropriate curative intervention, consequently improving patient survival.

Funding Statement

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Statement conflict of Interest

The authors declare no conflicts of interest associated with this manuscript.

Acknowledgements

The authors thank Dr. Kotaro Matsunaga and Professor Michihiro Suzuki for their valuable insight.

References

Akai H, Kiryu S, Matsuda I, et al (2011). Detection of hepatocellular carcinoma by Gd-EOB-DTPA-enhanced liver MRI: comparison with triple phase 64 detector row helical CT. *Eur J Radiol*, **80**, 310-5.

Bertuccio P, Turati F, Carioli G, et al (2017). Global trends and predictions in hepatocellular carcinoma mortality. *J Hepatol*, **67,** 302-9.

Best J, Schotten C, Theysohn JM, et al (2017). Novel implications in the treatment of hepatocellular carcinoma. *Ann Gastroenterol*, **30**, 23-32.

Bruix J, Sherman M (2011). Management of hepatocellular carcinoma: an update. *Hepatology*, **53**, 1020-2.

Cheng AL, Kang YK, Chen Z, et al (2009). Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-

blind, placebo-controlled trial. *Lancet Oncol*, **10**, 25-34.
Di Martino M, Marin D, Guerrisi A, et al (2010). Intraindividual comparison of gadoxetate disodium-enhanced MR imaging and 64-section multidetector CT in the Detection of hepatocellular carcinoma in patients with cirrhosis. *Radiology*, **256**, 806-16.
Forner A, Vilana R, Ayuso C, et al (2008). Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: Prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. *Hepatology*, **47**, 97-104.
Goh GB, Chang PE, Tan CK (2015). Changing epidemiology of hepatocellular carcinoma in Asia. *Best Pract Res Clin Gastroenterol*, **29**, 919-28.
Goverment Kanagwa Prefecture (2016). Annual report of Kanagawa cancer registry 40th edition, 53.
Hayashi N, Izumi N, Kumada H, et al (2014). Simeprevir with peginterferon/ribavirin for treatment-naive hepatitis C genotype 1 patients in Japan: CONCERTO-1, a phase III trial. *J Hepatol*, **61**, 219-27.
Huo TI, Huang YH, Chiang JH, et al (2007). Survival impact of delayed treatment in patients with hepatocellular carcinoma undergoing locoregional therapy: is there a lead-time bias? *Scand J Gastroentero*l, **42**, 485-92.
Ikeda K, Saitoh S, Arase Y, et al (1999). Effect of interferon therapy on hepatocellular carcinogenesis in patients with chronic hepatitis type C: A long-term observation study of 1,643 patients using statistical bias correction with proportional hazard analysis. *Hepatology*, **29**, 1124-30.
Izumi N (2010). Diagnostic and treatment algorithm of the Japanese society of hepatology: a consensus-based practice guideline. *Oncology*, **78**, 78-86.
Izumi N, Hayashi N, Kumada H, et al (2014). Once-daily simeprevir with peginterferon and ribavirin for treatment-experienced HCV genotype 1-infected patients in Japan: the CONCERTO-2 and CONCERTO-3 studies. *J Gastroenterol*, **49**, 941-53.
Kan M, Hiraoka A, Uehara T, et al (2010). Evaluation of contrast-enhanced ultrasonography using perfluorobutane (Sonazoid((R))) in patients with small hepatocellular carcinoma: comparison with dynamic computed tomography. *Oncol Lett*, **1**, 485-88.
Kim HD, Lim YS, Han S, et al (2015). Evaluation of early-stage hepatocellular carcinoma by magnetic resonance imaging with gadoxetic acid detects additional lesions and increases overall survival. *Gastroenterology*, **148**, 1371-82.
Kojiro M, Roskams T (2005). Early hepatocellular carcinoma and dysplastic nodules. *Semin Liver Dis*, **25**, 133-42.
Kudo M, Izumi N, Kokudo N, et al (2011). Management of hepatocellular carcinoma in Japan: Consensus-based clinical practice guidelines proposed by the Japan Society of Hepatology (JSH) 2010 updated version. *Dig Dis*, **29**, 339-64.
