ORIGINAL ARTICLE
Oncology & Hematology

JKMS

http://dx.doi.org/10.3346/jkms.2016.31.3.403 • J Korean Med Sci 2016; 31: 403-409

Trends and Patterns of Hepatocellular Carcinoma Treatment in Korea

Young Mi Hong,[1] Ki Tae Yoon,[1] Mong Cho,[1] Dae Hwan Kang,[1] Hyung Wook Kim,[1] Cheol Woong Choi,[1] Su Bum Park,[1] Jeong Heo,[2] Hyun Young Woo,[2] and Won Lim[2]

[1]Department of Internal Medicine, Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan, Korea; [2]Department of Internal Medicine, Pusan National University Hospital, Busan, Korea

Received: 23 September 2015
Accepted: 9 November 2015

Address for Correspondence:
Ki Tae Yoon, MD
Department of Internal Medicine, Pusan National University School of Medicine, Pusan National University Yangsan Hospital, 20 Geumo-ro, Mulgeum-eup, Yangsan 50612, Korea
E-mail: ktyoon@pusan.ac.kr

Multiple therapeutic modalities are available for hepatocellular carcinoma (HCC) treatment. We aimed to evaluate the trends for HCC treatment in Korea. Recent trends and patterns in treatment modalities were assessed in HCC patients who first registered for the Health Insurance Review Assessment Service between 2008 and 2012. From 2009 to 2012, 57,690 patients were diagnosed with HCC. Transcatheter arterial chemoembolization (TACE) was the most common treatment modality for initial treatment. Curative treatment modalities like hepatic resection, liver transplantation, and local ablation therapy increased gradually. The 3 most common treatment modalities (hepatic resection, local ablation therapy, TACE) used after initial treatment in 2009 were studied. Following initial hepatic resection, 44.5% of patients required re-treatment. TACE was the most common modality (in 48.3% of cases), while 15.0% of patients received local ablation therapy. After local ablation therapy, 55.4% of patients were re-treated, wherein 45.0% of patients received TACE and 31.5% received local ablation therapy. Following initial TACE, 73.9% patients were re-treated, most commonly with TACE (57.7%) followed by local ablation therapy (12.8%). While there were no significant differences between the initial and re-treatment modalities, various multiple treatments followed the initial treatment. The treatment modalities were interchangeable.

Keywords: Carcinoma; Hepatocellular; Treatment; Trend; Korea

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer-related deaths worldwide (1,2). In Korea, HCC is the fourth and sixth most common cancer in men and women, respectively, and over 15,000 new cases occurred in 2009 (3). HCC accounts for 75%-90% of all primary liver cancers (3-5). HCC was the second leading cause of cancer mortality in Korea, but the overall 5-year survival rate of HCC patients has improved from 10.7% to 28.6% in 2013, according to the national cancer center (6).

There are various treatment options for HCC. The proportion of patients undergoing curative therapies including hepatic resection, liver transplantation, and locoregional therapy has been increasing over the last decade. Several studies have demonstrated that transarterial chemoembolization (TACE) improves the survival rate (7,8). Radiotherapy for HCC has become more common as radiation technology has developed rapidly and high-dose radiotherapy without broad liver damage became available. The introduction of sorafenib, which lengthened survival, opened a new era of chemotherapy for HCC patients (9,10).

The treatment of HCC is very complicated since HCC is heterogeneous and treatable by various modalities in the same stage. The Barcelona Clinic Liver Cancer staging system, which is used commonly, is helpful for conceptualizing the different treatment options, but may not be applicable in all settings. Moreover, the Barcelona Clinic Liver Cancer staging system guideline is only for initial treatment. There are no re-treatment guidelines for HCC patients.

There is no large-scale population-based study on HCC treatment trends. We aimed to assess the trends of initial treatment and re-treatment modalities for Korean HCC patients on the basis of data taken from national data from the Health Insurance Review and Assessment Service (HIRA) between 2008 and 2012.

MATERIALS AND METHODS

Data source

We used data from the Korean HIRA, which includes adjusted medical and pharmacy claims for almost the whole Korean population. Korea has a health care system that is managed and supervised by the government; 97.0% of the population is legally obliged to register in the Korean National Health Insurance Program. All medical clinics and hospitals must submit data of inpatients' and outpatients' care, including diagnoses (coded according to the International Classification of Disease, Tenth Revision [ICD-10]), procedures, prescription records, demographic information, and direct medical costs, to HIRA to claim back

pISSN 1011-8934
eISSN 1598-6357

medical costs from the government.

