Incidence and pattern of second primary cancer in patients diagnosed with primary cancer

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Abstract. The long survival of patients with primary cancer increases the chance of such patients developing second primary cancer (SPC). The development of SPC in cancer survivors exerts a large psychological, social and economic burden on patients and their families. The aim of the present study was to assess the risk of cancer survivors developing SPC. The study included patients who had been diagnosed with a first primary cancer in five organs (stomach, colorectum, lung, breast and thyroid), which are the five most common sites of cancer in patients from Korea, at the regional cancer center in Jeonbuk National University Hospital between January 2007 and December 2009. The standardized incidence ratio (SIR) of SPC according to sex and site was calculated from 5,209 patients who were followed up to September 2017. General incidence was acquired from the National Cancer Registry of Republic of Korea. SPC occurred in 6.2% (323/5,209) of patients, and the incidence of SPC among the five major types of cancer was in the order of breast (8.8%, 46/524), colorectum (8.6%, 86/1,003), gastric (6.6%, 89/1,358), thyroid (4.7%, 67/1,437) and lung cancer (3.9%, 35/887). When all SPC sites were included, the SIRs of SPC in patients with colorectal cancer and breast cancer were >1.0 (1.21 and 1.66, respectively). Breast cancer and thyroid cancer exhibited a high site relationship ($P<0.05$), and colorectal cancer had a high site relationship with gastric cancer ($P<0.05$). The present study analyzed the incidence and pattern of SPC in patients with cancer who were diagnosed with primary carcinoma in five organs. The results of the study may be useful for effective follow-up and early detection of SPC in patients with cancer.

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Introduction

Second primary cancer (SPC) is the development of a second, unrelated cancer in a person who has previously experienced the first cancer. SPC in cancer survivors has become relatively common rather than a rare event (1-6). One of the earliest studies of SPC was carried out in 1934 by Bugher (1). Several studies on SPCs were subsequently reported (2-6). The incidence of SPC in cancer survivors are reported in the range of 2 to 17% (2-6) and the incidence of the SPCs is increasing. In a study cohort in Osaka, Japan, the incidence of SPCs within 10 years after first diagnosis was 2.0% during 1966-1989 (7) and the incidence increased to 3.8% during 1985-2005 (5). The lengthening of the survival period of cancer patients and the aging of the population are assumed to contribute to the increased incidence of the SPCs among cancer patients. The overall lifetime probability for developing any type of cancer is 39% in men and 33.9% in women in Korean (8), and 71.5% of the cancer patients in Korea survive for at least 5 years (8). Additionally, the improved detection techniques and screening programs for early detection of cancer can also lead to the increased incidence of SPCs.

The development of SPC in cancer survivors leads to a large psychological, social, and economic burden on patients and their families. Therefore, in the current situation where the occurrence of SPC is increasing, research on SPC in cancer patients may provide insight into the common etiological factors and basic mechanisms of carcinogenesis among cancers and also help manage the follow-up of cancer patients with a greater risk of SPC. However, variability exists among researchers regarding the types and frequencies of SPCs across different cancer populations. Therefore, reaching a consensus through continued data accumulation is essential. This process is expected to produce accurate follow-up guidelines for cancer patients.

In the current study, we studied patients with the five most common cancer in general Koreans. The risk of SPC occurring in this patient group was investigated, and the organs in

which SPC was more prevalent in each primary cancer patient were studied.

Materials and methods

Patient selection and definition of multiple primary cancers. This study included patients who had been diagnosed with a primary cancer in 5 organs (stomach, colorectum, lung, breast, and thyroid), the five most common sites of cancer in Koreans. The patients were diagnosed between January 2007 and December 2009 in the regional cancer institute in Jeonbuk National University Hospital (JNUH). The incidence of SPCs among the subjects was surveyed through to the end of the September of 2017. We obtained the patients' clinical and survival information by reviewing medical records of Jeonbuk National University Hospital (JNUH). According to the criteria established by Warren and Gates, double primary cancer is defined by the following conditions: i) Both the index and secondary tumors must have histological confirmation of malignancy; ii) There must be at least 2 cm of normal mucosa separating the tumors. If the tumors are located in the same region, they must be separated by a time interval of at least five years; iii) The possibility that one tumor is a metastasis of the other must be excluded (9). Both primary and SPCs were confirmed as malignant by histological examination. When selecting SPC cases, we compared the first primary cancer and SPC under microscope and included only those cases in the study that exhibited different histopathological features or immunohistochemical staining, thereby excluding metastasis. Exceptionally hepatic cancer confirmed only by radiologic evaluation was included, because it is clinically accepted as malignancy without histologic diagnosis. Both synchronous and metachronous cancer were included in this study. The criteria to differentiate between synchronous or metachronous cancer was based on the definition of Moertel *et al* (10). Synchronous cancers were defined as those occurring within 6 months of the first primary cancer, while metachronous cancers were defined as those occurring more than 6 months later. The inclusion and exclusion criteria for each type of cancer included in the study are described in detail below.

