 doi:10.20944/preprints202106.0330.v1

Article

Effect of chemotherapy and radiotherapy on cognitive function in colorectal cancer: evidence from national representative longitudinal database

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Simple Summary: Results from representative longitudinal data suggests heterogeneous associations between various chemotherapy agents and cognitive impairment. While capecitabine and irinotecan was associated with increased risk of cognitive impairment, oxaliplatin and 5-fluorouracil was not. In addition, adverse cognitive effect of irinotecan was larger in elderly patient than in their younger counterparts. Radiotherapy was not associated with cognitive impairment in rectal cancer.

Abstract:

Background: We aimed to assess the risk of chemotherapy- and radiotherapy-related cognitive impairment in colorectal cancer patients.

Methods: We randomly selected 40% of colorectal cancer patients from Korean National Health Insurance Database (NHID), 2004-2018 (N=148,848). Patients with one or more ICD-10 diagnostic codes for dementia or mild cognitive impairment was defined as cognitive impairment cases. Patients who were aged 18 or younger, diagnosed with cognitive impairment before colorectal cancer (N=8,225) and did not receive primary resection (N=45,320) were excluded. The effects of each chemotherapy agent on cognitive impairment were estimated. We additionally estimated the effect of radiotherapy in rectal cancer patients. Time-dependent competing risk Cox regression was conducted to estimate overall and age-specific hazard ratios (HR) separately for colon and rectal cancer.

Results: In colon cancer, capecitabine and irinotecan was associated with higher cognitive impairment, while 5-fluorouracil was not. In rectal cancer, no chemotherapy agents increased the risk of cognitive impairment, nor did radiotherapy. Hazardous association of irinotecan was estimated larger in elderly patients compared with younger counterparts.

Conclusion: Heterogeneous associations between various chemotherapy agents and cognitive impairment were observed. Elderly patients were more vulnerable to possible adverse cognitive effects. Radiotherapy did not increase the risk of cognitive impairment.

Keywords: Chemotherapy; Radiotherapy; Cognitive dysfunction; Big data; Cohort studies; Survival analysis

 doi:10.20944/preprints202106.0330.v1

1. Introduction

Cancer treatment, including chemotherapy and radiotherapy, is continuously questioned for being associated with cognitive impairment. Although cognitive impairment after chemotherapy, known as "chemo-brain", has attracted great attention among researchers, it is still yet to be understood. [1-3] "Chemo-brains" were primarily identified and studied in patients with breast cancer who underwent chemotherapy in 1980s. [2] Some studies reported potential adverse cognitive effects of chemotherapy, [2] but a meta-analysis of studies on breast cancer survivors in 2017 reported no overall association. [1]

However, research in "chemo-brain" in colorectal cancer is relatively sparse. A single-arm study which enrolled about 80 Spanish colorectal cancer patients reported 50% increased incidence of cognitive decline. In this study, patients received oxaliplatin/fluorouracil regimen. [4] However, the following prospective US study including 362 colorectal cancer patients reported that chemotherapy did not increase the risk of cognitive impairment in cancer patients. [5]

In case of radiotherapy, fewer studies have assessed "post-radiotherapy cognitive impairment" or "radio-brain" in colorectal cancer patients. Two studies conducted in Norther Europe (N = 324, N = 532 respectively) suggested that radiotherapy induces cognitive impairment in rectal cancer patients. [6, 7] However, other two studies indicated contradicting results: a Swiss study on 60 patients indicated that there is no increased risk of cognitive impairment after radiotherapy. [8] Therefore, the evidences for "radio-brain" in rectal cancer is yet inconclusive, and further in-depth in a more extensive population setting is required.

It has been hypothesized that older patients with cancer are vulnerable to cognitive impairment after chemotherapy, [9] as their cognitive reserve, the capacity of the brain that helps it sustain the external and internal neuropathological burden, [10] are diminished. [11] A meta-regression from our previous systematic review and meta-analysis on cognitive decline after chemotherapy in colorectal cancer patients suggested that older colorectal cancer patients are more likely to suffer from cognitive impairments after receiving chemotherapy, [12] further supporting the hypothesis. However, previous studies that our group reviewed consisted of studies utilizing relatively small and selected population (N<500), so epidemiologic evidence from nationwide representative population with large sample is warranted.

In this study, we aimed to evaluate the adverse cognitive effect of cancer treatment by conducting a longitudinal analysis on representative population of South Korea. Additionally, we investigated age heterogeneity in the effects of chemotherapy and radiotherapy in patients with colorectal cancer.

