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증/하부 직장암에서 항암방사선치료 후 의도되지 않은 비광범위절제요법의 종양학적 위험성:

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송광섭



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# **Oncologic catastrophe of unintended non-radical management after chemoradiotherapy for mid or low rectal cancer: a multicentre comparative study with intended non-radical management**

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**Background:** non-radical management after chemoradiotherapy for rectal cancer may increase oncologic uncertainty. This study aimed to compare the oncologic outcomes of intended non-radical management and unintended non-radical management against medical advice.

**Methods:** The study population consisted of cases in which organs were preserved after chemoradiotherapy for clinical stage I-III mid or low rectal cancer between May 2003 and August 2017 ( $n=2883$ ) and was divided into intended non-radical management (group A,  $n=41$ ) and unintended non-radical management (group B,  $n=101$ ), defined as non-operative management or local excision against medical advice of radical surgery. The primary endpoint was 3-year overall survival.

**Results:** The tumor distance, age and performance status of patients were not significantly different between the groups, while the clinical T stage before chemoradiotherapy was lower in group A than in group B ( $P<0.001$ ). The percentage of cases in group B increased from 2.8% of 1450 in period I (May 2003–December 2010) to 4.3% of 1433 in period II (January 2011–August 2017) ( $P=0.037$ ). During the median follow-up period of 34 months (interquartile range 18.3–72.0), the 3-year overall survival in group B (59.7%) was worse than that in group A (90.1%;  $P<0.001$ ), and 80.2% of group B patients had residual or unknown disease status.

**Conclusions:** This study confirmed that unintended non-radical management increases oncologic risk after chemoradiotherapy for rectal cancer regardless of short-term follow-up. Therefore, these findings should be shared with rectal cancer patients who choose to ignore medical advice after chemoradiotherapy.

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**Keywords :** rectal cancer, neoadjuvant chemoradiotherapy, non-radical management, oncologic outcome

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## INTRODUCTION

Neoadjuvant chemoradiotherapy (nCRT) increases therapeutic compliance and decreases local recurrence in locally advanced rectal cancer.<sup>1</sup> Approximately 11.3–78.4% of patients show a clinical complete response (ycCR) after nCRT<sup>2, 3</sup> and 15–30% of patients experience a pathologic complete response (ypCR).<sup>4, 5</sup> Within these good responders, previous studies have shown excellent oncologic results of non-radical management including non-operative management and local excision.<sup>6, 7</sup> However, the scientific evidence is limited due to the presence of highly selective or small non-randomized studies as well as the uncertainty of long-term oncologic outcomes.<sup>4, 6, 7</sup> In addition, there is no definite diagnostic modality for predicting ypCR after nCRT for rectal cancer,<sup>8, 9</sup> and concerns exist that non-radical management might increase disparities in rectal cancer management.<sup>10</sup> Nevertheless, non-radical management by avoiding radical resection after nCRT for rectal cancer has increased in clinical practice.

Although refusal of radical surgery after nCRT occurs in rectal cancer patients,<sup>11</sup> which is considered ‘unintended non-radical management’ by surgeons, little is currently known about the actual oncologic outcome of unintended non-radical management and its proportional changes. We hypothesized that the unintended non-radical management increases oncologic risk. Therefore, this study aimed to compare the oncologic outcomes between intended and unintended non-radical management without radical resection after nCRT for mid or low rectal cancer.

## MATERIALS AND METHODS

This was a multicenter, retrospective, cross-sectional study performed in 3 referral hospitals (Seoul National University Bundang Hospital, Seoul National University Hospital, and National Cancer Center, Korea). The study included mid or low rectal cancer patients with local excision or non-operative management after nCRT for biopsy proven rectal cancer located lower than 10 cm from the anal verge (AV) from May 2003 to August 2017. We excluded patients who underwent radical resection for rectal cancer and those with a history of previous malignancy, concurrent distant metastasis, or concomitant unrelated malignant disease. This study was approved by the Institutional Review Board of the three included hospitals.

