Global Health & Medicine. 2024; 6(6):416-419.
BRIEF REPORT
DOI: 10.35772/ghm.2024.01061

Analysis of recent changes in treatment options for patients with hepatocellular carcinoma using data from a highly comprehensive Japanese national database: Impact of advances in systemic therapy and minimally invasive surgery

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Abstract: In 2011, the Ministry of Health, Labour and Welfare started providing data from the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) for research purposes. The NDB is an exhaustive and valuable database for health policymaking and research. It provides an accurate and most recent visualization of the burden of hepatocellular carcinoma (HCC) in Japan. In this study, we analyzed the trend in HCC treatments using data from the NDB. The NDB data were retrospectively analyzed to calculate the number of patients who were diagnosed with HCC (International Classification of Diseases, version 10 code of C22.0) and underwent treatment from fiscal year (FY) 2016 to 2020. We observed the following trends in HCC treatments during the past 5 years: a slight increase in the number of liver resection (LR) cases (+5.4%), a decrease in the number of radiofrequency ablation cases (−15.2%), and a considerable decrease in the number of transarterial chemoembolization/transarterial embolization cases (−38.2%). However, the number of patients who received systemic therapy dramatically increased from 471 in FY 2016 to 1,584 in FY 2020 (+236%). Among LR cases, there was a remarkable increase in the number of laparoscopic procedures from 1,227 in FY 2016 to 2,057 in FY 2020 (+67.6%). This analysis of a national highly comprehensive database revealed a very recent visualization of HCC management in Japan, wherein the impact of recent advances in systemic therapy and minimally invasive surgery was prominent.

***Keywords*:** hepatocellular carcinoma, systemic therapy, minimally invasive surgery

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer mortality worldwide (*1*). National cancer mortality data in Japan have been reported previously (*2*), showing that the recent decrease in mortality was primarily attributable to stomach, liver, and lung cancers. Furthermore, several Japanese nationwide registries, including the Japan Liver Cancer Association formerly Liver Cancer Study Group of Japan (LCSGJ), have reported a 5-year survival rate of 53.6% (*3,4*). Nevertheless, the nationwide follow-up survey conducted by the LCSGJ was based only on data from approximately 500 specialized member institutions in Japan.

In 2011, the Ministry of Health, Labour and Welfare (MHLW) started providing data from the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) for research purposes (*5*). The NDB is an exhaustive and valuable database for health policymaking and research and provides an accurate visualization of HCC burden in Japan.

We conducted this study to analyze data from the NDB to reveal trends in HCC treatments in Japan.

Materials and Methods

Data source

This repeated cross-sectional study used data from the NDB, which compiles and stores nationwide electronic insurance claims data for all medical goods and

services provided under the national health insurance system (*6*). Researchers can apply to the MHLW for access to NDB data and will be provided with all the data deemed necessary for their study. The MHLW provides accumulated data that contain no personally identifiable information. Details regarding insurance claims and health checkups from all hospitals and clinics in Japan are recorded in the NDB, which includes the demographics, health, diagnosis, medical and dental practice, and drug prescription information of all patients.

For the present study, we requested and obtained data with International Classification of Diseases, version 10 (ICD-10) codes related to liver cancer recorded between April 2015 and September 2021. The MHLW provided 323 million medical records, 130 million diagnostic procedure combination records, and 384,000 prescription records to our research group. The study protocol was reviewed and approved by the ethical committee of the National Center for Global Health and Medicine (approval number 004253).

Patient selection

Because the NDB is one of the most comprehensive national databases in the world and used for health policymaking and research, we did not establish exclusion criteria in this study. However, we excluded certain patients without data regarding the type of treatments from the analysis.

Measurements

Diagnostic data in the NDB are classified using ICD-10 codes. Patients who had C22.0 (liver cell carcinoma) were considered as having HCC. Patients who first had the diagnosis code in the database with a lookback period of ≥ 12 months were considered as having a new diagnosis of HCC.

