***Original Article***

# Neoadjuvant Concurrent Chemoradiotherapy Might Not be Necessary for Stage III Upper-third Rectal Adenocarcinoma

Ming-Hung Lee
Jui-Ho Wang
Tai-Ming King
Min-Chi Chang
Chao-Wen Hsu
*Division of Colorectal Surgery, Department of Surgery, Kaohsiung Veteran General Hospital, Kaohsiung, Taiwan*

***Key Words***
Upper-third rectal cancer;
Neoadjuvant chemoradiotherapy;
Adenocarcinima

***Purpose.*** The necessity of neoadjuvant concurrent chemoradiotherapy in stage III upper-third rectal cancer patients has not yet been definitively proven. The aim of this study was to compare the oncological outcomes and clinical results of neoadjuvant concurrent chemoradiotherapy and primary radical surgery in upper-third rectal cancer patients.
***Methods.*** Between January 2004 and December 2012, we examined 222 pathological stage III rectal cancer patients. These patients were separated into two groups based on their treatment modality: the neoadjuvant concurrent chemoradiotherapy group and the primary radical surgery group. The clinicopathological and surgical data of the two groups were then collected and retrospectively analyzed.
***Results.*** In our study cohort, men were predominant in both groups. The mean age of all patients was 63.2 years. After a three-year follow-up period, no significant statistical differences were found in the local recurrence rate or cancer-specific survival. Based on the Kaplan-Meier curve, the *p*-values for local recurrence, distant metastasis, and cancer-specific survival were 0.526, 0.087, and 0.127, respectively. The complication rate for neoadjuvant concurrent chemoradiation therapy was 25.7% and 8% for primary radical surgery; the *p*-value was 0.002. The most common complications for patients were anastomotic leakage and rectovesical fistula.
***Conclusions.*** Based on our data, neoadjuvant concurrent chemoradiation therapy for stage III upper-third rectal tumors is not necessary. Both the clinical results and the long-term oncological outcomes indicated that there were no significant statistical differences between the two groups. However, a higher rate of complications was observed in the patients who received neoadjuvant concurrent chemoradiotherapy.
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The question of whether carcinomas located in the upper-third of the rectum should be treated as colon cancers or as rectal cancers remains unanswered.[1,2] Several retrospective studies have shown that onco-

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Correspondence to: Dr. Jui-Ho Wang, Division of Colorectal Surgery, Department of Surgery, Kaohsiung Veteran General Hospital, No. 386, Dazhong 1st Rd., Zuoying Dist., Kaohsiung City 81362, Taiwan. Tel: 886-7-342-2121 ext. 3025; Fax: 886-7-342-2288; E-mail: hik008@hotmail.com

logical outcomes between recto-sigmoid junction cancers, sigmoid cancers, upper-third rectal cancers and middle-third rectal cancers share several key characteristics.[3-5]

Upper-third rectal tumors are located above the peritoneal reflection. The surgical technique as the intraperitoneal lesion such as colon cancer for well training surgeons.[6] Typically, less touch-based techniques are used to prevent the spread of upper-third rectal tumors during intraoperative periods. Both national guidelines and randomized trials suggest that all rectal cancers should be treated via the use of neoadjuvant concurrent chemoradiotherapy (CCRT) and radical intervention.[7] However, the European Society for Medical Oncology (ESMO) suggests that radical surgery alone is enough for early (cT1-2, some cT3) upper-third rectal tumors.[8]

However, it is standard procedure in our clinic to treat patients with upper-third rectal cancers with only radical surgery and without any neoadjuvant CCRT. Few studies exist that directly compare treatment outcomes for upper-third rectal tumors. Therefore, we retrospectively analyzed the treatment outcomes for patients with upper rectal cancers (10~15 cm from the anal verge) and cancers of the recto-sigmoid junction (15~18 cm from the anal verge), who had been treated from 2004 to 2012 in Kaohsiung Veterans General Hospital (VGHKS) with two separate treatment modalities.

# Materials and Methods

## Patients

Between January 2004 and December 2012, 1020 patients were diagnosed with rectal cancer in the Kaohsiung Veterans General Hospital. Among them, 222 patients were diagnosed with stage III rectal cancer located at the upper-third of the rectum. Patients with distant metastases and tumors that were not histologically identified as adenocarcinomas were excluded (Fig. 1).

Stage III upper-third rectal cancers were defined as tumors that were located within 10~15 cm from the anal verge (1) and pathologically staged as stage III tumors, including the tumor deposit (2).

