

## Executive Summary

### The Impact of the National Liver Cancer Surveillance Program on the Early detection, Mortality and Medical cost

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#### □ Background

Liver cancer has the second highest mortality rate in Korea. It is the leading cause of death among people in their 40's and 50's, and consequently the socioeconomic loss from liver cancer is high. To reduce this loss, the National Cancer Screening Program has been underway since 2003. However, there has been no evaluation of the effectiveness of the National Liver Cancer Surveillance in reducing the disease burden of liver cancer.

#### □ Objective

This study aims to evaluate the health and economic benefits of implementation of the National Liver Cancer Surveillance for patients at risk of liver cancer (patients with liver cirrhosis, those who are hepatitis B/C antigen-positive, or those with chronic liver disease caused by hepatitis B or C virus). The research objectives are listed below:

- (1) To evaluate the status and diagnostic accuracy of the National Liver Cancer Surveillance.
- (2) To investigate whether the National Liver Cancer Surveillance enables early detection of liver cancer, and improves the survival rate.

- (3) To evaluate changes in healthcare expenses due to liver cancer as a result of the National Liver Cancer Surveillance.

## □ Methods

Customized database (NHIS-2016-1-023) of the National Health Insurance Service (referred to as NHIS hereafter) was used in this study. This study was approved by the Institutional Review Board of the National Evidence-based healthcare Collaborating Agency (NECA IRB16-003).

### 1. Surveillance status

We investigated the surveillance status of patients at risk of liver cancer aged 40 years or above who underwent the National Liver Cancer Surveillance from 2004 to 2015 by linking cancer screening data, health insurance claims data, and eligibility data obtained from the NHIS. We investigated socioeconomic and clinical factors that influence the number of patients who receive surveillance for liver cancer among patients with hepatic disease each year.

### 2. Diagnostic accuracy

We analyzed the diagnostic accuracy of the National Liver Cancer Surveillance by using liver cancer screening data and health insurance claims data collected from 2005 to 2014. Sensitivity, specificity, and positive predictability values (PPV) were analyzed based on patients who were diagnosed with liver cancer within 3, 6, or 12 months after undergoing liver cancer surveillance during the study period.

### 3. Early detection, survival, and medical costs

To investigate the early-stage liver cancer detection rate, survival rate, and health care costs as a result of the National Liver Cancer Surveillance, we analyzed liver cancer screening data, eligibility data, and health insurance

claims data collected from 2004 to 2015.

First, we performed a logistic regression analysis to evaluate differences in the stages of liver cancer according to whether liver cancer patients underwent the National Liver Cancer Surveillance or not in the past two years, where the patients were diagnosed with liver cancer from 2006 to 2010. Since our data did not contain information about cancer staging, it was determined that patients who underwent surgery or radiofrequency ablation (RFA) as the first cancer treatment had early-stage liver cancer.

Second, changes in the survival rate as a result of the National Liver Cancer Surveillance were examined using a log-rank test and Cox proportional hazards model. The survival period was defined as the time from the development of liver cancer to death. A lead-time bias that occurred due to the National Liver Cancer Surveillance was adjusted for in the models.

Third, we analyzed changes in medical costs as a result of the National Liver Cancer Surveillance by using a generalized linear model (GLM) to investigate whether the surveillance program influences liver cancer medical expense.

## □ Results

- High risk group for liver cancer was defined out of the patients who had hepatic disease and were eligible for the National Liver Cancer Surveillance. The annual surveillance rate resulted that individuals undergoing the National Liver Cancer Surveillance have increased from 2.41% in 2004 to 41.16% in 2014.
- The sensitivity, specificity, and PPV of the liver cancer surveillance program for 6 months intervals between surveillance and liver cancer diagnosis in 2014 was 37.0%, 99.8%, and 40.4%, respectively.
- The rate of early-stage liver cancer detection was 1.82 times higher for patients who underwent the liver cancer surveillance once within the 2 years prior to being diagnosed with liver cancer compared with

the non-surveillance group. In addition, patients who received the surveillance more than twice throughout the same period were 2.58 times more likely to be diagnosed with early-stage cancer.

- The risk of mortality for patients who underwent the liver cancer surveillance once within the 2 years prior to being diagnosed with liver cancer was 22.1% lower (HR: 0.779, 95% CI: 0.758-0.800) compared with the patients who did not undergo the surveillance. Moreover, the risk of mortality for patients who received surveillance more than twice throughout the same period was 29.7% lower (HR: 0.703, 95% CI: 0.654-0.756) compared with the patients who did not undergo the surveillance.
- The total cost of medical care for patient diagnosed with early stage liver cancer in the untreated group was 46.6 million Korean won (KRW) (median: 36.12 million KRW) and was 44.97 million KRW (median: 3,560 million KRW) for the surveillance group. It has been found that the total expenditure of medical expenses for patients who did not undergo surveillance was higher than that for patients who underwent surveillance and have been diagnosed with early stage liver cancer.
- The analysis of changes in medical costs related to liver cancer as a result of liver cancer surveillance showed that patients who underwent surveillance spent an average of 68.97 million KRW (median: 1,326 million KRW) per year compared with patients who did not undergo surveillance an average of 100.35 million KRW (median: 1,800 million KRW) per year.

