

Oncologic Results of Preoperative Chemoradiation in Low Rectal Cancer

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Oncologic Results of Preoperative Chemoradiation in Low Rectal Cancer

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저자 씀

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ABSTRACT

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Sphincter-saving operations for low rectal cancer are on the rise. Here, we investigated the oncologic outcomes of patients who underwent sphincter-saving operations following preoperative chemoradiation for low rectal cancer.

This study included 48 patients who underwent sphincter-saving operations after preoperative chemoradiation with curative intent for locally advanced rectal cancer that was located at less than 5.5 cm from the anal verge. All patients, initially considered for abdominoperineal resection (APR) underwent concurrent chemoradiation therapy (CCRT) consisting of preoperative 5-fluorouracil-based chemotherapy and pelvic radiation (4,500-5,040 cGy) and then followed by surgery 6

weeks after. The oncologic outcomes were investigated, and factors affecting survival were evaluated.

The median follow-up period was 42.1±25.5 (range 5 - 109) months. The mean distance from the anal verge to the lesion was 3.7±1.1 (range 1.0 - 5.5) cm. The overall postoperative complication rate was 32.6%. The recurrence developed in 9 patients (18.8%). The 5-year local recurrence rate was 0% in patients of pathologic (p) primary tumor (T) pT0-2 group and 13.4% in patients of pT3-4 group ($p = 0.075$). The 5-year survival rate was 100% for patients of pT0 group, 93.7% for patients of pT1-2 group, and 52.7% for patients of pT3-4 group ($p = 0.016$). In a multivariate analysis, the pathologic primary tumor stage was a statistically significant independent factor related to the disease-free survival ($p = 0.014$) and overall survival ($p = 0.033$).

In conclusions, sphincter-saving operation after preoperative chemoradiation is a mandatory option without deterioration of oncologic outcomes for the treatment of locally advanced low rectal cancer patients for whom initially APR are considered. Meanwhile pathologic primary tumor stage can be considered as a valuable clinical indicator in predicting prognosis of low rectal cancer.

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Key words: Low rectal cancer, Preoperative chemoradiation, Sphincter-saving operation

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I. INTRODUCTION

Abdominoperineal resection (APR) has been known as a standard treatment modality for lower rectal adenocarcinoma. Recent reports indicate, however, this procedure is associated with worse prognosis comparing to anterior resection (AR).^{1,2} The number of sphincter-saving operation for lower rectal cancer is increasing related to improved surgical techniques, application of preoperative neoadjuvant chemoradiation therapy

(CCRT), and realization of the fact 1 cm of distal resection margin is sufficient enough to achieve cure.³⁻⁶ A recent prospective randomized trial demonstrated that preoperative chemoradiotherapy improves sphincter preservation. Specifically in those patients who were clinically determined to require APR for rectal cancer, sphincter preservation was significantly increased in the preoperative (39%) versus postoperative chemoradiotherapy group (20%).⁷

The aim of this study was to investigate the oncologic outcomes of patients who underwent sphincter-saving operations following preoperative chemoradiation for lower rectal cancer that has been treated by APR traditionally. Also factors affecting survival rate of low rectal cancer patients were evaluated.

II. PATIENTS AND METHODS

Between December 1995 and August 2004, 48 consecutive patients, who were treated at the Yongdong Severance Hospital and the Yonsei Medical Center, underwent sphincter-saving operation with curative intent for locally advanced (endorectal ultrasound T3/T4 or N1 and/or clinically bulky) low rectal cancer located at less than 5.5 cm from the anal verge. All patients in this study had histologically confirmed as primary adenocarcinoma of the rectum. Patients who were requiring local therapy for rectal cancer or patients with distant metastases were excluded in this study. Sphincter-saving operation was classified into an ultralow anterior resection/colorectal anastomosis with staplers (CRA) group and an ultralow anterior resection/handsewn coloanal anastomosis (CAA) group.

Diagnostic evaluations included physical examination, rigid proctoscopy, colonoscopy or double-contrast barium enema, endorectal ultrasound (ERUS) with abdominopelvic computed tomography (CT), abdominopelvic magnetic resonance imaging (MRI), chest X-ray, CBC with platelet count, liver function test and checking

of serum carcinoembryonic antigen level. The location of the tumor was defined as the distance from the anal verge to the caudal margin of the tumor which was measured by digital examination and rigid proctoscopy. Staging ERUS studies were performed whenever technically feasible. For those patients with an obstructing tumor that prevents passage of ultrasound probe for proper study of the entire lesion, abdominopelvic CT or pelvic MRI were performed to assess the extent of local tumor invasion.

