Original Article

Is the Tegafur/uracil and Leucovorin Adjuvant Chemotherapy Overused in Low-risk Group Stage II Colorectal Cancer Patients?

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Key Words
Low-risk stage II colorectal cancer;
Tegafur/uracil (UFT);
Adjuvant chemotherapy

Purpose. Colorectal cancer is one of the most common cancers and the third leading cause of cancer-related death in Taiwan. Because of the nationwide biennial fecal immunochemical screening, the number of colorectal cancer cases detected at an early stage is increasing. According to the National comprehensive cancer network (NCCN) clinical practice guidelines, adjuvant chemotherapy is suggested for patients with high-risk group stage II colorectal cancer; research in the low-risk group stage II colorectal cancer has been less specific. We aimed to review our hospital database to evaluate the effect of uracil-tegafur (UFT) and leucovorin adjuvant chemotherapy on low-risk group stage II colorectal cancer patients.
Materials and Methods. Between January 2004 and August 2009, 1273 stage II colorectal cancer patients underwent standard curative operations at the Linkou and Keelung Branch of Chang Gung Memorial Hospital in Taiwan. After excluding the patients with early recurrence within 6 months after the operation, and those who received intravenous adjuvant chemotherapy, the remaining 1107 patients were enrolled in the study. After analyzing the pathological and clinical characteristics of the patients, 515 were identified to have low-risk group stage II colorectal cancer. All patients in this group were followed up for at least 5 years postoperatively or until the date of patient death. Statistical analysis was performed with SPSS ver. 20.
Results. In our database, patients in the high-risk group (n = 592) had significantly worse overall survival and 5-year disease-free survival compared to those in the low-risk group (n = 515). In the low-risk group stage II colorectal cancer patients, 70 patients received UFT and leucovorin adjuvant chemotherapy, while 445 patients did not receive adjuvant chemotherapy. Comparing the two groups revealed that UFT and leucovorin adjuvant chemotherapy did not improve the overall survival or 5-year disease-free survival in the low-risk group stage II colorectal cancer patients.
Conclusion. Our data showed that low-risk group stage II colorectal cancer patients who received the UFT and leucovorin adjuvant chemotherapy might be overtreated. We should aim to avoid exposing these patients to the side effects of unnecessarily administered chemotherapy, and control its impact on the economy.
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In recent years, colorectal cancer has become the most common cancer in Taiwan. According to the Taiwan Cancer Registry, one person is diagnosed with colorectal cancer every 37 minutes. In addition, colorectal cancer is the third leading cause of cancer-related death in Taiwan.[1] With the introduction of a nationwide colorectal cancer screening program offering biennial fecal immunochemical testing to all Taiwanese aged 50-69 years, the early detection rate of colorectal cancer has increased.[2] In fact, more than 40% of the cases are defined as early stage (colon cancer, stage 0~2: 48.18%; rectal cancer, stage 0~2: 46.74%). Early detection could result in timely administration of treatment to cancer patients and reduction of mortality.

Currently, after complete preoperative staging, the main treatment for localized colorectal cancer (stages I-III) is radical resection.[3] Radical resection includes complete removal of the tumor and associated major lymphovascular pedicles of the affected colonic segment. This operative procedure provides specimens for pathological, histochemical, and genetic testing, which help determine the prognosis of colorectal cancer in patients.[4] Depending on the diagnosis, a treatment and surveillance plan is developed.

According to the National comprehensive cancer network (NCCN) 2014 guidelines, high-risk stage II colorectal cancer is characterized by T4 lesion, poor differentiation, lymphovascular invasion, perineural invasion, bowel obstruction, localized perforation, and less than 12 lymph nodes examined.[5] According to the NCCN guidelines, adjuvant chemotherapy is recommended for these patients.[6] Several chemotherapy protocols were considered for the treatment of high-risk stage II colorectal cancer patients, including intravenously administered 5-fluoropyrimidine (5-FU)-based chemotherapy, oxaliplatin, or orally administered chemotherapy (e.g. uracil-tegafur [UFT] and capecitabine).[5] Previous studies reported that UFT and leucovorin adjuvant chemotherapy was effective in high-risk stage II colorectal cancer patients.[7] However, the use of adjuvant chemotherapy in low-risk stage II colorectal cancer patients is controversial. In this study, we aimed to review our hospital database and evaluate the effectiveness/economics of UFT and leucovorin adjuvant chemotherapy in the treatment of low-risk stage II colorectal cancer patients.

