Original Article

Difference between Complete Oxaliplatin Based Adjuvant Chemotherapy and Incomplete Course in Stage III Colorectal Cancer Patients in Taiwan

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Key Words
FOLFOX;
Oxaliplatin;
Adjuvant chemotherapy;
Incomplete course;
Stage III colorectal cancer

Purpose. We have analyzed stage III colorectal patients who cannot receive complete course oxaliplatin based adjuvant chemotherapy (FOLFOX). We have followed up this group of patients, and have gained information for the patients who cannot complete adjuvant chemotherapy in the aspect of overall survival and recurrence rate.

Patients and Methods. This was a case control study. We retrospectively analyzed stage III colorectal cancer patients who received adjuvant chemotherapy at Taichung Veteran General Hospital (VGHTC) from Jan. 2005 to Dec. 2012. The patients were enrolled and classified according to the duration of chemotherapy. Consequence of disease free survival (DFS), overall survival (OS) will be analyzed.

Result. Two-year disease free survival (DFS) rates were 86.7% and 82.1% in patients' receiving incomplete course FOLFOX and complete course FOLFOX respectively (Hazard ratio: [HR] = 0.70, 95% CI, 0.38 to 1.30, p = 0.254). Five-year overall survival rates (OS) were 77.2% and 79.0% in patients' receiving incomplete course FOLFOX and complete course FOLFOX respectively (Hazard ratio: [HR] = 1.37, 95% CI, 0.69 to 2.78, p = 0.366). 49% patients cannot complete full-course adjuvant chemotherapy FOLFOX. The most frequent reasons of incomplete chemotherapy were severe gastrointestinal side effect and sensory neuropathy. The recurrent pattern were liver, lung metastasis, and peritoneum seeding in both groups. In the stage of 3A + 3B incomplete group, non-inferior trend in DFS and OS was noted. In the stage of 3C complete course group, superior trend in overall survival was noted.

Conclusion. For stage III colorectal cancer adjuvant chemotherapy setting, incomplete course FOLFOX didn't get worse in overall survival. There was also a leading trend toward complete course in DFS. But in the stage of 3C colorectal cancer patients, complete course FOLFOX was an indicator for better OS. The result was pending further larger randomized clinical trial.

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Colorectal cancer has been the first leading cause for the cancer in Taiwan for continuous 7 years, and the number of newly diagnosed cases has continuously been growing up in these years. In 2011, there was 4921 deaths caused by colorectal cancer (standardized mortality rate: 15/100 thousands) in Taiwan. In 2012, there were 14965 colorectal cancer cases being newly diagnosed (standardized cancer incidence rate: 45.1/100 thousands) in Taiwan.[1] Stool occult blood routine has been promoted by Health Promotion Administration, Ministry of Health with Welfare for colorectal cancer screening since 2004. Stage III colorectal cancer cases have been increased after this policy was promoted. The use of adjuvant chemotherapy was associated with 30% proportional reduction in risk of recurrence.[2] In the MOSAIC phase III trial, FOLFOX-4 provided better 5-year DFS rate to LV5FU2 (73.3% and 67.4%, HR = 0.80; 95% CI: 0.68 to 0.93; $p = 0.003$) and better 6-year OS (78.5% and 76% HR = 0.84, 95% CI: 0.71 to 1.00; $p = 0.046$).[2] Oxaliplatin was approved in FDA in 2003 and was introduced to Taiwan at the same time. National Healthy Insurance has covered 12 courses adjuvant FOLFOX for stage 3 colorectal cancer patient since 2009.[3]

Despite the efficacy of Oxaliplatin, it also leads to significant cost, toxicity, and patient inconvenience. In particular, cumulative dose-dependent neurotoxicity is usually clinically related to treatment compliance. In the MOSAIC trial, the incidence of neurotoxicity during treatment was estimated to be 92%, and grade 2 or 3 neurotoxicity was approximately 45% during treatment.[4] For the stage III colorectal cancer patients who could not complete standard six-month course FOLFOX, the efficacy of chemotherapy was eager to be known. We conducted this study to compare recurrence and mortality of incomplete course FOLFOX with a complete course.

Patients and Methods

This case control study has enrolled stage III colorectal cancer patients who received oxaliplatin based adjuvant chemotherapy within three months after curative surgery from Jan. 2005 to Dec. 2012. Cancer staging was AJCC edition 6 according to Taiwan cancer Registry manual.[5] The study was approved by the Ethics Committees of Institutional Review Board.