2. Materials and Methods

2.1 Participant selection

Administrative data for medical service usage of colorectal cancer patients were obtained from the Korea National Health Information Database (NHID), 2004-2018. The NHID is a public database on healthcare services constructed using the National Health Insurance System (NHIS) of South Korea, which is a universal health insurance system that covers the medical expenditure of approximately 98% of entire Korean citizens. [13] The database consists of representative and comprehensive information on medical use of Korean patients, including insurance eligibility, diagnostic codes, prescribed medications and procedures, and billing records. [14]

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Patients with two or more ICD-10 diagnostic codes for colorectal cancer (C18-C20) and one or more admission records were defined as colorectal cancer patients. From the original database, 40% of colorectal cancer patients was randomly selected (N=148,929). We excluded patients aged 18 or younger (N = 81), those diagnosed with cognitive impairment before colorectal cancer diagnosis (N = 8,225), and patients without administrative records for tumor resection (N = 45,320, Figure 1), and 95,303 patients were included in final analyses (66,733 colon cancer cases and 28,570 rectal cancer cases).

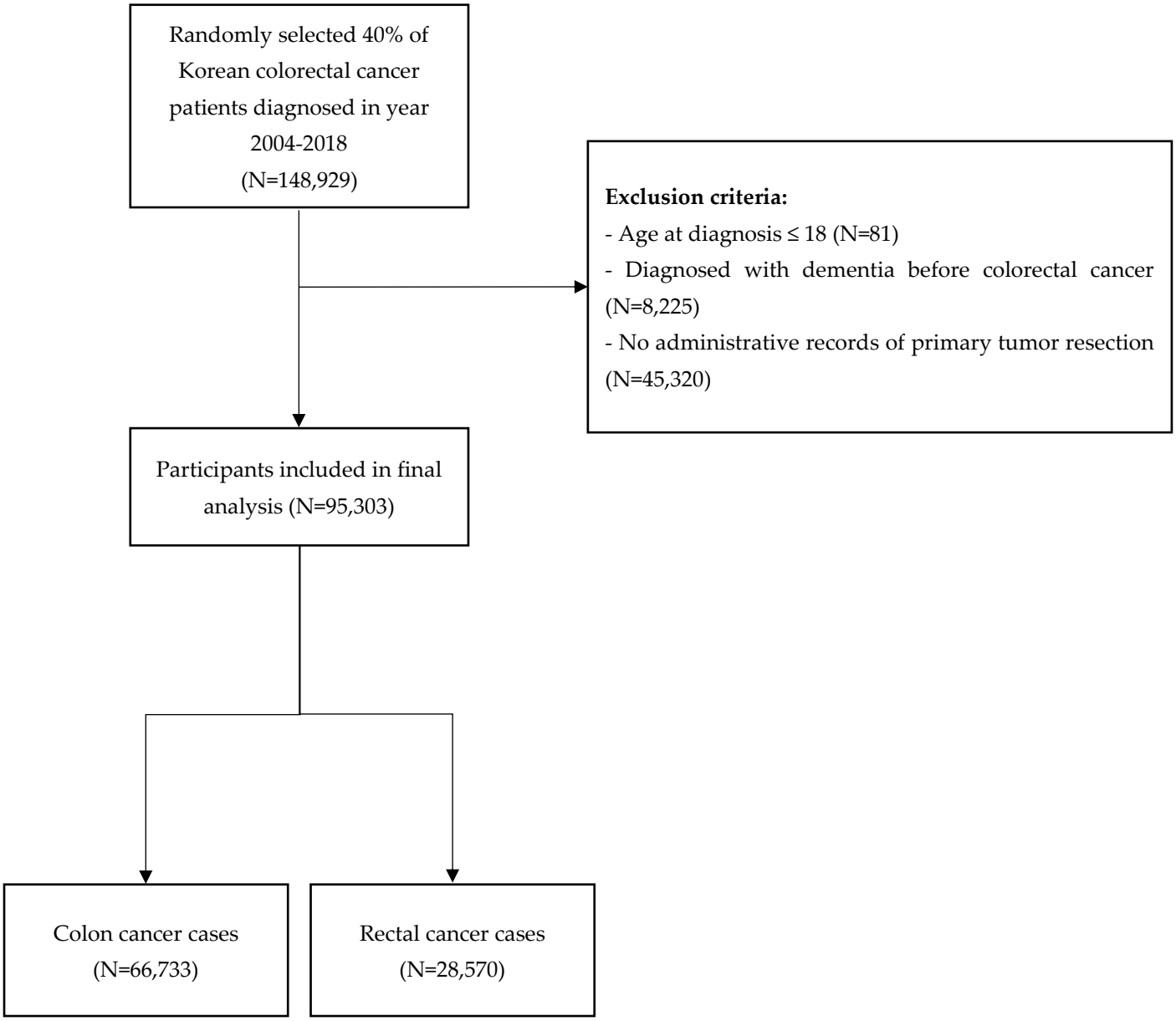

Figure 1. Flow chart of participant inclusion and exclusion.