Kumada H, Toyota J, Okanoue T, et al (2012). Telaprevir with peginterferon and ribavirin for treatment-naive patients chronically infected with HCV of genotype 1 in Japan. *J Hepatol*, **56**, 78-84.
Lavanchy D (2011). Evolving epidemiology of hepatitis C virus. *Clin Microbiol Infect*, **17**, 107-15.
Lencioni R, Llovet JM, Han G, et al (2016). Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: The SPACE trial. *J Hepatol*, **64**, 1090-8.
Llovet JM, Bruix J (2003). Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. *Hepatology*, **37**, 429-42.
Llovet JM, Ricci S, Mazzaferro V, et al (2008). Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*, **359**, 378-90.
Lopez PM, Villanueva A, Llovet JM (2006). Systematic review: evidence-based management of hepatocellular carcinoma-an updated analysis of randomized controlled trials. *Aliment Pharmacol Ther*, **23**, 1535-47.
Makuuchi M, Kokudo N (2006). Clinical practice guidelines for hepatocellular carcinoma: the first evidence based guidelines from Japan. *World J Gastroenterol*, **12**, 828-9.
Mandai M, Koda M, Matono T, et al (2011). Assessment of hepatocellular carcinoma by contrast-enhanced ultrasound with perfluorobutane microbubbles: comparison with dynamic CT. *Br J Radiol*, **84**, 499-507.
Matsuda M, Ichikawa T, Amemiya H, et al (2014). Preoperative gadoxetic Acid-enhanced MRI and simultaneous treatment of early hepatocellular carcinoma prolonged recurrence-free survival of progressed hepatocellular carcinoma patients after hepatic resection. *HPB Surg*, **2014**, 641685.
Mizokami M, Yokosuka O, Takehara T, et al (2015). Ledipasvir and sofosbuvir fixed-dose combination with and without ribavirin for 12 weeks in treatment-naive and previously treated Japanese patients with genotype 1 hepatitis C: an open-label, randomised, phase 3 trial. *Lancet Infect Dis*, **15**, 645-53.
Nishiguchi S, Kuroki T, Nakatani S, et al (1995). Randomised trial of effects of interferon-alpha on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. *Lancet*, **346**, 1051-5.
Oeda S, Iwane S, Takasaki M, et al (2016). Optimal follow-up of patients with viral hepatitis improves the detection of early-stage hepatocellular carcinoma and the prognosis of survival. *Intern Med*, **55**, 2749-58.
Okamoto N (2008). A history of the cancer registration system in Japan. *Int J Clin Oncol*, **13**, 90-6.
Pawlotsky JM (2013). NS5A inhibitors in the treatment of hepatitis C. *J Hepatol*, **59**, 375-82.
Singal AG, Pillai A, Tiro J (2014). Early detection, curative treatment, and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis: a meta-analysis. *PLoS Med*, **11**, e1001624.
Singal AG, Mittal S, Yerokun OA, et al (2017). Hepatocellular carcinoma screening associated with early tumor detection and improved survival among patients with cirrhosis in the US. *Am J Med*, **130,** 1099-106.
Suzuki Y, Ikeda K, Suzuki F, et al (2013). Dual oral therapy with daclatasvir and asunaprevir for patients with HCV genotype 1b infection and limited treatment options. *J Hepatol*, **58**, 655-62.
Tanaka H, Nouso K, Kobashi H, et al (2006). Surveillance of hepatocellular carcinoma in patients with hepatitis C virus infection may improve patient survival. *Liver Int*, **26**, 543-51.
Tanaka H, Imai Y, Hiramatsu N, et al (2008). Declining incidence of hepatocellular carcinoma in Osaka, Japan, from 1990 to 2003. *Ann Intern Med*, **148**, 820-6.
Umemura T, Ichijo T, Yoshizawa K, et al (2009). Epidemiology of hepatocellular carcinoma in Japan. *J Gastroenterol*, **44**, 102-7.
Zhu RX, Seto WK, Lai CL, et al (2016). Epidemiology of hepatocellular carcinoma in the Asia-Pacific region. *Gut Liver*, **10**, 332-9.