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Clinical characteristics of rectal cancer patients with neoadjuvant chemoradiotherapy: a nationwide population-based cohort study in South Korea

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Purpose: Neoadjuvant chemoradiotherapy has been accepted as a standard treatment for stage II–III rectal cancer. This study aimed to evaluate the clinical characteristics of patients who underwent neoadjuvant chemoradiotherapy for rectal cancer and effects on overall survival (OS) of neoadjuvant chemoradiotherapy in South Korea.

Methods: Patients who underwent curative resection for rectal cancer from 2014 to 2016 were retrospectively reviewed from the database of the National Quality Assessment program in South Korea. Patients were categorized into the upfront surgery group and neoadjuvant chemoradiotherapy group. We evaluated factors associated with the administration of neoadjuvant chemoradiotherapy and its effects on OS. Inverse probability of treatment weighting was performed to account for baseline differences between subgroups.

Results: A total of 6,141 patients were categorized into the upfront surgery group (n = 4,237) and neoadjuvant chemoradiotherapy group (n = 1,904). The neoadjuvant chemoradiotherapy was more frequently administered to male, midrectal cancer, and younger patients. In the neoadjuvant chemoradiotherapy group, old age, underweight, and pathologic stage were significant risk factors of OS, and male sex, the level of tumor and clinical stages were not associated with OS. After adjustment, the OS of the neoadjuvant chemoradiotherapy group followed the OS of the upfront surgery group of the same pathologic stage.

Conclusion: Male sex and the level of tumor were not related to the OS of rectal cancer patients with neoadjuvant chemoradiotherapy. The OS of patients who underwent neoadjuvant chemoradiotherapy was decided by their pathologic stages regardless of clinical stages.

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INTRODUCTION

Rectal cancer accounts for approximately 33.6% of all colorectal cancer cases in South Korea [1]. The treatment of rectal cancer differs from that of colon cancer as local control is important. Neoadjuvant chemoradiation therapy (NCRT) has been accepted as an effective treatment to prevent local recurrence of advanced rectal cancer [2]. In addition, it has been demonstrated that the tumor response to NCRT is associated with improved survival [3]. The National Comprehensive Cancer Network guidelines recommend NCRT as a priority treatment for stage II–III rectal cancer. NCRT followed by total mesorectal

excision (TME) is also the current standard of care for stage II–III rectal cancer patients in South Korea.

However, there are some disadvantages of NCRT. For example, it can increase surgical difficulty as tissue inflammation after radiation leads to congestion or edema [4]. Similarly, anastomosis leakage or perineal wound dehiscence can occur. In addition, NCRT may lead to distant metastasis, especially in tumors that respond poorly to radiation therapy [5]. Therefore, establishing specific indications is important to maximize the advantages and minimize unnecessary administration of NCRT. There is a lack of study about the treatment outcomes of NCRT for rectal cancer based on the national registry of the Asian countries. In this study, we aimed to investigate factors related to the administration of NCRT and its association with overall survival (OS) of rectal cancer patients using the national registry of South Korea.

METHODS

Data

Data from the National Quality Assessment program in South Korea was retrospectively reviewed. The Health Insurance Review and Assessment Service (HIRA) runs this program to evaluate the appropriateness of treatment for major diseases in medical institutions and ensure appropriate expenditure on health care. The HIRA collects information on patients with major diseases from institutions every year. This assessment program for colorectal cancer has been performed since 2011. Information on patients who were diagnosed with colorectal cancer and charged for surgery was collected. The data consisted of clinical characteristics including age, sex, height, weight, date and type of surgery, the American Society of Anesthesiologists (ASA) physical status (PS) classification, mortality, cell type, pathologic stages, and margin status. Positive resection margin is defined as the presence of malignant cells at the resection margin. The tumor height was recorded based on the location from the anal verge to the tumor and was categorized into high (above the peritoneal reflection), low (below the peritoneal reflection), and mid (at the peritoneal reflection). Clinical stage (cStage) was recorded if the patient had received neoadjuvant therapy and categorized into 3 groups (stage I: T1–T2, N0; stage II: T3–T4, N0; and stage III: T1–T4, N1–N2). Pathologic stage (pStage) was categorized into 5 groups (stage 0: no residual tumor; stage I: T1–T2, N0; stage IIA: T3, N0; stage IIB–C: T4, N0; stage III: any T, N+). TNM staging was performed according to the American Joint Committee on Cancer guidelines 7th edition.

