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Original Article

Pulmonary Metastasectomy in Colorectal Cancer: A Population-Based Retrospective Cohort Study Using the Korean National Health Insurance Database

Woo Sik Yu[1], **Mi Kyung Bae**[2], **Jung Kyu Choi**[3], **Young Ki Hong**[4], **In Kyu Park**[5]

[1]Department of Thoracic and Cardiovascular Surgery, Ajou University School of Medicine, Suwon, [2]Department of Thoracic and Cardiovascular Surgery, National Health Insurance Service Ilsan Hospital, Goyang, [3]Institute of Health Insurance and Clinical Research, National Health Insurance Service Ilsan Hospital, Goyang, [4]Department of General Surgery, National Health Insurance Service Ilsan Hospital, Goyang, [5]Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

Purpose The study aimed to investigate the current status and prognostic factors for overall survival in patients who had undergone pulmonary metastasectomy for colorectal cancer.

Materials and Methods The data of 2,573 patients who had undergone pulmonary metastasectomy after surgery for colorectal cancer between January 2009 and December 2014 were extracted from the Korean National Health Insurance Service claims database. Patient-, colorectal cancer–, pulmonary metastasis–, and hospital-related factors were analyzed using the Kaplan-Meier method, log-rank test, and Cox proportional hazards analysis to identify prognostic factors for overall survival after pulmonary metastasectomy.

Results The mean age of the patients was 60.9±10.5 years; 66.2% and 79.1% of the participants were male and had distally located colorectal cancer, respectively. Wedge resection (71.7%) was the most frequent extent of pulmonary resection; 21.8% of the patients underwent repeated pulmonary metastasectomies; 73% of pulmonary metastasectomy cases were performed in tertiary hospitals; 53.9% of patients were treated in Seoul area; 82% of patients received chemotherapy in conjunction with pulmonary metastasectomy. The median survival duration was 51.8 months. The 3- and 5-year overall survival rates were 67.7% and 39.4%, respectively. In multivariate analysis, female sex, distally located colorectal cancer, pulmonary metastasectomy-only treatment, and high hospital volume (> 10 pulmonary metastasectomy cases/yr) were positive prognostic factors for survival.

Conclusion Pulmonary metastasectomy seemed to provide long-term survival of patients with colorectal cancer. The female sex, presence of distally located colorectal cancer, and performance of pulmonary metastasectomy in high-volume centers were positive prognostic factors for survival.

Key words Survival, Prognosis, Lung, Metastasectomy, Colorectal neoplasms

Introduction

In Korea, as in other countries worldwide, colorectal cancer (CRC) constitutes a significant public health burden. In 2017, 28,111 newly diagnosed CRC cases were observed (12% of the total cancer cases). Especially, CRC was the second most frequently diagnosed cancer and the third most frequent cause of cancer-related death in Korea [1]. Lung is the most common extra-abdominal metastatic site of CRC development. In a French population-based study, 11% of patients with metastatic CRC had undergone synchronous pulmonary metastases, and the 5-year cumulative risk of developing metachronous pulmonary metastases after curative resection of CRC was 5.8% [2].

Pulmonary metastasectomy (PM) is considered a beneficial intervention for selected patients with CRC with limited metastases, and has been performed in routine clinical practice for decades. The 5-year overall survival rate after PM is estimated to be 30%-50% [3-5]. Several prognostic factors were proposed in earlier studies with most of them being single-center studies that included a small number of patients; only a few studies included a large number of patients [3,5-7].

The government of the Republic of Korea is operating the National Health Insurance Service (NHIS), a mandatory universal health insurance system, which covers more than 98% of the Korean population. All claims data are centralized under the NHIS, and the database provides a unique

Correspondence: In Kyu Park
Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel: 82-2-2072-2342 Fax: 82-2-764-3664 E-mail: ikpark@snu.ac.kr
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*Woo Sik Yu and Mi Kyung Bae contributed equally to this work.