Patient selection

All HCC-related hospital visits or admissions were recorded in the aforementioned system using ICD-10 codes between January 2008 and December 2012. To identify newly diagnosed HCC patients, ICD-10 codes (C220) were selected and patients with previously diagnosed HCC were excluded.

Data analysis

Data regarding age, gender, etiology, and underlying liver cirrhosis were ascertained by a medical records' review. The annual incidence was determined using the aforementioned patient selection criteria and the annual HCC prevalence was defined as the number of patients who retained the C220 code for 1 year. The following 3 institutional types were defined according to the national medical law: the clinic was defined as a facility with more than 30 beds, the general hospital was defined as a facility with more than 100 beds and a certain number of experts, and the tertiary hospital was defined as a general hospital with highly trained medical practitioners specializing in severe diseases.

Patients received 1 of the following treatments: hepatic resection, liver transplantation, radiofrequency ablation (RFA) therapy, percutaneous ethanol injection, transarterial chemoembolization (TACE) therapy, hepatic artery chemoinfusion therapy, external-beam radiation therapy, systemic cytotoxic chemotherapy, molecular-targeted therapy (sorafenib), and conservative management. All hospitals and clinics were listed in the HIRA database and used the same procedure, medicine, and surgery codes. The initial treatment modality was defined as the first treatment modality after diagnosis and was analyzed annually. Combination treatment was defined as 2 different treatment modalities administered within 30 days.

Treatment trends after initial treatment were only available from 2009 because HIRA only provided data for the most recent 5 years and analysis was performed according to the 3 most common modalities (hepatic resection, liver transplantation, and local ablation therapy). The follow-up period was 3-4 years.

Subgroup analysis of sorafenib therapy was performed in 2011 and 2012. The initial doses, 800 mg and 400 mg, were analyzed separately. The mean daily dose was calculated by dividing the total administration dose by the total number of patients and days. The median treatment duration was analyzed using each patient's total prescription days.

Ethics statement

The study was reviewed and approved by the institutional review board of Pusan National University Yangsan Hospital (PNUYH 05-2015-063). Informed consent was waived by the board.

RESULTS

From January 2009 to December 2012, 57,690 persons were newly diagnosed with HCC, which constituted the final study population. During the study period, the annual incidence of HCC was approximately 14,000 cases per year and did not significantly change over time, while the prevalence gradually increased (Table 1).

The mean age was the late fifties (57-60 years) and the majority of the patients were men. More than half of the patients were diagnosed in tertiary hospitals. The main etiology of HCC was hepatitis B virus (HBV) infection (47.9%-50.2%) and this proportion did not significantly change over time. Half of the patients had accompanying liver cirrhosis. Overall, the extrahepatic metastasis rate was about 10% and the most common site was the lung, followed by the bones and the lymph nodes (Table 2).

The initial treatment was usually performed in tertiary hospitals (approximately 70%) and there was no significant change during the study period. However, more patients visited tertiary hospitals after the diagnosis. The median period from diagnosis to initial treatment was 22 days (range 14-36 days). TACE was the most common initial treatment modality (29.3%-33.0%). The use of curative treatment modalities (hepatic resection, liver transplantation, and local ablation therapy) gradually increased from 17.6%-17.7% during the study period. Sorafenib therapy has been used in about 3.5% of HCC patients since 2011. Combination treatment accounted for about 4% of patients every year, and TACE plus radiotherapy and TACE plus RFA were performed commonly. The patients who did not receive treatment decreased over time, after the diagnosis (Table 3).

Re-treatment trends were evaluated in HCC patients who first received treatment in 2009 (Fig. 1). In patients who underwent hepatic resection initially, 44.5% of patients received the same or other treatments over the study period. The most common treatment modality was TACE (48.3%), followed by local ablation therapy (15.0%) and radiotherapy (14.4%). Hepatic resection was repeated in 6.8% of patients. In patients initially treated with local ablation therapy, 54.4% of patients received re-treatments during the study period. The most common modality was TACE (45.0%), followed by local ablation therapy (31.5%) and radiotherapy (8.4%). Hepatic resection was performed in 5.3% of patients. In patients initially treated with TACE, 73.9% of patients were re-treated and the most common mo-