Patient selection

Patients who underwent curative resection for rectal cancer between January 2014 and December 2016 were included. Patients who had distant metastasis, other malignancies within 5 years, or palliative resections were excluded. Patients with incomplete records were also excluded. Patients were classified into 3 age groups (>75 years, ≥65 and ≤75 years, and <65 years). We additionally calculated body mass index (BMI) of the patients and categorized it into 3 groups (underweight, <18.5 kg/m²; normal, 18.5–25 kg/m²; obese, >25 kg/m²) according to the Asia-Pacific standards [6]. The Institutional Review Board of Korea University Guro Hospital approved this study (No. 2019GR0416), which waived the requirement of informed consent. The datasets are generated from the Korean National Health Insurance database. The datasets are not allowed publicly without official permission.

Measured outcomes

Statistical comparison of the clinical characteristics of patients who underwent NCRT or upfront surgery was performed. The OS was defined as the period from the date of surgery to the date of death. Survival analysis was performed after excluding all cases of mortality, the follow-up period of <30 days, positive resection margin, or adjuvant radiotherapy. We analyzed the OS in patients who underwent upfront surgery according to the pStage and compared them with OS in patients treated with NCRT according to the corresponding pStage after neoadjuvant chemoradiotherapy (ypStage).

Statistical analysis

Discrete values, such as sex, TN categories, and primary tumor locations, were compared using the chi-square test. The odds ratios (ORs) for the association between NCRT administration and other clinical characteristics were investigated using logistic regression models. Cox proportional hazards regression analysis was used to evaluate the hazard ratios (HRs) for OS. The OS was analyzed using the Kaplan-Meier method and log-rank test. Before the analysis of Kaplan-Meier method, adjustments for differences in baseline characteristics between subgroups are performed using the inverse probability of treatment weighting (IPTW) method to reduce the selection bias and their confounding effects. The propensity score (PS) was estimated using a multivariable logistic regression model based on ages, sex, tumor height, BMI, ASA PS classification, cell type, and the number of harvested lymph nodes. IPTW for patients with NCRT were the inverse of PS, and IPTW for patients with upfront surgery were the inverse of 1 – PS. A standardized difference of <0.1 was considered to indicate a well-balanced result. A 2-sided P-value of <0.05 was considered statistically significant. All data were analyzed using SAS Enterprise Guide ver. 6.1 (SAS Institute, Cary, NC, USA) and R software ver. 3.0.2 (R Foundation for Statistical Computing, Vienna).
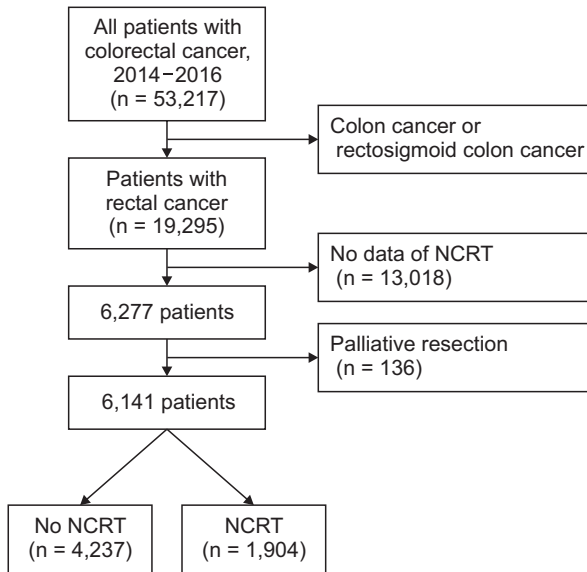
Fig. 1. Flowchart of patient selection from the database of the National Quality Assessment program. NCRT, neoadjuvant chemoradiation therapy.