Each patient received a colonoscopy, coupled with a biopsy, to locate the tumor and to confirm the histological diagnosis. Clinical stage of the tumor was determined before treatment via computed tomography (CT) scans or magnetic resonance imaging (MRI) of the abdomen and pelvis. If necessary, a chest CT scan and liver ultrasonography were performed to exclude the presence of distant metastases. We then analyzed the patients' clinicopathological characteristics and demographic features such as age, gender, tumor size, the number of harvested lymph nodes, post-operative chemotherapy, diverting colostomy, perioperative complications, local recurrence, distant metastasis,

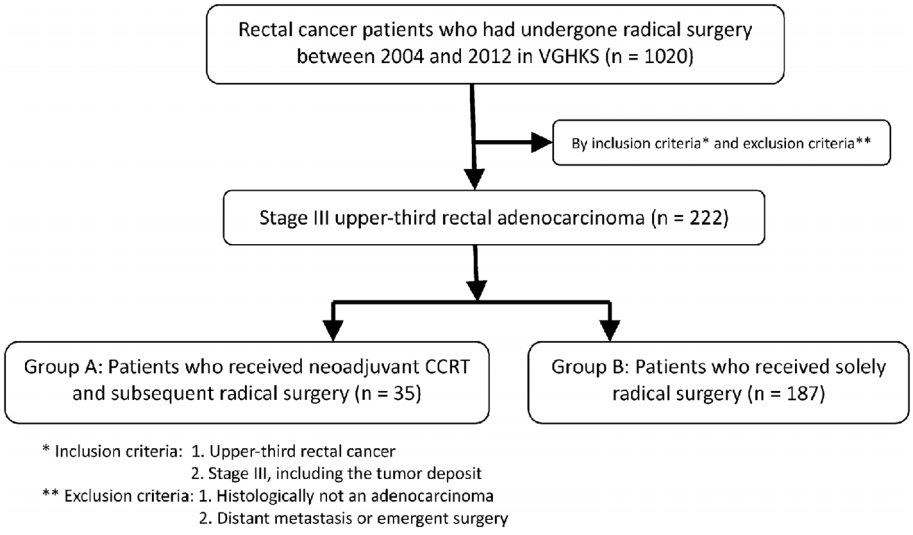


**Fig. 1.** Patient collection flow chart.

and overall survival. All patients were followed-up for at least 3 years from the date of diagnosis.

All data in this study were partly obtained from the Cancer Registry Database, provided by the Cancer Center of Kaohsiung Veterans General Hospital, and partly from patient charts.

### Neoadjuvant chemoradiotherapy group

Thirty-five patients underwent 5040 cGy of long-course radiotherapy. During this period, patients also received intravenous 5-Fluorouracil or oral Ufur (Tegafur 100 mg + Uracil 224 mg) as a form of chemotherapy.

### Surgical technique

Preoperative bowel preparation was performed in all patients. Conventional low anterior resections or laparoscopic low anterior resections were performed using the following steps. First, the inferior mesentery artery was ligated and divided at its origin. Second, the rectum was sharply mobilized along the anatomic plane to maintain the integrity of the mesorectum. Finally, either a temporary loop ileostomy or a transverse loop colostomy was performed, based on the surgeon's evaluation of the patient's quality of anastomosis.

### Statistical analysis

For each categorical variable, chi-square tests were used to detect significant differences between the two groups. Local recurrence and overall survival after treatment were analyzed using the Kaplan-Meier method, and statistically significant differences in survival were identified using the log-rank test. All statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

## Results

In our study cohort, composed of 222 patients, the mean age was 63.2 years and male predominance was seen in both groups. Additional clinical data are shown in Table1. Nine out of the 35 patients in the neoadjuvant CCRT group showed major complications including anastomotic leakage in 5, rectovesical fistulas in 1, rectovaginal fistulas in 1, and anastomosis stenosis in 2. Fifteen patients in the primary radical surgery group experienced major complications such as anastomotic leakage in 6, rectovesical fistulas in 3, rectovaginal fistulas in 1, anastomosis stenosis in 2, pelvic abscesses in 1, and ureteral injuries in 2. For treatment complications, the statistical value of the chi-square test was $p = 0.002$, which indicated a significant difference between two groups.