All 48 patients received preoperative concurrent chemoradiation therapy. The whole pelvic field received 25 fractions of 180 cGy/day over five weeks for total of 4,500 - 5,040 cGy. The four-field box technique was used. The upper border of the tumor bed field was the L5/S1 junction and the lower limit was the inferior border of the ischial tuberosity. The lateral borders were 1.5 cm lateral to the bony pelvis, and the posterior border encompassed the entire sacrum. The anal canal was included in all patients. Chemotherapy with oral fluorouracil (FU) was given to all patients who received radiotherapy. Oral doxifluridine (900 mg/m², Furtulon, Roche, Seoul, Korea) was administered in three dosages every eight hours during radiotherapy until

seven days before the operation. Surgery was performed six to eight weeks following completion of radiation therapy. When feasible, patients underwent CRA using the double-stapled technique and a circular stapling device (Autosuture, US Surgical, Norwalk, CT). However, a handsewn CAA was performed for tumors that could not be anastomosed with staplers due to limited distal margins or a narrow pelvis. A diverting stoma and a colonic reservoir with pouch were excluded in those who underwent CRA or CAA.

Standard pathologic analysis was performed on all radical rectal resection specimens. After the final histopathologic examination, the rectal tumor was staged according to the 6th UICC TNM staging system. Resection specimens were evaluated for depth of tumor penetration, lymph node involvement, differentiation, lymphovascular invasion, and distal resection margins. Patients with either lymph node involvement or tumors that invaded the muscularis propria received postoperative 5-fluorouracil-based chemotherapy, consisting of 425 mg/m² of 5-fluorouracil plus 30 mg leucovorin for 5 days every 28 days for 12 cycles. Patients were examined every 3 months for the first 2 years after the operation, every 6

months for the next 3 years, and annually thereafter. If the patient did not return for observation after one year, the information was obtained by a letter or telephone.

On a semiannual basis or when there was a suspicion of recurrence, follow-up examinations included clinical history, physical examination, serum carcinoembryonic antigen levels, chest x-ray, abdomino-pelvic computed tomography, colonoscopy, and positron emission tomography (PET) scanning was used if available. Determination of recurrence was made by clinical and radiologic examinations or by histological confirmation. Recurred patients were divided into three groups: local, systemic, and combined. Local recurrence was defined as recurrence within the pelvis; systemic recurrence was defined as disease outside of the pelvis. The main patterns of recurrence were recorded as the first site of detectable failure during the follow-up period.

Statistical evaluation was carried out using the statistics program SPSS 12.0[®] (SPSS, Chicago, IL, USA). The Kaplan-Meier methodology was used to estimate overall survival, disease-free survival, and local recurrence rates; the log-rank test was used to assess statistical significance. A Cox proportional hazards model was

generated by a forward stepwise selection of variables, and a P value of 0.1 was adopted as the limit for inclusion of a covariant. A value of $p < 0.05$ was considered statistically significant.

III. RESULTS

1. Summary of patients and extents of tumor

Male patients were predominant as of 62.5% (30/48). The mean distance from the anal verge to the caudal border of lesion was 3.7 ± 1.1 (range 1.0 - 5.5) cm. In clinical assessment based on ERUS using abdomino-pelvic CT scan and/or MRI, patients with T2 was 17 (35.4%), T3 was 28 (58.3%), and T4 was 3 (6.3%), respectively. In 40% of patients (19/48), lymph node involvement was suspected. In 11 patients (22.9%), pre-treatment serum carcinoembryonic antigen level was above 5 ng/mL. Patient and tumor characteristics before treatment for all 48 patients are summarized in Table 1.

Table 1. Patients and tumor characteristics before treatment

	Value
Mean age, years (range)	54 (31 – 80)
Sex (M:F)	30:18
Body Mass Index (kg/m ²)	23.5 ± 3.0
ASA I	18 (37.5)
II	28 (58.3)
III	2 (4.2)
Mean distance from anal verge, cm	3.7 ± 1.1 (1.0 – 5.5)
Histological type	
Well differentiated	8 (16.7)
Moderately-differentiated	34 (70.8)
Poorly-differentiated	4 (8.3)
Mucinous	2 (4.2)
Depth of invasion *	
T2	17 (35.4)
T3	28 (58.3)
T4	3 (6.3)
Node involvement *	
N-	29 (60.4)
N+	19 (39.6)
Preoperative carcinoembryonic antigen	
> 5 ng/mL	11 (22.9)
≤ 5 ng/mL	37 (77.1)

ASA = American Society of Anesthesiologists.