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2.2 Assessing colorectal cancer treatment and cognitive impairment

Cognitive impairment cases were defined as having at least one ICD-10 diagnostic code for dementia or minor cognitive impairments. [15, 16] ICD-10 codes for dementia and minor cognitive impairments are described in Table S1.

Claim codes for cancer treatment modality, including surgical resection, chemotherapy, and radiotherapy, were reviewed and confirmed by a colorectal surgeon (CWK), a medical oncologist (HK) and two epidemiologists (SJJ, KK). For chemotherapy, regimens that are recommended for first-line chemotherapy in the National Comprehensive Cancer Network (NCCN) Guidelines 2019 were included for analyses (oxaliplatin, capecitabine, 5-fluorouracil, irinotecan; administrative codes are listed in Table S2). Patients with one or more labels for corresponding chemotherapy regimens were considered to be chemotherapy recipients. The date of the first insurance claim for colorectal cancer was considered as the date of colorectal cancer onset.

2.3 Covariates

Monthly insurance premium was used as a proxy variable for socioeconomic status. Participants' monthly insurance premium payment records at baseline were collected, and the participants were divided into subgroups according to quintile values of monthly insurance premium (18,700, 31,110, 44,169, 63,749 KRW/month in year 2004). Medical aid receivers, who did not pay the premium due to poor economic situation, were classified into a separate subgroup. Charlson comorbidity index (CCI) at baseline was calculated to assess medical comorbidities. [17] Participants with corresponding ICD-10 diagnostic codes for each comorbidity was considered to have those comorbidities (Table S3).

2.4 Statistical analyses

We classified participants by cancer treatment modality in accordance of claim records for cancer treatment as follows: in colon cancer, 1) primary resection only and 2) primary resection with chemotherapy: in rectal cancer, 1) primary resection only, 2) primary resection with chemotherapy, 3) primary resection and radiotherapy, and 4) primary resection with CCRT. With these categories, we described the baseline characteristics of participants by presenting mean and standard deviation for continuous variables and numbers and percentage of participants for discrete variables.

We hypothesized that treatments were provided according to the 2019 NCCN guidelines for colorectal cancer treatment, and that participants with the same treatment modality were likely to have a similar tumor burden. [18,19] We estimated hazard ratios of each chemotherapy agents. To control possible confounding by tumor burden, we excluded patients without claims codes for surgical resection, excluding patients who were either having an inoperable tumor with higher tumor burden or chronic patients receiving palliative treatments only.

Hazard ratios (HRs) and their 95% confidence intervals (95% CIs) for each chemotherapy agent and radiotherapy were estimated using a time-dependent competing risk survival analysis model, with all-cause mortality considered as a competing risk. For consideration of left truncation, the mid-date of the birth year was used as the date of initiation. Age interaction terms were added to the model to assess moderating effects of age, and age-specific HRs of chemotherapy and radiotherapy were estimated. All models were adjusted for age, sex, comorbidities, and monthly insurance premium quintile. For sensitivity analyses, we applied landmark analyses; in these analyses, a certain lag time period is set, and only cases with onset after a lag time period are considered as

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cases. We performed landmark analyses with lag times of 6, 12, and 18 months. [20] All statistical analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Characteristics of the study population

Among the 66,733 patients with colon cancer included in the baseline (2004), 14,146 (21.20%) received adjuvant or neoadjuvant chemotherapy until 2018. The mean follow-up duration was longer in patients who did not receive chemotherapy than in those who received it (5.57 years vs. 3.21 years, p<0.001). Among chemotherapy recipients, capecitabine, oxaliplatin, 5-fluorouracil (5-FU), and irinotecan was administered to 3,228 (22.82%), 9,928 (70.18%), 7,709 (54.50%), and 2,444 (17.28%), respectively. The incidence rate of cognitive impairment was 22.17 per 1,000 person-years in chemotherapy non-recipients and 14.48 per 1,000 person-years in chemotherapy recipients. All-cause mortality rate was 49.05 per 1,000 person-years in chemotherapy non-recipients, and 96.52 per 1,000 person-years in patients who received chemotherapy (Table 1).