Table 1. Incidence and prevalence rates (per 100,000 people per year) of hepatocellular carcinoma

Incidence/prevalence	2009	2010	2011	2012
Incidence, n (per 100,000)	14,766 (29.7)	14,244 (28.5)	14,226 (28.1)	14,454 (28.4)
Prevalence, n (per 100,000)	40,908 (82.4)	43,176 (86.4)	45,292 (89.4)	49,221 (96.8)

http://dx.doi.org/10.3346/jkms.2016.31.3.403

Table 2. Demographic features of newly diagnosed hepatocellular carcinoma patients

Parameters	No. (%) of patients by year			
	2009	2010	2011	2012
Age, mean (standard deviation)	57 (11)	58 (12)	58 (10)	60 (8)
Gender, n (%)				
Men	11,108 (75.2)	10,743 (75.4)	10,873 (76.4)	11,042 (76.4)
Women	3,658 (24.8)	3,501 (24.6)	3,353 (23.6)	3,412 (23.6)
Etiology, n (%)				
Hepatitis B virus	7,118 (48.2)	6,926 (48.6)	7,148 (50.2)	6,926 (47.9)
Hepatitis C virus	1,561 (10.6)	1,430 (10.0)	1,516 (10.7)	1,532 (10.6)
Alcohol	1,449 (9.8)	1,435 (10.1)	1,544 (10.9)	1,600 (11.1)
Fatty liver	258 (1.7)	202 (1.4)	177 (1.2)	247 (1.7)
Others	4,380 (29.7)	4,251 (29.9)	3,841 (27.0)	4,149 (28.7)
Liver cirrhosis, n (%)	6,350 (43.0)	6,325 (44.4)	6,486 (45.6)	6,818 (47.2)
Extrahepatic metastasis, n (%)				
Lung	586 (4.0)	593 (4.2)	593 (4.2)	574 (4.0)
Bone	464 (3.1)	454 (3.2)	433 (3.0)	405 (2.8)
Lymph node	276 (1.9)	271 (1.9)	252 (1.8)	244 (1.7)
Adrenal gland	50 (0.3)	48 (0.3)	52 (0.4)	45 (0.3)
Brain	-	11 (0.1)	71 (0.5)	59 (0.4)
Institution, n (%)				
Tertiary hospital	8,093 (54.8)	7,855 (55.2)	7,705 (54.2)	8,050 (55.7)
General hospital	5,902 (40.0)	5,699 (40.0)	5,768 (40.6)	5,686 (39.3)
Clinic	771 (5.2)	690 (4.8)	753 (5.3)	718 (5.0)

Table 3. Initial treatment modalities

Treatment modality	No. (%) of patients by year			
	2009 (n = 14,766)	2010 (n = 14,244)	2011 (n = 14,226)	2012 (n = 14,454)
Hepatic resection, n (%)	1,431 (9.7)	1,655 (11.6)	1,818 (12.8)	1,886 (13.0)
Liver transplantation, n (%)	128 (0.9)	148 (1.0)	177 (1.2)	179 (1.2)
Local ablation therapy, n (%)	1,044 (7.1)	1,044 (7.3)	1,071 (7.5)	1,140 (7.9)
RFA	1,021 (6.9)	1,009 (7.1)	1,029 (7.2)	1,062 (7.3)
PEI	23 (0.2)	35 (0.2)	42 (0.3)	78 (0.5)
TACE, n (%)	4,815 (32.6)	4,661 (32.7)	4,688 (33.0)	4,235 (29.3)
HACI, n (%)	99 (0.7)	113 (0.8)	70 (0.5)	129 (0.9)
Radiation therapy, n (%)	238 (1.6)	224 (1.6)	187 (1.3)	180 (1.2)
Systemic chemotherapy, n (%)	237 (1.6)	213 (1.5)	129 (0.9)	173 (1.2)
Sorafenib, n (%)	0	0	503 (3.5)	527 (3.6)
Combination therapy, n (%)	611 (4.2)	604 (4.2)	631 (4.4)	550 (3.8)
TACE+RT	304 (2.1)	286 (2.0)	307 (2.2)	262 (1.8)
TACE+RFA	218 (1.5)	227 (1.6)	227 (1.6)	186 (1.3)
TACE+PEI	17 (0.1)	9 (0.1)	11 (0.8)	10 (0.1)
RT+HACI	45 (0.3)	60 (0.4)	64 (0.5)	57 (0.4)
RT+SC	27 (0.2)	22 (0.2)	22 (0.2)	35 (0.2)
Others, n (%)	110 (0.7)	190 (1.3)	155 (1.1)	166 (1.1)
Supportive care, n (%)	6,053 (41.6)	5,392 (37.9)	4,797 (33.7)	5,289 (36.6)

