Original Article

The Effectiveness of the Tegafur/uracil and Leucovorin Adjuvant Chemotherapy for Stage II Colorectal Cancer Patients Based on the Tumor Location

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Key Words
Right-sided colon cancer (RCC);
Left-sided colorectal cancer (LCRC);
High-risk/low-risk stage II colorectal cancer;
Tegafur/uracil (UFT) adjuvant chemotherapy

Introduction. Colorectal cancer is one of the most common cancers and the third leading cause of cancer-related death in Taiwan. Colorectal cancer can be characterized by the tumor location with proximal or right-sided colon cancer and distal or left-sided colorectal cancer. The distinction between the tumor locations is important because they have different clinical responses to chemotherapy. In this study, we compared the effectiveness of uracil-tegafur (UFT) as the adjuvant chemotherapy in stage II colorectal cancer between different tumor locations and variable risk levels.

Materials and Methods. The participants involved were 1320 stage II colorectal cancer patients who underwent standard curative operations at the Keelung and Linkou Branch of Chang Gung Memorial Hospital between January 2004 and August 2009. After excluding patients who received radiotherapy, surgical mortality during the same hospitalization, patients with early recurrence within 6 months, and those who received intravenous chemotherapy, the remaining 1149 patients were enrolled in the study. After analyzing the medical records, 363 patients were classified as right-sided colon cancer (31.6%) patients and 786 patients were classified as left-sided colorectal cancer (68.4%) patients depending on whether their location was proximal to the splenic flexure or not. All patients were followed up for at least 5 years postoperatively or until the death of the patient. Statistical analysis was performed with SPSS ver. 20.

Results. In our database, the right-sided colon cancer patients had higher proportion of females, poor differentiation, anemia, poor nutrition status, were a high-risk group, and constituted the UFT treatment group. The adjuvant chemotherapy for high-risk stage II colorectal cancer can improve the 5-year disease free survival and overall survival whether it be a right-sided colon cancer or a left-sided colorectal cancer. For low-risk stage II colorectal cancer patients, the UFT treatment can improved the overall survival in left-side colorectal cancer patients (with UFT vs. without UFT: 93.8% vs. 81.8%, log-rank $p = 0.038$).

Conclusion. Our data showed that UFT treatment had benefits in both high-risk stage II right-sided and left-sided colorectal cancer although they have different molecular pathways of carcinogenesis. Further, the low-risk stage II left-sided colorectal cancer patients had better outcomes from the UFT treatment.

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Colorectal cancer is the third most common cancer and the third leading cause of cancer deaths in the United States.[1] In Taiwan, colorectal cancer has become the most commonly malignancy and more than 15,000 cases were detected every year.[2] Colorectal cancer can be characterized by the location of the primary tumor distal or proximal to the splenic flexure known as left-sided or right-sided colorectal cancer, respectively.[3]

The proximal or right-sided colon is derived from the embryologic midgut, including the cecum, ascending colon, and transverse colon to the splenic flexure. The main blood supply is from the superior mesenteric artery. The distal or left-sided colorectum is derived from the embryologic hindgut, including the descending colon, sigmoid colon and rectum. The main blood supply comes from inferior mesenteric artery. According to the above definition, approximately 63% of colorectal cancer patients have left-sided colorectal cancer.[4] Apart from the anatomical differences, colorectal cancer at different locations have significantly different epidemiology, pathology, microbiome, molecular pathway, and outcomes.[5]

Adjuvant chemotherapy for patients with a curative intent resected stage III colon cancer is a standard treatment strategy.[6] However, the adjuvant chemotherapy is only recommended for stage II colorectal cancer patients with high-risk factors according to National comprehensive cancer network (NCCN) guidelines.[7] Over the past few years, the distinction between the tumor locations of colorectal cancer has been brought into focus because they each have different outcomes and clinical responses to chemotherapy.[8] In the present study, we aimed to review our hospital database in order to compare the effectiveness of oral uracil-tegafur (UFT) as the adjuvant chemotherapy in stage II colorectal cancer between different tumor locations and variable risk levels, presuming that tumor location affects the strategies of treatment.

Materials and Methods

The study included 1320 stage II colorectal cancer patients who underwent standard curative operations at the Keelung and Linkou Branch of Chang Gung Memorial Hospital, Taiwan, between January 2004 and August 2009. We aimed to investigate adjuvant oral UFT treatment and long-term outcomes of postoperative stage II colorectal cancer patients. Patients who received preoperative or postoperative radiotherapy (n = 105), another oral form of chemotherapy agent (Capecitabine) (n = 5), or intravenous 5-FU based chemotherapy (FOLFOX regimen or 5-FU only) (n = 32) were excluded from our study. Patients who suffered from surgical related mortality during the same hospitalization (n = 11) and those who experienced recurrence 6 months after curative intent surgery (n = 18) were also excluded from our study. The remaining 1149 patients were enrolled in the study. The patients were classified as right-sided colon cancer patients if the primary tumor was located in the cecum, ascending colon, transverse colon, and splenic flexure colon (n = 363, 31.6%) and left-sided colorectal cancer patients if the tumor was located in the descending colon, sigmoid colon, and rectum (n = 786, 68.4%). The patient selection flow chart is shown in Fig. 1.