Materials and Methods

Between January 2004 and August 2009, 1273 patients were diagnosed with stage II colorectal cancer and underwent standard curative operations at the Linkou and Keelung Branch of Chang Gung Memorial Hospital in Taiwan. Patients who received preoperative or postoperative radiotherapy (n = 105) or intravenous 5-FU based chemotherapy treatment (FOLFOX regimen or 5-FU only) (n = 32); patients who experienced risk of surgical mortality during the same hospitalization (n = 11); and those who relapsed within 6 months (n = 18) were excluded from the study. The remaining 1107 patients were included. According to the clinical and pathological characteristics defined by NCCN guidelines for stage II colorectal cancer patients, we divided 1107 patients into high-risk group (at least one of T4 lesion, poor differentiation, lymphovascular invasion, perineural invasion, bowel obstruction, perforation, and less than 12 lymph nodes examined), and low-risk group (no any poor features). 592 patients exhibited in high-risk groups and the remaining 515 patients were diagnosed as low-risk groups (Fig. 1).

Demographic data including sex, age, tumor location and size; pathological characteristics; and preoperative laboratory data, were all collected for analysis in these patients. The administration of UFT and leucovorin adjuvant chemotherapy depended on the surgeons' experience and patient performance. The treat-

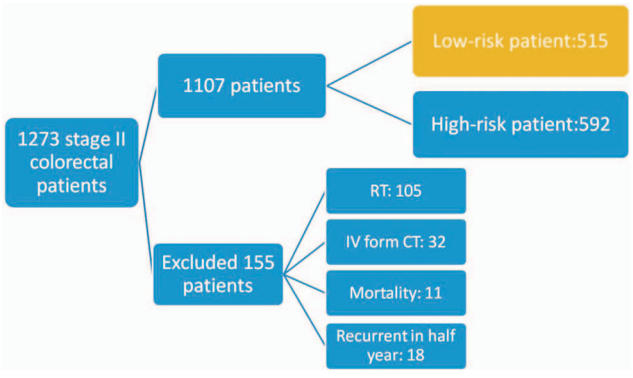

Fig. 1. Patients collecting and screening.

ment doses were UFT 300 mg/m^2/day PO and leukovorin 90 mg/day PO, from days 1 to 28, followed by 7 days rest, and repeated every 5 weeks for half to one year. The patients were continuously followed up for at least 5 years postoperatively or until death.

Categorical data like clinicopathological features were compared by using Pearson's chi-squared test and the numerical data like preoperative laboratory examinations were compared by using Student's t-test. The survival curves were calculated using the Kaplan-Meier method and compared with the log-rank test. Statistical significance was defined as $p < 0.05$. All analyses were performed using the Statistical Package for the Social Sciences version 20 (SPSS Inc. Chicago, USA).

Results

The high-risk group (n = 592) had significantly worse overall survival (83.7% vs. 74.3%; log-rank test: $p < 0.001$; Fig. 2), and 5-year disease-free survival (84.7% vs. 75.7%; log-rank test: $p < 0.001$; Fig. 3) compared to the low-risk group (n = 515). These results were consistent with those of other studies.

We further divided the low-risk group stage II colorectal cancer patients into two groups; those who received UFT and leucovorin adjuvant chemotherapy (n = 70), and those who did not (n = 445). There were no statistically significant differences in sex, tumor location (right or left colon), pathologic differentiation (well differentiated or moderately differentiated), or preoperative laboratory data (including hemoglobin level, white blood cell count, absolute neutrophil count, and albumin level) between the two groups. The group that received adjuvant treatment had younger patients and higher carcinoembryonic antigen (CEA) levels (Table 1).

After comparing patients with or without UFT and leucovorin adjuvant chemotherapy treatment in the low-risk group stage II colorectal cancer, we showed that UFT and leucovorin adjuvant chemotherapy did not prolong the patients' overall survival (82.2% vs. 92.9%; log-rank test: $p = 0.297$; Fig. 4) or 5-year disease-free survival (84.3% vs. 87.1%; log-rank test: $p = 0.526$; Fig. 5).