Following-up

Patients enrolled in this study were followed up according to NCCN guideline. History and physical in colorectal out patients department (OPD) was checked every 3 to 6 months for 2 years, then every 6 months for a total of 5 years. CEA was checked every 3 to 6 months for a total of 5 years. Abdomen CT was arranged annually up to 5 years. Colonoscopy was arranged in one year except no preoperative colonoscopy due to obstruction, and colonoscopy would be arranged in 3 to 6 months. The cutoff date for final analysis was in Dec. 2014. Adverse effect was assessed according to OPD record.

Statistic Analysis

We have retrospectively collected stage III colorectal cancer from Jan. 2005 to Dec. 2012 to receive an adjuvant oxaliplatin based chemotherapy in VGHTC. The patients were divided into 2 group: 6-11 times, and 12 times. DFS and OS curve between these groups was calculated by Cox proportional hazards model. DFS and Survival curves were presented according to Kaplan-Meier methods. The cutoff date for this analysis was in Dec. 2014.

Result

Patients and treatment

From Jan. 2005 to Dec. 2012, 780 patients were enrolled. Among them, 266 patients were not treated due to many reasons such as elderly, patient's preference and operation complication. 208 patients received oral form chemotherapy. 27 patients received other regimen clinical trial. 279 patients were intent to received oxaliplatin based adjuvant chemotherapy

within 3 months after curative surgery. 21 patients received less than 5 times of chemotherapy, 116 patients received 6-11 times (incomplete course), and 142 patients received complete 12 times oxaliplatin based chemorherapy. In the group of patients who received incomplete course, 21 patients were excluded because they changed adjuvant regimen due to progress of disease (Fig. 1). Incomplete courses FOLFOX group had more percentage in female patients (61.1% vs 41.5%), rectum cancer (45.3% to 35.4%), and lower percentage in the stage of 3C disease (33.7% vs 41.5%). Tumor location, tumor cell differentiation was not significant between these two groups (Table 1).

DFS in incomplete course and complete course

After an average follow-up time of 34.6 months and 35.2 months, 2-year DFS patients were 86.7% and 82.1% in incomplete course and complete course respectively (Hazard ratio: [HR]: 0.7, 95% CI, 0.38 to 1.30, $p = 0.254$) (Table 2). There was no statistic difference. The DFS curve showing complete course got leading position in the first year but fell behind to incomplete group after 2 years. (Fig. 2A). Trend of superiority in DFS curve in incomplete course group was noted. We sub-classified the patients in both group into stage 3A + 3B and stage 3C. Incomplete course group got superior trend of DFS curve in stage 3A + 3B patients. There was no obvious difference in stage 3C between these groups. (Fig. 2B)

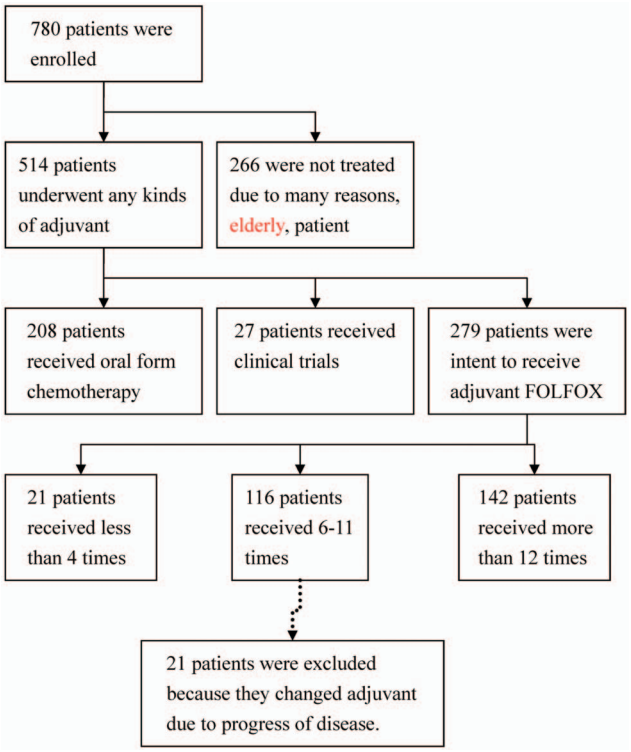

Fig. 1. Stage III colorectal cancer patients underwent adjuvant chemotherapy in VGHTC. The figure illustrated patient groups of this study.