An initial evaluation of the rectal cancer was performed before nCRT. Colonoscopy with a biopsy was performed to confirm the pathologic diagnosis. Rectal magnetic resonance imaging (MRI) and/or endorectal ultrasonography (US) were used to determine the depth of tumor invasion and lymph node evaluation. Abdominopelvic computed tomography (CT) and chest CT with or without positron emission tomography (PET) were used to identify distant metastasis.

The patients received a long-course nCRT regimen as described in our previous paper.<sup>12</sup> A dose of 50.4 Gy was provided over 5.5 weeks as long-course radiation therapy. The common chemotherapy regimens were 5-fluorouracil or capecitabine-based. Two cycles of an intravenous 5-fluorouracil bolus with leucovorin were administered in weeks 1 and 5 of radiotherapy, or oral capecitabine was administered continuously during radiotherapy. Short-course radiotherapy using an institutionally approved protocol with 25 Gy or 33 Gy in 5 or 10 fractions with concurrent chemotherapy was performed in some patients as part of an experimental study.<sup>13, 14</sup>

The tumor response was assessed 6-8 weeks after nCRT completion. The protocol was similar to the baseline work-up. Local excision or non-operative management was offered as an alternative treatment for some patients with a ycCR or near ycCR at the surgeon's discretion.<sup>15, 16</sup> The criteria used to determine a ycCR were 1) no residual tumor, including a scar or small ulcer on digital rectal examination (DRE) or colonoscopy and 2) a subtle or small hypointense wall thickening without isointense signal on T2-weighted MRI.<sup>8, 17</sup> Local excision included the excision of a full thickness mesorectum and an adequate safety margin distance

using direct vision or transanal minimally invasive surgery.<sup>15</sup> We defined non-operative management or local excision against the medical advice of radical surgery as unintended non-radical management.

The study population was categorized into 2 groups: intended non-radical management (group A) and unintended non-radical management (group B). The study period was divided into two periods to identify the proportional change in each group: period I from May 2003 to December 2010 and period II from January 2011 to August 2017.

The follow-up surveillance protocols were generally similar in all three hospitals. The patients visited the hospital every 3 or 6 months for the first 2 years and every 6 months thereafter. DAE and laboratory tests including carcinoembryonic antigen (CEA) were performed at every visit. An abdominopelvic CT scan with or without chest CT was performed every 6 months. A colonoscopy was performed 1 year after treatment and then biennially. A group of patients undergoing non-operative management were under close follow-up surveillance at the discretion of the surgeon using sigmoidoscopy and rectal MRI in addition to the routine protocol.

The survival status of all eligible patients was confirmed based on the extinction of a resident registration number from Statistics Korea (KOSTAT, [mdis.kostat.go.kr](http://mdis.kostat.go.kr)). The time interval for overall survival was determined from the final day of nCAT to death from any cause.

Mann-Whitney U test was used to compare continuous variables. Fisher's exact test was used to compare categorical variables. Two-sample z-test was used to compare proportions. The survival outcome was assessed using the Kaplan-Meier curve and a log-rank test. A P-value <0.05 was considered statistically significant. Statistical analyses were performed using the R program for Statistical Computing Version 3.2.3 software (R Development Core Team, Vienna, Austria).

## RESULTS

### ***Patient selection and clinicopathologic characteristics***

Among 2883 patients who received nCRT for mid or low rectal cancer during the study period, 142 patients were identified as eligible for this study. Group A included local excision ( $n=28$ ) and non-operative management ( $n=13$ ). Group B consisted of 5 patients with unintended local excision and 96 patients with unintended non-operative management. The reasons for unintended non-radical management were avoidance of radical surgery including permanent colostomy ( $n=69$ ), poor physical condition ( $n=8$ ), old age ( $n=4$ ), personal problems ( $n=4$ ) and unknown reasons ( $n=16$ ). Both groups showed significant proportional changes from period I to period II: from 0.9% (13 of 1450) to 2.0% (28 of 1433) in group A ( $P=0.025$ ) and from 2.8% (40 of 1450) to 4.3% (61 of 1433) in group B ( $P=0.037$ ) (Table 1).

nCRT was administered to all patients except for 6 who received radiotherapy alone because of reluctance to receive chemotherapy. Total radiation doses ranging from 34.2 Gy to 66.0 Gy were administered due to an incomplete radiotherapy course or radiotherapy without surgery. Two patients received short-course radiotherapy.