There was also a significant difference in the rate of diverting colostomies as we typically constructed diverting enterostomies in the neoadjuvant CCRT

**Table 1.** Basic characteristics of the study group

| Variables | Group A (n = 35) | Group B (n = 187) | *p* value |
|---|---|---|---|
| Gender | | | 0.047* |
| Male | 28 (80.0%) | 117 (62.6%) | |
| Female | 7 (20.0%) | 70 (37.4%) | |
| Age | | | 0.310 |
| ≤ 50 years | 3 (8.6%) | 17 (9.1%) | |
| 51~69 years | 13 (37.1%) | 94 (50.3%) | |
| ≥ 70 years | 19 (54.3%) | 76 (40.6%) | |
| Tumor size | | | 0.455 |
| ≤ 5 cm | 26 (74.3%) | 127 (67.9%) | |
| > 5 cm | 9 (25.7%) | 60 (32.1%) | |
| Complication | | | 0.002* |
| Yes | 9 (25.7%) | 15 (8.0%) | |
| No | 26 (74.3%) | 172 (92.0%) | |
| Chemotherapy$^{+}$ | | | 0.128 |
| Yes | 32 (91.4%) | 151 (80.7%) | |
| No | 3 (8.6%) | 36 (19.3%) | |
| Colostomy | | | < 0.001* |
| Yes | 35 (100%) | 7 (3.7%) | |
| No | 0 (0%) | 180 (96.3%) | |
| Clinical T stage | | | 0.253 |
| cT2 | 2 (5.7%) | 26 (13.9%) | |
| cT3 | 25 (71.4%) | 134 (71.6%) | |
| cT4 | 8 (22.9%) | 27 (14.5%) | |
| Clinical N stage | | | 0.659 |
| cN0 | 2 (5.7%) | 63 (33.7%) | |
| cN1 | 21 (60%) | 104 (55.6%) | |
| cN2 | 12 (34.3%) | 20 (10.7%) | |

* Indicated significant difference. $^{+}$ Chemotherapy for adjuvant or salvage, included oral form and intravenous form.

group for avoiding stool pass through the anastomosis. Advanced local upper rectal cancers usually have a large tumor burden prior to treatment with neoadjuvant chemotherapy. Adjacent organs may also be involved due to local desmoplastic reactions or direct invasions from difficult surgical planes, which results in the injury of nearby organs (such as the ureter or the bladder). Pathological outcomes for our study cohort are shown in Table 2. All observed parameters showed no significant differences between the two groups.

The mean follow-up period was 56.4 months (range: 2.4-142 months). The rate of recurrence and metastasis in the neoadjuvant group (Table 3) was 11.4% (4/35) and 28.6% (10/35), respectively. In the radical surgery group, the rates of recurrence and metastasis were 15.5% (29/187) and 43.9% (82/187), respectively. The corresponding *p*-values obtained from chi-square tests were 0.534 (recurrence) and 0.092 (metastasis). Cancer-specific survival rate during the following-up period was 82.9% for the neoadjuvant group and 66.3% for the primary radical surgery group. However, there were no significant statistical differences between the two groups in terms of local recurrence, distant metastasis, orcancer-specific survival. Furthermore, a Kaplan-Meier survival curve study was used to examine local recurrence-free survival, metastasis-free survival, and 3-year cancer specific overall survival and further confirmed the results obtained via earlier statistical testing (Fig. 2).

**Table 2.** Pathological outcomes for the two groups based on chi-square tests

| Variables | Group A (n = 35) | Group B (n = 187) | *p* value |
|---|---|---|---|
| Tumor size | | | 0.455 |
| ≤ 5 cm | 26 (74.3%) | 127 (67.9%) | |
| > 5 cm | 9 (25.7%) | 60 (32.1%) | |
| Tumor grading | | | 0.773 |
| Moderate-differentiated | 32 (91.4%) | 168 (89.8%) | |
| Poor-differentiated | 3 (8.6%) | 19 (10.2%) | |
| Lymph nodes harvest | | | 0.786 |
| n > 12 | 22 (62.9%) | 122 (65.2%) | |
| n < 12 | 13 (37.1%) | 65 (34.8%) | |
| Node positive | | | 0.991 |
| N1 | 21 (60.0%) | 112 (59.9%) | |
| N2 | 14 (40.0%) | 75 (40.1%) | |
| Tumor deposit | | | 0.142 |
| Positive | 13 (37.1%) | 47 (25.1%) | |
| Negative | 22 (62.9%) | 140 (74.9%) | |

A statistically significant difference was not observed between the two groups.