Discussion

According to the American Joint Committee on Cancer (AJCC) staging system, localized cancer lesions were categorized as stage II, and lesions with regional lymph node involvement were categorized as stage III.[8] In theory, stage II and stage III colorectal cancer are potentially eligible for curative resection (R0 resection). However, some cases had local/re-

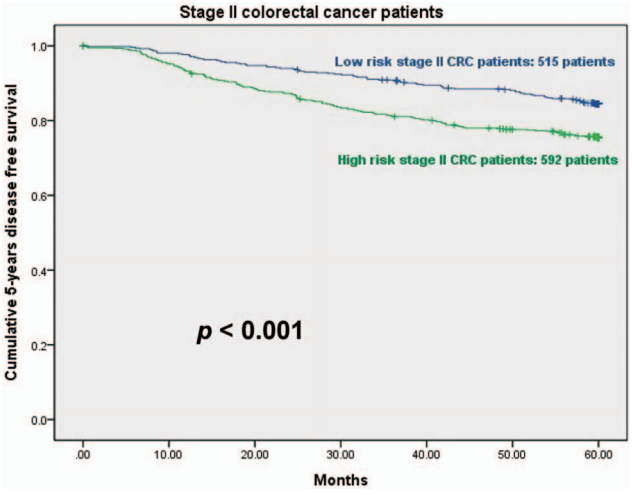

Fig. 2. The 5-years disease free survival in high-risk group and low-risk group stage II colorectal cancer patients.

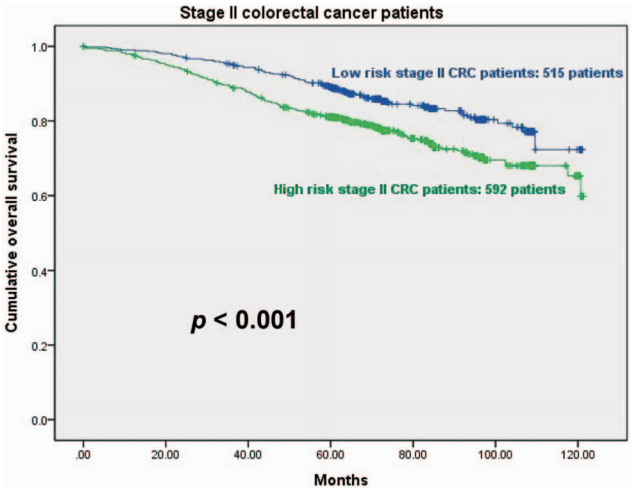

Fig. 3. The overall survival in high-risk group and low-risk group stage II colorectal cancer patients.

Table 1. Characteristics of stage II colorectal cancer patients with UFT treatment or not

Stage II colorectal cancer Low risk patients (515)	UFT treatment (70)	No UFT treatment (445)	*p* value
Sex			0.814
Male	41 (58.6%)	254 (57.1%)	
Female	29 (41.4%)	191 (42.9%)	
Location			0.724
Right	19 (27.1%)	112 (25.2%)	
Left	51 (72.9%)	333 (74.8%)	
Differenation			0.982
Well	8 (11.6%)	52 (11.7%)	
Moderate	64 (88.7%)	393 (88.3%)	
Age (years)	61.74	66.28	0.003*
Pre-operative CEA (ng/mL)	14.049	7.834	0.008*
Hb (g/dL)	11.847	12.043	0.509
WBC (/mm^3)	7734	7329	0.159
ANC (/mm^3)	5115	4802	0.260
Albumin (g/dL)	3.98	4.04	0.295

CEA: Carcinoembryonic Antigen, Hb: Hemoglobin, WBC: While blood cell, ANC: absolute neutrophil count.

gional/distant recurrence. In 2007, the ACCENT Database revealed that stage II and stage III colorectal cancer patients had the highest recurrence rates within 2.5 years after operation.[9] Reducing the risk of recurrence in the time period after the operation is a big challenge for surgeons.

In order to reduce the risk of recurrence, eradication of micrometastases is the goal of postoperative adjuvant chemotherapy. Postoperative adjuvant chemotherapy is a well-accepted treatment strategy for stage III colorectal cancer patients. However, the effectiveness of adjuvant chemotherapy in the treatment of stage II colorectal cancer remains controversial. Schcrag et al. showed that chemotherapy improves the absolute 5-year survival by 3% in stage II colorectal cancer patients; however, this improvement is not statistically significant.[10]

As previously mentioned, T4 lesion, poor differentiation, lymphovascular invasion, perineural invasion, bowel obstruction, perforation, and less than 12 lymph nodes examined enable to differentiate between high- and low-risk stage II colorectal cancers. According to these criteria, the National Cancer Institute's SEER database showed 75% of the patients are classified as high-risk stage II colorectal cancer.[11] In our database, the high-risk group accounted for 53.5%, and the low-risk group for 46.5% of all stage II colorectal cancer patients.