Significantly more patients had elevated initial CEA levels in group B than in group A ( $P=0.002$ ). The initial clinical T stage was lower in group A patients than in groups B ( $P<0.001$ ). The P-value did not reach statistical significance in the analysis of the initial clinical N stage ( $P=0.059$ ). Age, performance status and tumor height were not significantly different between groups (Table 2).

### ***Clinical course***

Among patients who underwent local excision in group A, 5 patients had recurrence. Among them, four patients received a salvage operation, and one patient was treated with palliative chemotherapy due to distant bone metastasis. Of the 4 patients who received a salvage operation, only one patient exhibited no evidence of disease (NED) at the end of hospital follow-up. Two patients undergoing non-operative management in group A experienced tumor regrowth. One patient showed regrowth 28 months after the end of neoadjuvant therapy and NED status after abdominoperineal resection (APR), but the other patient was recommended for palliative chemotherapy because of multiple lung metastases (Fig. 1a). Among 5 patients who underwent unintended local excision in group B, 3 patients developed recurrence, one of whom underwent a salvage operation because of lung metastasis. The two

other recurrent patients refused a salvage operation. The majority of group B refused surgery after neoadjuvant therapy (n=96). Seven patients maintained ycCR status over a median hospital follow-up period of 66 months. Eighteen patients later decided to undergo a salvage operation. Salvage operations included one pelvic exenteration, one Hartmann's operation and 9 APRs. Of the 18 patients who underwent a salvage operation, 10 patients were NED status at the end of hospital follow-up. The remaining 71 patients discontinued their regular visits, and 43 patients were confirmed to have died at the end of this study (Fig. 1b).

### ***Survival outcome***

The median follow-up period was 34 months (interquartile range 18.3-72.0). The 3-year overall survival rate of 59.7% (95% CI 50.1-71.1%) in group B was worse than the rate of 90.1% (95% CI 79.8-100%) in group A ( $P<0.001$ ) (Fig 2). In group B, 80.2% (81 of 101) of patients had remaining disease or an unknown disease status at the last hospital visit.

## **DISCUSSION**

This study showed that unintended non-radical management against medical advice increased oncologic risk compared to intended non-radical management after nCRT despite short-term follow-up, even after a salvage operation. Therefore, we suggest that these findings should be shared with rectal cancer patients who act against medical advice after chemoradiotherapy.

To the best of our knowledge, no report has addressed oncologic outcomes in a group with unintended non-radical management. In this study, we assessed the possible harm of non-radical management against medical advice after chemoradiotherapy. Although non-radical management after nCRT is a promising treatment for rectal cancer, clinicians should be cautious and estimate the potential negative effect to prevent patient harm as this option is increasingly used clinically. Recent surveys revealed that surgeons favor non-operative management and wish to discuss options with patients when a ycCR is suspected.<sup>18, 19</sup> In addition, one prospective study showed that patients are also more likely to accept local excision than radical surgery and a considerable number

of patients refused completion total mesorectal excision.<sup>7</sup> Further investigation is warranted to determine whether inappropriate non-radical management is increasing as shown in this study.

According to previous studies, the potential reasons for refusing surgery or standard treatment included the avoidance of radical surgery,<sup>20</sup> older and sicker populations,<sup>21, 22</sup> patient preferences,<sup>23</sup> and communication problems between patients and their physicians.<sup>24, 25</sup> In our study, the main reason for unintended non-radical management was the avoidance of radical surgery, including permanent colostomy. Although the unintended non-radical management group showed a more advanced disease status, their age and general performance were not different from the intended non-radical management group, and many of them could have been cured if they had received radical surgery. We considered that losing an organ and requiring a permanent stoma are overestimated by patients as important reasons to avoid radical surgery. However, there is no clear evidence comparing quality of life after APR with permanent stoma placement to inter-sphincteric resection with low anterior resection syndrome. Therefore, future studies should compare the quality of life and functional outcome between APR and sphincter preservation surgery in low rectal cancer patients.