According to the NCCN 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 when examined. We classified the patients into the high-risk stage II colorectal cancer group if patients had at least one of above risk factors and low-risk stage II colorectal cancer group if patients had neither of the risk factors (Fig. 1). The administration of uracil-tegafur (UFT) and

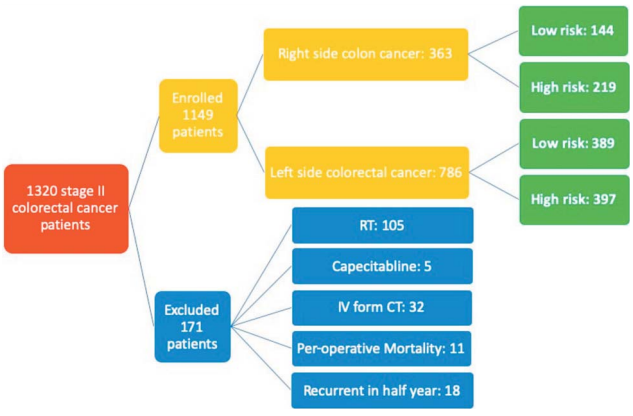

Fig. 1. Patient collecting and screening.

leucovorin adjuvant chemotherapy after operation depended on the surgeons' experience and patient performance but not according to the high or low risk stage II colorectal cancer group. The treatment doses were UFT 300 mg/m^2/day PO and leucovorin 90 mg/day PO, from days 1 to 28, followed by 7 days' rest, and repeated every 5 weeks for 6 to 12 months.

The data including demographic data (sex, age, and tumor location), tumor pathologic characteristics, preoperative laboratory data, duration of adjuvant chemotherapy, and survival time were retrospectively collected from inpatient and outpatient electronic records from our hospital. The patients were continuously followed-up for at least 5 years postoperatively or until death.

Categorical data such as clinicopathological features were compared using Pearson's chi-squared test and numerical data such as preoperative laboratory examinations were compared using one-way analysis of variance (ANOVA). 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).

Result

Patient characteristics

We included 1149 stage II colorectal cancer patients in our study, divided into groups according to tumor locations and risks described in the materials and methods section. Of the patients enrolled, 363 (31.6%) and 786 (68.4%) had right-sided colon cancer and left-sided colorectal cancer, respectively. The characteristics of the 1149 patients are shown in Table 1. There was a higher proportion of females among patients with right-sided colon cancer (RCC vs. LCRC = 48.5% vs. 41.0%, $p = 0.017$). Patients with right-sided colon cancer had a relatively higher proportion of poor differentiation (16.0%) in pathological finding than those with left-sided colorectal cancer (4.2%). Regarding symptoms, the right-sided colon cancer patients had higher proportions of anemia (Hb: RCC vs. LCRC = 10.71 vs. 12.28 g/dL, $p < 0.001$) and poor nutrition status (albumin: RCC vs. LCRC = 3.76 vs. 3.97 g/dL, $p < 0.001$). The right-sided colon cancer patients had a higher proportion of high-risk factor rates (60.3%) than the left-sided colorectal cancer patients (50.5%), and higher adjuvant UFT treatment rates (RCC vs. LCRC = 26.2% vs. 20.1%, $p = 0.021$). There was no significant difference in age, proportion of perineural invasion, lymphovascular invasion, T4 stage, number of lymph node sampling, obstruction, and perforation between right-sided and left-sided colon cancer patients (Table 1).

Right-sided colon cancer patients

We further divided the stage II right-sided colon cancer patients into two groups; those who had no risk factors (low-risk group = 144, 39.7%) and those who had at least one risk factor (high-risk group = 219, 60.3%). There were no statistically significant differences in sex, age, preoperative CEA levels, or preoperative hemoglobin level between the two groups. The high-risk group had poor immunonutrition status, and higher adjuvant UFT treatment rates (Table 2).

Left-sided colorectal cancer patients

We also divided the stage II left-sided colorectal cancer patients into two groups; those who had no risk factors (low-risk group = 389, 49.5%) and those who had at least one risk factor (high-risk group = 397, 50.5%). There were no statistically significant differences in sex, age and preoperative CEA level between the two groups. But the high-risk group had lower pre-operative hemoglobin levels, poor immunonutrition status and higher adjuvant UFT treatment rates (Table 3).

