Original Article

Clinical Outcome of Rectal Cancer in Patients with or without Pathologic Complete Response after Preoperative Neoadjuvant Chemoradiotherapy: A Retrospective Analysis of a Single Institution in Taiwan

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Key Words
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Neoadjuvant chemoradiation therapy;
Outcome;
Survival

Purpose. Preoperative concurrent chemoradiation (CCRT) is an important part of the therapeutic regimen to treat locally advanced rectal cancer. Patients who achieved a pathological complete response (pCR) after preoperative CCRT were shown to have a better clinical outcome compared to patients who did not. In this study, we investigated clinical outcome and survival in Taiwanese rectal cancer patients who achieved pCR after preoperative CCRT (ypT0N0M0 group) with patients who did not (non-ypT0N0M0 group).
Methods. In this retrospective study, we analyzed the records of 227 patients who presented with rectal adenocarcinoma. Preoperative concurrent chemo-radiation therapy (CCRT) consisted of a total dose of 50.4 Gy delivered in 25 fractions, five times per week. The chemotherapy regimen for preoperative CCRT consisted of an intravenous infusion of 5-fluorouracil (1,500 mg/m2) and leucovorin (120 mg/m2) weekly for 6 weeks. All patients underwent radical resection 6-8 weeks after preoperative CCRT treatment. Differences between patients with or without pCR were compared using two-sample t-tests in continuous data and Chi-square test/or Fisher's exact test with Yate's correction in categorical data. Overall survival (OS) and disease-free survival (DFS) were compared using log-rank test and Kaplan-Meier curves, respectively.
Results. A total of 121 patients are eligible for analysis. 19 patients pertained to ypT0N0M0 and 102 patients belonged to non-ypT0N0M0 group. There was no significant association between demographics and clinical characteristics of the patients and pCR. There was no significant association between clinical outcome and pCR in the two groups. The log-rank test showed no significant difference in OS and DFS between the ypT0N0M0 and non-ypT0N0M0 groups.(OS: p-value = 0.643; DFS: p-value = 0.196).
Conclusions. There was no significant difference in clinical outcome or survival between Taiwanese patients who achieved pCR after preoperative CCRT and those who did not.
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Colorectal cancer is among the leading causes of cancer-related deaths in Asia,[1] and rectal cancers comprise almost one third of all colorectal carcinomas.[2] Resection of the primary tumor is the standard treatment for early stage rectal cancer, and patients with metastatic tumors have a poor prognosis.[3] The current treatment option for patients with locally advanced T3 and/or node-positive rectal cancer includes a combination of preoperative chemo-radiotherapy (CRT), total mesorectal excision (TME) and adjuvant chemotherapy.[4,5] Preoperative (neoadjuvant) chemotherapy has been reported to be more effective than postoperative therapy to treat locally advanced rectal cancer.[6] A continuous infusion of 5-FU is the most commonly used preoperative chemotherapy regimen, although a number of other drug combinations including leucovorin and oxaliplatin, capecitabine.[7-9]

The challenges of postoperative therapy include increased growth factor activity postoperatively, which could promote tumor growth and progression.[10] This could be overcome by using preoperative chemotherapy. Preoperative chemotherapy also offers the advantage of shrinking the tumor prior to surgery, and a means of designing postoperative therapy based on the response to preoperative therapy.[11] Although associated with a risk of increased postoperative complications,[12] the potential effect of preoperative CCRT in achieving pathologic complete response (defined as tumor regression and absence of residual neoplasia), tumor down-staging and sphincter preservation makes it an important part of the therapeutic regimen for rectal cancer. Interestingly, patients who achieved a pathological complete response (pCR) after preoperative CCRT were shown to have a better clinical outcome compared to patients who did not.[13,14]

A number of studies have investigated the clinical outcome of rectal cancer patients who had pCR in response to to preoperative CCRT.[15-20] However, there is not many information on the association between pathologic complete response to preoperative CCRT and clinical outcome and survival in Taiwanese rectal cancer patients.[21,22] In this study, we compared clinical outcome and survival in rectal cancer patients who had a pCR after preoperative CCRT with patients who did not have a pCR after preoperative CCRT.