In some cases, radical surgery is not possible, and an alternative treatment method is needed. Among older or morbid patients, radical surgery-related risks may outweigh the oncologic risks.<sup>26</sup> Additionally, some patients refuse radical surgery even if they understand that their survival outcome will be poor.<sup>27</sup> Local excision may be a possible alternative treatment instead of radical surgery if the patient's condition and disease status are acceptable. One notable finding of our study was the considerable number of unintended non-operative management cases and the few unintended local excisions during the study period, which was much lower than expected. We believe that local excision may be considered more often as an alternative treatment to non-operative management. However, the knowledge that no solid evidence exists regarding the safety of local excision after nCRT for rectal cancer should be shared with patients.

Non-operative management has increased, especially among certain races and populations with poor medical insurance backgrounds.<sup>10</sup>

<sup>28</sup> Previous studies revealed that the decision making of rectal cancer patients is affected by their socioeconomic and educational

status.<sup>29, 30</sup> Taken together, the process of adopting non-operative management in clinical practice might aggravate the disparity in rectal cancer management. There is little information about the survival outcome of unintended non-operative management in rectal cancer patients,<sup>11, 27</sup> and one recent study reported a poor 5-year overall survival rate of 58.3% in rectal cancer patients who refused any surgery after nCRT, which is similar to the results of our study.<sup>27</sup> Therefore, non-operative management should be employed cautiously with consideration of patient compliance.

Although this study was limited to three large volume centers, our data showed a gradual but distinct trend of increasing intended non-radical management in rectal cancer management.<sup>31, 32</sup> This change might reflect surgeon preference, but there is no standardized indication for each non-radical management method to date.<sup>18</sup> Additional collaborative work is required to form a consensus or standardized criteria for non-radical management.

Our study has several limitations. First, inevitable selection bias was present due to the retrospective nature of the study. Clinical data were also limited, especially for post-nCRT evaluation and follow-up surveillance, due to the lack of compliance in the unintended non-radical management group. However, this study adds clinical value because it is not feasible for a comparative prospective study to identify clinical outcomes for unintended non-radical management. Second, the sample size was insufficient to draw firm conclusions, even though we collected study populations from three referral centers. This was based on practical constraints due to the uncertainty of current diagnostic modalities for predicting ypCR after nCRT for rectal cancer. Third, the disease-free survival in the unintended non-radical management group could not be estimated because most of the patients still had disease despite the short follow-up period. However, we confirmed their survival status at the end of the study period using the national registration system.

In conclusion, our study confirms the poor oncologic outcomes of unintended non-radical management compared to the acceptable results of intended non-radical management. Therefore, this finding should be shared with rectal cancer patients who desire inappropriate non-radical management against a doctor's recommendation of radical surgery. In addition, well-designed studies are necessary to confirm the oncologic safety of intended non-radical management compared with that of radical management.

after nCRT for rectal cancer.

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**Table I.** Percentage of patients in each group based on study period.

	Period I (n=1208)	Period II (n=1588)	P *
Radical surgery	1,155 (95.6)	1,499 (94.4)	0.172
Non-radical management			
Group A	11 (0.9)	17 (1.1)	0.819
Group B	2 (0.2)	11 (0.7)	0.080
Group C	40 (3.3)	61 (3.8)	0.521

Values in parentheses are percentages unless indicated otherwise.

period I, January 2005 to December 2010; period II, January 2011 to August 2017.

\*Two-sample z-test.