RFA, radiofrequency ablation; TACE, transarterial chemoembolization; HACI, hepatic artery chemoinfusion; PEI, percutaneous ethanol injection; RT, radiation therapy; SC, systemic chemotherapy.

dality was TACE (57.7%), followed by local ablation therapy (12.8%) and radiotherapy (11.8%). TACE was performed 0.8 times/year. Hepatic resection was performed in 6.2% of patients who initially underwent TACE.

Sorafenib has been used widely since 2011, when the reimbursement policy was applied. In 2011 and 2012, the majority of HCC patients received sorafenib in the general or tertiary hospitals. About 25% of patients had extrahepatic metastases. The majority of patients received the standard dose of 800 mg (81%). The mean daily doses were 667 mg and 680 mg in 2011 and 2012, respectively. The median treatment durations were 10.7 weeks and 8.7 weeks, respectively (Table 4).

DISCUSSION

This study is a nationwide cross-sectional study undertaken to evaluate the trends and patterns of HCC treatment in Korean patients. The prevalence of HCC has gradually increased from 40,908 in 2009 to 49,221 in 2012. The increasing prevalence of HCC seems to be caused by the increased survival time of Ko-

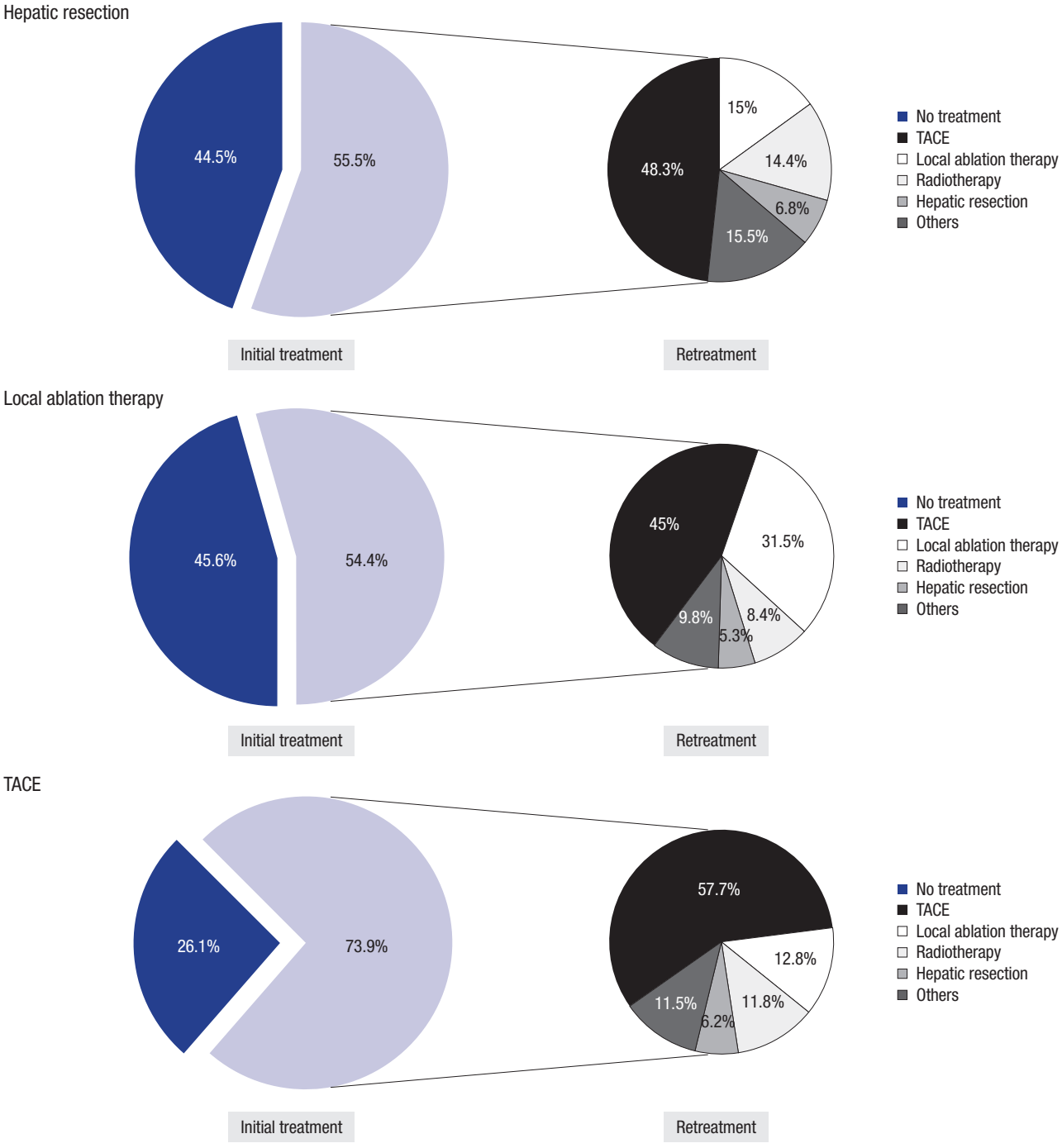

Fig. 1. Treatment trends after initial treatment in 2009. Treatment trends after initial treatment were analyzed for 3 of the most common initial treatment modalities (hepatic resection, local ablation therapy, and transarterial chemoembolization [TACE]).

rean HCC patients according to the national cancer registry's report (6).

The etiology of HCC was mostly HBV infection. HBV infection caused 50%, while hepatitis C virus infection and alcohol caused 11% and 10%-11% of HCCs, respectively. The proportion of cases accounted for by HBV infection was lower than that reported by other studies (11,12). However, considering that the etiology for about 30% of cases was not known and that HBV infection accounted for about 50% of the cases reported in this study, this study is not different from other reports. Extrahepatic metastases of HCC occurred in 9%-10% of the patients and HCC frequently spread to the lungs, bones, lymph nodes, adrenal glands, and brain. The rate of metastasis was lower than that in other reports; about 30%-50% of patients presented with metastases (13). The lower rate might be due to lower recording as a result of physicians' unawareness of clinically insignificant