Among the 28,570 patients with rectal cancer included in the analyses, 2,604 (9.11%) received chemotherapy, 8,098 (28.34%) received radiotherapy, and 3,161 (11.06%) received CCRT before or after surgical resection. Mean follow-up duration (in years) was relatively longer in the primary resection group and resection - radiotherapy combination group and shorter in the resection - chemotherapy combination group and resection - CCRT combination group. Among 5,765 chemotherapy and CCRT recipients, capecitabine, oxaliplatin, 5-fluorouracil (5-FU), and irinotecan were administered to 1,734 (30.08%), 3,289 (57.05%), 3,499 (60.69%), and 1,228 (21.30%), respectively. The incidence rate of cognitive impairment was highest in the resection only group (23.16 per 1,000 person-years), while mortality was highest in the resection - CCRT combination group (123.66 per 1,000 person-years) (Table 1).

Table 1. Characteristics of colon cancer patients from Korea National Health Insurance Database, 2002-2018 (N = 95,303).

	Colon cancer (N = 66,733)		Rectal cancer (N = 28,570)			
	Primary resection only (N = 52,587)	Resection with chemotherapy (N = 14,146)	Primary resection only (N = 14,707)	Resection with chemotherapy (N = 2,604)	Resection with radiotherapy (N = 8,098)	Resection with concurrent chemoradiotherapy (N = 3,161)
Age, Mean (SD)	64.52 (11.99)	61.31 (11.05)	65.10 (11.55)	61.52 (10.78)	60.56 (11.16)	59.34 (10.99)
Male, N (%)	30,588 (58.17)	8,474 (59.90)	8,940 (60.79)	1,726 (66.28)	5,282 (65.23)	2,185 (69.12)
Charlson comorbidity index, Mean (SD)	6.85 (2.51)	6.00 (2.29)	6.87 (2.47)	5.89 (2.25)	5.98 (2.32)	5.56 (2.19)
2	1,243 (2.36)	552 (3.90)	323 (2.20)	92 (3.53)	335 (4.14)	161 (5.09)
3	3,235 (6.15)	1,376 (29.84)	830 (5.64)	273 (10.48)	818 (10.10)	424 (13.41)
4	5,218 (9.92)	2,069 (28.39)	1,419 (9.65)	407 (15.63)	1,205 (14.88)	532 (16.83)
5	7,094 (13.49)	2,440 (17.25)	1,928 (13.11)	467 (17.93)	1,359 (16.78)	566 (17.91)
6	7,999 (15.21)	2,255 (15.94)	2,295 (15.60)	428 (16.44)	1,317 (16.26)	509 (16.10)
7	7,886 (14.99)	1,940 (13.71)	2,377 (16.16)	358 (13.75)	1,090 (13.46)	377 (11.93)

 doi:10.20944/preprints202106.0330.v1

8	6,848 (13.02)	1,456 (17.53)	1,952 (13.27)	246 (9.45)	790 (9.76)	259 (8.19)
9	5,222 (9.93)	997 (7.05)	1,446 (9.83)	151 (5.80)	531 (6.56)	176 (5.57)
≥10	7,842 (14.91)	1,061 (7.50)	2137 (14.53)	182 (6.99)	653 (8.06)	157 (4.97)
Insurance premium, KRW/month, N (%)						
0	2,361 (4.49)	545 (3.85)	744 (5.06)	115 (4.42)	290 (3.58)	115 (3.64)
<20p (<18,700)	9,910 (18.85)	2,832 (20.02)	2,876 (19.56)	547 (21.01)	1,531 (18.91)	680 (21.51)
20 - 40p (18,700 - 31,109)	9,314 (17.71)	2,682 (18.96)	2,669 (18.15)	520 (19.97)	1,561 (19.28)	655 (20.72)
40 - 60p (31,110 - 44,169)	10,280 (19.55)	2,743 (19.39)	2,882 (19.60)	516 (19.82)	1,656 (20.45)	596 (18.85)
60 - 80p (44,170 - 63,749)	10,671 (20.29)	2,841 (20.08)	2,969 (20.19)	482 (18.51)	1,657 (20.46)	604 (19.11)
≥80p (≥63,750)	10,051 (19.11)	2,503 (17.70)	2,567 (17.45)	424 (16.28)	1,403 (17.33)	511 (16.17)
Mean follow-up years	5.57 (3.95)	3.21 (2.79)	6.08 (4.14)	3.07 (2.81)	6.36 (3.82)	3.52 (2.59)
Incidence rate of cognitive impairment, per 1,000 person-years.	22.17	14.48	23.16	12.65	13.12	10.69
Mortality rate, per 1,000 person-years	49.05	96.52	47.50	107.33	54.75	123.66
Chemotherapy regimen, N (%)						
Capecitabine		3,228 (22.82)		608 (23.35)		1,126 (35.62)
Oxaliplatin		9,928 (70.18)		1,684 (64.67)		1,605 (50.78)
5-fluorouracil		7,709 (54.50)		1,546 (59.37)		1,953 (61.78)
Irinotecan		2,444 (17.28)		545 (20.93)		683 (21.61)