Inclusion and exclusion criteria for primary cancer patients. SPC is defined as a new malignancy occurring in an individual with a prior cancer diagnosis, which is distinct from the initial cancer and not a recurrence or metastasis. To differentiate SPC from recurrence or metastasis, clinical, radiological, and histopathological assessments are employed. We primarily enrolled patients suspected of SPC based on clinical and radiological evaluations using medical records. Cases suspected of SPC, according to clinical and radiological findings, met the following criteria: i) An interval of at least 6 months between the diagnosis of the initial primary cancer and SPC (latency); ii) a different primary site between the initial cancer and SPC; iii) distinct growth patterns compared to the initial cancer; and iv) non-disseminated primary cancer (11). The diagnosis of SPC was confirmed through histological examination. When histological findings differed from those of the initial cancer, the diagnosis was confirmed as SPC. When differentiation based on hematoxylin and eosin (HE) staining alone was challenging, immunohistochemical (IHC) staining was performed. IHC to distinguish between SPC and metastasis was predominantly performed at the initial diagnosis, with results obtained from medical records. The antibodies used as site-specific markers for major organs are as follows: i) thyroid transcription factor-1 (TTF-1) or thyroglobulin for thyroid cancer; ii) cytokeratin 7 (CK7), cytokeratin 20 (CK20), mucin 5AC (MUC5AC), or mucin 6 (MUC6) for gastric cancer; iii) CK20 or caudal homeobox 2 (CDX2) for colorectal cancer (CRC); iv) TTF-1 for lung cancer; v) GATA-binding protein 3 (GATA3), estrogen receptor (ER), or progesterone receptor (PR) for breast cancer. In the case of squamous cell carcinoma, where organ-specific markers are limited, the inclusion criteria based on clinical and radiological findings are crucial. Cases in which SPC occurred in the same organ were excluded from this study due to difficulties in distinguishing from recurrence or metastasis. Synchronous cancers diagnosed within 2 months of each other were excluded from this study due to challenges in identifying the initial primary cancer.

Statistical analysis. The standardized incidence ratio (SIR), which is the ratio of the observed SPCs to the expected number of SPCs, was evaluated. To calculate the expected number of SPCs, we acquired sex-specific, age-specific, and year of cancer diagnosis-specific incidence rates of the general population in Korea from National Cancer Registry data (12). Next, person-years at risk for each sex, age group, and year of cancer diagnosis group in patients diagnosed with a first primary cancer were calculated. They were calculated from the date of diagnosis of the first primary cancer to whichever of the following occurred first: the date of diagnosis of the SPC, the date of death, or 30 September 2017. Incidence rates in the general population and person-years in patients were multiplied, and all sex, age group, and year of cancer diagnosis expected incidences were summed to obtain the expected number of SPCs. The P-value and 95% confidence intervals (CIs) of SIRs were calculated by Fisher's exact test. The difference in SPC occurrence between the sexes was determined using the χ^2 test or Fisher's exact test. SPSS software (version 26.0; IBM Corporation) was used for statistical analyses, while the SIR P-value and 95% CIs were calculated using the OpenEpi online web calculator (https://www.openepi.com/SMR/SMR.htm). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. A total 5,209 patients diagnosed with first primary cancer from January 2007 to December 2009 were included in this study. The distributions of first primary cancers were as follows: 1,437 thyroid cancer cases (men: 203, women: 1,234), 1,358 gastric cancer cases (men: 912, women: 446), 1,003 colorectal cancer cases (men: 637, women: 366), 887 lung cancer cases (men: 672, women: 215), and 524 breast cancer cases (men: 2, women: 522). During the follow-up period, SPC occurred in 6.2% of the overall group (323/5,209), and the difference in incidence between males and females were minimal (male: 164, 6.8%; female: 159, 5.7%). The incidence of SPC among the five cancer types was in order of breast (8.8%, 46/524), colorectum (8.6%, 86/1,003), gastric (6.6%, 89/1,358), thyroid (4.7%,