Treatments

Treatments performed within 180 days after diagnosis were considered treatments for HCC. Liver resection (LR) cases were divided into open liver resection (OLR, procedure code K695) and laparoscopic liver resection (LLR, K695-2). Microwave ablation and radiofrequency ablation (RFA) were considered RFA (K697-2, K697-3). Transarterial embolization (TAE, K615) and transarterial chemoembolization (TACE, G003-3) were considered together. Patients who received sorafenib (medication code 620006778), regorafenib (622225801), lenvatinib (622416001, 622416101), ramucirumab (622417901, 622418001), atezolizumab (622594601, 629900601), bevacizumab (620004872, 620004873), and cabozantinib (622796901, 622797001) were considered as receiving systemic therapy.

Statistical analysis

The number of patients who underwent HCC treatment was analyzed in terms of number and percentage. The number of patients was calculated for each FY, which begins every April, from FY 2016 to 2020. Statistical analyses were conducted using JMP software, version 17.0 (SAS Institute Inc., Cary, NC).

Results and Discussion

We observed a gradual decrease in the number of patients who were diagnosed with HCC and underwent treatment over time (FY 2016, 14,267; FY 2017, 13,845; FY 2018, 13,246; FY 2019, 12,921; and FY 2020, 12,760). The trend of treatments is shown in Table 1 and Figure 1. The number of patients who underwent OLR, RFA, and TACE/TAE decreased over time (FY 2016, 3,449/2,650/6,470; FY 2017, 3,284/2,651/5,809; FY 2018, 3,115/2,437/5,115; FY 2019, 2,993/2,419/4,375; and FY 2020, 2,871/2,248/4,000). Nevertheless, the number of patients who underwent LLR increased (FY 2016, 1,227; FY 2017, 1,548; FY 2018, 1,644; FY 2019, 1,960; and FY 2020, 2,057), and the number of patients who received systemic therapy increased considerably (FY 2016, 471; FY 2017, 553; FY 2018, 935; FY 2019, 1,174; and FY 2020, 1,584).

Given that there was a significant increase in the number of patients who underwent LLR, we further analyzed the combination of treatments in that group. The number of patients who underwent TACE/TAE

Table 1. Trend in treatments for hepatocellular carcinoma

Treatment	2016 (*n* = 14,267)	2017 (*n* = 13,845)	2018 (*n* = 13,246)	2019 (*n* = 12,921)	2020 (*n* = 12,760)
Open liver resection	3,449 (24.2)	3,284 (23.7)	3,115 (23.5)	2,993 (23.2)	2,871 (22.5)
Laparoscopic liver resection	1,227 (8.6)	1,548 (11.2)	1,644 (12.4)	1,960 (15.2)	2,057 (16.1)
Radiofrequency ablation	2,650 (18.6)	2,651 (19.1)	2,437 (18.4)	2,419 (18.7)	2,248 (17.6)
Transarterial chemoembolization/ transarterial embolization	6,470 (45.3)	5,809 (42.0)	5,115 (38.6)	4,375 (33.9)	4,000 (31.3)
Systemic therapy	471 (3.3)	553 (4.0)	935 (7.1)	1,174 (9.1)	1,584 (12.4)

Data are reported as numbers (%).

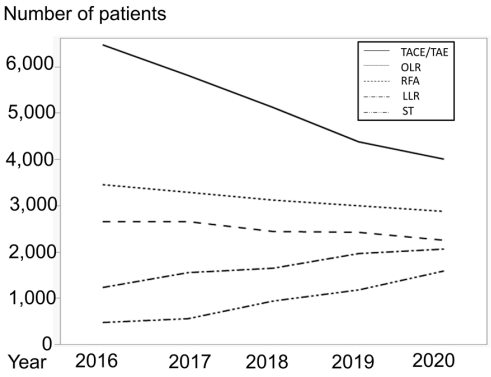

Figure 1. Trend in treatments for hepatocellular carcinoma in the national database. TACE/TAE: transarterial chemoembolization/transarterial embolization; OLR: open liver resection; RFA: radiofrequency ablation; LLR: laparoscopic liver resection; ST: systemic therapy.

and LLR was not significantly different during the study periods (FY 2016, 167; FY 2017, 135; FY 2018, 165; FY 2019, 142; and FY 2020, 144). Moreover, the number of patients who underwent RFA and LLR was not significantly different during the study periods (FY 2016, 50; FY 2017, 57; FY 2018, 76; FY 2019, 68; and FY 2020, 64).