**Table 2.** Patient characteristics.

Characteristic	Group A (n=41)		P value
	n (%)	n (%)	
Age (IQR), years	66 (55-77)	72 (62-78)	0.130*
Gender			0.712†
Male	21 (51.2)	56 (55.4)	
Female	20 (48.8)	45 (44.6)	
Performance status			0.541†
ECOG 0-1	30 (93.8)	63 (87.5)	
ECOG 2-3	2 (6.2)	9 (12.5)	
Missing	9	29	
Tumor height (IQR), cm	3 (1-4)	3 (2-5)	0.112*
Initial CEA, ng/ml			0.002†
<5	37 (90.2)	65 (65.0)	
≥ 5	4 (9.8)	35 (35.0)	
Missing	0	1	
Differentiation			0.724†
WD	12 (30.0)	22 (22.9)	
MD	26 (65.0)	68 (70.8)	
PD/SAC	2 (5.0)	6 (6.2)	
Missing	1	5	
Initial clinical T stage			< 0.001†
T1-2	16 (40.0)	14 (13.9)	
T3	24 (60.0)	72 (71.3)	
T4	0 (0.0)	15 (14.9)	
Missing	1	0	
Initial clinical N stage			0.059†
Negative	23 (57.5)	39 (38.6)	

Positive	17 (42.5)	62 (61.4)	
Missing	1	0	
Chemotherapy agent			0.110 †
FL	9 (23.1)	40 (41.7)	
X	26 (66.7)	49 (51.0)	
Other agents ‡	4 (10.3)	7 (7.3)	
RT alone/missing	2	5	
RT dose (range), Gy	50.4 (37.8–50.4)	50.4 (25.0–66.0)	0.034*
Missing	1	0	

Missing information was excluded from data analysis.

