

The outcomes of therapeutic decision in lower 3rd rectal cancer patients

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Abstract

To investigate the outcomes of the selective neoadjuvant concurrent chemoradiotherapy (CCRT) in lower 3rd rectal cancer patients in different groups (with or without neoadjuvant CCRT), especially in survival rate, local recurrence rate, and sphincter preservation rate.

From January 1999 to December 2012, 69 consecutive patients who had histologically proven adenocarcinoma of lower 3rd rectum, defined preoperatively as lower tumor margin within 7 cm from the anal verge as measured by rigid sigmoidoscopy, received total mesorectum excision (TME). Our inclusion criteria of neoadjuvant CCRT are lower 3rd rectal cancer, stage II/III, and large (diameter >5 cm or >1/2 of circumference). Neoadjuvant concurrent CCRT had begun to apply lower 3rd rectal cancer patients or not. The radiation techniques of neoadjuvant CCRT for lower 3rd rectal cancer patients were all conventional fraction intensity modulated radiotherapy (IMRT) and concurrent fluoropyrimidine chemotherapy.

Five-year overall survival rate, disease-free survival rate, and local recurrence rate for lower 3rd rectal cancer patients in group I were 51%, 45%, and 25%, respectively. On the contrary, 5-year overall survival rate, disease-free survival rate, and local recurrence rate for lower rectal cancer patients in group II were 70%, 70%, and 3%, respectively. The 5-year sphincter sparing rate was increased from 38.2% to 100% after the beginning of neoadjuvant CCRT. Analyzing local recurrence, overall survival rate, disease-specific survival rate, and sphincter sparing rate in group II were statistically significant superior to group I.

Five-year overall survival rate, disease-free survival rate, and sphincter sparing rate for lower 3rd rectal cancer patients were improved after the addition of neoadjuvant CCRT. No unacceptable toxicity was noted after conventional fraction IMRT and concurrent fluoropyrimidine chemotherapy. Our study showed neoadjuvant CCRT could be valuable for lower 3rd rectal cancer patients.

Abbreviations: CCRT = concurrent chemoradiotherapy, CT = chemotherapy, DRE = digital rectal examination, IMRT = intensity modulated radiotherapy, RT = radiotherapy, TME = total mesorectum excision.

Keywords: CCRT, low 3rd, neoadjuvant, rectal cancer

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C-HC and P-LW contributed equally to this work.

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1. Introduction

The treatment of lower 3rd rectal cancer is still a challenge problem including how to reduce permanent stoma, local recurrence, and improve survival. The improvements in surgical technique, total mesorectum excision (TME), described by Heald et al in 1982,^[1–3] have resulted in local recurrence rate of 4% to 10%.^[1,2,4,5]

Today, the entire removal of the mesorectum by sharp dissection under direct vision along the visceral fascia of the mesorectum is accepted as the standard approach in rectal cancer surgery. Otherwise, the German rectal cancer study trial, published in 2004, demonstrated that TME combined neoadjuvant concurrent chemoradiotherapy (CCRT) could improve local control and was associated with reduced toxicity, compared with TME plus adjuvant CCRT.^[6,7] And then, neoadjuvant CCRT combined with TME has been adopted as standard treatment of rectal cancer worldwide in patients with preoperatively staged as II and III rectal cancer. However, side effect of radiotherapy (RT) such as fecal incontinence, sexual dysfunction, bowel dysfunction, and secondary malignancy can impair quality of life and may shorten life expectancy.^[6,8,9]

The techniques of RT are also improved. Intensity modulated radiotherapy (IMRT) is an advanced form of 3-dimensional conformal radiotherapy (3D-CRT) that changes the intensity of radiation in different parts of a single radiation beam while the treatment is delivered. Early data from retrospective series and phase II trials suggest good compliance, low rates of acute bowel toxicity, and high complete pathologic response rates after preoperative IMRT with concurrent fluoropyrimidine

therapy.^[10–13] However, there are no randomized trials comparing IMRT with conventional 3D-CRT, and its routine use cannot yet be recommended.

