Original Article

Neoadjuvant Long Course CCRT Significantly Increases Disease Free Survival among Pathological Stage III Rectal Cancer Patients as Compared to Short Course RT Alone

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Key Words
Concurrent chemoradiotherapy;
Radiotherapy;
Advanced rectal cancer

Purpose. Both pre-operative short course radiotherapy and long course radiotherapy with concurrent chemotherapy have been used with the purpose of better local control and survival for locally advanced rectal cancer. However, the selection of patients for these two treatment modalities has remained unclear.
Methods and Materials. Patients diagnosed with locally advanced rectal adenocarcinoma from 2002/1/1 to 2006/12/31 and have received complete preoperative short course radiotherapy or long course chemoradiotherapy followed by curative surgery were included. These patients were followed up until 2009/12/31. Variants between gender, age, tumor location, initial CEA level, and tumor differentials were compared. Overall survival, disease free survival, local recurrent rate and distant metastasis rate were also compared by Log Rank test.
Results. Tumor location (63.4% vs. 81.0% for low rectum, $p = 0.049$) was the only difference between short course and long course subgroups in terms of clinicopathological characteristics. Significant differences are found between groups according to whether there is a presence of pathological proven lymph node metastasis or not. The overall survival (89.3% vs. 62.2% 5 years survival, $p = 0.009$) is better in the short course group only for the subgroup without lymph node metastasis. As for the subgroup with lymph node metastasis, better diseases free survival (27.8% vs. 64.7% 5 years survival, $p = 0.018$) and metastasis free rate (26.8% vs. 76.5% 5 years survival, $p = 0.003$) and a trend of significant difference in overall survival ($p = 0.059$) is noted in the long course CCRT group. However, there is no significant difference for local recurrence (83.0% vs. 87.5% 5 years survival, $p = 0.557$).
Conclusions. To achieve better disease free survival, long course CCRT should be considered for patients with middle and low rectal cancer with lymph node metastasis. However, for patients without evidence of lymph node metastasis, short course radiotherapy may achieve the same disease control.
[*J Soc Colon Rectal Surgeon* (*Taiwan*) *2017;28:18-26*]

Received: June 2, 2016. Accepted: September 12, 2016.
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Adjuvant therapy such as chemotherapy or radiotherapy have become the standard treatment for stages II and III rectal cancer after favorable results were reported by several prospectively randomized trials in the 1980s. Although some utilized postoperative chemoradiation, many other centers favored preoperative radiotherapy. A prospective randomized German study by Sauer et al.[1] compared preoperative and postoperative chemoradiotherapy for rectal cancer. It concluded that preoperative neoadjuvant chemoradiation followed by surgery is associated with less toxicity, lower rate of local recurrence, and higher rate of sphincter preservation. In the EORTC trial,[2,3] patients who received preoperative radiotherapy and either concurrent or postoperative chemotherapy had significantly lower rates of local recurrence compared with patients who received preoperative radiotherapy alone. Based on these trials, neoadjuvant therapy in the management of rectal cancer has been widely used over the past years with the purpose of better local control and survival.

Traditionally, patients receive radiotherapy in the way of 1.8 or 2 Gy per day, and 5 days per week till the total dose 50.4 Gy were administered. 5-FU based chemotherapy, either oral or intravenous infusion, is combined through the whole course of radiotherapy (RT).[4-7] Recently, other advancing chemotherapy agents such as oxaliplatin or irinotecan have been added. Acute toxicity related to either radiotherapy or chemotherapy is obvious. However, decreased late toxicity could be achieved due to a lower dose of radiotherapy which was received during each fraction. In contrast, the short-course RT, as used in theSwedish rectal trial[7] and the Dutch experience,[8] the radiation dose rose to 5 Gy per day. The time of the whole treatment decreased to 5 days only to limit the risk of normal tissue damage from the higher dose per fraction. Decreased early toxicity is thus noted without compromising long-term survival.[2,3,8,9]