 http://dx.doi.org/10.3346/jkms.2016.31.3.403

Table 4. Subgroup analysis of sorafenib administration in 2011 and 2012

Parameters	No. (%) of patients by year	
	2011 (n = 503)	2012 (n = 526)
Age, mean (standard deviation)	57 (11)	56 (10)
Men, n (%)	435 (86.5)	434 (82.5)
Institution, n (%)		
Tertiary hospital	275 (54.67)	296 (56.3)
General hospital	210 (41.74)	207 (39.2)
Clinic	18 (3.57)	24 (4.5)
Liver cirrhosis, n (%)	126 (25.0)	165 (31.4)
Initial dose of 800 mg, n (%)	408 (81.1)	427 (81.2)
Initial dose of 400 mg, n (%)	72 (14.3)	81 (15.4)
Mean daily dose, mg	667	680
Median treatment duration, weeks	10.7	8.7

metastatic lesions.

Initial treatment seems to start early in Korea. The period from diagnosis to initial treatment was 14-36 days. The majority of patients received initial treatment within 30 days of diagnosis. The proportion of patients who received curative treatments (hepatic resection, liver transplantation, local ablation therapy) increased slightly from 17.7% in 2009 to 22.1% in 2012. At the same time, the proportion of patients who received supportive care decreased during the study period, from 41.6% to 36.6%. The increase in curative treatment is probably caused by earlier HCC detection due to physicians' awareness of HCC surveillance in high-risk patients and the nationwide check-up program.

TACE was the most common modality for initial treatment in Korea and is used more frequently than in other countries (14). Generally, single drug chemotherapy was used with TACE. Doxorubicin accounted for 80% and cisplatin for 15% of cases. TACE with 3 chemotherapeutic agents is routinely administered in other countries and a recent large randomized controlled trial showed that TACE with 3 chemotherapeutic agents increased the overall survival (15). The reimbursement policy permits the use of only 1 chemotherapeutic agent in Korea, which possibly led to a different practice environment.

Combination treatments accounted for about 4% of cases every year. TACE plus radiotherapy and TACE plus RFA were performed commonly. Combination therapies are expected to increase based on several recent studies, which report that combination therapies including TACE plus radiotherapy, showed better results for advanced HCC patients compared to monotherapy and combination of TACE with RFA could improve the survival rate (16).