OS in incomplete course and complete course

After an average follow-up time of 32.3 months and 31.0 months, the probabilities of 5-years overall

Table 1. Patients characteristics in incomplete course FOLFOX (6-11 times) and complete course (12 times)

	< 12		= 12		
Gender					
Male	37	38.9%	83	58.5%	0.005
Female	58	61.1%	59	41.5%	
Primary site					
Cecum	7	7.4%	14	9.9%	0.177
A-colon	7	7.4%	11	7.7%	
Hepatic flexure	2	2.1%	8	5.6%	
T colon	9	9.5%	3	2.1%	
Splenic flexure	1	1.1%	4	2.8%	
D colon	3	3.2%	8	5.6%	
S colon	18	18.9%	27	19.0%	
Overlapping site	2	2.1%	1	0.7%	
R-S colon	3	3.2%	10	7.0%	
Rectum	43	45.3%	56	39.4%	
Differentiation					
Moderate	71	74.7%	114	80.3%	0.366
Poor	18	18.9%	24	16.9%	
Undifferentiated	6	6.3%	4	2.8%	
Pathology stage					
3A	7	7.4%	9	6.3%	0.474
3B	56	58.9%	74	52.1%	
3C	32	33.7%	59	41.5%	
Survival					
Death	15	15.8%	17	12.0%	0.516
Alife	80	84.2%	125	88.0%	
Recurrence					
N	80	84.2%	110	77.5%	0.267
Y	15	15.8%	32	22.5%	

Table 2. Patients DFS of incomplete course FOLFOX and complete course. 2-years DFS in incomplete course and complete course group was 86.7% to 82.1%. incomplete course group DFS was slightly superior to complete course group

	Total	Recurrence	1st yr	2nd yr	3rd yr	4th	5th yr	6th yr
< 12	95	15	93.6%	86.7%	83.3%	81.1%	77.2%	77.2%
= 12	142	32	93.4%	82.1%	70.9%	67.8%	67.8%	67.8%

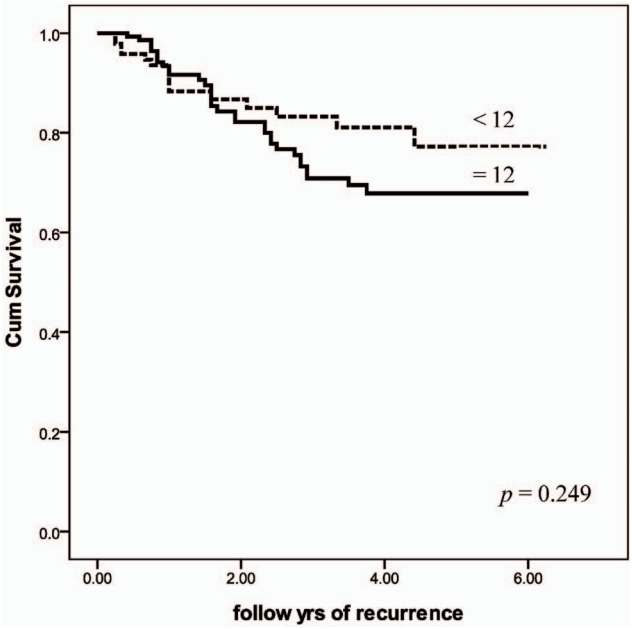

Fig. 2. (A) DFS curve between complete course and incomplete course. There was no statistical significance. (p = 0.249) But the paragraph showed the trend of superiority in DFS curve in incomplete course group.

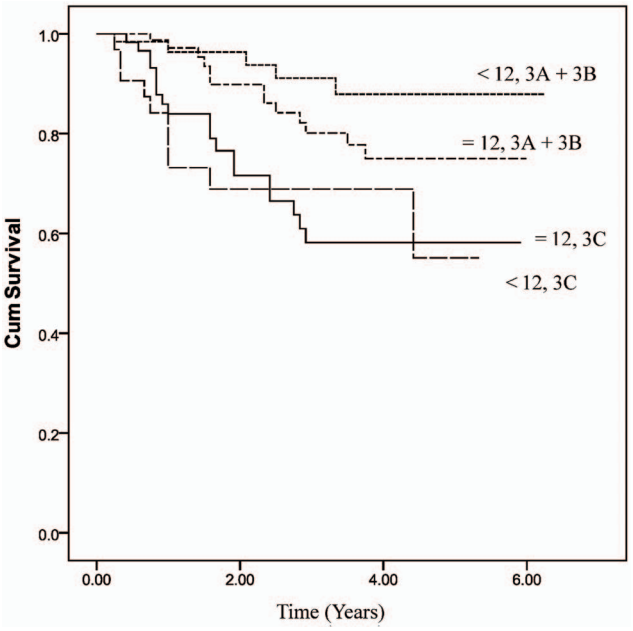

Fig. 2. (B) DFS curve between complete course and incomplete course, the patients were sub-classified in stage 3A + 3B group and stage 3C. In stage 3A + 3B, incomplete course group got superiority in DFS to complete course group. In stage 3C group, there was no superiority noted.