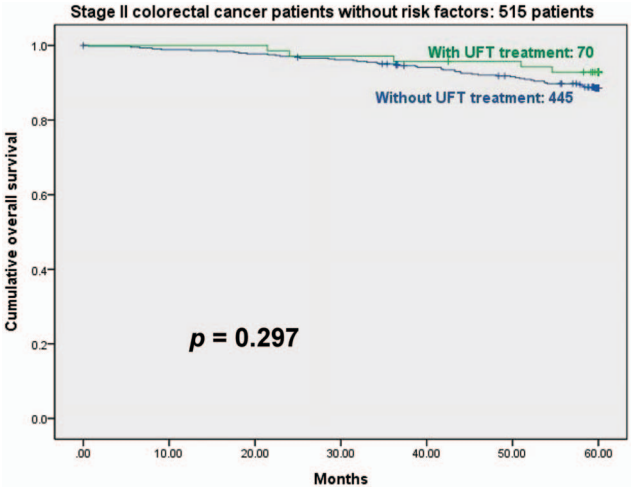

Fig. 4. UFT treatment did not prolong the overall survival in low-risk group stage II colorectal cancer patients.

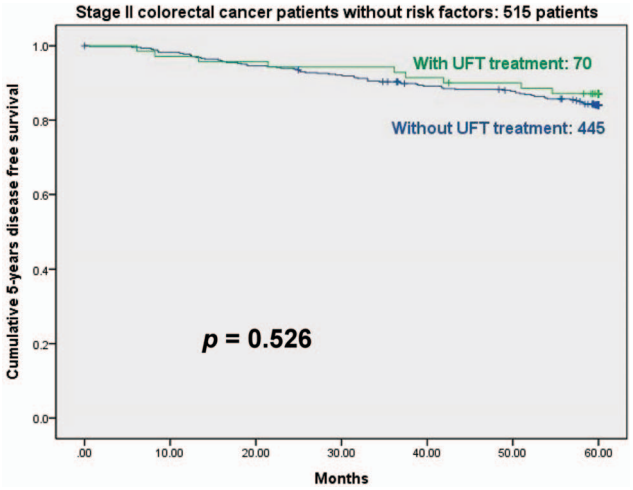

Fig. 5. UFT treatment did not prolong the 5-year disease free survival in low-risk group stage II colorectal cancer patients.

According to NCCN guidelines, adjuvant chemotherapy is recommended for stage II colorectal cancer patients with high-risk factors.[6] UFT and leucovorin adjuvant chemotherapy is one of the treatment choices.[7] The efficacy and economy of using adjuvant therapy in the treatment of low-risk stage II colorectal cancer patients has to be clinically evaluated.

Kato et al. suggested that consecutive administration of UFT at 400 mg/day was an effective and highly safe postoperative adjuvant chemotherapy for stage II and stage III colorectal cancer patients in 2002.[12] Lembersky et al. showed that UFT plus leucovorin had similar effects with intravenously administered 5-FU based chemotherapy after primary surgery in stage II and III colorectal cancer patients in 2006.[13] UFT treatment had some advantages during the course of the treatment, including convenience (oral absorption), and reduction of treatment time and costs.[14]

UFT was first prescribed in Japan. It was a combination of tegafur and uracil at a molar ratio of 1:4. Tegafur is a precursor of 5-FU. It can be metabolized to active 5-FU in the human body. Uracil can inhibit dihydropyrimidine dehydrogenase, which can degrade 5-FU, and prolong the action time of 5-FU in the body. UFT is not only used in the treatment of colorectal cancer, but also in the treatment of gastric cancer,[15] breast cancer,[16] lung cancer,[17] and head and neck squamous cell carcinoma.[18] However, UFT still has some side effects. In 2000, Roy E. Smith et al. revealed that UFT and leucovorin in treatment of colon cancer patients would cause about 38% grade 3 hematologic and non-hematologic toxicity, including diarrhea (29%), nausea (7%), vomiting (4%), leucopenia (1%), thrombocytopenia (< 1%) , and stomatitis (1%).[19]

The low-risk stage II colorectal cancer patients in our database were divided into two groups; those who received UFT and leucovorin adjuvant chemotherapy and those who did not. These two groups exhibited similar epidemiological and pathological features, as well as similar preoperative white cell counts, absolute neutrophil count (ANC), albumin, and hemoglobin level (Table 1). Although the low-risk stage II colorectal cancer patients received UFT and leucovorin adjuvant chemotherapy, the patients in this group had higher CEA levels. Some previous studies reported that an elevated CEA level is a marker of poor prognosis in colorectal cancer patients. Kirat et al. suggested that a high preoperative CEA level is not associated with the oncologic outcome in adequately staged patients.[20] Using our data, we showed that UFT and leucovorin adjuvant chemotherapy could not prolong the overall or 5-year disease-free survival in low-risk stage II colorectal cancer patients.