67/1,437), and lung cancer (3.9%, 35/887). The median interval from the initial diagnosis of primary cancer to the diagnosis of the second cancer was 32±28.4 months in the primary breast cancer group, followed by 40±25.2 months in the lung cancer group, 47±26.6 months in the stomach cancer group, 48.5±27.6 months in the colon cancer group, and 61±54.3 months in the thyroid cancer group. SPC sites occurring in each organ are summarized in Table SI.

SPCs of the thyroid cancer patients. In the thyroid cancer group, SPC occurred in 15 out of 203 males (7.4%) and 52 out of 1,234 females (4.2%); the incidence of SPC was higher in men compared with women (P=0.047) (Table SI). The observed SPC incidences and expected thyroid cancer incidences according to the cancer incidences of the general population in Korea are summarized in Table SII. The SIR of SPC in patients with primary thyroid cancer was 0.928 [95% confidence interval (95% CI); 0.719-1.179, P=0.591] for all patients, 1.469 (95% CI; 0.822-2.423, P=0.190) for males, and 0.831 (95% CI; 0.620-1.089, P=0.196) for females (Table SIII). The SIR of SPC in thyroid cancer patients was not significantly different from the cancer incidence of the general Korean population. The SIR of the SPC in patients with primary thyroid cancer was analyzed by organ. The two most common SPC sites of the primary thyroid cancer patients were breast and stomach (Table SIV). The breast cancer patients were all women and the SIR was 3.112 (95% CI; 1.901-4.807, P<0.001), which was significantly higher than the breast cancer incidence of the general Korean population (Table SIV). However, the SIR of gastric cancer did not show a significant difference from the gastric cancer incidence of the general Korean population (Table SIV).

SPCs of the gastric cancer patients. In the gastric cancer group, SPC occurred in 63 out of 912 males (6.9%) and 26 out of 446 females (5.8%); there was no statistical difference between SPC occurrence according to sex (P=0.451) (Table SI). The observed SPC incidences and expected gastric cancer incidences according to the cancer incidences of Korean general population are summarized in Table SV. The SIR of SPC in patients with primary gastric cancer was 0.955 (95% CI; 0.767-1.175, P=0.713) for all patients, 0.788 (95% CI; 0.605-1.008, P=0.058) for males, and 1.067 (95% CI; 0.697-1.564, P=0.793) for females (Table SVI). SIR of SPC in primary gastric cancer patients was not significantly different from the cancer incidence rates of the general population of Korea. The two most common SPC sites were colorectum and lung (Table SVII). The SIR for second colorectal cancer was 1.869 (95% CI; 1.221-2.738, P=0.005) for all patients, which was significantly higher than the colorectal cancer incidence of the general Korean population. In males, the SIR was 1.650 (95% CI; 1.021-2.522, P=0.041), which was significantly higher than the colorectal cancer incidence of the general male Korean population. In females, the SIR was 1.508 (95% CI; 0.490-3.520, P=0.480), which did not show statistical difference from the colorectal cancer incidences of the general female Korean population (Table SVII). The SIR of the second lung cancer was not significantly different from the lung cancer incidence of the general Korean population (Table SVII).

SPCs of the colorectal cancer patients. In the colorectal cancer group, SPC occurred in 57 out of 637 males (8.9%) and 29 out of 366 females (7.9%); there was no statistical difference between SPC occurrence according to the sex (P=0.577) (Table SI). The observed SPC incidences and expected colorectal cancer incidences according to the cancer incidences of Korean general population are summarized in Table SVIII. The SIR of SPC measured in patients with primary colorectal cancer was 1.214 (95% CI; 0.971-1.499, P=0.088) for all patients, 0.991 (95% CI; 0.750-1.284, P=0.986) for males, and 1.404 (95% CI; 0.941-2.017, P=0.095) for females (Table SIX). The SIR of SPC in primary colorectal cancer patients was not significantly different from the cancer incidence rates of general Korean population. The two most common SPC sites of primary colorectal cancer patients were stomach and lung (Table SX). The SIR of second gastric cancer was 1.888 (95% CI; 1.169-2.887, P=0.011) for all patients, which was significantly higher than the gastric cancer incidence of the general Korean population. However, when analyzing according to gender, it was not statistically significant. The SIR of the second lung cancer was not significantly different from the lung cancer incidence of the general Korean population (Table SX).