## Discussion

In Taiwan, many surgeons believe that patients with locally advanced (T3/4 or N+) rectal cancers, located in the upper-third of the rectum, should be treated identically to colon cancer patients. In the 7th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, upper rectal tumors are defined as partially peritonealized, compared to tumors located in the middle and lower rectum, which are not peritonealized.[1] Adenocarcinomas of the upper-third of the rectum and the rectosigmoid junction seem to have a similar prognosis to colon cancers.[5] For our patient data, which were collected using ICD-9 codes, we chose the ICD-9: 154.0 (indicated rectosigmoid junction cancer) and 154.1 (indicated rectal cancer) codes to pick up additional cases by reviewing medical charts and surgical reports. The mean follow-up period was 56.4 months. This was mainly due to a number of cases that were only identified as rectal tumors in 2012. In addition, few cases had short follow-up times due to perioperative complications (such as pneumonia and anastomotic leakage) or due to previous systemic diseases. For our primary radical surgery group, patients who demonstrated positive surgical margins or local recurrence received further postoperative radiation and adjuvant chemotherapy.

**Table 3.** Oncological outcomes between the two groups

| Variables | Group A (n = 35) | Group B (n = 187) | *p* value |
|---|---|---|---|
| Local recurrence | | | 0.534 |
| Yes | 4 (11.4%) | 29 (15.5%) | |
| No | 31 (88.6%) | 158 (84.5%) | |
| Metastasis | | | 0.092 |
| Yes | 10 (28.6%) | 82 (43.9%) | |
| No | 25 (71.4%) | 105 (56.1%) | |
| Cancer specific survival | | | 0.052 |
| Alive | 29 (82.9%) | 124 (66.3) | |
| Death | 6 (17.1%) | 63 (33.7) | |