Materials and Methods

Patient population

In this retrospective study, we analyzed the records of 227 consecutive patients who presented with adenocarcinoma of the rectum at the Division of Colorectal Surgery, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei, between January 2005 and December 2010. A total of 121 patients were diagnosed with locally advanced cancer of the rectum and were treated with preoperative chemoradiation followed by total mesorectal excision (TME) and R0 resection.

Eligibility criteria included 1) presence of histologically confirmed primary adenocarcinoma of the rectum, 2) clinical Stage T3-T4 or N1-N3 according to the AJCC TMN staging system (7th edition, 2010), 3) tumor location with the lower pole of the tumor ranging between 0 and 15 cm from the anal verge, 4) no evidence of metastases, 5) no prior chemotherapy, immunotherapy, or radiotherapy (RT) to the pelvis, 6) no prior malignancy, 7) Eastern Cooperative Oncology Group 0-2 performance score, 8) granulocyte count > 3,000/mL, 9) platelet count > 100,000/mL, 10) hemoglobin concentration > 10 g/mL, 11) serum creatinine value < 1.5 mg/mL, 12) no major concurrent disease, and 13) adequate heart function. All patients were subjected to digital examination, endoscopy with biopsy, chest X-ray, abdominal CT and blood analysis.

Patients with stage I or IV rectal cancer, transanal excision, and previous radiotherapy or chemotherapy were excluded.

The study was approved by the IRB of the Tri-Service Hospital and a waiver of informed consent was obtained from the IRB for this retrospective study.

Treatment protocol

Preoperative concurrent chemo-radiation therapy

(CCRT) consisted of a total dose of 50.4 Gy delivered in 25 fractions, five times per week. The radiation fields included pelvic fields (45 Gy) and boost fields (5.4 Gy) in 3 fractions. The boost fields enclosed a 3-cm margin around the tumor but had to include the whole presacral space. No postoperative radiotherapy was given for fear of severe long-term complications. The chemotherapy regimen for preoperative CCRT consisted of an intravenous infusion of 5-fluorouracil (1,500 mg/m2) and leucovorin (120 mg/m2) weekly for 6 weeks. Standard chemotherapy with 5-fluorouracil and leucovorin for 4 months (biweekly regimen) was recommended for patients with stage II-III disease after surgery. Surgery was performed 6-8 weeks after completion of preoperative CCRT. All study patients underwent radical resection based on the TME principles, irrespective of whether they received abdominoperineal resection (APR) or low anterior resection (LAR). All surgeries were performed by sharp pelvic dissection under direct vision along the Holly plane. The choice of the surgical procedure (APR or LAR) was at the surgeon's discretion (5 senior surgeons were involved in all the procedures). Patients were seen at routine follow-up visits every 3 months for the first 2 year, every 6 months for the subsequent 3 years, and yearly thereafter. At each follow-up visit, digital rectal examination and proctoscopy were performed, if feasible. Liver ultrasonography, chest X-ray, pelvic CT, and carcinoembryonic antigen (CEA) values were obtained at 3-12-month intervals.

Histopathology

Pathologic evaluation was performed by two senior pathologists. All resected specimens were stained with hematoxylin and eosin, and evaluated for tumor differentiation and invasion, lymph node metastases and lymphovascular invasion. The pathologic stage of rectal cancer was evaluated according to the 7th AJCC TNM Staging System.

Statistical analysis

All statistical analyses were performed using the SAS 9.0 (SAS Institute Inc., Cary, NC, USA) and PASW statistics 18.0 software (SPSS Inc, Chicago, IL, USA). Subjects' demographics and clinical characteristics were summarized as mean with range (min. to max.) for continuous data and n (%) for categorical data. The differences between the two groups with different pathologic complete responses were compared using two-sample t-tests in continuous data and Chi-square test/or Fisher's exact test with Yate's correction if any cell number was less than five or close to zero in the categorical data. The overall survival (OS) time and disease-free survival (DFS) time were summarized as median with range (min. to max.) by pathologic complete responses (ypT0N0M0 vs. non-ypT0N0M0) and compared using Log-rank test. Kaplan-Meier curves for OS and DFS times were also presented by pathologic complete responses, respectively. A p value < 0.05 was considered statistically significant.