RESULTS

A total of 53,217 colorectal cancer patients were included, of whom 19,295 patients (36.3%) were diagnosed with rectal cancer (Fig. 1). Finally, 6,141 patients were included in the analysis, of which 4,237 (69.0%) and 1,904 (31.0%) patients underwent upfront surgery and NCRT, respectively.

The baseline characteristics of the patients are presented in Table 1. The proportion of patients with young ages, obesity, ASA PS classification of I or II, male sex, midrectal cancer, and abdominoperineal resection was higher in the NCRT group than in the upfront surgery group. The rate of positive resection margin in NCRT group was marginally lower than the upfront surgery group. The most common chemotherapeutic regimens during NCRT were intravenous fluorouracil based chemotherapy (n = 921, 48.3%) and capecitabine (n = 847, 44.5%), and other regimens including oxaliplatin or irinotecan were used in 136 patients (7.1%).

The ORs for the association between NCRT administration and several factors (Table 2) revealed a tendency for less frequent administration of NCRT to older or ASA PS classification of III patients. In addition, NCRT was more frequently administered to patients with male sex and midrectal cancer.

The HRs for OS of each group were analyzed (Table 3). Older age, male sex, underweight, tumor height, ASA PS classification of III or IV, and pStage were significant risk factors for OS in patients who underwent upfront surgery. In patients who underwent NCRT, older age, underweight, and pStage were risk factors for poor OS and male sex; tumor height and cStage were not significantly associated with OS. Table 4 shows the changes

Table 1. Baseline characteristics of patients

Characteristic	Upfront surgery	NCRT	P-value
No. of patients	4,327	1,904	
Age (yr)			<0.001
<65	1,750 (41.3)	1,059 (55.6)	
65–75	1,353 (31.9)	619 (32.5)	
>75	1,134 (26.8)	226 (11.9)	
Male sex	2,552 (60.2)	1,341 (70.4)	<0.001
ASA PS classification			<0.001
I, II	3,454 (81.6)	1,652 (86.8)	
III	744 (17.6)	241 (12.7)	
IV	33 (0.8)	11 (0.6)	
Body mass index (kg/m^2)			0.043
<18.5	290 (6.8)	102 (5.4)	
18.5–25.0	2,464 (58.2)	1,104 (58.0)	
>25.0	1,461 (34.5)	698 (36.7)	
Tumor height			<0.001
High	1,776 (41.9)	284 (14.9)	
Middle	1,846 (43.6)	1,356 (71.2)	
Low	615 (14.5)	264 (13.9)	
Pathologic stage			<0.001
0	0 (0)	188 (9.9)	
I	1,457 (34.4)	432 (22.7)	
II	1,115 (26.3)	600 (31.5)	
III	1,665 (39.3)	684 (35.9)	
Cell type			0.862
Adenocarcinoma	3,842 (90.7)	1,624 (85.3)	
Others (MAC, SRCC)	114 (2.7)	46 (2.4)	
Harvested lymph node			0.074
≥12	3,958 (93.4)	1,754 (92.1)	
<12	279 (6.6)	150 (7.9)	
Positive resection margin	89 (2.1)	24 (1.3)	0.059
Type of surgery			<0.001
Low anterior resection	3,797 (89.6)	1,609 (84.5)	
Abdominoperineal resection	303 (7.2)	265 (13.9)	
Proctocolectomy	17 (0.4)	8 (0.4)	
Hartmann procedure	120 (2.8)	22 (1.2)	
Stoma, yes	1,641 (38.7)	1,495 (78.5)	<0.001
Mortality	50 (1.2)	7 (0.4)	0.003

Values are presented as number only or number (%).
NCRT, neoadjuvant chemoradiation therapy; ASA, American Society of Anesthesiologists; PS, physical status; MAC, mucinous adenocarcinoma; SRCC, signet ring cell carcinoma.

of stages of patient in NCRT group. The proportions of patients whose ypStage were lower than cStage were 59.8%, 41.0%, and 40.0% in patients with cStage III, II, and I, respectively.