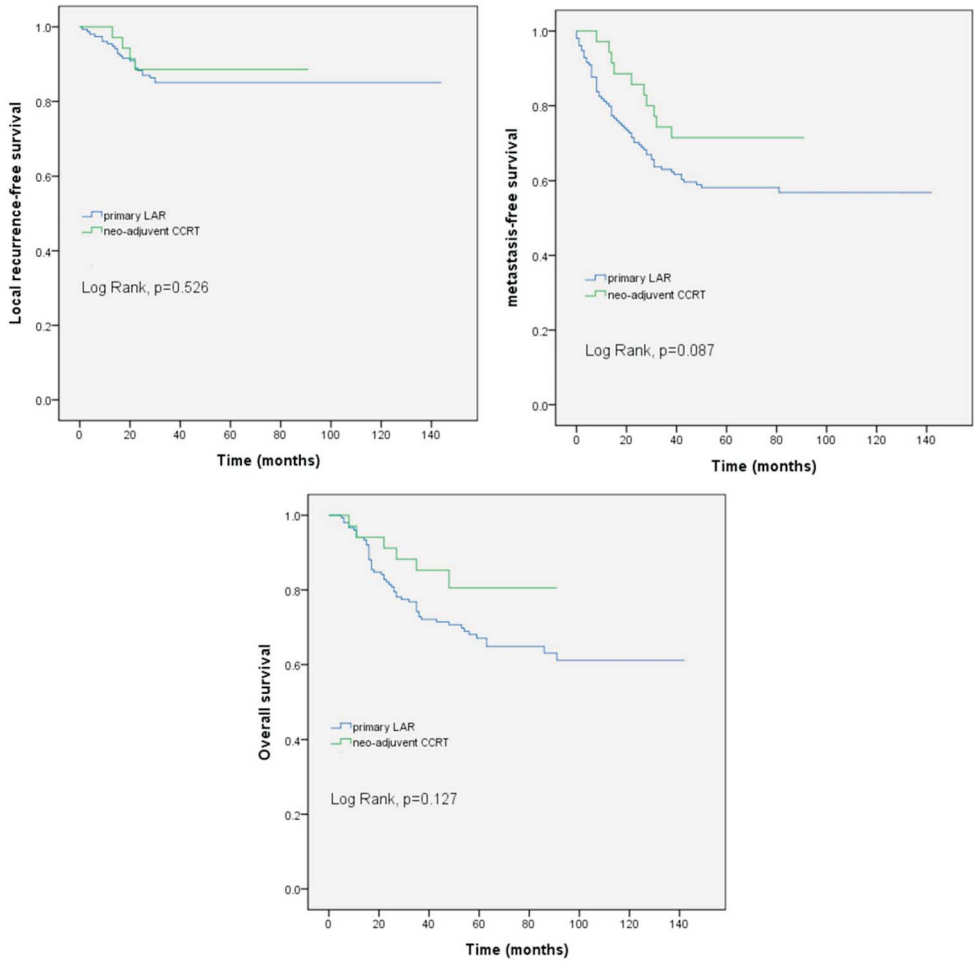


**Fig. 2.** The Kaplan-Meier survival curves for oncological outcomes.

In our study, we found that there were no statistical differences in oncological outcomes between two groups. Based on previous article,[3] upper-third rectal adenocarcinomas seem to have more similarities with rectal tumors located in the middle-third of the rectum than with sigmoid tumors.[4] However, certain study had demonstrated that most upper rectal tumors can be treated with partial mesorectal excisions and without the systematic use of preoperative chemoradiation.[5] Few articles focus on the efficacy of differential treatments (such as neoadjuvant treatments) in stage III upper-rectal tumors.[1] We reviewed data obtained from a single medical center (VGHKS). We believe that the results obtained might increase confidence in treating upper-rectal tumors with more aggressive treatments.

Neoadjuvant CCRT has been suggested as a treatment for local recurrence in the NSABP R-03 trial.[9] This was further corroborated by our own data, which also indicated a tendency for increased local-regional control when neoadjuvant CCRT was used. However, our data also suggest that neoadjuvant CCRT may cause an increase in the number of patient complications. We hypothesize that this increase in complications may be due to out-of-date facilities, which may cause additional damage to intraperitoneal organs during the radiotherapy procedure. In VGHKS, we typically performed a diverting colostomy in neoadjuvant CCRT group, as a temporary stool diversion could have masked immediate complications, such as microleakage or intraperitoneal abscess. In our study, patients with anastomotic stenosis usually required further surgical treatment and had a poor quality of life. Published articles show that anastomotic leakage

makes up approximately 11% of all major perioperative complications,[10] However, our data indicate that there was no difference in the occurrence rate of major complications between neoadjuvant radiotherapy and radical surgery.[10] Therefore, more data are needed to confirm whether the oncological outcome and risk of complications for neoadjuvant CCRT in patients with upper-third rectal tumors are comparable between the two groups, thereby assisting in choosing the appropriate procedure to be performed.

### Limitations

This is a retrospective analysis of data collected in a prospective randomized study and thus, unknown bias is theoretically possible. There was also a potential bias for choosing patients during the pre-op evaluation whose nodules were positive for upper rectal cancer. Furthermore, the sample size is relatively small.

## Conclusions

Oncological results (local recurrence interval and cancer-specific overall survival) for patients with stage III upper-third rectal cancers, who have been treated with neoadjuvant chemoradiotherapy and primary radical surgery, indicate that there are no significant statistical differences between the two treatment modalities. Primary radical surgery for patients with upper-third rectal tumors may be viable treatment choice, which would not compromise long-term oncological results and would result in fewer patient complications.

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**原　著**

# 對於第三期上位直腸癌的病患是否需要手術前放射線及化學治療

李明泓　王瑞和　金台明　張敏琪　許詔文

高雄榮民總醫院　外科部　大腸直腸外科

**目的**　對於第三期上位直腸癌患者接受新輔助性同步電化療的必要性沒有明確的建議。這項研究的目的是要探討在第三期上位直腸癌在單一醫學中心比較腫瘤成果和新輔助同步放化療和先施行根治性手術的臨床效果。

**方法**　從 2004 年 1 月至 2012 年 12 月，我們收集了 222 位病理結果為第三期上位直腸癌的病人，分為兩組，分別給予新輔助性電化療然後行低前位切除手術及直接接受低前位切除術治療，回溯性收集相關臨床和病理資料併分析。

**結果**　222 位病人中，新輔助性電化療組及先接受手術組皆以男性病患佔多數，平均年齡為 63.2 歲，在追蹤至少三年以上，比較兩組的局部復發率，腫瘤特異性存活率 Kaplan-Meier curve 的統計局部復發率 *p* 值為 0.526，遠端轉移率為 *p* 值為 0.087，整體存活率為 *p* 值為 0.127。在併發症上，新輔助性電化療組 (9/35) 比上先接受手術組 (15/187) 發生併發症之機率 *p* 值為 0.002，在統計學上達到顯著之差異。主要以腸道吻合滲漏，直腸膀胱廔管為主。

**結論**　在第三期上位直腸癌新輔助放化療同步治療是沒有必要的。臨床效果和長期的腫瘤學結果兩組間無顯著統計學差異。然而，在我們的研究中發現在新輔助同步電化療組併發症較多。

**關鍵詞**　上位直腸癌、新輔助放化療同步治療、腺癌。