SPCs of the lung cancer patients. In the lung cancer group, SPC occurred in 29 out of 672 males (4.3%) and 6 out of 215 females (2.8%); there was no statistical difference between SPC occurrence according to sex (P=0.318) (Table SI). The observed SPC incidences and expected lung cancer incidences according to the cancer incidences of Korean general population are summarized in Table SXI. The SIR of SPC in patients with primary lung cancer was 0.943 (95% CI; 0.657-1.312, P=0.811) for all patients, 0.797 (95% CI; 0.534-1.144, P=0.249) for males, and 0.787 (95% CI; 0.289-1.712, P=0.722) for females (Table SXII). SIR of SPC in primary lung cancer patients was not significantly different from the cancer incidences of Korean general population. The two most common SPC sites were stomach and liver (Table SXIII). The SIR for second gastric cancer was 1.190 (95% CI; 0.478-2.452, P=0.750) for all patients, which was not significantly different from the gastric cancer incidence of the general Korean population. The SIR of second liver cancer was 2.011 (95% CI; 0.738-4.377, P=0.165) for all patients, which also did not show significant difference from the liver cancer incidence of the general Korean population (Table SXIII).

SPCs of the breast cancer patients. In the breast cancer group, SPC occurred in 0 out of 2 males (0%) and 46 out of 522 females (8.8%); there was no statistical difference between SPC occurrence according to sex (P=0.660) (Table SI). The observed SPC incidences and expected breast cancer incidences according to the cancer incidences of the general Korean population are summarized in Table SXIV. The SIR of SPC in patients with primary breast cancer was 1.660 (95% CI; 1.215-2.214, P=0.002) for all patients and 1.703 (95% CI; 1.247-2.2272, P=0.001) for females (Table SXV). The SIR of SPC in primary breast cancer patients was significantly higher than the cancer incidence of the general Korean population. The two most common SPC sites were thyroid and stomach (Table SXVI). All the SPCs of the primary breast cancer

patients were in female patients. The SIR of second thyroid cancer was 4.013 (95% CI; 2.544-6.022, P<0.001) for all patients and 2.454 (95% CI; 1.556-3.682, P<0.001) for females; both SIR was significantly higher than the thyroid cancer incidence of the general and female Korean population. The SIR of second gastric cancer did not show statistical difference from the gastric cancer incidence of the general Korean population (Table SXVI).

Discussion

In this study, we investigated the SPCs of cancer patients that were diagnosed through 2007 to 2009 at the regional cancer center in JNUH; the patients were followed until 2017. During the follow-up, 6.2% cancer patients developed SPC. This result was similar to a previous study that reported an incidence of 5.8% in a cohort of Japanese cancer patients during 2000-2015 (13). The incidence of SPCs of cancer survivors is increasing. Three reports investigated the incidence of SPCs of the same regional population from 1966 to 2015 and found that the incidence increased from 2.0 to 5.8% during the nearly 50 years of duration (5,7,13). One of the reasons for this increase in incidence is thought to be the increase in the survival rate of cancer patients. The 5-year survival rate of the cancer patient has dramatically increased from 42.9% in 1993-1995 to 70.7% in 2015-2019 (14). In 2015-2019, the 5-year survival rate of Korean cancer patients was 70.7% in both sexes, 64.5% in men, and 77.3% in women (14). This increase in the survival rate of cancer patients likely has a significant impact on the aging of cancer patients who survive. Thus, the elderly population will include a large number of cancer survivors and developing SPC will not be an uncommon event. Therefore, it is necessary for clinicians to recognize that the occurrence of SPC in cancer patients is increasing and refer to it in follow-up methods and strategies.