Table 1 (Continued)

Radiotherapy, N (%)						
Single port					4,775 (58.97)	1,023 (32.36)
Parallel port					4,970 (61.37)	1,013 (32.05)
Rotation radiation					29 (0.36)	2 (0.06)
3D radiotherapy					3,860 (47.67)	1,985 (62.86)
Brachytherapy					33 (0.41)	8 (0.25)
Density-modulated radiotherapy					320 (3.95)	685 (21.67)
Proton therapy					11 (0.14)	16 (0.51)

SD, standard deviation; KRW, Korean Won

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3.2 Effects of chemotherapy and radiotherapy on cognitive impairment

In colon cancer patients, capecitabine (HR = 1.44, 95% CI 1.23-1.68) and irinotecan administration (HR = 1.90, 95% CI 1.29-2.80) increased the risk of cognitive impairment. Oxaliplatin (HR = 0.76, 95% CI 0.64-0.89) and 5-FU (HR = 0.69, 95% CI 0.52-0.92) were negatively associated with cognitive impairment. In rectal cancer patients, chemotherapy regimens did not increase the risk of cognitive impairment. Radiotherapy decreased the risk of cognitive impairment (HR = 0.91, 95% CI 0.83-0.99; Table 2).

Age-specific hazard ratio of irinotecan was larger in older patients than in younger patients ($HR_{Age=80}$ = 2.23, 95% $CI_{Age=80}$ 1.29-3.38; $HR_{Age=40}$ = 1.19, 95% $CI_{Age=40}$ 0.22-6.38; Figure 2A). Effects of capecitabine was estimated to be less severe in older patients, but the effect size difference was statistically insignificant. In interaction analyses among rectal cancer patients, age-specific hazard ratio of irinotecan administration increased as the age of participants increased, but the hazard ratio was not statistically significant ($HR_{Age=80}$ = 1.69, 95% $CI_{Age=80}$ 0.80-3.58; $HR_{Age=40}$ = 0.69, 95% CI $_{Age=40}$ 0.13-3.62, Figure 2B). The association regarding capecitabine, oxaliplatin, 5-FU, and radiotherapy did not change by age (Figure 2B).

In sensitivity analyses, we found no significant differences in the results. The association between irinotecan and cognitive impairments in colon cancer patients was significant in landmark analysis with lag times of 6 (HR=1.44, 95% CI 1.01-2.06), 12 (HR=1.75, 95% CI 1.20-2.56), and 18 months (HR=2.10, 95% CI 1.39-3.18). Oxaliplatin and 5-FU were negatively associated with cognitive impairment (Table S4). In rectal cancer patients, the association between irinotecan and cognitive impairment was detected in landmark analysis with lag time of 12 months (HR=1.99, 95% CI 1.17-3.38), but not in analyses with lag times of 6 or 18 months. Negative associations between cognitive impairments and 5-FU administration were detected (Supplemental Material 4). In both colon and rectal cancer patients, age at diagnosis modified the effect of irinotecan on cognitive impairments in landmark analyses (Supplemental Material 5-7).

Table 2. Estimated hazard ratios of chemotherapy regimens and radiotherapy in colorectal cancer

	Colon cancer, HR (95% CI)		**Rectal cancer, HR (95% CI)**	
	Fully adjusted model	**Interaction model**	**Fully adjusted model**	**Interaction model**
Capecitabine	**1.44 (1.23 - 1.68)**	1.81 (0.47 - 7.01)	1.04 (0.81 - 1.34)	0.59 (0.08 - 4.05)
Oxaliplatin	*0.76 (0.64 - 0.89)*	0.55 (0.12 - 2.50)	0.87 (0.67 - 1.13)	0.31 (0.03 - 2.71)
5-FU	*0.69 (0.52 - 0.92)*	0.24 (0.02 - 3.78)	0.75 (0.55 - 1.01)	1.44 (0.12 - 17.07)
Irinotecan	**1.90 (1.29 - 2.80)**	0.63 (0.02 - 25.09)	1.32 (0.82 - 2.13)	0.28 (0.01 - 12.33)
Radiotherapy			*0.91 (0.83 - 0.99)*	0.71 (0.36 - 1.37)
Interaction terms				
Capecitabine*Age		1.00 (0.98 - 1.02)		1.01 (0.98 - 1.04)
Oxaliplatin*Age		1.00 (0.98 - 1.03)		1.02 (0.98 - 1.05)
5-FU*Age		1.01 (0.98 - 1.05)		0.99 (0.96 - 1.03)
Irinotecan*Age		1.02 (0.97 - 1.07)		1.03 (0.97 - 1.08)
Radiotherapy*Age				1.00 (0.99 - 1.01)