Previous studies comparing recurrences and survival between short-course radiation and long-course chemoradiotherapy found no difference in 5-year survival between the two methods, but better local control is noted in the long course group.[4,5] Some non-comparative studies showed similar long-term survival, local control and late morbidity for both methods.[1-3,6-8] Few reports compared differences between standard fractionated RT and "Short-course" RT.[9-12] A review article[4] comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer did not show an increase in survival, local control or late toxicity for chemoradiation compared with short-course radiotherapy alone. Another meta-analysis reported by Wim Ceelen et al. noted better local control in the long course group although this result has not translated to better overall survival. Both studies showed no difference in the distant control between the two groups. In short, both types of neoadjuvant therapies for rectal cancer decrease local recurrence. However, inconsistent overall survival and disease free survival (incidence of local control and distant metastases) were observed among different series.[2-4,8,9] While short-course irradiation has less early toxicity, is less expensive, and more convenient, which means better compliance, conventional fractionated chemoradiation might be better at reducing local recurrence.[4,5]

In this study, we retrospectively analyzed treatment results of the preoperative neoadjuvant therapy followed with surgery for mid and low third rectal cancer in terms of overall survival, diseases free survival, local recurrence and distant metastases during the periods of 2002-2006 in Linkou Chang Gung Memorial Hospital. We did further comparison on whether significant differences exists between clinicopathological factors or not.

Material and Methods

Patients

From January 2002 to December 2006, patients with locally advanced low or middle rectal cancer underwent neoadjuvant therapy were chosen as members of this study. Locally advanced tumors were defined as T3, T4, tumors with or without lymph node metastasis or Any T stage with lymph node metastasis. Low and middle rectal cancer was defined as a tumor located 0 to 5 cm and 5 to 10 cm above the anal

verge respectively. All patients that were diagnosed as rectal cancer with histopathologically proved adenocarcinoma. Pre-operative staging was performed by a physical examination, chest to abdominal computed tomography (CT), and/orendorectal ultrasound. Patients with distant metastases that showed in the CT study were excluded.

During this period (Between Jan. 2002 to Dec. 2006), 352 stage III patients diagnosed with rectal adenocarcinoma located below 10 cm from the anal verge underwent resection in Linkou Chung Gang Memorial Hospital. Of them, 129 patients received preoperative neoadjuvant therapy, either short course radiotherapy or long course chemoradiation depending on the attending surgeon's preference and disease status. 185 patients underwent post operative adjuvant CCRT and the remaining 38 patients did not receive pre-operative or post-operative CCRT due to patient's co-morbidity or reluctance. Any lymph node larger than 0.5 cm was considered as a positive lymph node metastases according to previous reports.[12-14]

Treatment protocol

All patients in the short course radiotherapy group received 5 Gy × 5 days, total 25 Gy, followed by an operation one week later. All patients in the long course chemoradiation group received 1.8 Gy × 28 days, and with 5-Fu based chemotherapy either IV form or oral form followed by an operation around 4 to 8 weeks later. Post operation adjuvant chemotherapy was applied to most patients with pathology proved lymph node metastases, except patients who refused to receive further chemotherapy. For node negative patients, post operation adjuvant chemotherapy was only given to high risk patients.

Follow up

We followed up these patients till December 31 2009 using colonoscopy, CT scan, abdominal sonogram and chest X-ray to survey both local recurrence and distant metastasis. Patients who did not return for a follow up for more than one year were counted as patients with a loss of follow up.

Statistic method

Regarding clinicopathological parameters, patients were compared by dividing them into two groups, that is, with or without lymph node metastasis, according to postoperative pathology staging. Different subgroups were compared using Pearson chi-square test and $p < 0.05$ is taken as a significant difference for the comparison of variant factors. Kaplan-Meier estimates and log-rank tests were used to assess the association of radiation doses with overall survival and diseases free survival.

Results

129 patients were chosen to be members of this study between year 2002 and 2006. Among these patients, 18 patients were excluded, including: 8 patients with distant metastasis noted intraoperatively; 5 patients whose operation had been delayed for more than half a year due to searching for other treatment modalities by patients themselves such as traditional Chinese herbal medicine; 3 patient lost follow up; and peri-operative mortality was found in 2 patients both due to acute myocardial infarction. Finally, 111 patients were analyzed for comparisons of overall survival and recurrence free survival in terms of clinic-pathological features and treatment modalities.