Table 5 shows the baseline characteristics of patients in the NCRT and upfront surgery groups after the adjustment. Fig. 2 shows the comparison of OS of patients in 2 groups according to the same pStage. Regardless of cStage, the OS rate of the NCRT group was not statistically different from the OS rate of patients in the upfront surgery group with the same pStage (Fig. 2A: 5-year OS, pStage III = 64.6%, ypStage III [cStage II] = 57.4%,

Table 2. Association of administration of neoadjuvant chemoradiation therapy with patient characteristics

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (yr)				
<65	1		1	
65–75	0.76 (0.67–0.85)	<0.001	0.79 (0.69–0.89)	<0.001
>75	0.33 (0.28–0.39)	<0.001	0.36 (0.31–0.43)	<0.001
Sex				
Female	1		1	
Male	1.57 (1.40–1.76)	<0.001	1.44 (1.28–1.63)	<0.001
Body mass index (kg/m²)				
<18.5	0.79 (0.62–0.99)	0.045	0.89 (0.70–1.15)	0.385
18.5–25	1		1	
>25	1.07 (0.95–1.20)	0.270	1.06 (0.94–1.20)	0.326
ASA PS classification				
I, II	1		1	
III	0.65 (0.55–0.77)	<0.001	0.82 (0.69–0.98)	0.032
IV	0.53 (0.23–1.22)	0.134	0.91 (0.38–2.18)	0.824
Tumor height				
High	1		1	
Middle	4.61 (3.99–5.32)	<0.001	4.64 (4.01–5.37)	<0.001
Low	2.69 (2.22–3.25)	<0.001	2.77 (2.28–3.36)	<0.001

OR, odds ratio; CI, confidence interval; ASA, American Society of Anesthesiologists; PS, physical status.
ORs were obtained from logistic regression model.

ypStage III [cStage III] = 63.2%; Fig. 2B: 5-year OS, pStage II = 78.6%, ypStage II [cStage II] = 78.7%, ypStage II [cStage III] = 77.5%; Fig. 2C: 5-year OS, pStage I = 90.1%, ypStage I [cStage II] = 87.7%, ypStage I [cStage III] = 90.1%).

DISCUSSION

The benefits of NCRT have been demonstrated in other randomized controlled studies, NCRT has been accepted as a standard treatment for stage II and III rectal cancer [7]. Previous studies have reported on the maximization of NCRT effect, such as modulation of the waiting periods after radiation therapy prior to surgical resection or introduction of consolidation/induction chemotherapy with chemoradiation therapy [8,9]. These studies will eventually make it possible to selectively perform TME after NCRT with strict indications to avoid overtreatment or undertreatment of disease through the evaluation of multiple factors related to treatment outcomes. In this large retrospective cohort study, we evaluated the current status of NCRT in South Korea using the national registry data and identified multiple factors related with the treatment strategies and survivals. Our results showed that NCRT was more frequently administered to younger, male, and midrectal cancer patients. Additionally, NCRT reduced the negative effects of male sex and the tumor height on OS. The OS in patients who underwent NCRT was not different from that of patients who underwent upfront surgery with corresponding pStage.