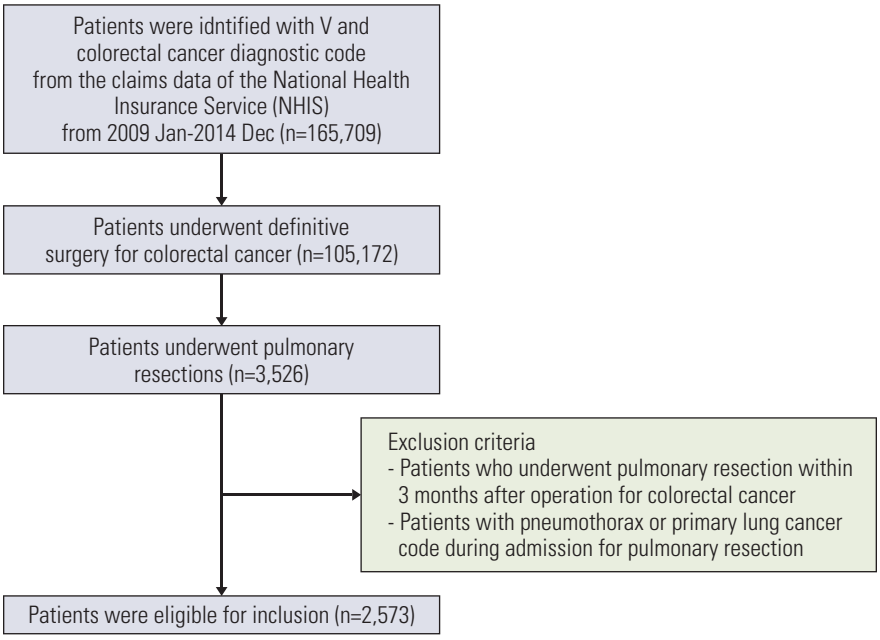

Fig. 1. Diagram of study cohort selection process.

nationwide source of information on specific diseases and treatments [8].

This study aimed to describe the patient and treatment characteristics and the survival outcomes, and to investigate the prognostic factors of PM for CRC cases, which were recorded in the Korean NHIS database.

Materials and Methods

1. Participants

We used customized data recorded by the NHIS (NHIS-2016-1-041) between January 2009 and December 2014. Among the patients registered as V codes in the NHIS with the CRC codes (C18, C19, and C20), we identified patients who underwent an operation for CRC, using operation codes listed in S1 Table. In Korea, the V code is a special code for patients with International Classification of Diseases, 10th revision cancer and was established by the Korean Ministry of Health and Welfare in 2008. We identified patients who underwent pulmonary resection after CRC surgery by using operation codes (O1401-2, O1410, 1421-4, and O1431-2) (S2 Table). We excluded patients with pneumothorax (J93) and/or primary lung cancer (C34) during hospitalization for pulmonary resections to exclude the causes of pulmonary resection besides pulmonary metastasis. To identify patients with metachronous pulmonary metastasis, we excluded those who received pulmonary resection within 3 months after CRC (Fig. 1).

2. Data collection

All data were collected from the NHIS claims database. Demographic data included sex, age at the time of pulmonary resection, income level, and type of health insurance. The income level was grouped into low (0-8), medium (9-16), and high (17-20), using 20-quantile data from the NHIS. The cases of surgery for CRC were categorized to distal (QA921-6) and proximal (QA671-3 and QA679) resection by using the operation code (S1 Table). Pre- and postoperative treatments were identified with chemotherapy (KK059, KK151-156, and KK158) or radiotherapy (HD051-9, HD061, HD071-3, HD080-093, HD110-5, HD211-2, HD121, and HZ271) codes within 3 months before/after the operation. Data related to PM included the time to PM, chemotherapy in conjunction with PM, the extent and number of lung resections, number of PM, type of hospital, and annual hospital procedure volume of PM for CRC cases. The time to PM was defined as the interval between the date of operation for CRC and that of the first PM performance. We measured the time to PM instead of the disease-free interval because the NHIS claims data only provide information regarding the time of intervention. Chemotherapy in conjunction with PM were identified according to the chemotherapy codes and included in the analysis when they occurred within 3 months before and after pulmonary resection. When the patient had more than two operation claims data on the same day, the extent

and number of pulmonary resections were classified based on more extended resection and as ≥ 2, respectively. Moreover, the operation code for "wedge resection, two or more (O1402)" was classified as indicating ≥ 2 pulmonary resections. The number of PM performances was defined as the sum of the pulmonary resections performed on different dates. Overall survival was measured from the date of PM to that of death or last follow-up. The follow-up period ended on December 31, 2015.