Highly selective use of neoadjuvant CCRT to those who had lower 3rd rectal cancer or fixed tumor was recommended in 2003 by Heald and Simunovic to limit the need for RT because RT may cause severe side effect.^[14] But they had no definite inclusion criteria. In the 2001 Dutch TME trial,^[15] RT has not shown significant benefit of 2-year local recurrence rate in stage II patients and upper rectal cancers (10–15 cm from anal verge).

Because upper rectal cancer patients had no definite improvement after neoadjuvant RT, the purpose of our study focused on lower 3rd rectal cancer patients. The optimal therapeutic decision for lower 3rd rectal cancer patients is still unclear. The techniques of RT is improving over time and the value of conventional fractions IMRT with concurrent fluoropyrimidine chemotherapy (CT) is vague. We investigated the outcomes of the selective neoadjuvant CCRT to lower 3rd rectal cancer patients in different 2 groups (with or without neoadjuvant CCRT), especially in survival rate, local recurrence rate, and sphincter preservation rate.

2. Patients and methods

2.1. Study participants

From January 1999 to December 2012, 69 consecutive patients who had histologically proven adenocarcinoma of lower 3rd rectum, defined preoperatively as lower tumor margin within 7 cm from the anal verge as measured by rigid sigmoidoscopy, and received surgery at the Taipei Medical University-Wanfang Hospital and Taipei Medical University Hospital. Our inclusion criteria of neoadjuvant CCRT are lower 3rd rectal cancer, stage II/III, and large (diameter >5 cm or >1/2 of circumference). All enrolled patients were Taiwanese patients (Asian people). Therapeutic decision was very different in 2 groups (neoadjuvant CCRT first or surgery first). To evaluate the outcomes and value of neoadjuvant CCRT to lower 3rd rectal cancer patients, we analyze these patients. As a result, 69 patients were enrolled into this study. Clinical data were reviewed. Our protocols were reviewed and approved by the institutional review board at our hospital (TMU-JIRB No. 2015).

2.2. Protocol of neoadjuvant CCRT

Neoadjuvant CCRT had begun to be applied rectal cancer patients in the 2 hospitals since June, 2006. We divided group I (34 patients) and group II (35 patients) as surgery first or neoadjuvant CCRT first. In group I, there were no lower 3rd rectal cancer patients have neoadjuvant CCRT. And in group II, all lower rectal cancer patients receive neoadjuvant CCRT. There were scarcely studies about optimal therapeutic strategy for lower rectal cancer patients till now. In group II, we constructed a combined committee which included colorectal surgeon, gastroenterologist, radiologist, pathologist, medical oncologist, and radiation oncologist to discuss whether lower 3rd rectal cancer (defined as within 7 cm from anal verge) patients underwent neoadjuvant CCRT or not. Abdomen and pelvic computed tomography was used to the patients preoperatively. The inclusion criteria of neoadjuvant CCRT are stage II/III lower rectal cancer and large (>5 cm in diameter of > 1/2 of circumference or regional lymphadenopathy) in 2 Taipei Medical University hospitals.