A small proportion of HCC patients received systemic cytotoxic chemotherapy. The most frequently used monotherapeutic agent was 5-fluorouracil. Combination therapy with 5-fluorouracil and cisplatin, or cisplatin and gemcitabine was used most frequently. These chemotherapeutic agents have not demonstrated efficacy in HCC, although they reportedly increased survival time in several solid gastrointestinal tumors. Physicians still seemed to prefer systemic chemotherapy for treatment-refractory advanced HCC patients. This practice lasted until 2012, even after sorafenib, an effective molecular-target agent, was introduced in Korea. This study did not show whether systemic chemotherapies were administered in patients who were sorafenib-naïve or sorafenib-refractory.

Sorafenib, a molecular target therapy, was introduced in 2007 in Korea, while the reimbursement policy has been implemented since 2011. According to the reimbursement policy data, sorafenib accounted for about 3.5% of all treated patients in 2011 and 2012. Subsequently, sorafenib use has presumably become more common due to the expanded reimbursement policy in force since 2013.

In HCC patients, there are several treatment modalities that are curative or palliative. The curative treatment modalities are hepatic resection, liver transplantation and locoregional ablation therapy. Unlike other solid gastrointestinal tumors, multiple treatments are administered to HCC patients, and treatment modalities are not hierarchical. They can be used interchangeably in the same patients. Although there are several guidelines for the treatment of HCC patients, they are limited to initial treatment. There is no study about how often and which treatment modalities are selected after initial therapy. Ignoring treatment modalities following initial treatment in HCC patients may lead to confusing results, as many studies that compared curative treatment modalities have demonstrated (17,18). The re-treatment rate was much lower in patients who initially underwent curative treatments such as hepatic resection and local ablation therapy than in patients who received TACE, a palliative treatment. TACE was the most common re-treatment modality regardless of the initial treatment modality. In a significant proportion of HCC patients, re-treatment modalities were selected interchangeably with the first treatment modalities, regardless of whether they were curative or palliative treatments. This study demonstrated the overall pattern of re-treatments 3-4 years after initial treatment.

On analysis of sorafenib administration, we found that the majority of patients had received sorafenib in general or tertiary hospitals consistent with the institutional pattern of initial treatment; however, long-term follow-up was not possible. Most (70%-90%) HCC cases are known to involve underlying liver cirrhosis (19), but in the present report, only 25% and 31% of HCC cases were accompanied by liver cirrhosis in 2011 and 2012, respectively. The lower rate is believed to be because of the enrolled patients' criteria, as unlike other studies, only Child Pugh-A patients were enrolled in this study. The majority of patients received the recommended initial dose (800 mg) and mean daily dose (about 680 mg) of sorafenib. Thus, the majority of Korean physicians have tried to administer the recommended dose during HCC treatment. The median treatment duration in

our study was relatively shorter than that in Child-Pugh A patients, as reported in the final analysis of the global investigation of therapeutic decisions in HCC and of its treatment with sorafenib (20). This can be explained by a limited follow-up period in our study.

There are some limitations to this population-based study. First, the HIRA database provided limited information about the patients. Because the available data are age, gender, year, diagnostic code, procedure code, and medication code, we could not identify associated diseases and treatment methods, such as combination treatment, accurately by reviewing medical records. It is possible that clinicians had missed final diagnosis records such as underlying disease or extrahepatic metastasis sites. Second, the incidence of HCC may have been overestimated. Cases for 5 years (January 2008-December 2012) were obtained from the HIRA database. Although we excluded the same patient prior to the patient's registration during the study period, we could not isolate the first diagnosed patients accurately, because the 5-year overall survival rate of HCC is greater than 20%.

Even though we could not identify the patterns of re-treatment accurately and sequentially due to these limitations, our study may highlight the current situation of HCC treatment. There are no data on re-treatment trends after initial treatment or for the entire population. Therefore, our study may provide new insights regarding the patterns and trends of HCC treatment.

DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Conception & design of the study: Hong YM. Drafting: Yoon KT. Acquisition, analysis, interpretation of the data: Choi CW, Park SB, Heo J, Woo HY, Lim W. Critical revisions of the manuscript: Cho M, Kang DH, Kim HW. Approval of the final manuscript: all authors.