Results

In this study, we compared pathologic complete responders (ypT0N0M0) and patients who did not have ypT0N0M0 to evaluate differences in the outcomes, overall survival (OS) rates and disease free survival (DFS) rates after preoperative CCRT. Of the 225 patients, 40 patients were excluded because they did not have clinical stages T3-T4 or N1-N3; 21 patients were excluded for not receiving preoperative CCRT; 34 patients were excluded because they did not receive surgery and 9 patients were excluded for receiving transanal excision. Of the 121 patients who were evaluated, 19 patients showed pCR (pT0N0M0), while 102 patients did not (Fig. 1).

We evaluated the relationship between patients' demographics and clinical characteristics and pathologic response after CCRT as follows: The patients included 71 males (58.7%) and 50 females (41.3%). The mean age was 64 years (range: 26 to 94 years). Our data showed no significant association between demographics and clinical characteristics of the patients and pCR (all p-values > 0.05) (Table 1).

We also evaluated the relationship between post-

CCRT pCR status and clinical outcomes, including survival status, recurrence status, OS and DFS (Table 2). OS was defined as the duration from the date of initial diagnostics until death or the last follow-up visit. DFS was defined as the duration from the date of surgery until treatment failure (death or recurrence). Our data showed that a total of 9 patients (7.4%) died in both groups, and 13 patients (10.7%) in the non-ypT0N0M0 group had recurrence during the follow-up period. There was no significant difference in mortality rate and recurrence rate between the ypT0N0M0 and non-ypT0N0M0 groups (both p-values > 0.05).

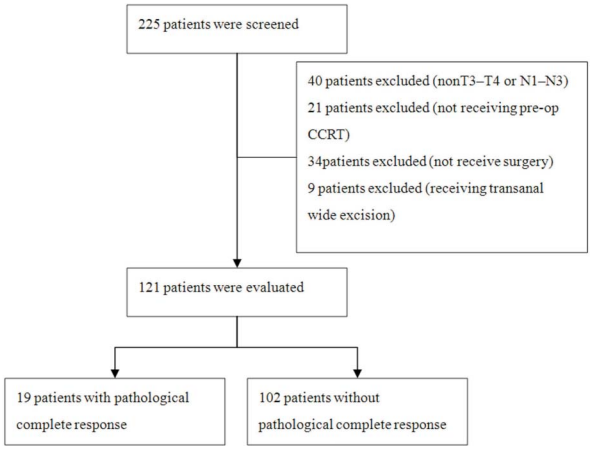

Fig. 1. Flow chart of patient disposition.

The median OS in both groups combined was 39.9 months (range: 4.2 to 85.3 months), while the median DFS in both groups combined was 35.4 months (range: 1.8 to 85.2 months). The estimated 6-month, 1-yr, 3yr, and 5yr OS rates were 99.2%, 99.2%, 91.5%, and 88.8%, respectively. The estimated 6-month, 1-yr, 3yr, and 5yr DFS rates were estimated as 98.3%, 95.6%, 84.1%, and 74.9%, respectively. The OS rate for overall was 94.7% in ypT0N0M0 and 92.2% in non-ypT0N0M0 groups; The DFS rate for overall was 94.7% in ypT0N0M0 and 81.4% in non-ypT0N0M0 groups. The log-rank test showed no significant difference in OS or DFS times between the ypT0N0M0 and non-ypT0N0M0 groups (both p-values > 0.05) (Figs. 2 and 3).

We analyzed pathological downstaging in a total

Table 1. Relationship between pathologic complete response and patient demographics and clinical characteristics

Variables	Total (n = 121)	ypT0N0M0 (n = 19)	Non-ypT0N0M0 (n = 102)	p-value
Sex				0.276
Male	71 (58.7%)	9 (47.4%)	62 (60.8%)	
Female	50 (41.3%)	10 (52.6%)	40 (39.2%)	
Mean age (yrs) (range)	64.0 (26-94)	64.4 (37-94)	64.0 (26-86)	0.460
Pre-Op CEA[a]				0.229
≧ 5 ng/ml	49 (80.3%)	8 (66.7%)	41 (83.7%)	
< 5 ng/ml	12 (19.7%)	4 (33.3%)	8 (16.3%)	
T/N clinical stage				1.000
T3/N0	37 (30.6%)	6 (31.6%)	31 (30.4%)	
T4/N0	3 (2.5%)	0 (0%)	3 (2.9%)	
T2N1-2	12 (9.9%)	2 (10.5%)	10 (9.8%)	
T3N1-2	63 (52.1%)	10 (52.6%)	53 (52.0%)	
T4N1-2	6 (4.9%)	1 (5.3%)	5 (4.9%)	
Primary site				1.000
RS colon tumor	18 (14.9%)	3 (15.8%)	15 (14.7%)	
Rectum tumor	103 (85.1%)	16 (84.2%)	87 (85.3%)	
R0 resection	121 (100%)	19 (100%)	102 (100%)	NA