Three-dimensional conformal RT or IMRT was planned on the PINNACLE treatment planning system (Philips, Amsterdam, Netherlands) using 10- or 6-MV X-rays to advanced lower rectal cancer patients. Clinical target volumes (CTVs) included the primary rectal tumor lesions and the 2 end portions of the rectum; the perirectal tissues; and the anterior sacral lymph, iliac lymph, obturator lymph, and true pelvis internal iliac lymph drainage areas. For patients with stage T4 lesions or tumors invading the bladder, the CTV also included the external iliac lymph drainage area. Planned target volume (PTV) is defined as CTV or gross tumor volume (GTV) +8 mm. The median total dose was 45 Gy delivered to the CTV in 25 fractions of 1.8 Gy without a boost dose. A 5.4-Gy boost comprising 3 fractions of 1.8 Gy to the GTV increased the total dose to 50.4 Gy. All techniques of RT with neoadjuvant CCRT were conventional fraction IMRT and concurrent fluoropyrimidine CT. During the 1st and 5th weeks of RT, fluorouracil was given as a 120-hour continuous infusion at a dose of 1000 mg per square meter per day. In patients who were assigned to neoadjuvant treatment, surgery was scheduled to take place 4 to 6 weeks after the completion of chemoradiotherapy. Four cycles of bolus fluorouracil (500 mg per square meter per day, 5 times weekly, every 4 weeks) were started 4 weeks after surgery (in the preoperative-treatment group) if there were pathologic risk factors such as margin positive, tumor size >5 cm, or pathologic lymph node positive. Adjuvant CT would be delivered for margin positive, tumor size > 5 cm or pathologic lymph node positive. And RT would be delivered for margin positive. There is no adjuvant CCRT if neoadjuvant CCRT was done. This is because no margin positive in group II (Table 1). In group I, adjuvant RT with 5040 cGy in 28 fractions will be done for margin positive. The radiation techniques of neoadjuvant CCRT for lower 3rd rectal cancer patients were all conventional fraction IMRT. RT-related complications were categorized using the Radiation Therapy Oncology Group Late

Table 1

Characteristics of the patients in different groups.

| | Group I (n=34) | Group II (n=35) | P |
|----------------------------------|----------------|-----------------|----------|
| Age, year | | | |
| <65 | 15 | 19 | 0.47 |
| >65 | 19 | 16 | |
| Sex | | | |
| Male | 19 | 23 | 0.46 |
| Female | 15 | 12 | |
| Stage | | | |
| Stage II | 15 | 15 | 0.97 |
| Stage III | 19 | 20 | |
| Size, cm | | | |
| Neoadjuvant CCRT | 4.7 ± 1.2 | 5.1 ± 1.3 | 0.741 |
| Yes | 0 | 35 | 0.0001** |
| No | 34 | 0 | |
| Adjuvant RT | | | |
| Yes | 13 | 0 | 0.0001** |
| No | 21 | 35 | |
| Adjuvant CT | | | |
| Yes | 30 | 18 | 0.01 |
| No | 4 | 13 | |
| Location (cm from anal verge) | 5.0 ± 1.5 | 4.8 ± 1.4 | 0.752 |
| Sphincter preservation procedure | 13 | 35 | 0.0001** |
| APR | 21 | 0 | 0.0001** |

APR=abdomino-perineal combined resection, CCRT=concurrent chemoradiotherapy, CT=chemotherapy, RT=radiotherapy.

Radiation Morbidity Scoring Criteria and the Common Terminology Criteria for Adverse Events (Version 3.0).

2.3. Surgery and follow-up

Total mesorectal excision (TME) was performed in all lower rectal cancer patients included high ligation of inferior mesentery artery and vein, mobilization of sigmoid colon, descending colon or splenic flexure, and mobilization of rectum by sharp dissection with diathermy or scissors under direct vision in the avascular plane between the visceral fascia of mesorectum and the parietal fascia of the pelvis, as had been originally described by Heald.^[2]

Pathological staging of the disease was performed according to the American Joint Cancer Committee on cancer staging manual, 6th edition. Following surgery, all patients were entered into a surveillance program designed to detect recurrent local and distant disease. Clinic visits were scheduled every 3 months for the 1st 2 years, then at 6-month intervals for 3 years. At each visit, pelvic examination was performed and carcino-embryonic antigen was measured. Abdomen ultrasound or computed tomography was performed every 6 months. Colonoscopy was done after 1 and 3 years. If the patients lost in follow-up visit at out-patient department, we will contact the patients by telephone or mail. Any symptom potentially related to local tumor recurrence was investigated with digital rectal examination (DRE), colonoscopy, and computed tomography or magnetic resonance imaging. Recurrence was confirmed by biopsy if possible, but any pelvic mass with progressively increasing size in image study was classified as recurrence unless this was clearly disproved.