ORCID

Young Mi Hong http://orcid.org/0000-0001-5427-7505
Ki Tae Yoon http://orcid.org/0000-0002-8580-0239
Mong Cho http://orcid.org/0000-0002-0498-6300

REFERENCES

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 2009; 59: 225-49.
2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; 127: 2893-917.
3. Jung KW, Won YJ, Park S, Kong HJ, Sung J, Shin HR, Park EC, Lee JS. Cancer statistics in Korea: incidence, mortality and survival in 2005. *J Korean Med Sci* 2009; 24: 995-1003.
4. Ahmed F, Perz JF, Kwong S, Jamison PM, Friedman C, Bell BP. National trends and disparities in the incidence of hepatocellular carcinoma, 1998-2003. *Prev Chronic Dis* 2008; 5: A74.
5. Kim SR, Kudo M, Hino O, Han KH, Chung YH, Lee HS; Organizing Committee of Japan-Korea Liver Symposium. Epidemiology of hepatocellular carcinoma in Japan and Korea. A review. *Oncology* 2008; 75 Suppl 1: 13-6.
6. National Cancer Information Center [Internet]. Available at http://www.cancer.go.kr/mbs/cancer/ [accessed on 20 August 2015].
7. Llovet JM, Real MI, Montaña X, Planas R, Coll S, Aponte J, Ayuso C, Sala M, Muchart J, Solà R, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002; 359: 1734-9.
8. Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, Fan ST, Wong J. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002; 35: 1164-71.
9. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; 359: 378-90.
10. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, et al. 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* 2009; 10: 25-34.
11. The Korean Liver Cancer Study Group [Internet]. Available at http://www.klcsg.or.kr/ [accessed on 20 August 2015].
12. Kwak HW, Park JW, Nam BH, Yu A, Woo SM, Kim TH, Kim SH, Koh YH, Kim HB, Park SJ, et al. Clinical outcomes of a cohort series of patients with hepatocellular carcinoma in a hepatitis B virus-endemic area. *J Gastroenterol Hepatol* 2014; 29: 820-9.
13. Terada T, Maruo H. Unusual extrahepatic metastatic sites from hepatocellular carcinoma. *Int J Clin Exp Pathol* 2013; 6: 816-20.
14. Park JW, Chen M, Colombo M, Roberts LR, Schwartz M, Chen PJ, Kudo M, Johnson P, Wagner S, Orsini LS, et al. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. *Liver Int* 2015; 35: 2155-66.
15. Shi M, Lu LG, Fang WQ, Guo RP, Chen MS, Li Y, Luo J, Xu L, Zou RH, Lin XJ, et al. Roles played by chemolipiodolization and embolization in chemoembolization for hepatocellular carcinoma: single-blind, randomized trial. *J Natl Cancer Inst* 2013; 105: 59-68.
16. Meng MB, Cui YL, Lu Y, She B, Chen Y, Guan YS, Zhang RM. Transcatheter arterial chemoembolization in combination with radiotherapy for unresectable hepatocellular carcinoma: a systematic review and meta-analysis. *Radiother Oncol* 2009; 92: 184-94.
17. Wang Y, Deng T, Zeng L, Chen W. Efficacy and safety of radiofrequency ablation and transcatheter arterial chemoembolization for treatment of hepatocellular carcinoma: a meta-analysis. *Hepatol Res* 2016; 46: 58-71.
18. Yang HJ, Lee JH, Lee DH, Yu SJ, Kim YJ, Yoon JH, Kim HC, Lee JM, Chung JW, Yi NJ, et al. Small single-nodule hepatocellular carcinoma: comparison of transarterial chemoembolization, radiofrequency ablation, and hepatic resection by using inverse probability weighting. *Radiology* 2014;

 http://dx.doi.org/10.3346/jkms.2016.31.3.403

271: 909-18.
19. Okuda H. Hepatocellular carcinoma development in cirrhosis. *Best Pract Res Clin Gastroenterol* 2007; 21: 161-73.
20. Marrero JA, Lencioni R, Ye SL, Kudo M, Bronowicki JP, Chen XP, Dagher L, Furuse J, Geschwind JF, de Guevara LL, et al. Final analysis of GIDEON (Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma [HCC] and of Its Treatment with sorafenib [Sor]) in >3000 Sor-treated patients (pts): clinical findings in patients with liver dysfunction. *J Clin Oncol* 2013; 31: abstr 4126.