In NCRT group, there were 30 patients with cStage I and 284 patients with high tumors. In addition, among the patients with midrectal or low-rectal cancer, there were 563 and 872 patients with pStage II and III, respectively, who underwent upfront surgeries. We could not evaluate how statistically cStage was consistent with pStage because there was no information related to cStage of the upfront surgery group in this database. Nevertheless, considering these patients, it could be estimated that about 32.9% (n = 2,019) of all rectal cancer patients (n = 6,141) did not follow the standard guideline of treatment for rectal cancer. Thus, even with the same cStage or tumor height, it was found that the treatment policy for rectal cancer could be determined differently in consideration of various factors including age, sex, or side effects of radiation therapy.

Male sex was an independent risk factor for poor OS in patients who underwent upfront surgery in our study, which is consistent with results of a previous cohort study, reporting that men had poorer long-term outcomes than women [10]. There have been several explanations for better survival in female patients than in male patients. The protective effect of female sex hormones has already been reported in previous studies [11]. It has been hypothesized that female hormones have stimulatory effects on immunologic response, in contrast to the detrimental effects of testosterone [12]. In addition, colorectal surgeons recognized that women typically have wider

Table 3. Multivariate analysis of hazard ratio for overall survival in patients according to administration of the NCRT

Variable	Upfront surgery		NCRT	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (yr)				
<65	1		1	
65–75	2.27 (1.89–2.73)	<0.001	1.72 (1.38–2.14)	<0.001
>75	4.60 (3.85–5.49)	<0.001	2.78 (2.12–3.63)	<0.001
Sex				
Female	1		1	
Male	1.47 (1.28–1.69)	<0.001	1.15 (0.92–1.44)	0.196
ASA PS classification				
I, II	1		1	
III	1.68 (1.42–1.99)	<0.001	1.31 (0.98–1.74)	0.063
IV	4.33 (2.60–7.20)	<0.001	1.52 (0.48–4.79)	0.469
Body mass index (kg/m^2)				
<18.5	1.72 (1.40–2.11)	<0.001	1.64 (1.15–2.3)	0.006
18.5–25	1		1	
>25	0.77 (0.66–0.90)	0.001	0.69 (0.55–0.87)	0.001
Tumor height				
High	1		1	
Middle	1.26 (1.09–1.45)	0.001	1.31 (0.98–1.76)	0.062
Low	1.25 (1.02–1.52)	0.025	1.13 (0.78–1.65)	0.499
Pathologic stage				
I	1		1	
II	1.93 (1.56–2.38)	<0.001	2.48 (1.73–3.51)	0.006
III	3.64 (3.02–4.38)	<0.001	3.93 (2.77–5.56)	0.001
Clinical stage				
II	NA		1	
I	NA		0.25 (0.04–1.84)	0.175
III	NA		1.15 (0.86–1.54)	0.358

NCRT, neoadjuvant chemoradiation therapy; HR, hazard ratio; CI, confidence interval; ASA, American Society of Anesthesiologists; PS, physical status; NA, not available.
HRs were obtained from Cox regression model adjusted for age, sex, BMI, level of tumor, pathologic and clinical stage.

Table 4. Changes of stages of patients after neoadjuvant chemoradiotherapy

ypStage	cStage		
	III (n = 1,562)	II (n = 312)	I (n = 30)
III	627 (40.1)	55 (17.6)	2 (6.7)
II	469 (30.0)	129 (41.3)	2 (6.7)
I	324 (20.7)	94 (30.1)	14 (46.7)
0	142 (9.1)	34 (10.9)	12 (40.0)

Values are presented as number (%).
cStage, clinical stage; ypStage, pathologic stage after neoadjuvant chemoradiotherapy.

pelvic dimensions, and the female pelvis is generally more accessible than the male pelvis, especially for mid and low-rectal cancer [13]. These anatomical differences may contribute to the difference in prognosis between male and female rectal cancer patients.