3. Statistical analysis

Statistical analyses were performed using SAS ver. 9.2 (SAS Institute Inc., Cary, NC). The survival analysis was performed using the Kaplan-Meier method, and comparisons were made using the log-rank test. Cox proportional hazard analysis was performed to identify the prognostic factors. Variables with $p \leq 0.05$ were included in the multivariable analysis. The level of significance was set at $p < 0.05$.

Results

1. Baseline characteristics of patients with CRC

We identified 165,709 patients who registered with V codes in the NHIS (indicating CRC cases) during the study period. Then, we extracted the data of 105,172 patients who underwent an operation for CRC. Among them, 3,526 patients underwent pulmonary resection. After excluding patients who underwent pulmonary resection within 3 months after CRC resection, the data of 2,573 patients (2.45% of those who underwent curative surgery for CRC) were analyzed (Fig. 1). The mean age of the patients was 60.9±10.5 years and 66.2% of the study population were male. The baseline characteristics of the patients are summarized in Table 1. Low anterior resection was the commonest operation for CRC cases, and 79.1% of patients had distally located tumors. Most of the patients received adjuvant treatment after CRC surgery (99.5%), which implied that they had pathologically proven advanced CRC.

2. Characteristics associated with pulmonary resection

The characteristics associated with pulmonary resection are summarized in Table 2. Approximately 85% of patients underwent PM within 36 months after CRC surgery, and those with time to PM between 12 and 36 months accounted for 57.6% of this population. Approximately 82% of patients received chemotherapy before and/or after pulmonary resection. Wedge resection (71.7%) was the most frequently performed procedure. Ninety-three point one percent of the patients underwent a single pulmonary resection during each PM. 21.8% of the patients underwent repeated PM (2 episode, 15.6%; ≥ 3 episode, 6.2%). 73% and 53.9% of the resection cases and total procedures were performed in tertiary hospitals and in hospitals located in Seoul city, respectively. Nine hospitals, which performed more than 10 PMs

Table 1. Baseline characteristics of the patients

Variable	No. (%)[a]
Sex	
Male	1,601 (62.2)
Female	972 (37.8)
Age (yr)	
< 39	119 (4.6)
40-49	351 (13.6)
50-59	762 (29.6)
60-69	881 (34.2)
70-79	439 (17.1)
≥ 80	21 (0.8)
Income level, quantiles	
High (17-20)	969 (37.7)
Medium (9-16)	1,021 (39.7)
Low (0-8)	583 (22.7)
Type of health insurance	
National health insurance (self-employed)	658 (25.7)
Health insurance (employed)	1,752 (68.3)
Medical aid	155 (6.0)
Missing value	8
Operation for colorectal cancer	
1. Anterior resection of rectal and sigmoid	619 (24.1)
2. Low anterior resection of rectal and sigmoid	1,276 (49.6)
3. A-P resection of rectal and sigmoid (miles operation)	127 (4.9)
4. Rectal and sigmoid resection (abdominal pull through)	1 (0.0)
5. Total coloproctectomy with ileostomy	6 (0.2)
6. Total coloproctectomy with pouch anastomosis	6 (0.2)
7. Colectomy (right or left hemicolectomy)	466 (18.1)
8. Total colectomy	9 (0.4)
9. Colectomy (segmental resection)	24 (0.9)
10. Hartmann's operation	39 (1.5)
Location of colorectal cancer	
Distal (1, 2, 3, 4, 5, 6)	2,035 (79.1)
Proximal (7, 8, 9, 10)	538 (20.9)
Type of treatment for colorectal cancer	
Surgery only	3 (0.1)
Preoperative treatment+surgery	11 (0.4)
Surgery+postoperative treatment	841 (32.7)
Preoperative treatment+surgery+postoperative treatment	1,718 (66.8)

[a]Missing values are excluded.