This study demonstrated a gradual decrease in the number of patients who were diagnosed with HCC and underwent treatment over time, which in turn led to a decrease in the number of patients who underwent OLR, RFA, and TACE/TAE. Nevertheless, there was an increase over time in the number of patients who received systemic therapy and those who underwent LLR.

The global incidence of viral hepatitis-related malignancies has decreased since the 2000s because of the implementation of neonatal hepatitis B virus (HBV) vaccination programs and the availability of highly effective antiviral treatments, including nucleoside analogs and direct-acting antiviral agents for HBV and hepatitis C virus (HCV), which have been approved and publicly covered in Japan since 2008. Although several other underlying liver diseases cause HCC, such as alcohol abuse or alcoholic steatohepatitis and nonalcoholic fatty liver disease or nonalcoholic steatohepatitis, which constitutes 17.2% of patients with HCC (*7*), viral hepatitis remains one of the most important causes of HCC. This information is consistent with our finding of the gradual decrease in the total number of patients who were diagnosed with HCC and underwent treatment from FY 2016 to 2020.

Although the LCSGJ reports the number of treated patients with HCC, there is a slight delay because of inherent technical issues for data collection. The most recent report included patients from 2014 to 2015 (*4*). Moreover, the nationwide survey included only some 500 specialized member institutions treating HCC. Therefore, it would be valuable to analyze this sub-real-time exhaustive database to understand the current treatments for HCC.

The number of patients diagnosed with liver cancer recorded in cancer statistics in Japan (*8*), was 42,762 in FY 2016, 39,401 in FY 2017, 38,312 in FY 2018, and 37,296 in FY 2019. These values are comparable with those obtained from the NDB.

Sorafenib was the first approved molecular targeted drug for treating HCC (*9*). In Japan, almost all drugs were generally covered by public health insurance soon after their approval. After the approval of sorafenib in 2009, multiple regimens, including lenvatinib, regorafenib, cabozantinib, and ramucirumab, formed the mainstay of systemic therapies for advanced HCC in Japan (*10*). This may be the reason for the significant increase in the number of patients who received systemic therapy. The most recent nationwide survey conducted by the LCSGJ included patients between 2014 and 2015 (*4*), and 217 patients received systemic chemotherapy as an initial treatment, which is considered equal to systemic therapy in this study. This is probably the first report demonstrating a considerable increase in the number of patients who received systemic therapy.

Another remarkable recent trend was an increase in the number of patients who underwent minimally invasive surgery. Technical developments in LLR have enabled its wide application due to the advantages of a shorter hospital stay and reduced intraoperative blood loss and postoperative pain, especially for minor LR (*11*). This trend is consistent with our finding of an increase in the number of patients who underwent LLR irrespective of the decrease in the number of patients who underwent OLR.

The number of patients receiving TACE decreased during the study period. TACE is the first-line treatment for intermediate-stage HCC (*12*); therefore, this is probably due to the decrease in number of patients with HCC.

Regarding the limitations of our study, the data were retrospectively analyzed, and there were patients with disease overlapping with less common types of primary liver cancer. Although detailed patient characteristics and precise prognosis were unavailable, we could demonstrate the recent dynamic change of daily practice in Japan for HCC treatments based on this comprehensive database. As more promising systemic therapy regimens for HCC are being developed after the introduction of immune-checkpoint inhibitors, a follow-up survey of the NDB after 2020 will be necessary.

In conclusion, according to the national exhaustive database, there was a gradual decrease in the number of patients diagnosed with HCC over time, probably due to the decrease in the incidence of chronic hepatitis B and C infections. On the other hand, the development of treatments has resulted in an increase in the number of patients who underwent systemic therapy and LLR over time.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received August 7, 2024; Revised October 4, 2024; Accepted October 15, 2024.

Released online in J-STAGE as advance publication October 17, 2024.

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