Given the increasing incidence of SPC, research on SPC is being actively conducted. Researchers are exploring various aspects of SPC, including its underlying mechanisms, risk factors, and potential interventions, to better understand and address this growing clinical concern. A study conducted on breast cancer survivors within the Kaiser Permanente cohort revealed that these individuals have a significantly higher risk of developing SPCs compared to the general population (15). Another study examined the incidence and outcomes of second primary colorectal cancer using data from the Surveillance, Epidemiology, and End Results (SEER) Program database. It found that although the overall incidence of second primary colorectal cancer has decreased over time, the risks remain substantial for survivors of initial primary gastrointestinal cancers (16).

In this study, we observed a strong relationship between breast and thyroid cancer. The thyroid cancer patients of this study showed a 3.112-fold increased risk (95% CI; 1.901-4.807, P<0.001) for developing breast cancer compared with the normal population. The breast cancer patients have a 4.013-fold increased risk (95% CI; 2.544-6.022, P<0.001) for developing thyroid cancer. The breast and thyroid are organs that are commonly regulated by hypothalamic-pituitary axis. Previous studies already reported the strong association between thyroid and breast carcinoma (17,18). While the mechanism of the association is not fully understood, there are some suggested explanations for the strong relationship between the two cancers. First, dietary iodide deficiency as well as intracellular iodide deficiency caused by mislocalization of iodine transporter is a well-established risk factor for developing thyroid cancer (17). Additionally, a previous study reported that breast cancer cells also show mislocalization of iodine transporters from the basolateral membrane to the intracellular region, but this does not occur in normal breast cells (19). This indicates that altered iodine metabolism may contribute to the development of not only thyroid cancer but also breast cancer (17). Another study showed that iodine deficiency can cause a hyperestrogenic state and an increased risk of breast cancer (20).

A second explanation is that the sex hormones during a woman's menstrual cycle and pregnancy can affect the development of not only breast cancer but also thyroid cancer. A previous study showed that the estradiol enhances the proliferation of estrogen receptor-positive papillary thyroid carcinoma (21). Other studies reported that the estrogen and progesterone receptor are expressed in 66.5 and 75.8% of papillary thyroid carcinoma cases, respectively (17,22). The expressions of estrogen and progesterone receptor are significantly associated with larger tumor size and local metastasis (22). Thus, iodine intake and transport and sex hormones represent common factors in the development of both thyroid and breast cancer. Factors that are associated with the initiation of thyroid cancer, such as low dietary iodine and mislocalization of iodine transporter, can increase the risk for breast cancer. Additionally, factors that play key roles in breast cancer such as estrogen are also reported to affect the development of thyroid cancer. These findings may explain the significant association of breast and thyroid cancer observed in the present study. While further clinical studies are needed, based on these results, new screening strategies can be developed in breast and thyroid cancer patients to enhance the early diagnosis of SPC.

However, there are also differences when compared to earlier reports on SPCs. In our study, primary thyroid cancer patients showed the highest incidence of secondary primary cancers as breast cancer. However, previous study reporting on SPCs in primary thyroid cancer patients have indicated that hematologic cancers as having the highest relative risk associated with radioactive iodine treatment in differentiated thyroid cancer survivors, which differs from our findings where breast cancer was the most prevalent secondary malignancy (23). Additionally, there was a study that reported differences when comparing our results with the findings of an analysis on SPCs in primary breast cancer patients. In our study, primary breast cancer patients showed the highest incidence of SPCs as thyroid cancer. This finding contrasts with the previous study, which reported that hematologic cancers, such as acute myeloid leukemia (AML), had the highest incidence among SPCs in breast cancer survivors (24). The differences between our results and the findings reported in the attached studies could be attributed to variations in the characteristics of the cohorts studied and the treatment methods used. These discrepancies suggest that additional research is needed to better understand the factors influencing the development of SPCs in these patient populations.