*Determined by endorectal ultrasound or abdominopelvic magnetic resonance imaging according to 6th AJCC staging system.

2. Postoperative complications

The overall postoperative complication rate was 32.6% (14/48). The most common complication was small bowel obstruction (9.3%, 4 patients), and followed by anal stenosis (7.0%, 3 patients), urinary retention, wound infection and so forth. There was no postoperative mortality within 30 days of operation.

Table 2. Postoperative complications

	Value
Small bowel obstruction	4 (9.3)
Urinary retention	2 (4.7)
Wound infection	2 (4.7)
Anal stenosis	3 (7.0)
Pneumonia	1 (2.3)
Atelectasis	1 (2.3)
Anastomotic leakage	1 (2.3)
Overall morbidity	14 (32.6)

3. Recurrence rate and survival rate

The median follow-up period was 42.1 ± 25.5 (range 5 - 109) months. The overall recurrence rate was 18.8% (9/48) as local of 4.2%, systemic of 12.5% and combined recurrence of 2.1%, respectively (Table 3). The 5-year local recurrence rate was 0% in patients of pathologic (p) primary tumor (T) pT0-2 group and 13.4% in patients of pT3-4 group ($p = 0.075$)(Fig. 1).

Table 3. Patterns of recurrence

	Value
Local recurrence	2 (4.2%)
Systemic recurrence	6 (12.5%)
Combined recurrence	1 (2.1%)
Total	9 (18.8%)

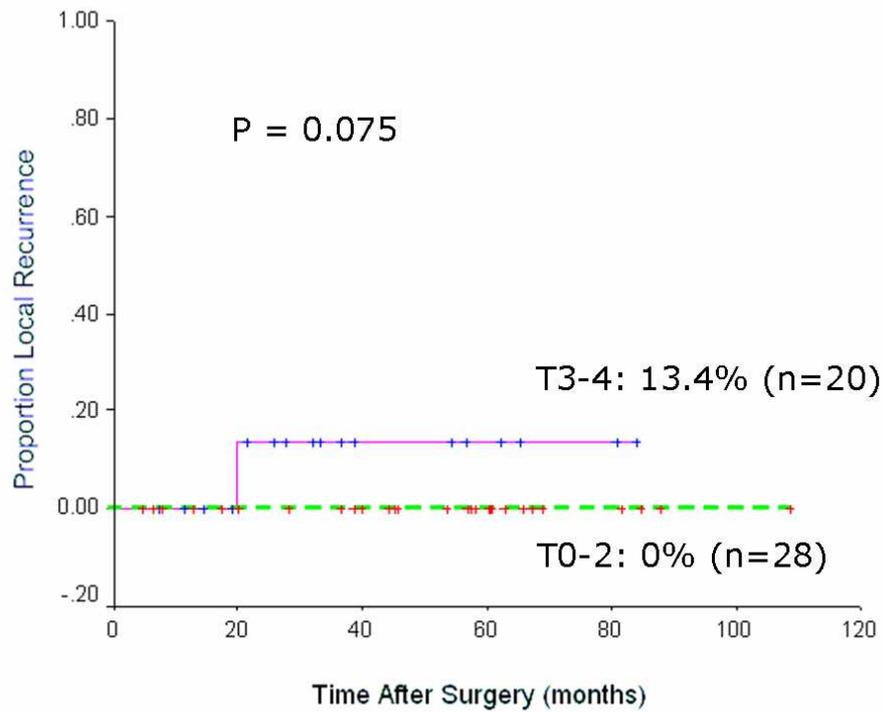


Fig. 1 Five-year local recurrence rates in T0-2 group and T3-4 group after combined sphincter saving operation and preoperative chemoradiation.

Survival rate was analyzed according to pathologic depth of rectal wall invasion (Fig. 2 and 3). There was significant difference in 5-year disease free survival rate and 5-year overall survival rate according to the pathologic primary tumor stage.