Data were summarized as n (%) in categorical variables, mean (Range: min.-max.) in age; Difference between pathologic complete responses were compared using two-sample t-test in age or Chi-square test/or Fisher's exact test with Yate's correction if any cell number less than five or close to zero in categorical ones.

Abbreviations: yrs., years old; Min., minimum; Max., maximum; Pre-Op CEA, preoperational carcinoembryonic antigen; NA, not assessed.

[a] Pre-OP CEA was not recorded in 61 patients.

Table 2. Relationship between pathologic complete response and follow-up outcomes, survival status, and recurrence status

Variables	Total (n = 121)	ypT0N0M0 (n = 19)	Non-ypT0N0M0 (n = 102)	*p*-value
Survival status				1.000
Dead	9 (7.4%)	1 (5.3%)	8 (7.8%)	
Alive	112 (92.6%)	18 (94.7%)	94 (92.2%)	
Total recurrence				0.438
No recurrence	108 (89.3%)	19 (100%)	89 (87.2%)	
Local recurrence	2 (1.6%)	0 (0%)	2 (2.0%)	
Distant recurrence	11 (9.1%)	0 (0%)	11 (10.8%)[a]	
OS time				
Months, median (range)	39.9 (4.2-85.3)	41.2 (19.4-61.7)	39.5 (4.2-85.3)	0.643
DFS time				
Months, median (range)	35.4 (1.8-85.2)	37.2 (15.0-57.8)	35.4 (1.8-85.2)	0.196

OS, overall survival; DFS, disease free survival time.

[a] Of the 11 non-ypT0N0M0 patients with distant recurrence of tumors, 5 were in lung, 4 in liver, 3 in bone, 2 in brain. In addition, a 36-yr old male patient had recurrence in multiple organs. Survival status and recurrence rate were summarized by n (%) and compared using Fisher's exact test; OS time and DFS time were summarized as median with range (min.-max.) by pathologic complete responses (ypT0N0M0 vs. non-ypT0N0M0) and compared using Log-rank test.

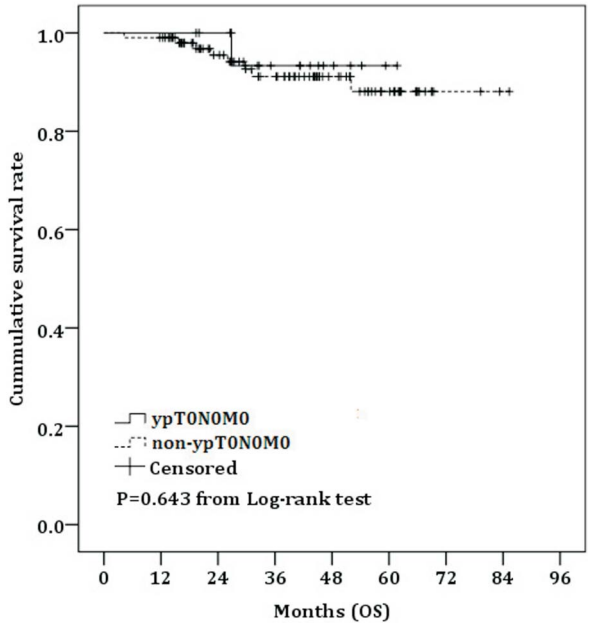

Fig. 2. Kaplan-Meier curves to show the relationship between overall survival (OS) time and pathological response. The *p*-value was derived through Log-rank test to identify the statistical significance of median OS time in the pathological complete response and non-complete response groups. Both groups had > 50% patients who survived during the follow-up period. The Log-rank test shows the OS time was not significantly different between ypT0N0M0 and non-ypT0N0M0 groups. (p = 0.643)