Table 2. Characteristics of pulmonary metastasectomy

Variable	No. (%)[a]
Time-to-PM (mo)	
< 12	703 (27.3)
12-36	1,482 (57.6)
> 36	388 (15.1)
Type of treatment for pulmonary metastasis	
PM only	461 (17.9)
Chemotherapy+PM	350 (13.6)
PM+chemotherapy	844 (32.8)
Chemotherapy+PM+Chemotherapy	918 (35.7)
Extent of lung resection	
Wedge resection	1,844 (71.7)
Segmentectomy	193 (7.5)
Lobectomy	530 (20.6)
Pneumonectomy	6 (0.2)
No. of lung resection(s)	
1	2,395 (93.1)
≥ 2	178 (6.9)
Episode of PM	
1	2,012 (78.2)
2	427 (16.6)
≥ 3	134 (5.2)
Type of hospital	
Private clinic	0
Hospital	1 (0)
Secondary hospital	622 (27.0)
Tertiary hospital	1,685 (73.0)
Missing value	265
Annual hospital PM volume	
≤ 5	742 (32.2)
6-10	296 (12.8)
11-20	435 (18.9)
> 20	835 (36.2)
Missing value	265
Hospital location	
Seoul	1,243 (53.9)
Incheon/Gyeonggi	415 (18.0)
Chungbuk	18 (0.8)
Daejeon/Sejong/Chungnam	65 (2.8)
Jeonbuk	64 (2.8)
Gwangju/Jeonnam	114 (4.9)
Daegu/Gyeongbuk	124 (5.4)
Busan/Ulsan/Gyeongnam	220 (9.5)
Gangwon	38 (1.7)
Jeju	7 (0.3)
Missing value	265

PM, pulmonary metastasectomy. [a]Missing values are excluded.

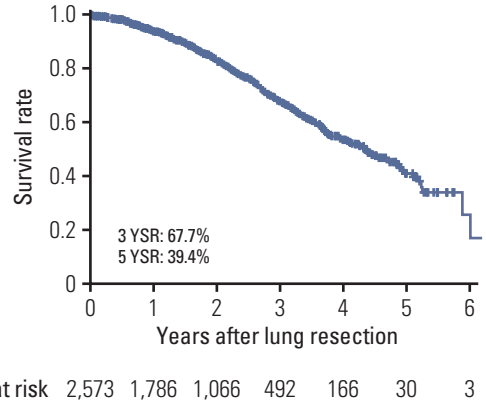

Fig. 2. Kaplan-Meier curve of overall survival after pulmonary metastasectomy in colorectal cancer. YSR, year survival rate.

per year, performed approximately 55% of the total number of PMs.

3. Survival and prognostic factors

The median survival time was 51.8 months, and the 3-year and 5-year overall survival rates were 67.7% and 39.4%, respectively (Fig. 2). In univariate analysis, sex, age, location of CRC, treatment method for lung metastasis, repeated PM (three or more PMs), type of hospital, annual hospital procedure volume, and hospital location were significant prognostic factors (Table 3). In the multivariate analysis, female sex, CRC distal location, surgery-only treatment, and larger hospital procedure volume were positive prognostic factors for survival after PM, but not for repeated PM (Table 4).

Discussion

To the best of our knowledge, this study comprised the largest number of patients who underwent PM for metastatic CRC. In this study, we examined the data of 2,573 patients who underwent PM out of 105,172 patients who underwent curative resection for CRC. Approximately 2.5% of those who underwent CRC surgery also underwent PM. The 5-year overall survival rate after PM was 39.4%, which was consistent with the outcomes reported in previous studies [3-5]. In this study, female sex, distal location of primary CRC, larger hospital volume, and surgery-only treatment were positive prognostic factors for survival after PM in patients with CRC.