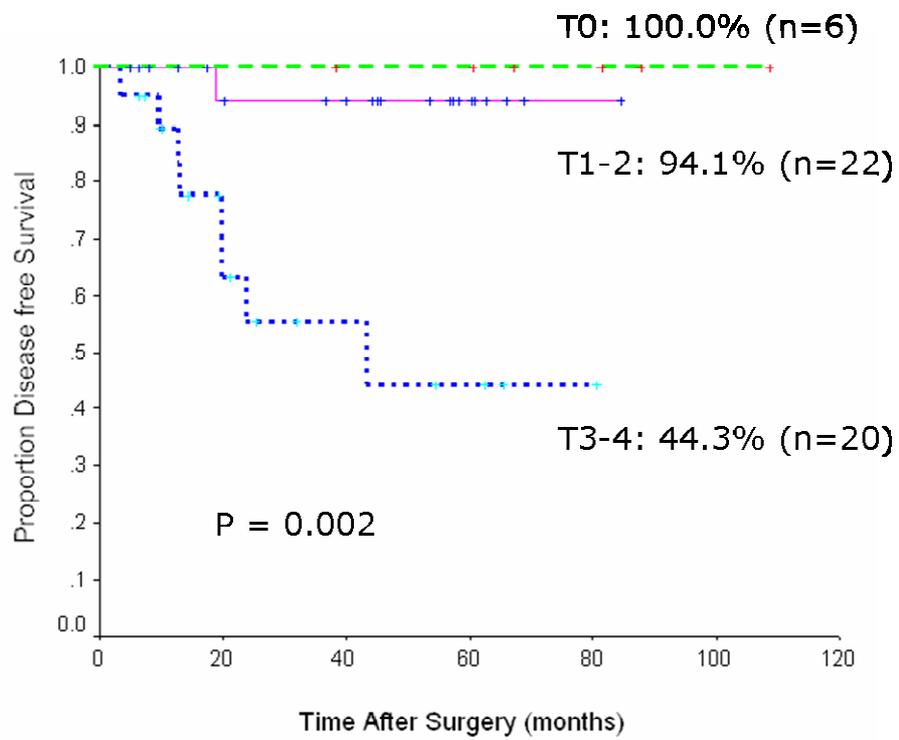


Fig. 2 Five-year disease free survival rates after combined sphincter saving operation and preoperative chemoradiation.

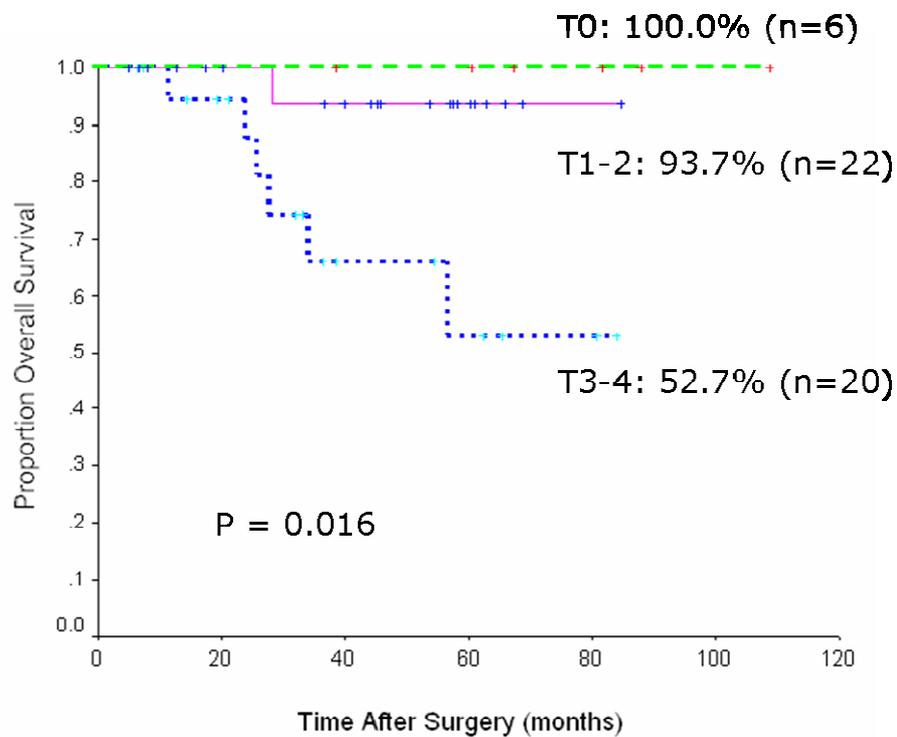


Fig. 3 Five-year overall survival rates after combined sphincter saving operation and preoperative chemoradiation.