Outcome comparisons based on pathological staging

According to the post-operative histopathological evaluation, there are 6 patients counted as in complete remission; 52 patients were diagnosed without lymph node metastasis and 55 patients showed lymph node metastases. Of them, 71 patients received short-course radiotherapy and 42 patients received long course radiotherapy. Clinico-pathological parameters including gender, age, tumor location, tumor differentiation and preoperative CEA level are shown in Table 1. No significant variation between these two radiation subgroups in terms of these clinic-pathological features

Table 1. Clinical features between short-course group and long course CCRT group

	25 Gy		50.4 Gy		*p*-value
	No.	%	No.	%	
Gender					0.307
Male	44	62.0	30	71.4	
Female	27	38.0	12	28.6	
Age					0.398
> 65 y/o	24	33.8	11	26.2	
≤ 65 y/o	47	66.2	31	73.8	
Location					0.049
≤ 5 cm	45	63.4	34	81.0	
5<~< 10 cm	26	36.6	8	19.0	
CEA					0.694
≤ 5 ng/mL	43	60.6	27	64.3	
> 5 ng/mL	28	39.4	15	35.7	
Differentiation					0.646
Well	12	16.9	5	11.9	
Moderate	56	78.9	34	81.0	
Poor	3	4.2	3	7.1	
Lynmph node involvement					0.234
Present	29	40.8	22	52.4	
Absent	42	59.2	20	47.6	
Tumor invasion depth					0.766
T3	41	57.7	27	63.4	
T4	23	32.4	12	28.6	
Unknown*	7	9.9	3	7.1	

* Ten patients were noted of advanced rectal cancer, but can hardly define T3 or T4 due to poor image quality.

were found. The patients with lower rectal lesions had a trend to receive long course chemoradiotherapy before the surgery.

Significantly improved overall survival and disease free survival was noted among pathological lymph node negative subgroups compared with the node positive subgroup (Table 2).

In general, there is no significant difference of overall survival and disease free survival between short and long course radiotherapy (5 yrs 58.5 vs. 68.3, p = 0.948). Significantly improved overall survival (p = 0.009) was noted in the short-course preoperative radiotherapy patients in the subgroup without pathologically lymph node metastases. However, no significant difference was noted when it came to disease free survival, local recurrence rate and distant metastasis rate. Furthermore, among the pathologically lymph node metastases proven subgroup, there are significant differences in the disease-free survival (p = 0.018) and distant metastasis rate (p = 0.003) (Fig. 1A and 1B). Marginal significant difference were noted in overall survival (p = 0.059) but no difference in local recurrence rate (p = 0.557).

Table 2. Outcomes between short course and long course CCRT groups and subgroups

	Short course (25Gy)			Long course (50.4Gy + CT)			*p*-value
	1 year	3 year	5 year	1 year	3 year	5 year	
All patients together							
OS	98.6	82.3	58.5	97.6	71.9	68.3	0.984
DFS	81.4	57.1	55.6	85.4	62.6	62.6	0.554
Local recurrence free rate	97.1	89.4	87.3	92.7	84.8	81.1	0.497
Metastases free rate	81.4	54.1	52.5	87.8	70.2	70.2	0.108
Clinical without lymph node involvement							
OS	100	84.2	63.6	100	73.4	73.4	0.811
DFS	82.9	58.5	55.9	85.0	69.6	69.6	0.344
Local recurrence free rate	97.6	86.9	83.5	85.0	80.0	80.0	0.729
Metastases free rate	85.4	56.0	53.2	90.0	80.0	80.0	0.064
Clinical with lymph node involvement							
OS	100	82.4	59.1	95.2	74.3	66.0	0.965
DFS	79.3	55.2	55.2	85.7	55.5	55.5	0.900
Local recurrence free rate	96.4	92.9	92.9	100	88.9	80.9	0.390
Metastases free rate	75.9	51.7	51.7	95.2	60.5	60.5	0.648
Pathology without lymph node involvement							
OS	100	97.0	89.3	100	62.2	62.2	0.009
DFS	97.1	85.3	85.3	77.8	65.3	65.3	0.082
Local recurrence free rate	97.1	91.1	91.1	83.3	83.3	83.3	0.338
Metastases free rate	97.1	79.2	79.2	83.3	65.5	65.5	0.235
Pathology with lymph node involvement							
OS	97.2	68.5	35.5	100	81.6	72.5	0.059
DFS	66.7	30.6	27.8	94.1	64.7	64.7	*0.018*
Local recurrence free rate	100	97.9	83.0	100	87.5	87.5	0.557
Metastases free rate	66.7	30.6	27.8	94.1	76.5	76.5	*0.003*

Difference of recurrence patterns between short course radiotherapy and long course CCRT

Clinical features of a total of 113 patients between patients that underwent short course radiotherapy and long course CCRT were compared and shown in Table 1. Generally, there was no significant difference between these two subgroups (short course radiotherapy and long course chemotheradiation therapy) related to gender, age, tumor differentiation, tumor staging and initial CEA level. The only significant difference between these two subgroups was more patients with low third rectal cancer received long course CCRT compared to patients with mid-third rectal cancer (34 of 42, 81.0% vs. 45 of 71, 63.4%, $p = 0.049$). Meanwhile, sphincter preservation rate and perioperative mortality between the short course and long course subgroups were not statistically different (Table 3).