The International Registry of Lung Metastases study reported favorable long-term outcomes (5-year overall survival rate, 36%) after PM in 5,206 cases with various types of cancer in 1997 [9]. After the publication of those results,

Table 3. Univariate analysis for the prognostic factors of overall survival after pulmonary metastasectomy in colorectal cancer

Variable	HR	95% CI	p-value
Sex			
Male	1		
Female	0.783	0.655-0.937	0.008
Age (yr)			
< 65	1		
≥ 65	1.252	1.057-1.483	0.009
Income level[a], quantiles			
High (17-20)	1		
Medium (9-16)	0.933	0.768-1.133	0.49
Low (0-8)	1.115	0.898-1.384	0.33
Type of health insurance[a]			
Medical aid	1		
Health insurance (self-employed)	0.775	0.539-1.116	0.17
Health insurance (employed)	0.782	0.558-1.096	0.15
Location of colorectal cancer			
Distal (1, 2, 3, 4, 5, 6)	1		
Proximal (7, 8, 9, 10)	1.357	1.120-1.644	0.002
Treatment for colorectal cancer			
Surgery only	1		
Preoperative treatment+surgery	0.474	0.053-4.248	0.50
Surgery+postoperative treatment	0.443	0.062-3.166	0.42
Preoperative treatment+surgery+postoperative treatment	0.401	0.056-2.861	0.36
Time-to-PM (mo)			
< 12	1		
12-36	0.859	0.717-1.029	0.10
> 36	1.112	0.803-1.540	0.52
Treatment for pulmonary metastasis			
PM only	1		
Preoperative chemotherapy+PM	2.921		< 0.001
PM+postoperative chemotherapy	3.097	1.755-5.465	< 0.001
Preoperative chemotherapy+PM+postoperative chemotherapy	4.215	2.650-6.705	< 0.001
Extent of lung resection			
Wedge resection	1		
Segmentectomy	0.962	0.696-1.331	0.82
Lobectomy	0.987	0.802-1.214	0.90
Pneumonectomy	1.343	0.335-5.386	0.68
No. of lung resections			
1	1		
≥ 2	1.222	0.902-1.655	0.20
Episode of PM			
1	1		
2	0.941	0.758-1.168	0.58
≥ 3	0.678	0.479-0.960	0.029
Type of hospital			
Hospital/Secondary hospital	1		
Tertiary hospital	0.775	0.638-0.942	0.011

(Continued to the next page)

Table 3. Continued

Variable	HR	95% CI	p-value
Annual hospital procedure volume			
≤ 5	1		
6-10	0.869	0.661-1.143	0.32
> 10	0.564	0.464-0.687	< 0.001
Hospital location			
Seoul	1		
Others	1.256	1.028-1.534	0.026

CI, confidence interval; HR, hazard ratio; PM, pulmonary metastasectomy. [a]At the time of pulmonary resection.

Table 4. Multivariate analysis of the prognostic factors for overall survival after pulmonary metastasectomy in colorectal cancer

Variable	HR	95% CI	p-value
Sex			
Male	1		
Female	0.701	0.566-0.868	0.001
Age (yr)			
< 65	1		
≥ 65	1.178	0.960-1.446	0.12
Location of colorectal cancer			
Distal (1, 2, 3, 4, 5, 6)	1		
Proximal (7, 8, 9, 10)	1.491	1.187-1.872	0.001
Treatment for pulmonary metastasis			
PM only	1		
Chemotherapy+PM	2.139	1.111-4.119	0.023
PM+chemotherapy	2.478	1.510-4.065	0.001
Chemotherapy+PM+chemotherapy	3.939	2.415-6.427	< 0.001
Episode of PM			
1	1		
2	1.142	0.888-1.467	0.30
≥ 3	0.829	0.563-1.220	0.34
Type of hospital			
Hospital+general hospital	1		
Advanced general hospital	0.843	0.653-1.089	0.19
Annual hospital PM volume			
≤ 5	1		
6-10	1.032	0.742-1.435	0.85
> 10	0.645	0.508-0.818	0.001
Hospital location			
Seoul	1		
Others	0.889	0.700-1.129	0.34