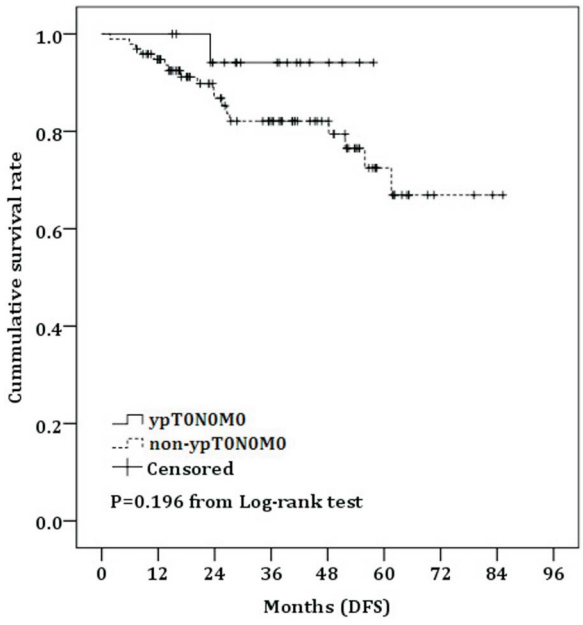

Fig. 3. Kaplan-Meier curves to show the relationship between disease-free survival (DFS) time and pathological response. The *p*-value was derived through Log-rank test to identify the statistical significance of median DFS time in the pathological complete response and non-complete response groups. Both groups had > 50% patients with DFS during the follow-up period. The Log-rank test showed that DFS time was not significantly different between the ypT0N0M0 and non-ypT0N0M0 groups. (p = 0.196)

of 103 patients (Table 3). Our data showed that one of the two patients with T1 tumor (50%) experienced downstaging to ypT0. Twenty seven percent of patients with T2 tumor experienced downstaging to ypT0 or ypT1, while 60.9% of patients with T3 tumor experienced downstaging to ypT0, ypT1 or ypT2, and totally 48.5% of our patients experienced downstaging. Two patients with T3/N0 experienced local recurrence would be noted.

Table 3. Pathological downstaging in a total of 103 patients

Clinical stage	Pathological stage				Downstaging[a] (%)
	ypT0	ypT1	ypT2	ypT3	
T1 (2)	1	0	1	0	1/2 (50)
T2 (37)	1	9	20	7	10/37 (27)
T3 (64)	2	16	21	25	39/64 (60.9)
Total (103)	4	25	42	32	50/103 (48.5)

18 subejcts were not considered for calculating downstagting that included 2 subjects with undefined clinical stage and 16 with pathological stages.

[a] Comparison of postoperative pathological stage and clinical stage.

Discussion

In this study, we compared the clinical outcomes, OS and DFS of Taiwanese rectal cancer patients who had achieved pCR after preoperative CCRT with those patients who did not have a pCR after preoperative CCRT. Our data showed that OS and DFS were not significantly associated with complete pathological response.

Pathological complete response has increasingly become the surrogate marker for long-term, favorable outcome after preoperative CCRT. However, neoadjuvant CCRT has been reported to achieve a significant regression only in around two-thirds of all tumors and a complete eradication in approximately 15% of tumors.[23] A number of rectal cancer patients do not achieve a complete response.[24,25] One recent study analyzing molecular mechanisms underlying a pathological complete response showed that patients with a p53 mutation, KRAS mutation, CCND1 G870A (AA) polymorphism or MTHFR C677T (TT) polymorphism were associated with non-pCR.[26] Pretreatment relative lymphocyte count > 26% was shown to be a predictor of downstaging.[27] Additionally, expression levels of Bax, MMP-9 and VEGF have been shown to correlate with pCR in rectal cancer patients.[28] Identification of such profiles that could predict pCR is especially important while selecting the optimal therapeutic regimen in patients with rectal cancer.

A number of studies have explored different means of increasing the rate of complete response to neoadjuvant CCRT. Addition of oxaliplatin to the fluorouracil based preoperative CCRT was found to achieve higher rates of pCR.[7] Addition of chemotherapy after neoadjuvant therapy was also found to achieve higher response rates.[29] Preoperative long-course radiotherapy in combination with chemotherapy was found to be more advantageous in treating patients with rectal cancer compared to short-course radiotherapy.[30] Our study patients received a total radiation dose of 50.4 Gy delivered in 25 fractions, five times per week, combined with an intravenous infusion of 5-fluorouracil (1,500 mg/m2) and leucovorin (120 mg/m2) weekly for 6 weeks.