2.4. Statistical analysis

End points for the study were documentation of recurrent local disease, distant spread without local recurrence, death from cancer recurrence, and death without recurrence. Patients lost follow-up were censored from the time of last follow-up. Frequency tables are used for the presentation of patient and treatment characteristics. Differences in proportions were analyzed with 2-tailed Chi-squared test. Numerical values were compared using the Student *t* test. The cumulative proportions of local recurrence and survival rates were performed according to the Kaplan–Meier method, Kaplan–Meier survival curves were compared using Log-rank test. Statistical analyses were performed with SPSS version 13.0 for windows (SPSS Inc, Chicago, IL).

3. Results

In the study of 69 patients, there were all lower 3rd rectal cancers. The patient population was composed of 42 men (61%) and 27 women (39%). There was no statistical significance in age between 2 groups (Table 1). The distribution of cancer stage was as follows: 30 stage II (43.5%) and 39 stage III (56.5%). The mean (5.0+/-1.5) distance from anal verge (cm) was provided for period 1 and 4.8+/-1.4 cm for period 2 patients (Table 1). Mean size of tumors was also provided and there were no statistical differences (Table 1). All patients underwent total mesorectal excision in group I and II. In group I, there were 61.8% lower rectal patients need abdomino-perineal combined resection (APR) and there were only 38.2% sphincter-preservation rate. Compared with group II, the most difference is neoadjuvant CCRT for lower 3rd rectal cancer patients. There were 0% lower

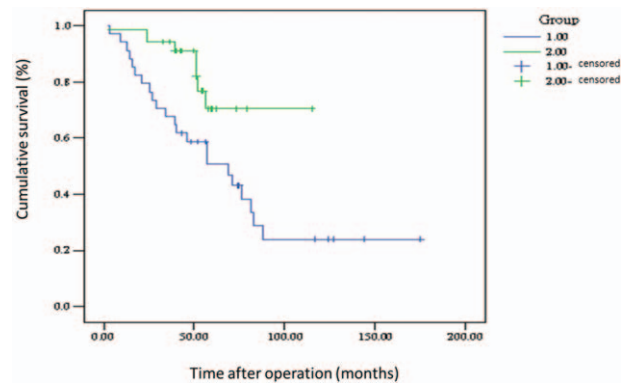


Figure 1. Overall survival for 2 groups.

rectal patients need APR and there were 100% sphincter-preservation rate. In our study, there was no correlation between the distance to anal verge and the OS or DFS rate. Response rate (partial and complete response rate based on Response Evaluation Criteria in Solid Tumors) and down stage rate were 100% and 76% in group II.

There was no association between tumor location, size, age, gender, stage, surgical techniques for group I (surgery first), and group II (neoadjuvant CCRT first) (Table 1). The patients who had lower 3rd rectal cancer underwent more APR and suffered from more local recurrence, death rate, and less sphincter sparing rate (Table 1 and Fig. 1). The median duration of follow-up was 67 months (range, 1–150 months). There was no one clinical anastomotic leakage who underwent emergent colostomy and 30-day mortality. There were no more grade 2 radiation-related complications noted in our medical review.

Five-year overall survival rate, disease-free survival rate, and local recurrence rate for lower 3rd rectal cancer patients in group I were 51%, 45%, and 25%, respectively. On the contrary, 5-year overall survival rate, disease-free survival rate, and local recurrence rate for lower 3rd rectal cancer patients in group II were 70%, 70%, and 3%, respectively (Figs. 1–3). The 5-year sphincter sparing rate was increased from 38.2% to 100% (Table 2) after the beginning of neoadjuvant CCRT. Analyzing local recurrence, overall survival rate, disease-specific survival rate, and sphincter sparing rate in group II were statistically significant superior to group I (Table 2).

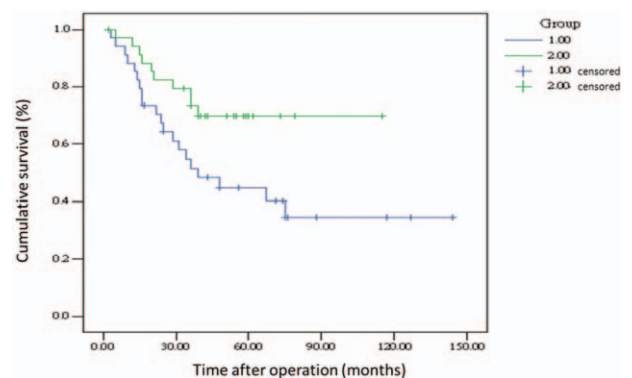


Figure 2. Disease-free survival for 2 groups.