4. Prognostic factors affecting survival

Univariate analyses of factors affecting survival showed pathologic primary tumor and pathologic lymph node stages to be significant factors. Multivariate analysis of these factors revealed that pathologic primary tumor stage was one of the most significant factor affecting survival rates (Table 4).

Table 4. Analysis for predicting favorable 5-year overall survival (OS)

	No.	OS (%)	P-Value	
			Univariate	Multivariate
Sex				
Male	30	86.6	0.557	
Female	18	83.3		
Age				
> 55 yr	23	86.9	0.958	
≤ 55 yr	25	84.0		
Histological type				
WD & MD	42	88.1	0.196	
PD & Mucinous	6	66.7		
Operation method				
LAR/CCRT	42	83.3	0.253	
CAA/CCRT	6	100.0		
Pathologic T stage				
T0	6	100.0	0.016	0.033
T1-2	22	95.4		
T3-4	20	70.0		
Pathologic N stage				
N0	37	91.9	0.031	0.551
N1-2	11	63.6		
LVI				
No	47	85.1	0.673	
Yes	1	100.0		
Preoperative CEA				
> 5 ng/mL	11	81.8	0.487	
≤ 5 ng/mL	37	86.5		
Distal resection margin				
> 1 cm	20	85.0	0.834	
≤ 1 cm	28	85.7		

WD = well differentiated; MD = moderately differentiated; PD = poorly differentiated; LVI = lymphovascular invasion; CEA = carcinoembryonic antigen.

IV. DISCUSSION

APR with a permanent colostomy has been the classical operation for cancer in the distal third of the rectum. The rate of performing APR, however, has been falling and was recently quoted at 10% for all rectal cancers.⁸ The absolute indication in APR for a patient with rectal cancer has changed with improvements in surgical techniques, employment of preoperative chemoradiation, and enhanced understanding of distal tumor spread.³⁻⁶ Fucini et al.⁹ reported that selected patients with very low-lying rectal cancers infiltrating the levator muscles and responding to preoperative chemoradiation therapy could still be treated with an advanced sphincter-sparing procedure, instead of an abdominoperineal excision. Furthermore, oncologic and functional results in those patients seemed to be satisfactory. Although some authors have questioned the advantages of sphincter saving operation for lower rectal cancer in terms of quality of life,¹⁰ permanent stoma must be considered a serious handicap. Engel et al.¹¹ reported that patients undergoing an low anterior resection had a significantly better body image, decreased sexual problems, and increased physical

functioning at 4 years, as compared with those who had treated by APR. In our study, postoperative morbidity rates such as small bowel obstruction and urinary retention was 32.6%, however there was no postoperative morbidity.

This practice of sphincter preservation is acceptable only if the long-term oncologic outcomes are not worse than for APR. Rullier et al.¹² reported a series of 43 advanced low rectal cancers (40 T3 and 3 T4), 70% of which were within 2 cm of the anal sphincter. All patients underwent sphincter-saving operations after preoperative chemoradiation. The authors concluded that the preoperative chemoradiation and downstaging allowed sphincter preservation. Our current study is in agreement that preoperative chemoradiation for the purpose of sphincter preservation may be the preferred approach in selected patients. It has not been settled whether oncologic outcomes for sphincter-saving operation are better than those of APR.^{1,13-16} Wibe et al.¹³ showed that survival was significantly worse in patients who underwent APR compared with those who received AR (55% vs. 68%; $p < 0.001$). Another study by Law and Chu¹⁴ also reported significantly worse local control and survival for patients who underwent APR, with APR emerging as an independent factor for poor

cancer-specific survival. In contradistinction to these studies, Chuwa and Seow-Choen¹⁵ noted that a well-conducted total mesorectal excision (TME) in the setting of an APR did not result in worse oncologic outcomes than those of AR; moreover, the type of operation did not affect the oncologic outcomes if consistent standardized surgical techniques were performed in a specialty unit. In general, the evidence appears to suggest that local recurrence is a reflection of the initial tumor biology (stage, histologic grade, and lymphovascular invasion) rather than the type of procedure initially performed.^{17,18} In our study, the depth of rectal wall invasion was statistically significant factor affecting recurrence and survival. Our results showed that the 5-year survival rate of patients with complete response (pT0) was 100%, pT1-2 was 93.7%, and pT3-4 was 52.7% ($p = 0.016$). Multivariate analysis revealed that the pathologic T stage was the independent prognostic factor. Thus, we propose that depth of rectal wall invasion status in the postirradiated tumor specimen was the strongest factor affecting prediction of long-term oncologic outcomes.