CI, confidence interval; HR, hazard ratio; PM, pulmonary metastasectomy.

the number of performed PMs in cases of CRC and other malignancies increased [10]. Numerous studies have reported favorable outcomes after PM in patients with CRC. Especially, Iida et al. [5] reported the survival outcomes of 1,030 patients who received PM for CRC, and the estimated overall survival was 53.5% and 38.4% at 5 and 10 years, respectively. The National Comprehensive Cancer Network (NCCN) guidelines for colon and rectal cancer recommend that cases of patients with resectable lung metastases in isolation or together with liver metastases should be considered for

metastasectomy [11]. Nonetheless, the evidence of the prognosis after PM is insufficient, and the role of PM remains controversial. Most of the previous studies were not randomized-controlled trials, had pervasive selection bias, and did not have well-matched control groups [12]. Therefore, the multicenter randomized clinical trial study (PulMiCC) was performed, and the results were reported recently [13,14]. The study was completed early because of poor recruitment, as it enrolled only 93 patients (18% of the planned sample size) in total. There was no survival difference between the PM and control groups (5-year survival rate: PM group, 36.4%; control group, 29.6%). Moreover, the study was unable to reach the desired statistical endpoints and answer the question regarding the value of performing PM. Given the lack of randomized studies, a population-based study may provide insights into the current practice, the role of PM, and the prognostic factors of PM in CRC cases.

Distal colon cancer accounted for 79.1% of the study population and distal colon cancer was associated with a better survival outcome compared with proximal colon cancer in multivariate analysis. In a recent population-based study, distal colon cancer (left colon and rectum) accounted for 62% of total primary CRC resection cases in Korea [15]. Rectal cancer is more frequently associated with lung metastasis compared to colon cancer [2,16], and the findings of this study supported this relationship. This is frequently explained by the different venous drainage of the rectum and colon. Rectal cancer can drain through the iliac system, which facilitates access to the lung rather than the liver. Conversely, most of the colon cancer lesions drain primarily through the liver via the portal vein and, then, enter the lung [17]. Thus, pulmonary metastasis from proximal colon cancer suggests a more advanced disease stage than that from rectal cancer and, therefore, is associated with worse survival rates. However, the aforementioned rationale cannot fully explain the poor prognosis of patients with proximal colon cancer. Venous drainage of only a part of the rectum (low-lying rectum) occurs through the iliac vein. Therefore, besides the venous drainage, the differences in molecular and pathological characteristics reported between proximal and distal colon cancer cases can result in different clinical features, which could be responsible for the worse survival in proximal colon cancer [18,19].

Retrospective studies have shown that chemotherapy is associated with better survival rates in patients who have undergone PM [20,21]. Moreover, the NCCN guidelines recommend the performance of perioperative chemotherapy, especially in chemotherapy naïve patients [11]. Contrarily, perioperative chemotherapy was associated with poor survival in this study. The NHIS claims database does not have detailed information regarding the disease status, such as the tumor size, number of metastases, carcinoembryonic antigen level, and pathologic results. Thus, the effect of selection bias could not be controlled. The patients who did not receive perioperative chemotherapy might have had low disease burden, such as smaller and fewer metastases. Therefore, in this study, perioperative chemotherapy might be a confounding factor.

Previous nationwide or multicenter studies did not find any significant survival differences by sex with regard to PM for CRC [2,5,22]. In this study, however, female sex was associated with better survival outcomes in the multivariate analysis. The sex differences in survival after PM in patients with CRC may reflect a higher comorbidity burden in men, at least with respect to a higher incidence of smoking and alcohol consumption. Population-based studies included patients with CRC in Sweden and Korea, and showed better overall survival rates in female than in male participants [23,24].