There are several structures below the peritoneal reflection, such as the seminal vesicles, prostate, vagina, and neurovascular bundles that are important for maintaining genitourinary functions. Since the OR for the association between NCRT administration and the tumor height was higher in midrectal cancer than in low-rectal cancer, we concluded that, with sphincter preservation, preservation of these structures was also an important factor affecting the decision of NCRT administration. However, preservation of these structures can make it difficult to perform R0 resection, especially in advanced rectal cancer. It is challenging for surgeons to acquire a safe resection margin without injuring these structures. Those structures in narrow pelvis can affect a negative effect on the treatment outcomes of patients with low-lying tumors.

Low-lying tumor and male sex are both related to the narrow pelvis and are important factors of rectal cancer to secure a circumferential resection margin (CRM) of safe width [14]. Although many studies regarded CRM > 1 mm of patients who received NCRT and TME as positive, it is also true that the optimal width after NCRT still has been unclear. Previous

Table 5. Baseline characteristics of patients after adjustment using the inverse probability of treatment weighting method

| Variable	Upfront surgery	NCRT	P-value	SMD
No. of patients	4,691	4,743		
Age (yr)			0.819	0.024
<65	2,024 (43.1)	2,002 (42.2)		
65–75	1,516 (32.3)	1,532 (32.3)		
>75	1,151 (24.5)	1,766 (37.2)		
Male sex	2,965 (63.2)	2,978 (62.8)	0.824	0.009
ASA PS classification			0.965	0.011
I, II	3,895 (83.0)	3,934 (82.9)		
III	768 (16.4)	777 (16.4)		
IV	28 (0.6)	33 (0.7)		
Body mass index (kg/m^2)			0.681	0.033
<18.5	293 (6.2)	288 (6.1)		
18.5–25	2,752 (58.7)	2,715 (57.2)		
>25	1,646 (35.1)	1,740 (36.7)		
Tumor height			0.905	0.015
High	1,710 (36.5)	1,764 (37.2)		
Middle	2,338 (49.8)	2,314 (49.4)		
Low	643 (13.7)	638 (13.5)		
Pathologic stage			<0.001	0.423
0	0 (0)	67.5 (1.4)		
I	1,970 (42.0)	1,128 (23.8)		
II	1,286 (27.4)	1,673 (35.3)		
III	1,435 (30.6)	1,874 (39.5)		
Cell type			0.862	0.002
Adenocarcinoma	4,591 (97.9)	4,644 (97.9)		
Others (MAC, SRCC)	100 (2.1)	99 (2.1)		
Harvested lymph node			0.220	0.040
≥12	4,357 (92.9)	4,452 (93.9)		
<12	334 (7.1)	291 (6.1)		
Type of surgery			0.002	0.148
Low anterior resection	4,227 (90.1)	4,117 (86.8)		
Abdominoperineal resection	339 (7.2)	547 (11.3)		
Proctocolectomy	24 (0.5)	17 (0.4)		
Hartmann procedure	101 (2.2)	73 (1.5)		

Values are presented as number only or number (%).
NCRT, neoadjuvant chemoradiation therapy; SMD, standardized mean difference; ASA, American Society of Anesthesiologists; PS, physical status; MAC, mucinous adenocarcinoma; SRCC, signet ring cell carcinoma.
The propensity score was estimated based on the age, sex, tumor height, BMI, ASA PS classification, cell type, and harvested lymph nodes.

studies demonstrated that a wider width of CRM in rectal cancer of 2 mm might be essential to achieve less-distant metastasis and patients with 1.1–5 mm showed the prognosis in a gray zone comparing those of ≤1 mm and ≥5 mm [15,16]. In this study, the rates of positive resection margin were 2.3% and 1.4% (upfront surgery group and NCRT groups, respectively; P = 0.059). Additional analysis was performed with patients of midrectal and low-rectal cancer with the same method. Midrectal and low-rectal cancer patients who underwent NCRT showed a lower rates of positive resection margin than patients who underwent upfront surgery (midrectal cancer: 58 patients [3.4%] with upfront surgery vs. 21 patients [1.8%] with NCRT, P = 0.015; low-rectal cancer: 13 patients [2.3%] with upfront

surgery vs. 0 patients [0%] with NCRT, P = 0.041). According to the results of the proportion of positive resection margin and risk factors for worse OS of patients in NCRT group, we could estimate that NCRT could be helpful in enhancing the surgical completeness of patients with male sex and low-lying rectal cancer by helping to secure safe resection margin length.