Sphincter preservation is the primary goal of preoperative irradiation for locally advanced rectal cancer. Preoperative chemoradiation causes tumor regression, as

manifested by downsizing and downstaging of the tumor.¹⁹⁻²¹ Prospective randomized trials by the German Rectal Cancer Study Group identified that preoperative chemoradiotherapy, as compared with standard postoperative chemoradiotherapy, improved local control but did not improve overall survival.⁷ Furthermore, this neoadjuvant therapy combined with advanced surgical techniques facilitates pelvic dissection and affords direct visual control for the transection of the distal resection margin.¹² Guillem et al.²² analysed 297 patients with locally advanced rectal cancer treated with preoperative chemoradiation followed by total mesorectal excision. The authors documented that a pathologic response greater than 95%, absence of lymphovascular invasion and/or perineural invasion, and negative lymph nodes in the post-CCRT pathologic specimen are independently predictive of improved long-term overall and recurrence-free survival. In the present multivariate analysis, pathologic T stage was the only independent factor affecting overall survival ($p = 0.033$). Our current data suggest that the pathologic T stage can provide valuable prognostic information about survival in patients undergoing curative resection for locally advanced lower rectal cancer.

V. CONCLUSION

We suggest that sphincter-saving operation after preoperative chemoradiation is a mandatory option without deterioration of oncologic outcomes for the treatment of locally advanced low rectal cancer patients for whom initially APR are considered. Meanwhile pathologic primary tumor stage can be considered as a valuable clinical indicator in predicting prognosis of low rectal cancer.

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ABSTRACT (IN KOREAN)

하부 직장암에서 수술 전 화학방사선 요법의 치료 효과

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허 정 욱

최근 하부 직장암에 대한 괄약근 보존술의 빈도가 크게 증가하고 있다. 본 연구의 목적은 국소 진행성 하부 직장암에서 수술 전 화학방사선 요법으로 병기 하강을 유도하여 괄약근 보존술을 시행 받은 환자들의 종양학적인 결과를 알아보고자 하였다.

본 연구는 직장연에서 5.5 cm 미만에 위치한 국소 진행성 직장암 환자 48 명을 대상으로 하였다. 전체 환자는 괄약근 보존을 목적으로 수술 전 5-fluorouracil 을 기본으로 한 항암치료 및 방사선 치료(4,500-5,040 cGy)를 받았으며, 6 주 후에 근치적인 괄약근 보존술을 시행받았다. 종양학적인 결과 및 생존에 영향을 미치는 요인들에 대해서 조사하였다.

중앙 추적기간은 42.1 ± 25.5 (5-109) 개월이었다. 항문연에서 중앙까지의 평균 거리는 3.7 ± 1.1 (1.0-5.5) cm 였다. 수술 후 합병증은

총 14 예(32.6%)가 발생하였으며, 총 9 예(18.8%)의 수술 후 재발이 발생했다. 5년 국소 재발률을 병리학적 T 병기에 따라 구분해보면 T0-2에서는 0%, T3-4에서는 13.4%였다 ($p = 0.075$). 5년 전체 생존율은 T0에서 100%, T1-2에서 93.7%, T3-4에서 52.7%였다 ($p = 0.016$). 다변량 분석 시 병리학적 T 병기만이 무병 생존율 ($p = 0.014$)과 전체 생존율 ($p = 0.033$) 양측 모두에 영향을 미치는 예측 인자로 판명되었다. 결론적으로 기존 복회음절제술을 시행해야만 했던 국소 진행성 하부 직장암이라도 수술 전 화학방사선 요법으로 병기하강을 유도하고 이후 괄약근 보존술을 시행하는 방법으로 치료함으로써 항문의 기능을 유지하면서도 안전하고 우수한 치료 성적을 얻을 수 있었다. 또한 방사선 조사 후의 병리학적 T 병기는 생존율에 영향을 미치는 가장 직접적인 예측인자임을 확인할 수 있었다.

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