## 1. Surveillance status

Annual surveillance rate of the patients at high risk of liver cancer demonstrated that individuals undergoing the National Liver Cancer Surveillance have increased significantly from 2.41% in 2004 to 41.16% in 2014. We investigated socioeconomic and clinical factors that influence the number of patients who receive surveillance among patients. The surveillance rate of men were 0.878 times lower than that of women and the surveillance rate was lower as the age increased. The surveillance rate of patients with cirrhosis was 0.786 times lower than that of patients without cirrhosis. Compared to National Health Insurance (NHI) district subscribers, NHI

employee subscribers and medical aid recipients had a higher surveillance rate.

## 2. Diagnostic accuracy

In 2014, the sensitivity of the National Liver Cancer Surveillance was 37.0% in 6 months interval between surveillance and cancer diagnosis (25.7% for 12 month ~ 46.3% for 3 month). The specificity was 99.8%, and the PPV was 40.4% in 6 months (43.6% for 12 month ~ 38.6% for 3 month). In addition, there was a significant improvement in diagnostic accuracy throughout the 10 years.

## 3. Early detection, survival rate, and health care costs

The rate of early-stage liver cancer detection was 1.824 (95% CI: 1.73-1.923) times higher among patients who underwent liver cancer surveillance once in a two-year period than among those who did not undergo liver cancer surveillance. The rate of early liver cancer detection was 2.583 (95% CI: 2.269-2.941) times higher among patients who underwent liver cancer surveillance twice or more in the same period than among those who did not undergo liver cancer surveillance. Compared to NHI district subscribers (over 50%), the rate of early liver cancer diagnosis in medical aid recipients were 0.59 times lower and 1.13 times higher in NHI employee subscribers (over 50%). The risk of mortality for patients who underwent the liver cancer surveillance once within 2 years prior to being diagnosed with liver cancer was 22.1% lower (HR: 0.779, 95% CI: 0.758-0.800) compared with the patients who did not undergo surveillance. In addition, the risk of mortality for patients who received surveillance more than twice throughout the same period was 29.7% lower (HR: 0.703, 95% CI: 0.654-0.756) compared with the patients who did not undergo surveillance. After lead-time bias adjustment, patients who underwent liver cancer surveillance once within the 2 years prior to being diagnosed with liver cancer had a 17.8% lower risk of mortality and for patients who received surveillance more than twice throughout the same period had a 23.8% lower risk of mortality.

The total cost of medical care for patient diagnosed with early stage liver cancer in the untreated group was 46.6 million KRW (median: 36.12 million KRW) and was 44.97 million KRW (median: 3,560 million KRW) for the surveillance group. It has been found that the total expenditure of medical expenses for patients who did not undergo surveillance was higher than that for patients who underwent surveillance who have been diagnosed with early stage liver cancer. The changes in medical costs related to liver cancer as a result of the surveillance showed that patients who underwent the surveillance spent an average of 68.97 million KRW (median: 1,326 million KRW) per year compared with patients who did not undergo surveillance an average of 100.35 million KRW (median: 1,800 million KRW) per year. The GLM analysis resulted that patients who underwent surveillance had a significantly lower medical cost per day compared with patients who did not undergo surveillance ( $p < 0.0001$ ).

## □ Conclusions

Although the National Liver Cancer Surveillance has been in effect since 2003, no systematic research has been conducted to evaluate its effectiveness. In this study, data from public sources were used to investigate the status of liver cancer surveillance, diagnostic accuracy, early-stage liver cancer detection rate, and mortality. The results showed that the early liver cancer detection rate was increased, while the mortality was significantly decreased, among patients who actively underwent the National Liver Cancer Surveillance.

However, there is still areas for improvement in the technical and institutional aspects of the liver cancer surveillance to enhance these positive effects. It is necessary to increase the diagnostic accuracy through the quality control of the ultrasound and AFP test used for screening. There is also a limitation that it does not specify the criteria to make comprehensive judgment based on the ultrasound and AFP test at present and it depends on expert opinion. Patients undergoing the National Liver Cancer Surveillance

are those who already have liver disease such as cirrhosis, hepatitis B and hepatitis C, and are regularly undergoing ultrasound examinations at medical institutions, other than the national liver cancer surveillance examinations. Therefore, linking screening from the clinical sector with the National Liver Cancer Surveillance will be critical to increase the effectiveness of the National Liver Cancer Surveillance.

The findings of this study can be used as a basis for the evaluation of the National Liver Cancer Surveillance, and as a useful source of information needed for policy improvement in liver screening programs. This study is limited in that it did not include all liver diseases covered in the National Liver Cancer Surveillance program for the surveillance status analysis, and used information from public sources that had limited clinical parameters. Thus, care should be taken in interpreting the results of the study.

## **Acknowledgement**

This research was supported by National Evidence-based Healthcare Collaborating Agency (NECA) funded by the Ministry of Health and welfare (grant number: NB16-001).

## **Key words**

: Liver Neoplasms, National Liver Cancer Surveillance, Outcomes Research