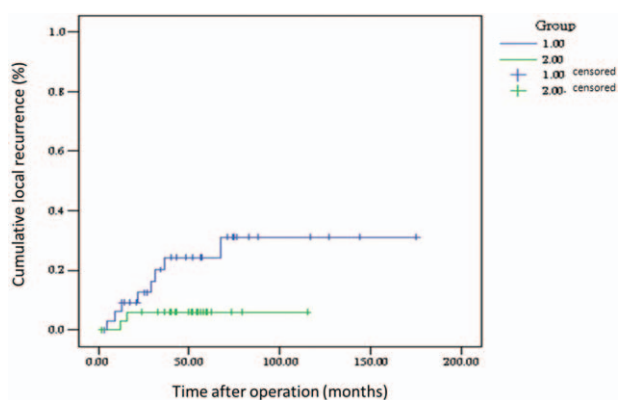


Figure 3. Local recurrent rate for 2 groups.

4. Discussion

Although flexible sigmoidoscopy is superior to rigid sigmoidoscopy in terms of patient comfort, diagnostic value, and ease of doing procedures like biopsy and polypectomy,^[16] but to assess the true height (distance from anal verge) of rectal cancers, rigid sigmoidoscopy is still the standard procedure. Rigid rather than flexible sigmoidoscopy can most accurately determine the distance between the distal tumor margin, the top of the anorectal ring, and the dentate line as well as the orientation within the rectum (e.g., anterior, posterior, left, and right). In our study, all lower 3rd rectal cancers were diagnosed by rigid sigmoidoscopy and estimate the true distance from anal verge. The definition of lower 3rd rectal cancers in our studies were diagnosed by consistence tool and superior to diagnosed by inconsistency diagnosed tools such as flexible sigmoidoscopy, magnetic resonance imaging,^[17] DRE, transrectal ultrasound, or transrectal endoscopic ultrasound.^[7,8,18,19] According to our best knowledge, all lower 3rd rectal cancer confirmed by the same tool with rigid sigmoidoscopy in scarcely studies. In our study, the true lower 3rd rectal cancer could be presented truly.

Analyzing local recurrence in all locations rectal cancer whatever upper, middle, or lower 3rd rectal cancer, the risk factor of local recurrence was lower 3rd rectal cancer, and patients who had T4 tumor or undergoing APR (data not shown and not published). At the same time, patients who had lower 3rd rectal cancer suffered from more distant/systemic recurrence and death.^[20] Venous drainage of the lower rectum is through the hemorrhoidal veins to the vena cava, bypassing the liver, and lung metastases might be more common.^[20] So, the high risk group for local recurrence and survival was stage II/III lower 3rd rectal cancer. Compared with largest series of lower 3rd rectal cancers in stage II and III, our outcomes of 5-year sphincter sparing rate and 5-year disease free survival rate in group II were superior to Lavery et al.^[21] And our study had longer follow-up time; the median duration of follow-up was 67 months (range, 1–150 months). The major therapeutic change before surgery between group I and II is neoadjuvant CCRT. Adjuvant therapy usually depended on pathologic risk factors. In group II, adjuvant RT or CT is statistically significantly less (Table 1). The neoadjuvant CCRT improved the outcomes of lower 3rd rectal cancer including overall survival rate, disease-free survival rate, and sphincter sparing rate. The medical progression with time is corresponding with the outcome. And this might be the 1st article

Table 2

Survival rate of the population in different groups.

| | Group I, % | Group II, % | P |
|--------------------------------------|------------|-------------|---------|
| Five-year overall survival rate | 51 | 70 | 0.0139* |
| Five-year disease-free survival rate | 45 | 69 | 0.0275* |
| Five-year local recurrence rate | 25 | 3 | 0.0369* |

to estimate the optimal therapeutic policy for lower 3rd rectal cancers.