Fully adjusted model: Adjusted for age, sex, Charlson Comorbidity Index, and monthly insurance premium;

Interaction model: Interaction between cancer treatment and age was estimated by each treatment modality.

HR, hazard ratio; CI, confidence interval.

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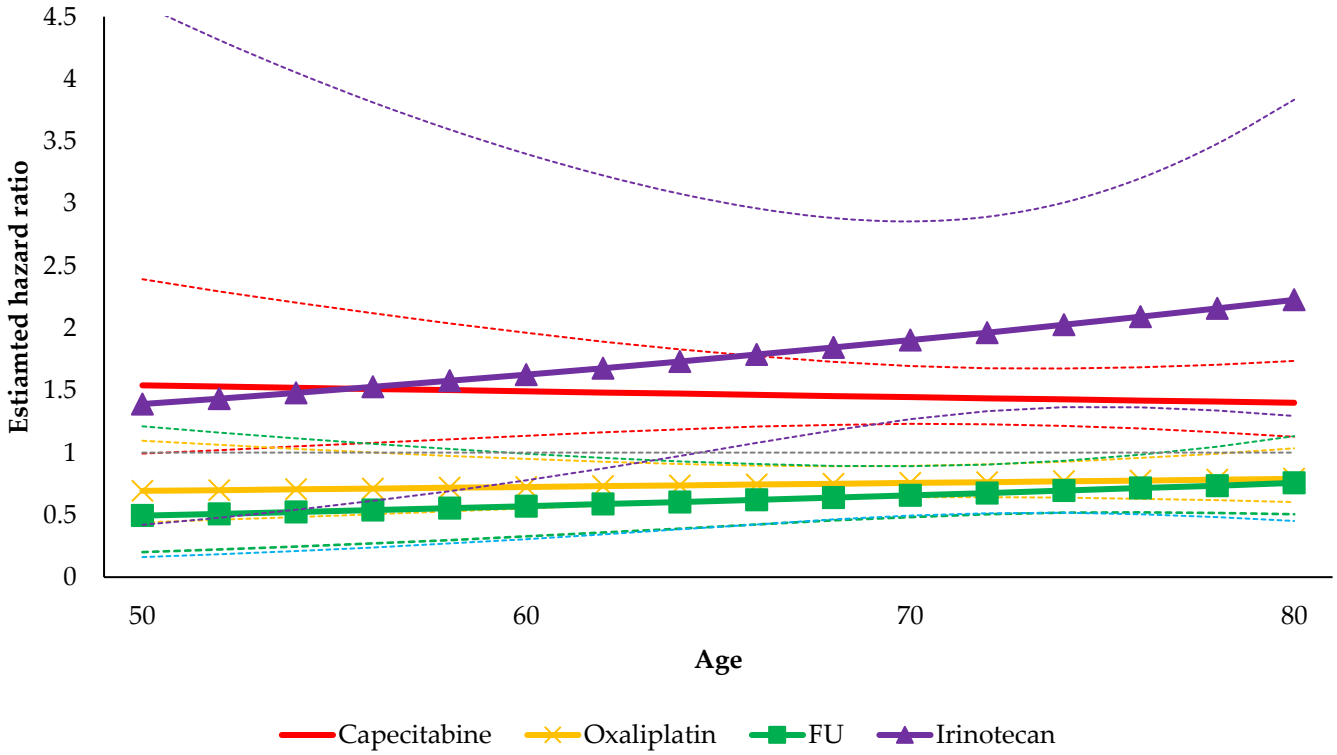
A. Colon cancer