The monthly cost for this treatment is about 8,000 NTD, and the 6-month cost is equivalent to approximately 50,000 NTD for each patient. From our data, we noted the use of Uracil-Tegafur (UFT) and leucovorin as adjuvant chemotherapy cannot prolong the overall survival and 5-year disease free survival in low-risk stage II colorectal cancer patients. The economical burden conferred by unnecessary treatment in low-risk patient should be avoided. Lowering the burden on national insurance budget is crucial for strengthening social welfare.

Our study had some limitations. First, it is a retrospective study and not a randomized control trial. Second, the UFT treatment period in our records largely depended on the experience of the surgeons and the performance of the patients, and a standard treatment protocol was not followed. In the future, it is imperative to develop a standard protocol for the administration of adjuvant therapy and for the avoidance of unnecessary exposure to chemotherapy.

In conclusion, we confirm that using UFT and leucovorin adjuvant chemotherapy in the treatment of low-risk group stage II colorectal cancer patients qualifies as overtreatment. UFT has some side effects including fatigue, anorexia, nausea, vomiting, diarrhea, leucopenia, thrombocytopenia, anemia, pigmentation, and fulminant hepatitis. Therefore, if the adjuvant chemotherapy cannot improve the overall or 5-year disease-free survival, unnecessary exposure to chemotherapy should be avoided.

References

1. Cancer prevention and control: cancer incidence [http://www.hpa.gov.tw/BHPNet/English/ClassShow.aspx?No=201401280006]
2. Chiu HM, Chen SL, Yen AM, Chiu SY, Fann JC, Lee YC, et al. Effectiveness of fecal immunochemical testing in reducing colorectal cancer mortality from the One Million Taiwanese Screening Program. *Cancer* 2015;121:3221-9.
3. West NP, Hohenberger W, Weber K, Perrakis A, Finan PJ, Quirke P. Complete mesocolic excision with central vascular