We showed no significant difference in clinical outcome between patients who achieved pCR and those who did not. It was recently shown that tumor cells can be found up to 3 cm distal from the gross ulcer in patients who have an apparent complete response[31] and residual tumor cells after CCRT were located close to the invasive front.[32] These data suggested that particular care must be taken while diagnosing a pathologic complete response.

Tumor stage after neoadjuvant CCRT was previously shown to be a prognositic factor for DFS and OS.[23] In our present study, we evaluated the association between pathological complete response after neoadjuvant CCRT and survival. We showed no significant difference in OS or DFS times between the ypT0N0M0 and non-ypT0N0M0 groups. Although pCR after neoadjuvant therapy has been shown to be an independent predictor of clinical outcome, some data suggest that it is not a prognostic factor for DFS and OS.[33] It is not clear if partial tumor regression is associated with better clinical outcomes and survival. Partial tumor regression was shown to predict pro-

gression only in lymph node-negative rectal cancer.[34] We would like to further stratify our results based on specific tumor grading data for patients who did not achieve pCR.

Patients with local recurrence of rectal cancer have poor survival rates with almost zero 5-year survival rates and chemoradiotherapy has been shown to be an attractive curative option for local recurrence.[35] In this study, two patients (both with T3/N0) had local recurrence, but one was lost to follow-up. Because all patients in this study were R0 resection, so this is not the reason of recurrence, however, we cannot perform any other statistical analysis because there were only two patients. The survival times of the two patients were 36.57 months and 46 months, respectively; the DFS times of the two patients were 23.87 months and 7.23 months, respectively. We showed that of a total of 103 patients, 48.5% experienced pathological downstaging. Pathological downstaging has previously been shown to be an important factor predicting survival.[36,37] It will be interesting to compare OS and DFS in the patients who experienced downstaging and the patients who did not.

The main limitations of this study are that 1) it is a retrospective, single center study and 2) the sample size was small. To further validate our finding, a prospective study with adequate sample size from multiple centers is expected.

Conclusions

In conclusion, we compared the clinical outcome and the survival in Taiwanese rectal cancer patients who had a pCR after preoperative CCRT with those who did not have a pCR after preoperative CRT. Our data suggested that there was no significant difference in clinical outcome, OS or DFS between the two groups.

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原　著

直腸癌患者接受術前同步放射及化學治療後有達到與未達到病理完全緩解的臨床預後之比較：在台灣單一機構的回顧性分析

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目的　本研究探究接受術前放射及化學治療 (CCRT) 達到 pCR (ypT0N0M0 組) 與未達完全緩解的患者 (non-ypT0N0M0 組) 的療效和存活狀況。

方法　回顧性分析了 227 位直腸癌患者的病歷。術前同步放射及化學治療 (CCRT) 中，放射線治療的總劑量是 50.4 Gy，分 25 次完成，一周 5 次；化療則是每週靜脈注射一次 5-氟尿嘧啶 (1500 mg/m2) 和亞葉酸鈣 (120 mg/m2)，共 6 周。所有患者在接受術前 CCRT 治療後 6-8 周內接受根治性切除術。比較兩組差異時，對連續型變項使用雙樣本 t-test，對類別變項使用 Chi-square test 或 Fisher's exact test。log-rank test 和 Kaplan-Meier 生存曲線分析則用以比較總生存率 (OS) 和無病生存期 (DFS)。

結果　共計 121 patients 符合條件進入比較分析，其中 19 位為 pCR (ypT0N0M0) 組，102 位為 non-ypT0N0M0 組。兩組患者的人口統計學和臨床特徵，療效與 pCR 無顯著相關性。兩組間的 OS 和 DFS 無顯著差異。兩組比較後，OS 的 *p*-value 為 0.643；DFS 的 *p*-value 為 0.196，均未顯著。

結論　術前接受 CCRT 的臺灣直腸癌患者的有無達到完全緩解和存活率無顯著差異。

關鍵詞　直腸癌、病理完全緩解、新輔助化學及放射治療、療效、存活分析。