B. Rectal cancer

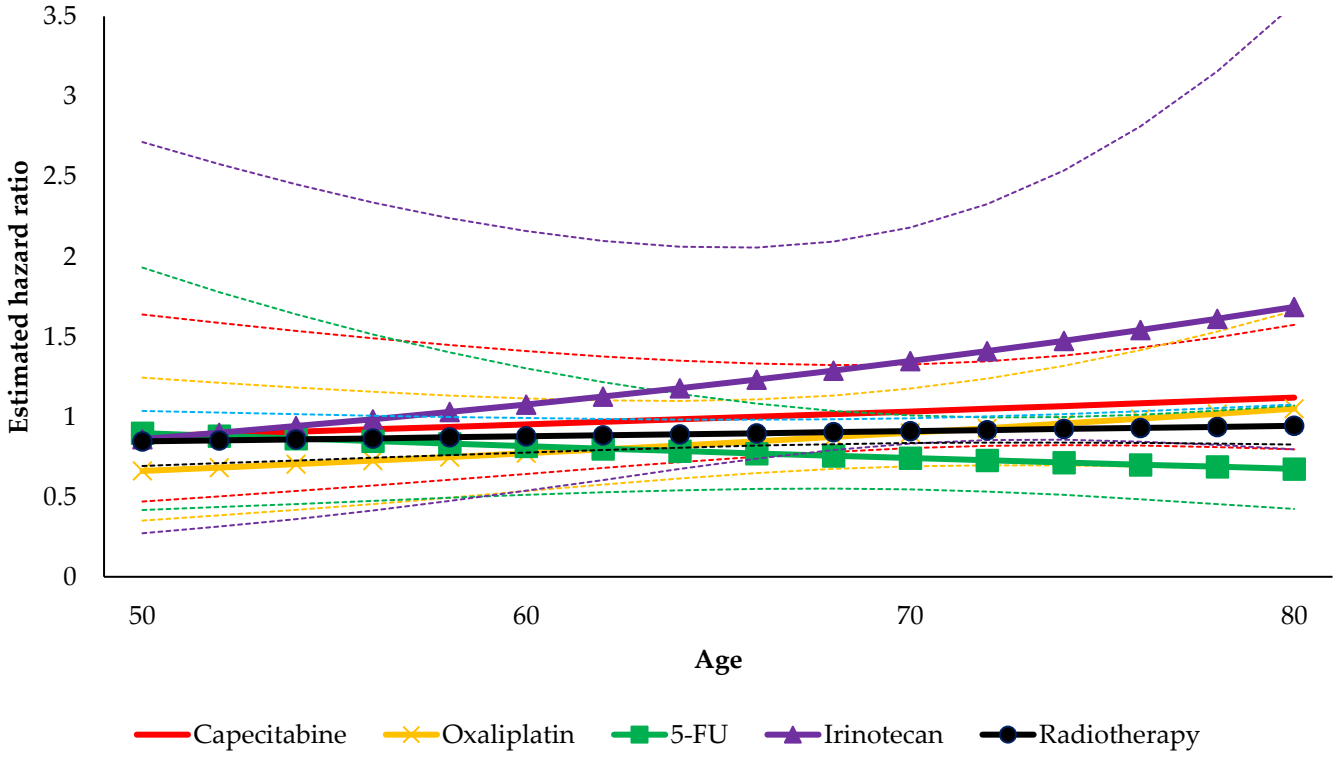


Figure 2. Age-specific hazard ratio of chemotherapy and radiothreapy on cognitive impairments

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4. Discussion

In colorectal cancer patients, chemotherapy agents such as irinotecan and capecitabin administration increased the risk of cognitive impairment in our nationwide representative population. In contrast, oxaliplatin or 5-FU did not increase the risk of cognitive impairment, nor did radiotherapy in rectal cancer patients. Additionally, the adverse effect of irinotecan appeared to be stronger in older patients.

Previous studies on "chemo-brain" in colorectal cancer patients did not suggest consistent direction of evidence4, 5. Our previous meta-analysis of previous studies showed that older patients are more likely to experience cognitive impairments after chemotherapy [12], but studies our groups reviewed had limited numbers of participants within each study, limiting the statistical power. Additionally, the effects of each chemotherapy agents were not described separately in previous studies. We tried to address this knowledge gap by estimating the adverse cognitive effects of each chemotherapy agents in a representative adult population of Korea.

A recent systematic review on cognitive impairment after cytotoxic chemotherapy demonstrated that two out of three studies on colon cancer treated with FOLFOX had not observed cognitive changes, whereas 21 out of 25 studies on breast cancer had detected cognitive impairment after cytotoxic chemotherapy. [21] The findings imply that characteristics of primary tumor, both biological and psychosocial, play important role on manifestation of chemotherapy-related cognitive impairment. It is well known that a significant proportion of breast cancer patients suffer from depression and anxiety, which leads to dysfunctional cognition and general fatigue. [22] A recent meta-analysis reported that around 32% of breast cancer patients suffer from depression. [23] In contrast, results from a systematic review on depression and anxiety in colorectal cancer patients reported that only around 6% of colorectal cancer patients were affected by depression. [24] These differences in psychological consequences of tumor, alongside variances in biological action of chemotherapy agents, [25,26] could have resulted in varying direction of association in our study. A large-scale randomized clinical trial on colorectal cancer patients and further study on mechanism of chemotherapy-related cognitive impairment is warranted for full understanding of the phenomenon.