Another notable finding from our current study is that gastric cancer and colorectal cancer have significant associations with each other. The most common SPC of gastric cancer patients was colorectal cancer and vice versa. The gastric cancer patients had a 1.869-fold increased risk (95% CI; 1.221-2.378, P=0.005) for developing colorectal cancer compared with the general population. Colorectal cancer patients showed a 1.888-fold increased risk (95% CI; 1.169-2.887, P=0.011) for developing gastric cancer compared with the general population. The strong association between gastric cancer and colon cancer observed in this study has also been reported in several previous studies (25-28). In the previous reports, the incidence of SPCs of gastric cancer patients ranged from 1.1 to 4.7% and the most frequent SPC was colorectal cancer (25,26). Gastric cancer was reported to be the most frequent SPC of colorectal cancer patients (29-32). Although the incidence of gastric and colorectal cancer is high in East Asian countries, the association of gastric and colorectal cancer observed in this study and previous studies is not fully explained. Previous reports indicated that the connection between gastric and colorectal cancer may be partially due to the germline loss of MSH2 expression (33). The proportion of patients with loss of MSH2 expression was higher in colorectal cancer patients having gastric cancer as SPC than patients with colorectal cancer without gastric cancer (33). Other studies reported that the well-known tumor suppressor p53 might also play a role in the development of gastric and colorectal double primary cancer (34). *TP53*, which is the gene encoding p53, is located on the short arm of chromosome 17 (35). A previous study reported that the translocation of chromosome 17 and/or TP53 translocation was statistically increased in patients with double primary cancer of gastric and colorectal cancer compared with those with a single cancer (34). Microsatellite instability is also suggested to be involved in the occurrence of the gastric and colorectal double primary cancer. Previous studies showed that microsatellite instability is more commonly observed in multiple primary gastric and colorectal cancer patients than single cancer patients (32,36). Data regarding MSH2, p53, and microsatellite instability were not available in the present study, and further study is necessary to identify the factor underlying the strong association between gastric and colorectal cancer observed in this study. Clinicians should be aware of the strong relationship between stomach and colorectal cancer and should carefully conduct screening tests for the gastric and colorectal cancer during the follow-up period for patients with primary gastric or colorectal cancer.

In our study, the most common SPC in primary gastric cancer patients was colon cancer. However, there were studies that reported results different from ours. One study analyzed 225,973 primary gastric cancer patients in Republic of Korea also found colorectal cancer to be the most common SPC, similar to our findings (37). However, in terms of SIR, the highest risks in male were for breast and esophagus cancers, while in female, the highest were for esophagus and tongue cancers (37). Another study analyzed based on the SEER 13 database of U.S. primary gastric cancer patients indicated a higher risk of thyroid cancer and pancreatic cancer in these patients (38). These differences could be attributed to various factors, including genetic background, environmental influences, and treatment methods. Further research is needed to understand the underlying causes of these discrepancies.

In this study, we examined the incidence rate of SPC according to the type of primary cancer. As a result, we found associations between thyroid and breast along with stomach and colon cancers. However, it is well known that multiple factors are involved in the occurrence of SPCs (39). Among these, there have been several reports indicating that the use of cytotoxic drugs is particularly involved in the occurrence of SPCs (40,41). Additionally, it has been reported that various environmental factors, particularly smoking (42), alcohol consumption (43), and red meat intake (44), can play significant roles in the occurrence of SPCs. However, this study did not analyze these factors, which is one of the limitations of this research.

In conclusion, this study showed that among cancer survivors in Korea, 6.2% (323/5,209) developed SPCs. The incidence for developing SPCs is increasing. While this study showed no significant difference in the risk of developing SPC among patients with the five most common cancer types in Korea compared with the general population, some specific relationships were observed between primary cancer and SPC site. A strong association was observed between breast and thyroid cancer and between stomach and colorectal cancer. The exact mechanism for the strong relationships between cancers occurring in these organs is still unknown and further research is needed. The results of this study are expected to serve as useful information for effective follow-up and early detection of SPC in cancer patients.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

JJS and KMK collected and analyzed the data, drew the tables and contributed in writing the manuscript. JJS, KMK and JHL performed the statistical analysis. JHL, KMK and MJC confirm the authenticity of all the raw data. WSM, MJC, ARA, HSP and KYJ participated in the design of the study, gave administrative or logistical support for this study, and reviewed drafts of the paper. All the authors agreed with the conclusions of this study. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of Jeonbuk National University Hospital (IRB number,

CUH 2019-04-053), including a waiver of consent for the patients' participation due to its retrospective nature, and was conducted in accordance with The Declaration of Helsinki.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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