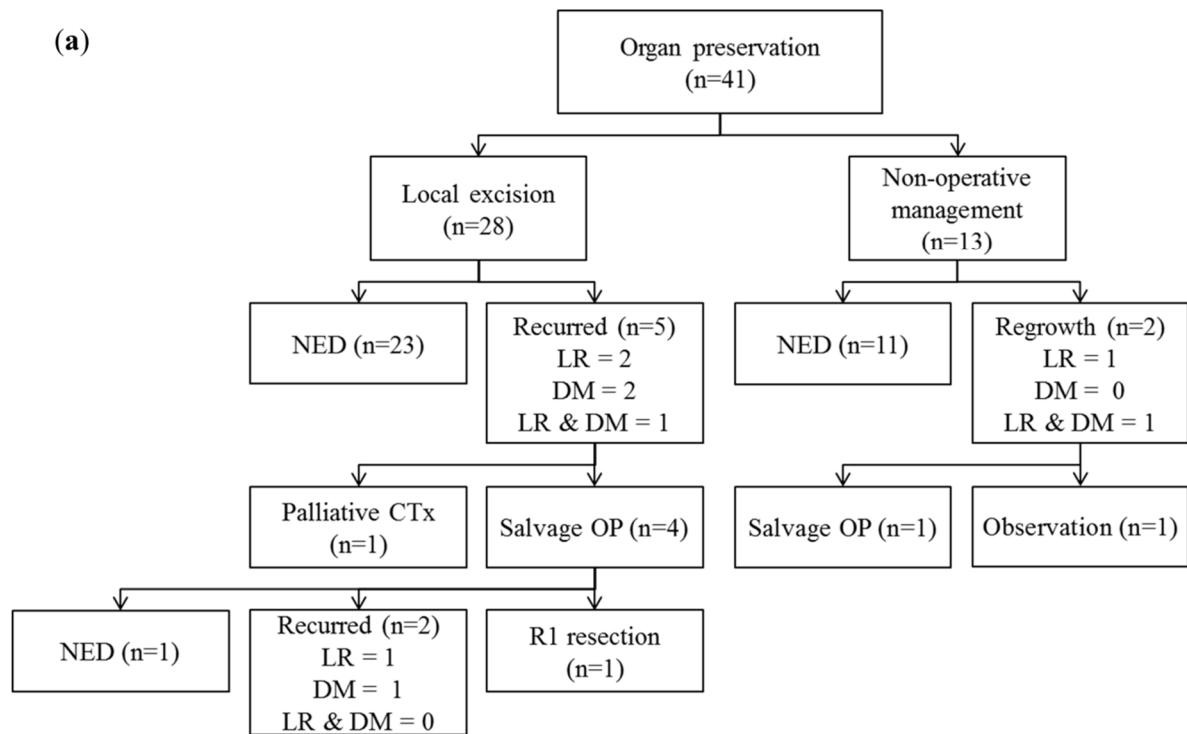
\*Mann-Whitney U test

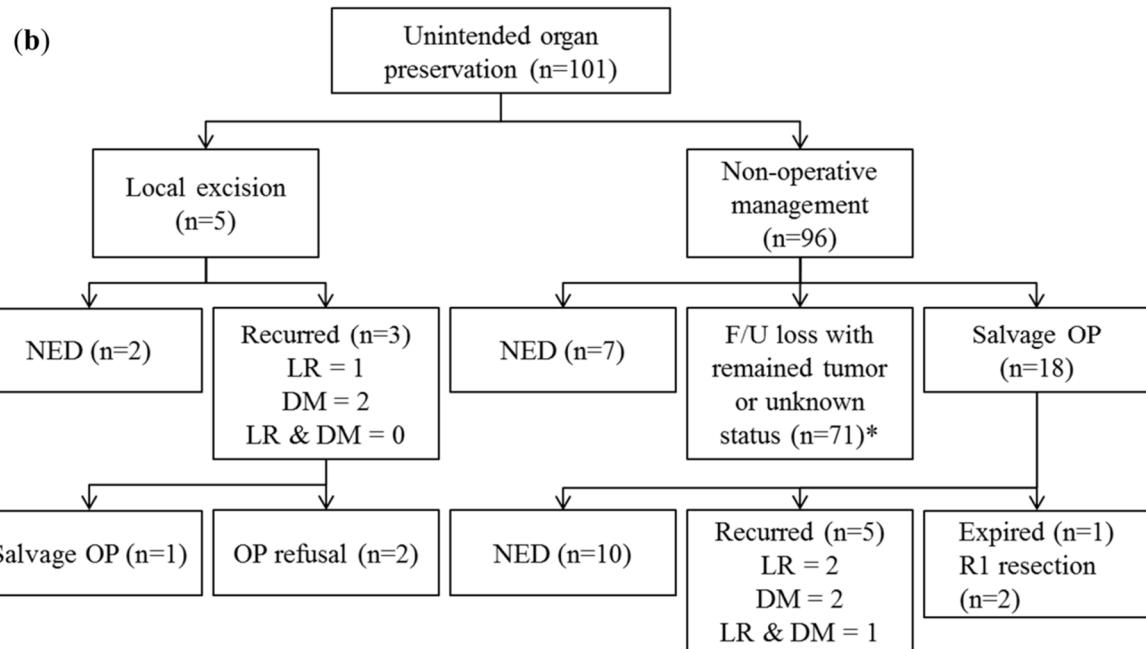
† Fisher's exact test

‡ Other agents included tegafur/uracil with leucovorin and xeloda with irinotecan.

IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; CEA, carcinoembryonic antigen; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; SAC, signet ring cell carcinoma; FL, 5-fluorouracil with leucovorin; X, xeloda; RT, radiotherapy; Gy, gray.