ligation produces an oncologically superior specimen compared with standard surgery for carcinoma of the colon. *J Clin Oncol: Off J Am Soc Clin Oncol* 2010;28:272-8.
4. Washington MK, Berlin J, Branton P, Burgart LJ, Carter DK, Fitzgibbons PL, et al. Protocol for the examination of specimens from patients with primary carcinoma of the colon and rectum. *Arch Pathol Lab Med* 2009;133:1539-51.
5. NCCN Clinicl Practice Guidelines in Oncology: Colon cancer Version 2.2014. *National Comprehesive Cancer Network* 2014.
6. Benson AB, 3rd, Schrag D, Somerfield MR, Cohen AM, Figueredo AT, Flynn PJ, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. *J Clin Oncol: Off J Am Soc Clin Oncol* 2004;22:3408-19.
7. Sadahiro S, Morita S, Sasaki K, Sakamoto K, Ohge H, Takahashi T, et al. Treatment rationale and study design for clinical trial on the efficacy of UFT/LV for stage II colorectal cancer with risk factors for recurrence (JFMC46-1201). *Clin Colorectal Cancer* 2015;14:277-80.
8. American Joint Committee on Cancer: Colon and Rectum Cancer Staging 7th Edition. 2009.
9. Sargent DJ, Patiyil S, Yothers G, Haller DG, Gray R, Benedetti J, et al. End points for colon cancer adjuvant trials: observations and recommendations based on individual patient data from 20,898 patients enrolled onto 18 randomized trials from the ACCENT Group. *J Clin Oncol: Off J Am Soc Clin Oncol* 2007;25:4569-74.
10. Schrag D, Rifas-Shiman S, Saltz L, Bach PB, Begg CB. Adjuvant chemotherapy use for Medicare beneficiaries with stage II colon cancer. *J Clin Oncol* 2002;20:3999-4005.
11. O'Connor ES, Greenblatt DY, LoConte NK, Gangnon RE, Liou JI, Heise CP, et al. Adjuvant chemotherapy for stage II colon cancer with poor prognostic features. *J Clin Oncol: Off J Am Soc Clin Oncol* 2011;29:3381-8.
12. Kato T, Ohashi Y, Nakazato H, Koike A, Saji S, Suzuki H, et al. Efficacy of oral UFT as adjuvant chemotherapy to curative resection of colorectal cancer: multicenter prospective randomized trial. *Langenbecks Arch Surg* 2002;386:575-81.
13. Lembersky BC, Wieand HS, Petrelli NJ, O'Connell MJ, Colangelo LH, Smith RE, et al. Oral uracil and tegafur plus leucovorin compared with intravenous fluorouracil and leucovorin in stage II and III carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project Protocol C-06. *J Clin Oncol: Off J Am Soc Clin Oncol* 2006; 24:2059-64.
14. Maroun J, Asche C, Romeyer F, Mukherjee J, Cripps C, Oza A, et al. A cost comparison of oral tegafur plus uracil/folinic acid and parenteral fluorouracil for colorectal cancer in Canada. *Pharmacoeconomics* 2003;21:1039-51.
15. Kinoshita T, Nakajima T, Ohashi Y: Adjuvant chemotherapy with uracil-tegafur (UFT) for serosa negative advanced gastric cancer: Results of a randomized trial by national surgical adjuvant study of gastric cancer. *J Clin Oncol* 2005;23:4021.
16. Noguchi S, Koyama H, Uchino J, Abe R, Miura S, Sugimachi K, et al. Postoperative adjuvant therapy with tamoxifen, tegafur plus uracil, or both in women with node-negative breast cancer: a pooled analysis of six randomized controlled trials. *J Clin Oncol: Off J Am Soc Clin Oncol* 2005;23:2172-84.
17. Kato H, Ichinose Y, Ohta M, Hata E, Tsubota N, Tada H, et al. A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. *N Engl J Med* 2004; 350:1713-21.
18. Mercke C: UFT/leucovorin in advanced squamous cell carcinoma of the head and neck administered with radiotherapy. *Oncology (Williston Park)* 2000;14(10 Suppl 9):79-81.
19. Smith RE, Lembersky BC, Wieand HS, Colangelo L, Mamounas EP. UFT/leucovorin vs 5-FU/leucovorin in colon cancer. *Oncology (Williston Park)* 2000;14(10 Suppl 9):24-7.
20. Kirat HT, Ozturk E, Lavery IC, Kiran RP. The predictive value of preoperative carcinoembryonic antigen level in the prognosis of colon cancer. *Am J Surg* 2012;204:447-52.

原　著

使用輔助性口服化療藥物於低風險第二期大腸直腸癌病人是否有過度使用的情形？

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目標　近年來大腸直腸癌是國內癌症發生率第一名、死亡率第三名的疾病。因為全國性的糞便潛血試驗檢查，有越來越多大腸直腸癌患者於早期被診斷發現。根據 NCCN guideline 的建議，術後的輔助性化學治療可用於高風險第二期大腸直腸癌的患者。但是輔助性化療對於低風險第二期大腸直腸癌的研究卻不多，我們希望可以藉由本院的資料庫進行輔助性口服化療藥物對於低風險第二期大腸直腸癌治療的成效評估。

方法　我們統計了從 2004 年 6 月到 2009 年 8 月共 1273 位在林口長庚紀念醫院、基隆長庚紀念醫院接受根治性手術治療的第二期大腸直腸癌患的資料，排除了六個月內復發以及接受靜脈注射化學治療的病人後，共記錄了 1107 位病人完整的臨床及病理特徵進行分析。其中 515 位病人屬於低風險第二期大腸直腸癌患者進行近一步的研究分析。

結果　在我們的資料庫中，屬於高風險第二期大腸直腸癌的患者有較差的總生存率及較差的 5 年無病生存率。低風險第二期大腸直腸癌的這組病人中，共有 70 名患者接受術後的輔助性口服化療藥物治療而 445 名病人未接受治療。經過分析後發現，接受輔助性口服化療藥物治療的低風險第二期大腸直腸癌的患者在總生存率及 5 年無病生存率上並無顯著的差異。

結論　我們的研究顯示，對於低風險第二期大腸直腸癌的患者而言，輔助性口服化療藥物屬於過度的治療，並無法延長病人的壽命以及五年無病生存率。相對之下，我們應該避免低風險第二期大腸直腸癌的患者暴露於不必要的化學治療風險中以及經濟效益。

關鍵詞　低風險第二期大腸直腸癌、優富多、輔助性化療。