survival were 77.2% and 79.0% in incomplete course and complete course respectively (Hazard ratio: [HR] = 1.37, 95% CI, 0.69 to 2.78, p = 0.366). (Table 3) There was no statistically difference (p = 0.362). The survival curve of complete course was slightly superior to the curve of incomplete course group (Fig. 3A). Furthermore, we sub-classified these patients into stage 3A + 3B and stage 3C. There was no obvious difference between complete course and incomplete course in stage 3A + 3B. But superior trend of OS curve of complete course in stage 3C was noted. (Fig. 3B)

Side effect

In incomplete course groups, the documented reasons for discontinuity of oxaliplatin were recorded (Table 4). The main reason of incomplete course was the adverse effect from chemotherapy. First, the peripheral neuropathy was recorded in 19 patients (20.0%) for the course to discontinue pre-planned therapy. Secondary, gastrointestinal discomfort including nausea, vomiting and poor appetite were noted in 18 patients. Besides toxicity of medication, complication of oncology operation and chemoport operation may also frustrate the patient to accept a completely adjuvant chemotherapy.

Recurrent pattern

The recurrent pattern of incomplete group and

Table 3. Patients OS of incomplete course FOLFOX and complete course. 5-years overall survival in incomplete course and complete course was from 77.2% to 79.0%. complete course group got superior overall survival to incomplete course group

	Total	mortality	1st yr	2nd yr	3rd yr	4th	5th yr	6th yr
< 12	95	15	96.7%	87.4%	81.2%	77.2%	77.2%	77.2%
≧ 12	142	17	99.1%	92.0%	86.5%	84.1%	79.0%	79.0%

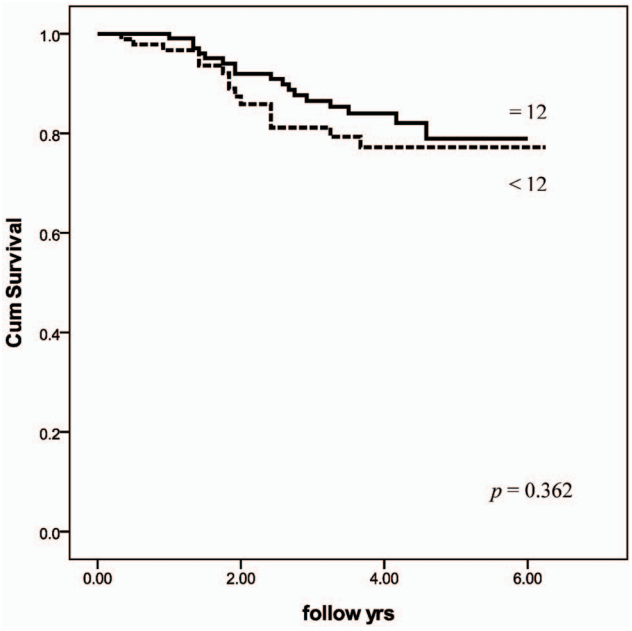

Fig. 3. (A) OS curve between complete course and incomplete course. There was no statistical significance. (p = 0.362). Superiority of survival curve in complete course group was not obvious. In the end, both groups were very close.