In this study cohort, 99.5% of the patients received adjuvant treatment for primary CRC. In cases of patients with CRC, adjuvant treatment can be considered for those with stage IIa (T3N0M0; cases of high-risk features) and stage IIb/c CRC and can also be routinely recommended for those with more advanced stages [11]. The extremely high rate of adjuvant treatment in this cohort suggested that pulmonary metastasis develops in patients indicated for adjuvant chemotherapy. The proportions of patients with advanced CRC who required adjuvant chemotherapy were also high in previous studies. Especially, Blackmon et al. [25] stated that approximately 93% of their participants had stage II CRC or higher. Kim et al. [6] stated that 85.3% of their patients had yp or p stage II and 92.2% of them received adjuvant chemotherapy. Additionally, the patients who received adjuvant treatment may undergo chest computed tomography examination. The latter is recommended for those with stage II CRC or higher and could result in early detection of asymptomatic pulmonary metastasis, thus leading to the performance of more PMs. It is uncertain whether the extremely high rate of adjuvant chemotherapy in this cohort was related with the aggressive application of adjuvant chemotherapy in Korea. The study cohort consisted of highly selected patients (i.e., only 2.45% of patients who have undergone surgery for CRC surgery in Korea), and selection bias could not be ruled out.

In Korea, approximately 55% of the performed PMs in patients with CRC were conducted in nine high-volume hospitals, which performed more than 10 PMs annually. Therefore, the high hospital PM volume was considered as an independent prognostic factor. The relationship between the hospital procedure volume and postoperative outcomes is well established [26,27]. Furthermore, the management of metastatic CRC involves various medical professionals

and should be based on a multidisciplinary team approach. High-volume centers may have a more experienced multidisciplinary team to facilitate the patient selection for surgery, adequate adjuvant treatment, and intensive follow-up examination, which may affect the postoperative survival [28]. More than half of the PMs were performed in hospitals located in Seoul, the capital city. This finding indicated a regional disparity regarding the accessibility to a high-volume center. Centralization and concentration of cancer surgery cases are spontaneous and are considered a common phenomenon in Korea. Indeed, approximately 60% of lung cancer surgeries are conducted in the capital area [29]. The concentration of the patients with pulmonary metastasis of CRC may improve the clinical outcomes of PM in CRC by increasing the experience of each hospital and decreasing the disparity in the management of metastatic CRC cases. Nevertheless, efforts should be made to lower the trend of centralization and reverse centralization, as excessive concentration would result in ineffective utilization of social resources.

Nevertheless, this study had several limitations. Especially, it was a retrospective study and did not include a control group of patients who did not undergo PM. Moreover, the NHIS claims database does not include detailed information on the disease status, such as the initial CRC stage, the number and size of pulmonary metastases, mediastinal lymph node involvement, completeness of resection, and the pathological results. We could only estimate the location and stage from operation codes and types of treatment. Therefore, these additional factors could not be included in the analysis, and the effect of confounding factors could not be controlled. The Health Insurance Review and Assessment Service database and the Korean Central Cancer Registry have detailed data regarding the cancer status and treatment procedures performed for patients with CRC. Nevertheless, we could not merge the data of these databases, as personal identifier information is missing from databases currently. When the NHIS claims database can be merged with other national databases, like the Surveillance, Epidemiology, and End Results and Medicare-linked databases in the United States, a more sophisticated analysis will be possible [30]. Social consensus followed by overhaul of the Personal Information Protection Law should be preceded to link data in these databases. Fundamentally, a prospective national registry specified for pulmonary metastases from CRC would be the best solution.

In conclusion, this population-based study showed a trend of centralization of the performed PMs in Korea. PM seemed to provide long-term survival of patients with CRC. Especially, the female sex, distally located CRC, and PM in a high-volume center (> 10 PMs per year) were considered positive prognostic factors for overall survival.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

This study was approved by the Institutional Review Board of National Health Insurance Service Ilsan Hospital (approval number: NHIMC 2016-03-022) and has been confirmed for waiver of informed consent.

Author Contributions

Conceived and designed the analysis: Yu WS, Bae MK, Choi JK, Park IK.
Collected the data: Hong YK.
Contributed data or analysis tools: Yu WS, Bae MK, Choi JK, Hong YK.
Performed the analysis: Yu WS, Bae MK, Hong YK.
Wrote the paper: Yu WS, Bae MK, Park IK.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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