There was no association between tumor location, size, age, gender, stage, surgical techniques for group I (surgery first), and group II (neoadjuvant CCRT first) (Table 1). The only definitive indication for neoadjuvant chemoradiotherapy, supported by data from prospective randomized trials, is locally advanced (T3/4) disease.^[8,19,22] The best regimen for neoadjuvant therapy has not been established. For all lower 3rd rectal cancer patients under neoadjuvant CCRT in our study, we used conventional fractionation RT with concurrent fluoropyrimidine CT (long-course chemoradiotherapy) rather than the short-course Swedish approach to RT alone.^[23] There were no more grade 2 radiation-related complications noted in our neoadjuvant CCRT patients. Compared with short course RT,^[24] gastrointestinal disorders, resulting in hospital admissions and bowel obstruction was not happened in our neoadjuvant CCRT patients. After neoadjuvant CCRT, there was no one clinical anastomotic leakage who underwent emergent colostomy and 30-day mortality. Our results imply neoadjuvant CCRT (conventional fraction RT with concurrent fluoropyrimidine CT) will be the feasible therapeutic policy for lower 3rd rectal cancer and improves overall survival, disease-free survival, and sphincter sparing rate.

With the evolution of treatment modalities, the techniques of RT are also improving. In our study, there were no more grade 2 radiation-related complications noted in our neoadjuvant CCRT patients categorized using the Radiation Therapy Oncology Group Late Radiation Morbidity Scoring Criteria and the Common Terminology Criteria for Adverse Events (Version 3.0). All techniques of RT with neoadjuvant CCRT were IMRT. Although experience with IMRT increases, its benefits in reducing acute morbidity (small and large bowel, genitalia, pelvic skin, and soft tissues) have been increasingly apparent when it is administered by experienced radiation oncologists, but long-term effects are not yet fully characterized. Most articles about IMRT were anal cancer or nonspecific locations of rectum.^[10,25,26] Till now, no article demonstrates the outcomes of neoadjuvant CCRT for lower 3rd rectal cancer with conventional fraction IMRT and concurrent fluoropyrimidine CT. Five-year overall survival rate, disease-free survival rate, and local recurrence rate for lower rectal cancer patients in group II were 70%, 70%, and 3%, respectively (Figs. 1–3). The 5-year sphincter sparing rate was increased from 38.2% to 100% (Table 2) after the beginning of neoadjuvant CCRT. Our treatment modality can achieve a very encouraging sphincter preservation rate and a favorable survival rate without excessive toxicity.

For patients undergoing either a sphincter-sparing procedure or an abdominal perineal resection of a rectal cancer, TME was done in our lower 3rd rectal cancer patients. TME is associated with improved local control and better survival rates. Improved local control appears to result in better survival. In the past, we have questioned the utility of neoadjuvant CCRT for patients with advanced rectal cancer, particularly those involving the

upper rectum, given the favorable low rates of local recurrence after TME alone in the Dutch TME trial and retrospective analyses.^[15,27-29] This is why we estimate the outcomes of lower 3rd rectal cancer after TME. For precise location of rectum, we used rigid sigmoidoscopy for height of rectum instead of various diagnostic tools such as DRE, an abdominopelvic computed tomography (CT), a transrectal ultrasound (TRUS), or colonoscopy. In our study, neoadjuvant CCRT could be valuable for lower 3rd rectal cancer patients in overall survival, local control, and sphincter sparing rate even after TME.

5. Conclusions

With the progress of time and the evolution of treatment modalities, there were less lower rectal patients need APR (61.8% in group I vs 0% in group II) after the addition of neoadjuvant CCRT. Five-year overall survival rate, disease-free survival rate, and sphincter sparing rate for lower 3rd rectal cancer patients in group II were improved. No unacceptable toxicity was noted after neoadjuvant conventional fraction IMRT and concurrent fluoropyrimidine CT. Our study showed neoadjuvant CCRT could be valuable for lower 3rd rectal cancer patients.

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