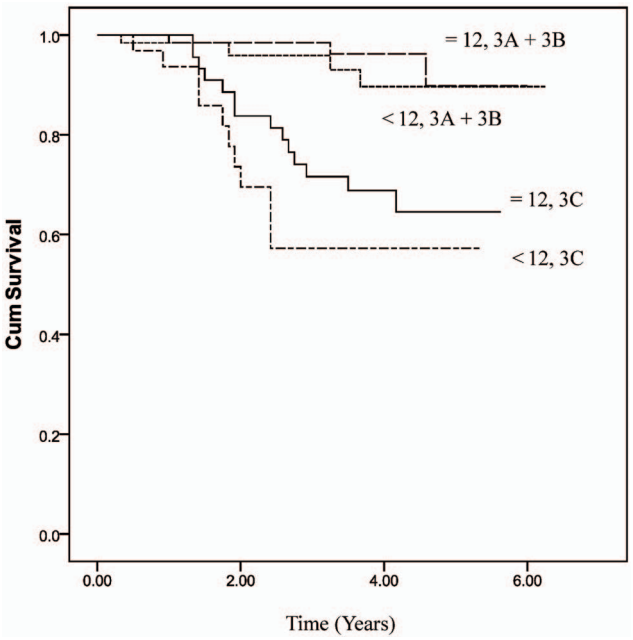

Fig. 3. (B) OS curve between complete course and incomplete course was sub-classified into stage 3A + 3C and stage 3C. In stage 3C, trend of superiority of overall survival in complete course group was noted. In stage 3A + 3B, no obvious difference between both groups.

complete group was calculated as following table (Table 5). peritoneum seeding, lung and liver metastasis were both documented in both group. There was no obvious difference between both groups.

Table 4. Reasons of patients of incomplete course

Reasons	Number	Percentage
Gastsrointestinal discomfort	18	18.9%
Thrombocytopenia	5	5.3%
Neutropenia	9	9.5%
Peripheral neuropathy	19	20.0%
Skin allergy	9	9.5%
Operation side effect	5	5.3%
Chemoport infection	4	4.2%
Patient hesitate	5	5.3%

Discussion

In the past, most literature discussion about what regimen was most benefited for the colorectal cancer patients in adjuvant setting. This time, proper chemotherapy duration was another issue that physicians wanted to know. The conductor of MOSAIC study Thierry André was handling The IDEA project to prospectively combine and analyze data from several randomized trials conducted around the world to answer whether a three-month course FOLFOX was non-inferior to the current standard six-month treatment.[6] We conducted this case-control study for stage III colorectal cancer patients receiving oxaliplatin based

Table 5. Recurrent pattern of complete course and incomplete course

	Incomplete		Complete	
Recurrent pattern				
Local	2	13.3%	5	15.6%
Peritoneum			2	6.2%
Lung	2	13.3%	6	18.8%
Liver	3	23.0%	9	28.1%
Distant	3	23.0%	2	6.2%
Multiple	5	33.3%	11	34.4%

adjuvant chemotherapy, retrospectively in VGHTC from Jan. 2005 to Dec. 2012.

The DFS curve of incomplete course fell behind in the first year but took a leading position after that. Proportion of stage 3C colorectal cancer was fewer in incomplete course group (33.7% vs 41.5%). Although better DFS was prospected in this group, the curve didn't fall behind if chemotherapy was not completed. So, there was no inferiority of recurrence rate in incomplete course. On the other hand, complete course didn't provide better warranty for tumor recurrence in this population although recurrence rate in the first year once got in fraction leading position, but it fell behind in a long term. No DFS advantage in complete course group was found. Since there was difference in the sample distribution, we sub-classified these groups into stage 3A + 3B and stage 3C. Incomplete course provided better trend in DFS curve in stage 3A + 3B group, and in stage 3C group, there was no difference between these groups. Incomplete course FOLFOX provided evenly warranty to recurrence in stage 3 colorectal cancer patients, except stage 3C.

Although complete course chemotherapy didn't provide obvious and better warranty for recurrence in this study. The OS curve of this group was slightly superior to that of incomplete course, but the curve of two groups met together after 5 years. There was no obvious advantage of complete course in OS.

In sub-classification study, complete course group's overall survival curve was better than that of incomplete course group in stage 3C patients. But the reasons for better survival rate of stage 3C patients were ambiguous. Nowadays, there were more choices of regiments or monoantibodies for salvage chemotherapy that would affect OS. The effect of these salvage chemotherapies interfered the life span from recurrence to death. We could only say that complete course was a good indicator for better survival rate in stage 3C patients. On the other hand, overall survival in incomplete course was not inferior to complete course. Incompletion of chemotherapy didn't affect survival rate of stage 3A + 3B patients compared with complete courses.