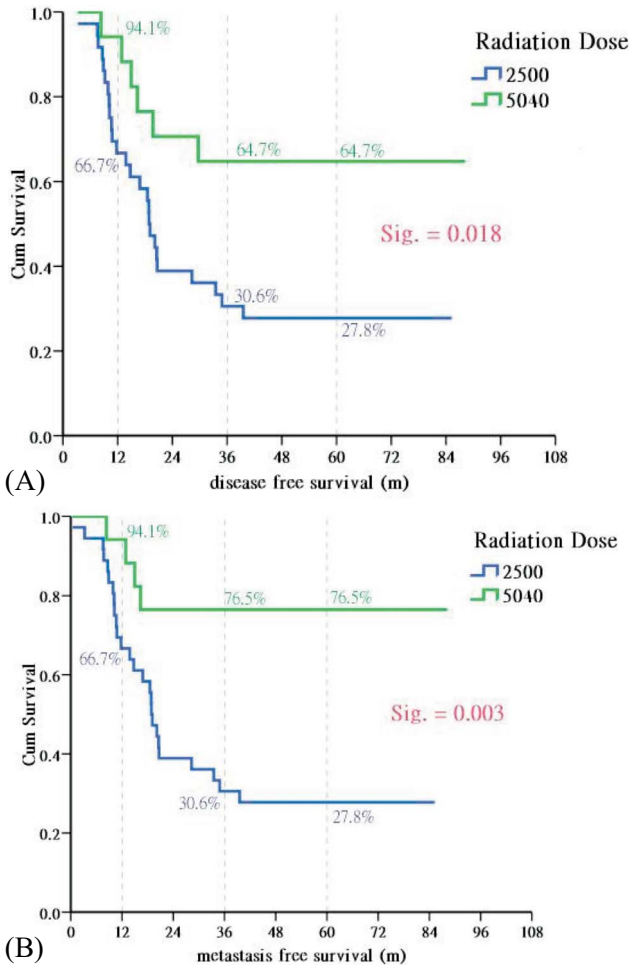


Fig. 1. Disease free survival difference (A) and distant metastases difference (B) between pathology lymph node positive subgroup.

In regards to down staging, we compared preoperative clinical staging with the postoperative pathology staging. If pathology staging is less advanced than the initial image staging, tumor regression is considered. If the pathology and clinical staging are the same, stationary is considered. If pathology staging is more advanced than clinical staging, progression is considered. The down-staging rate for the long course CCRT subgroup is 45.2% and 21.4% for tumor depth and lymph node involvement respectively. Concordance rates of short course radiotherapy are 28.2% and 52.1% for tumor depth and lymph node involvement respectively (Table 3).

Regarding treatment outcomes including overall survival, diseases free survival, local recurrent rate and distant metastasis rate, there is no significant difference between short course group and long course group shown in Table 2.

There are 6 patients out of 42 in the long course group that were noted of complete remission. Complete remission rate is 14.28%. Two of them did not receive an operation and the other 4 were pathological proved complete remission. They all survived till the end of our follow up, but only 3 of them remained dis-

Table 3. Hospital mortality, sphincter preservation and down staging comparison

	25 Gy		50.4 Gy		*p*-value
	No.	%	No.	%	
Hospital mortality					1.000
Yes	1	1.4	1	2.4	
No	70	98.6	41	97.6	
Sphincter preservation					0.105
Yes	57	80.3	28	66.7	
No	14	19.7	14	33.3	
T down staging					0.089
Progress	24	33.8	8	19.0	
Stationary	19	26.8	12	28.6	
Regression	20	28.2	19	45.2	
Uncertain	8	11.3	3	7.1	
N down staging					0.080
Progress	22	31.0	6	14.3	
Stationary	40	52.1	26	61.9	
Regression	9	11.3	10	21.4	

ease free, 1 from the non-OP group and the other 2 having been operated on. Distant metastasis to lung was noted in 2 of them. One was after 5 months and the other was after 20 months of follow up. One of the patients who did not receive an operation was noted with local recurrent after 14 months.