The reduced use of NCRT in patients of old age has been reported in other national registry-based studies and this tendency might be due to the higher rates of toxicity after NCRT in elderly patients than in younger patients [17,18]. However, according to a study based on the Swedish national database, old age (>75 years) affected treatment decisions, but it had no effect on the survival in patients [19]. The ACCORD12 phase

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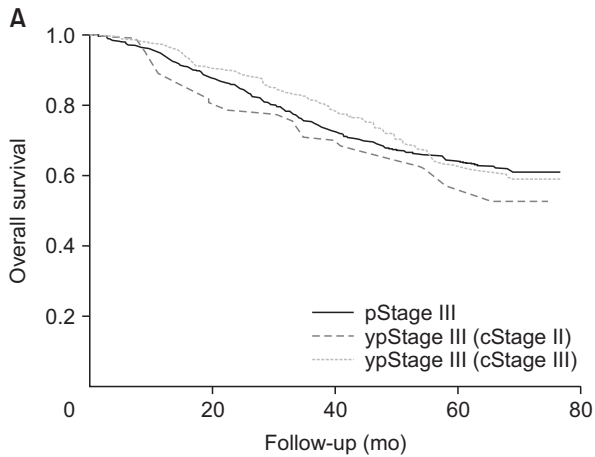
Stage	Number at risk			
	Month 0	Month 20	Month 40	Month 60
pStage III	1,435	1,262	1,045	466
ypStage III (cStage II)	164	135	117	25
ypStage III (cStage III)	1,708	1,551	1,346	479

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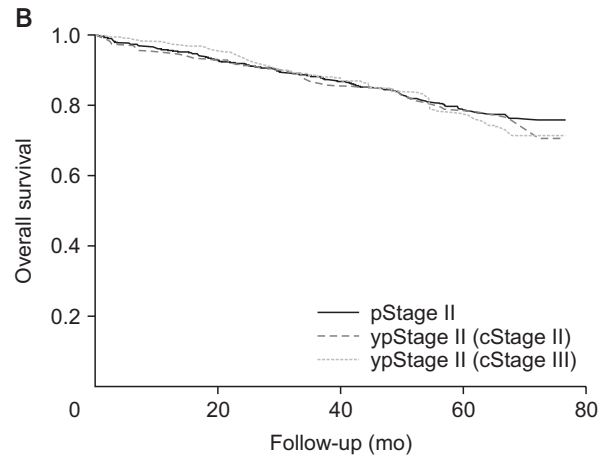
Stage	Number at risk			
	Month 0	Month 20	Month 40	Month 60
pStage II	1,286	1,194	1,115	537
ypStage II (cStage II)	319	301	277	188
ypStage II (cStage III)	1,349	1,291	1,184	445

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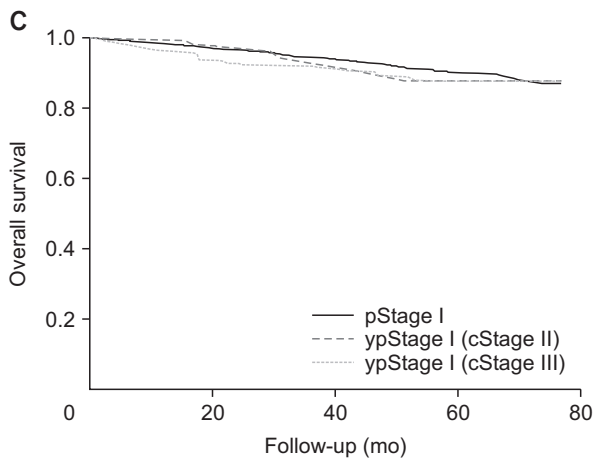
Stage	Number at risk			
	Month 0	Month 20	Month 40	Month 60
pStage I	1,970	1,917	1,852	987
ypStage I (cStage II)	243	241	234	148
ypStage I (cStage III)	856	804	783	388