The adverse effect of irinotecan was more profound in older patients. Cognitive reserve, a capacity of the brain to withstand the effects of external events, toxins, or diseases that can affect the cognitive function, [10] is known to be associated with vulnerability of brain to neurotoxicity of chemotherapy agents. [27] It is postulated that cancer treatments interact with aging of the brain and accelerate the process of cognitive decline; brain images of cancer treatment receivers showed structural changes in the brain that are indicative of aging. [28,29] However, since several chemotherapy agents did not increase the risk of cognitive impairment even in older patients, care must be taken during interpretation of our results.

Our study provides evidence of adverse cognitive effects of cancer treatment in colorectal patients from real-world data. Our results from a representative population of South Korea suggest age heterogeneities in cognitive decline of colorectal cancer patients after treatment. This is one of few studies that utilized nationwide data to understand chemotherapy-related and radiotherapy-related cognitive dysfunction in colorectal cancer.

However, this study had some limitations. First, several chemotherapy agents were not covered by NHIS, which might cause selection bias; most uncovered regimens are those from second-line treatment or for palliative treatment in advanced cancer. To

 doi:10.20944/preprints202106.0330.v1

minimize the selection bias, we excluded patients without primary cancer resection records, which can include substantial missing values.

Second, due to the administrative challenges in obtaining medical records, the validity of the date of cognitive impairment onset might be questioned. As the data were collected for medical insurance administration and not for research, information on disease and mortality might have been misclassified. [14] However, the reliability of cognitive impairment diagnosis is known to be valid in the Korean NHID. [30]

Lastly, in this study design, the selective survival bias is possible. Since the mean follow-up time is shorter in chemotherapy- or radiotherapy-recipients, their chances of developing cognitive impairments will be decreased. We applied time-dependent competing risk survival models, which can overcome the probable selective survival bias.31 Evidences from a randomized clinical trial on patients with comparative clinical cancer stages would provide a better understanding on the true association.

5. Conclusions

Despite these limitations, our results from the representative population of Korea provides evidence that can help understand the nature of cancer treatment-related cognitive impairments in colorectal cancer patients. Since our study suggests mixed direction in the effects of chemotherapy and radiotherapy, a large-scale randomized clinical trial with longer follow-up period is needed to fully interpret the complex mechanism of adverse effects in cancer treatment. Regular follow-up assessing cognitive functions after cancer treatment is needed, and especially for elderly patients, close monitoring is to be recommended.

Supplementary Materials: The following are available online, Figure S1: Estimated hazard ratios of chemotherapy and radiotherapy on cognitive impairment under time lag of 6 months, Figure S2: Estimated hazard ratios of chemotherapy and radiotherapy on cognitive impairment under time lag of 12 months, Figure S3: Estimated hazard ratios of chemotherapy and radiotherapy on cognitive impairment under time lag of 12 months, Table S1: Definition of colorectal cancer and cognitive disorders by ICD-10 diagnostic codes, Table S2: Insurance fee codes for colorectal cancer treatments, Table S3: Definition of comorbidities by ICD-10 diagnostic codes, Table S4: Estimated hazard ratios of chemotherapy and radiotherapy on cognitive impairment under landmark analyses.

Author Contributions: Conceptualization, Kim K and Jung; methodology, Kim K and Jung; software, Kim K; validation, Kim K, Kim CW, Shin, Jung; formal analysis, Kim K; investigation, Kim K, Jung; resources, Kim K and Jung; data curation, Kim K; writing—original draft preparation, Kim K; writing—review and editing, Kim K, Kim CW, Shin, Kang, Jung; visualization, Kim K; supervision, Jung; project administration, Kim K and Jung; funding acquisition, Jung. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the National Research Foundation of Korea (NRF) grant funded by the Ministry of Science and ICT, grant number 2020R1C1C1003502.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Yonsei University Health System, Seoul, Korea (protocol code: 4-2019-0425: date of approval: 24-June-2019).

Informed Consent Statement: Patient consent was waived since personal information that can be used to identify individuals registered to NHID have been removed

Data Availability Statement: The NHID is under control of National Health Insurance Service of Korea. The database is not open to the public, and only registered researchers of research projects are allowed to access.

Acknowledgments: None

Conflicts of Interest: The authors declare no conflict of interest.

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