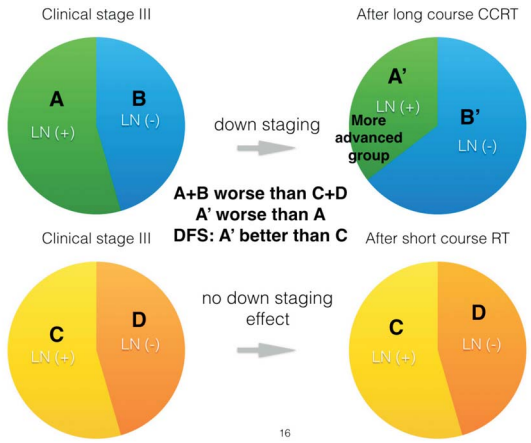
Discussions

In this study, the five-year overall survival of patients with locally advanced (T3/T4 with/without lymph node involved; any T stage with lymph node involvement) low and mid-rectum cancers is 58.5% in the short course radiotherapy group and 68.3% for the long course CCRT group, is comparable to the world's data, 54% to 81%.[1-5] There is no significant difference of treatment outcomes including overall survival rate, diseases free survival rate, local recurrence rate and distant metastasis rate between the short course and long course group. Interestingly, improved overall survival (89.3% vs. 62.2%, $p = 0.009$) is noted in the short course group among patients without pathologically proven lymph node involvement compared with those treated with long course CCRT. Furthermore, significantly improved disease free survival (64.7% vs. 27.8%, $p = 0.018$) and less distant metastases rate (23.5% vs.72.2%, $p = 0.003$) were observed in a long course CCRT group among pathological proven lymph node patients compared with those treated with short course radiotherapy.

In previous studies, better local control in the long course group but no difference in overall survival has been reported in the EORTC 22921,[3] Polish trial,[11,12] and the FFCD 9203 study.[10] A presence of a subclinical systemic disease at diagnosis is one of the hypotheses why no survival benefit is noted. There is also a study which reported that no differences in either overall survival or local control between the two groups,[12] which is the same as our study. Results in better distant control and marginal overall survival have also been reported before.[9] However, all of these studies mixed patients with or without lymph node metastases together and were based on clinical staging only. In our study, we divided patients into subgroups according to the presence or absence of lymph node involvement. In our study, average RT to OP interval is 13 days. An interval of less than 2 weeks from RT to OP had been reported with no down staging effects in different studies.[16,17] In other words, there is no down staging effect among the short course subgroup with pathologically negative lymph node involvement. The presence of better overall survival in pathologic negative lymph node subgroup after short course RT, implied the bias of patients with better clinical condition who had a better prognosis initially, may result in a better result.

As to the pathology proved lymph node involvement patients, improved disease free survival, less distant metastasis rate and marginal significance in better overall survival were noted in the long course group, while no significant difference related to local recurrence rate compared with short course radiotherapy. In our study, all surgeons agreed that long course CCRT was selected for the patients with a clinically more advanced condition. After long course CCRT, the remaining positive lymph node involvement subgroup stands for a clinically worse condition than the down staging one, which shifts into pathologic negative lymph nodes subgroups. In contrast, there is no down staging effect on short course radiation and the patients with positive lymph node stay in the same group. As a result, the groups with positive lymph node involvement after long course treatment have a more advanced condition than those in short course groups. The improved disease free survival and lower metastases rate in the more advanced group suggest the benefit of long course treatment, which may have a better distant control than short course RT. The schematic diagram was shown in Fig. 2.

The preoperative staging for rectal cancer is inaccurate compared with postoperative histopathology staging in previous studies. Smith et al. demonstrated an overall 60% and 62% predicted rate of preoperative CT scans for T-stage and nodal status respectively.[21] The accuracy of preoperative staging by CT scan may increase after using multiplanar reformations, especially for nodal stage, which was mentioned by Filippone et al.[22] Because of the inaccurate preoperative staging, the down staging effect after



The surgeons agreed long course CCRT was selected for the patients with a clinically more advanced condition (The A+B group was clinically worse than C+D group). After long course CCRT, the remaining positive lymph node involvement subgroup (A') stands for a clinically worse condition than the down staging one, which shifts into pathologic negative lymph nodes subgroups (B'). (Because of the down staging effect, the A' subgroup was the clinically worse part from the A subgroup) In contrast, there was no down staging effect on short course radiation and the patients with positive lymph node stayed in the same group, as a result, the groups with positive lymph node involvement after long course treatment have a more advanced condition than in short course group (A' subgroup was clinically worse than C subgroup). The better disease free survival and less metastases rate in the more advanced group suggest the benefit of long course treatment.