Fig. 2. Kaplan-Meier curve of overall survival of patients who underwent NCRT compared with patients who underwent upfront surgery after the adjustment using inverse probability of treatment weighting method. (A) The patients of pStage III (pStage III *vs.* ypStage III [cStage II], P = 0.579; pStage III *vs.* ypStage III [cStage III], P = 0.521). (B) The patients of pStage II (pStage II *vs.* ypStage II [cStage II], P = 0.853; pStage II *vs.* ypStage II [cStage III], P = 0.653). (C) The patients of pStage I (pStage I *vs.* ypStage I [cStage II], P = 0.693; pStage I *vs.* ypStage I [cStage III], P = 0.356). NCRT, neoadjuvant chemoradiotherapy; pStage, pathologic stage; ypStage, pathologic stage after neoadjuvant chemoradiotherapy; cStage, clinical stage.

III trial demonstrated that the surgical outcomes, including R0 resection rate and pathologic complete response, did not differ between old (≥70 years) and young (<70 years) patients [20]. We need to consider the utilization of NCRT for elderly patients positively with careful assessment and management of morbidity.

The cStage was not a risk factor for OS in patients who underwent NCRT; however, pStage was a significant risk factor for OS in both NCRT and patients who underwent upfront surgery. This was consistent with the results of previous studies and supports the idea of selecting patients who may acquire survival benefits from NCRT through downstaging [21]. In this study, the OS in ypStage I/II patients was similar to

that of the corresponding pStage I/II patients who underwent upfront surgery. Actually, before the adjustment, the OS in ypStage III patients was statistically better than that of pStage III patients who underwent upfront surgery. We speculated that this difference in OS was due to the tendency of the less administration of NCRT of old aged patients. In particular, the proportion of elderly patients was significantly higher in the upfront surgery group than in the NCRT group. This discrepancy in age might have resulted in poor survival in the upfront surgery group with pStage III. This difference became insignificant after adjustment for differences in clinical characteristics between the 2 subgroups.

This study has several limitations. First, there was no

information about the cStages of upfront surgery groups. Hence, it was not possible to evaluate the concordance of cStage with pStage; thus, the association (OR) of cStage with NCRT administration could not be evaluated. Second, a large proportion of patients (n = 13,018, 67.5%) were excluded from the analysis because there was no record of NCRT. Although the database was managed by HIRA, there were missing data of patients from many institutions, and the majority of data related to NCRT could not be analyzed. In addition, detailed information on clinical characteristics, including molecular profiling, local/systemic recurrence, and tumor regression grade was unavailable in the database. Moreover, the status of resection margins did not differentiate CRM and distal resection margin (DRM); thus, we could not evaluate the effect of resection margin according to the types of resection margin. HIRA revised the database to record the length of resection margins of CRM/DRM in 2018, and, for this reason, the database we utilized did not have information on the length of the resection margin of patients according to the types of resection margin. In spite of these shortcomings of this study, this study is the first study using the database from the National Quality Assessment program which is the only national registry of patients with colorectal cancer in South Korea. We hope that this study will not only provide information on neoadjuvant chemoradiotherapy in South Korea but also be a springboard for the national registry to be more informative.

In conclusion, NCRT was more frequently administered to young, midrectal cancer, and male patients, and old age, underweight, and pStage were independent risk factors for OS in patients who underwent NCRT. NCRT was helpful in controlling the negative effects of male sex and the tumor height on OS. The final pStage was a more reliable predictive factor of OS after NCRT than the cStage.

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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