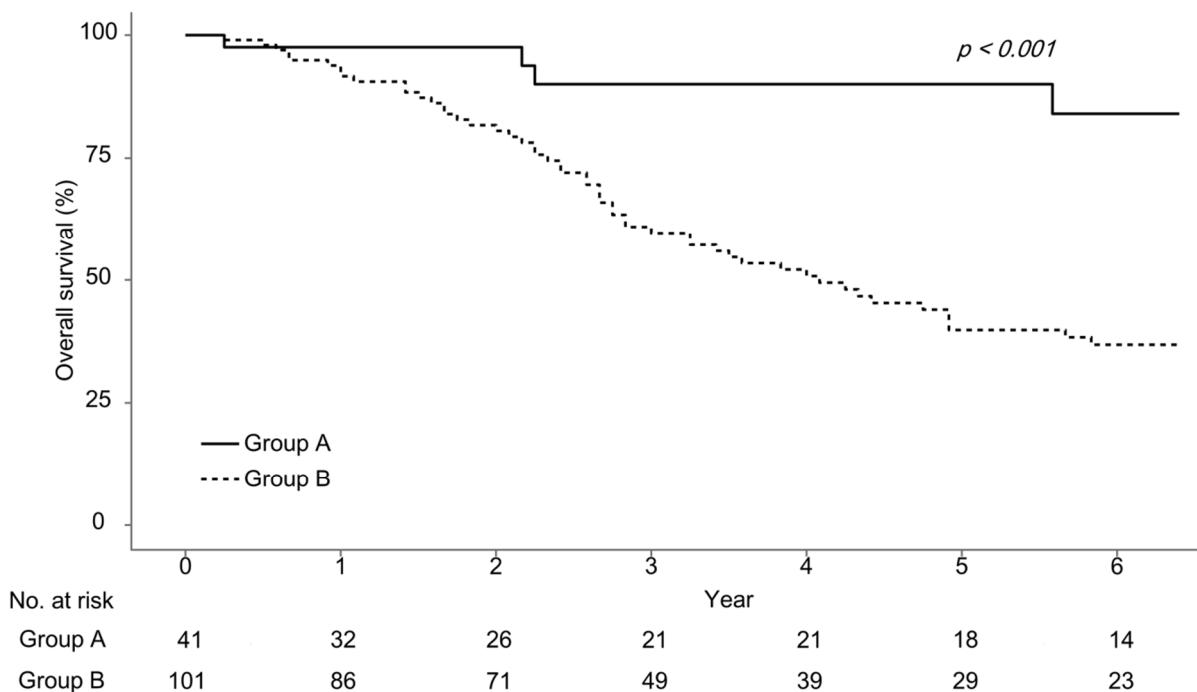
Figure 1. Clinical course of **a** group A and **b** group B.





\* Out of the 71 patients lost to follow-up, 43 patients were dead by the end of the study. NED: no evidence of disease, LR: local recurrence, DM: distant metastasis, OP: operation, CTX: chemotherapy, F/U: follow-up

Figure 2. overall survival according to each group



# Oncologic catastrophe of unintended non-radical management after chemoradiotherapy for mid or low rectal cancer: a multicentre comparative study with intended non-radical management

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배경 : 직장암에서 항암방사선치료 후 비광범위절제요법 (non-radical management)의 등장은 패러다임 전환 시대에 치료 방법을 결정하는데 불확실성을 증가시킬 수 있습니다. 이 연구는 수술자에 의해 계획된 경항문구소절제술 (transanal local excision) 및 관찰점검법 (watch and wait)과 수술자의 의학적 조언에 반하는 의도되지 않은 비광범위절제요법 (unintended non-radical management)의 치료결과를 비교하는 것이 목적이이다.

방법 : 연구 대상자는 2003년 5월과 2017년 8월 사이에 I-II 임상병기로 진단된 중/저위 직장암으로 항암방사선치료를 받은 2883 명의 환자 중 비광범위절제요법으로 항문관악근이 보존된 경우로, 치료방법에 따라 비광범위절제요법 (A 군, 41 명)과 의도되지 않은 비광범위절제요법 (B 군, 101 명)의 두 군으로 나눴다. 1차 평가 변수는 3년 생존율로 정했다.

결과 : 종양의 항문으로부터의 거리, 나이 및 수행되는 각 군간에 큰 차이가 없었으며, 항암방사선요법 전 T 병기는 B 군보다 A 군에서 낫았다. ( $p<0.001$ ). B 군이 연구기간 중 치료법에서 차지하는 비율은 전기 (2003-2010년) 1450 건 중 2.8%에서 후기 (2011-2017년) 1433 건 중 4.3%로 증가했다. 34 개월의 중앙 추적기간 동안 B 군의 3년 생존률은 (59.7%) A 군 (90.1%,  $p<0.001$ ) 보다 나빴으며, B 군 환자의 80.2%가 관찰의 종료시점에 잔류 종양이 있었다.

결론 : 이 연구에서 단기간의 추적기간에도 불구하고 수술자의 의학적 조언에 반하는 비광범위절제치료법이 항암방사선 후 직장암치료의 중앙학적 위험을 증가시킨다는 것을 확인했다. 이러한 결과는 의학적 조언을 거부하며 비광범위절제요법을 원하는 환자들에게 주지 되어야겠다.

주요어 : 지장암, 항암방사선치료, 비강방사선치료제, 생존율

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