Fig. 2. The schematic diagram to demonstrate the different effect of long course CCRT and short course RT on the pathologic proved lymph node involvement subgroups.

neoadjuvant treatment has less clinical significance. It is assumed that micro-metastasis may already exist at the time a patient is diagnosed with rectal cancer without clinically significant lymph node presentation. The combined usage of chemotherapy plus radiation may add better systemic control and results in less distant metastasis and thus better disease free survival. The concept provides us with an idea that a more aggressive neoadjuvant therapy may be better for patients with suspicious lymph node metastasis.

To our knowledge, there was no prospective randomized trial distinguishing treatment outcomes between the patients with or without lymph node involvement. In this retrospective study, most preoperative clinical staging examined by abdominal CT and/or endoscopic ultrasound is reported by different radiologists. Bias might be present due to different radiologist's judgment. Furthermore, radiologists evaluated lymph node involvement only by size of a lymph node larger than 0.5 cm, the sensitivity and specificity is around 80% when compared to final pathology.[13] Because of the unreliability of clinical staging, over treatment in about 40% of cases was reported. However, our study implied that patients with middle and low rectal cancer should be carefully evaluated to ensure whether lymph node is involved or not.

Thus, it is important to note that patients with proven lymph node metastasis may benefit from long course chemoradiotherapy for the better distant control, while patients without proven lymph node metastasis could gain similar local and distant control from either short course radiotherapy or long course CCRT.

Conclusions

In this retrospective analysis, patients with a presence of lymph node involvement showed a significantly better outcome in disease free survival and metastasis control when treated with long course chemoradiotherapy. Long course chemoradiotherapy may be considered as neoadjuvant therapy for patients with locally advanced middle and low-third rectal cancer with lymph node metastases. Either short course radiotherapy or long course chemoradiotherapy may achieve similar local control.

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原　著

手術前長程化學與放射治療較手術前短程放射治療對於第三期直腸癌病患的無病存活率有顯著的改善

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目的　對於局部晚期直腸癌的病患，為了達到更好的局部控制及存活率，無論是術前短程放射治療或是長程同步放化療皆被使用中。然而，如何選擇這兩個治療方法仍無定論。

方法　我們蒐集了 2002 年 1 月 1 日至 2006 年 12 月 31 日於林口長庚醫院診斷為局部晚期直腸癌的病患，所有病患皆接受完整術前短程放射治療或是長程同步放化療並接受根除性手術，術後追蹤日期至 2009 年 12 月 31 日。變異項目如病患的性別、年齡、術前 CEA 濃度及腫瘤位置皆被收集分析。總生存率，無病生存率，局部復發率和遠處轉移率也由統計分析比較。

結果　在臨床病理特徵方面，腫瘤位置是短程治療及長程治療唯一的差異項 (低位直腸 63.4% vs. 81.0%, $p = 0.049$)。針對淋巴結轉移與否的次族群分析存在許多統計上的差異。對於沒有淋巴結轉移的次族群，短程治療有較好的總生存率 (五年存活率 89.3% vs. 62.2, $p = 0.009$)。對於有淋巴結轉移的次族群，長程同步放化療則有較好的無病生存率 (五年存活率 27.8% vs. 64.7%, $p = 0.018$)，較低的遠處轉移率 (Metastasis free rate 26.8% vs. 76.5%, $p = 0.003$) 及趨向有較好的總生存率 ($p = 0.059$)。對於局部復發率，兩者並無顯著差異 (83.0% vs. 87.5%, $p = 0.557$)。

結論　基於我們的研究，對於中低位直腸癌且有淋巴結轉移的病患，為了達到更好的無病生存率，術前長程同步放化療是可以考慮的治療方式。對於沒有淋巴結轉移的病患，術前短程放療則與術前長程同步放化療有同樣的疾病控制。

關鍵詞　同步放化療、放射治療、局部晚期直腸癌。