The reasons for incomplete course were due to side effect of oxaliplatin. In our study, most frequent reasons were gastrointestinal discomfort: 18 (19.0%) and peripheral neuropathy: 19 (20.0%). Due to these side effects of oxaliplatin, only 50.7% (142/280) patients completed 6-month course chemotherapy in our study. Anna Wiela-Hojeńska1 et al. analyzed toxicity symptoms of FOLFOX, the most frequent ones were nausea/vomiting (41%), peripheral neuropathy (33%), hair loss (25%), leucopenia (13%), skin lesion (11%).[7] Anaphylactic shock was also clinically noted in our hospital but not included in this study because the patient quit FOLFOX after the second course. Thierry André reviewing 42 patients Allergic-type reactions to oxaliplatin. Anaphylactic case (2.4%) was noted.[8]

Rectum cancer was not excluded in this study. There was more percentage rectal cancer in incomplete course group (45.3% vs 39.4%). In recent years, the prognosis for rectal cancer has at least caught up with colon cancer, due to profound changes in treatment strategies which include introduction of TME and preoperative or neoadjuvant chemoradiotherapy. Fischer Joern1 & Hellmich Gunter et al. announced Outcome for stage II and III rectal and colon cancer were equally good after treatment improvement over three decades. They found a substantial increase of cause specific survival (CSS) from 65.0 to 88.1% (1981-1986 vs. 2007-2011) for stage II and III colon cancer. For stage II/III rectal cancer, the increase in CSS was even more pronounced (53.4 vs. 89.8%).[9] In our study, we didn't exclude rectal cancer patients due to similarity of outcome. Contrarily, more physicians discussed about difference between right side colon and left side colon. In our study, the proportion of right side colon was similar to both groups. (26.4% vs 25.3%)

Our study has some limitations that need to be addressed. First, this was not a randomized clinical trial, it was a retrospective case control study. Second, sample size was not enough, clinical information still did not have enough details. If Patients ECOG performance score was collected, correction of gender, ECOG score could be done under statistic software, and the larger scale sample number provided more sample power. We conducted this study for the patients who could not complete adjuvant FOLFOX, knowing the risk and consequence, and provided our clinical evidence in Taiwan population.

Conclusion

For stage III colorectal cancer adjuvant chemotherapy setting, complete course FOLFOX didn't provide obvious better survival benefit in stage III colorectal cancer patients, but it got better survival curve in stage 3C patients. Incomplete course FOLFOX seemed to have better DFS curve, especially for stage 3A + 3B patients. For patients who could not complete 12-time FOLFOX adjuvant setting, there was non-inferiority in disease free survival and overall survival for stage 3A + 3B group patients. Complete course and incomplete course had similar OS curve in stage III colorectal cancer patients, for stage 3C, complete course FOLFOX was a good indicator for better overall survival. Result of further larger scale clinical trail was pending to be known.

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原　著

台灣地區完整的輔助性化學治療與不完整的輔助性化學治療對於第三期大腸直腸癌復發率及存活率的差別

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目的　我們分析第三期大腸直腸癌病患接受不完整的輔助性化學治療 (FOLFOX)。追蹤這些病人的存活率復發率

病人及方法　這個 case control study 回顧式的分析台中榮民總醫院自 2005 年 1 月到 2012 年 12 月第三期大腸直腸癌接受手術後輔助性化學治療的病患，根據化學治療療程完成與否區分兩個族群，比較這兩組病患的存活率復發率。

結果　平均追蹤 34.6 月與 35.2 月，未完成化學治療與完成的兩年 DFS 分別是 86.7% vs 82.1% (Hazard ratio: [HR] = 0.70, 95% CI, 0.38 to 1.30, p = 0.254)。未完成化學治療與完成的五年存活率分別是 77.2% and 79.0% (Hazard ratio: [HR] = 1.37, 95% CI, 0.69 to 2.78, p = 0.366)。復發率與存活率在統計學上沒有意義，但未完整的療程在 DFS 有比較好的趨勢，49% 病人不能完成 12 次完整的化療，在不能完成化療的病人之中最常見的副作用是腸胃道症狀及神經感覺異常，復發型態在兩組沒有明顯差異。再進一步分析 stage 3A + 3B 與 3C 病人中，stage 3A + 3B 病患未完成化療的病患也有相當的存活率復發率，但 stage 3C 病患有完成化療的整體預後較佳。

結論　對第三期大腸直腸癌患者來說未完全的療程與完全的療程在 DFS 與 OS 上沒有誰比較好的顯著意義，但未完全的療程在 DFS 曲線反而可看到較好的趨勢，對於第三期大腸癌病患，即使無法完成化療，也不會有較差的復發率，但 stage 3C 患者，有完成 12 次 FOLFOX 療程的還是有較好的預後，還是建議儘量完成。

關鍵詞　Oxaliplatin、FOLFOX、輔助性化療、不完整療程、第三期大腸直腸癌。