Disease free survival and overall survival

We performed Kaplan-Meier analysis to determine the disease free survival and overall survival curve according to tumor location and adjuvant chemotherapy. For stage II right-sided colon cancer patients with

Table 1. Characteristic of stage II colorectal cancer patients with right-side or left-side

Stage II colorectal cancer (1149)	Right-sided colon cancer (363) 31.6%	Left-sided colorectal cancer (786) 68.4%	*p* value
Gender			0.017*
Male	187 (51.5%)	464 (59.0%)	
Female	176 (48.5%)	322 (41.0%)	
Age (years)	65.33	65.99	0.427
< 65	156 (43.0%)	322 (41.0%)	0.521
≥ 65	207 (57.0%)	464 (59.0%)	
Perineural invasion			0.660
No	285 (78.5%)	626 (79.6%)	
Yes	78 (21.5%)	160 (20.4%)	
Lymphovascular invasion			0.563
No	321 (88.4%)	704 (89.6%)	
Yes	42 (11.6%)	82 (10.4%)	
Differentiation			< 0.001*
W/M	305 (84.0%)	753 (95.8%)	
Poor	58 (16.0%)	33 (4.2%)	
T stage			0.409
T3	305 (84.0%)	675 (85.9%)	
T4	58 (16.0%)	111 (14.1%)	
Lymph node sampling			0.066
> 12	339 (93.4%)	708 (90.1%)	
< 12	24 (6.6%)	78 (9.9%)	
Obstruction			0.263
No	308 (84.8%)	686 (87.3%)	
Yes	55 (15.2%)	100 (12.7%)	
Perforation			0.719
No	348 (95.9%)	756 (96.3%)	
Yes	15 (4.1%)	29 (3.7%)	
Risk			0.002*
Low	144 (39.7%)	389 (49.5%)	
High	219 (60.3%)	397 (50.5%)	
UFT			0.021*
No	268 (73.8%)	628 (79.9%)	
Yes	95 (26.2%)	158 (20.1%)	
Pre-operative CEA (ng/mL)	10.43	10.86	0.784
Hb (g/dL)	10.71	12.28	< 0.001*
WBC (/mm^3)	7855	7613	0.183
ANC (/mm^3)	5786	5150	0.003*
Albumin (g/dL)	3.76	3.97	< 0.001*

UFT, uracil-tegafur; CEA, carcinoembryonic antigen; Hb, hemoglobin; WBC, while blood cell; ANC, absolute neutrophil count.

Table 2. Characteristic of right-sided colon cancer patients with low risk or high risk

Right-sided colon cancer (363)	Low risk group (144) 39.7%	High risk group (219) 60.3%	*p* value
Gender			0.212
Male	80 (55.6%)	107 (48.9%)	
Female	64 (44.4%)	112 (51.1%)	
Age (years)	65.82	65.00	0.588
< 65	63 (43.8%)	93 (42.5%)	0.809
≥ 65	81 (56.2%)	126 (57.5%)	
UFT			< 0.001*
No	122 (84.7%)	146 (66.7%)	
Yes	22 (15.3%)	73 (33.3%)	
Pre-operative CEA (ng/mL)	8.00	12.04	0.140
Hb (g/dL)	10.74	10.70	0.878
WBC (/mm^3)	7481	8099	0.038*
ANC (/mm^3)	5155	6186	0.026*
Albumin (g/dL)	3.93	3.64	< 0.001*

UFT, uracil-tegafur; CEA, carcinoembryonic antigen; Hb, hemoglobin; WBC, while blood cell; ANC, absolute neutrophil count.

Table 3. Characteristic of left-sided colorectal cancer with low risk or high risk

Left-sided colorectal cancer (786)	Low risk group (389) 49.5%	High risk group (397) 50.5%	*p* value
Gender			0.598
Male	226 (58.1%)	238 (59.9%)	
Female	163 (41.9%)	159 (40.1%)	
Age (years)	65.42	66.55	0.216
< 65	168 (43.2%)	154 (38.8%)	0.210
≥ 65	221 (56.8%)	243 (61.2%)	
UFT			0.012*
No	325 (83.5%)	303 (76.3%)	
Yes	64 (16.5%)	94 (23.7%)	
Pre-operative CEA (ng/mL)	9.41	12.30	0.091
Hb (g/dL)	12.48	12.07	0.008*
WBC (/mm^3)	7357	7864	0.014*
ANC (/mm^3)	4763	5515	< 0.001*
Albumin (g/dL)	4.08	3.86	< 0.001*

UFT, uracil-tegafur; CEA, carcinoembryonic antigen; Hb, hemoglobin; WBC, while blood cell; ANC, absolute neutrophil count.

high risk, taking the oral UFT medication led to a significant improvement in the five-year disease free survival (with UFT vs. without UFT: 83.6% vs. 67.1%, log-rank $p = 0.041$) (Fig. 2) and overall survival (with UFT vs. without UFT: 91.8% vs. 71.2%, log-rank $p = 0.003$) (Fig. 3). However, for stage II right-sided colon cancer with low risk, taking oral UFT medication had no benefit in the five-year disease free (Fig. 4) or overall survival (Fig. 5).

For stage II left-sided colorectal cancer with high risk, taking oral UFT improved the five-year disease free survival (with UFT vs. without UFT: 79.8% vs. 60.7%, log-rank $p = 0.0048$) (Fig. 6) and overall survival (with UFT vs. without UFT: 87.2% vs. 65.3%, log-rank $p < 0.001$) (Fig. 7). However, for stage II left-sided colorectal cancer with low risk, taking oral UFT medication had no benefit in the five-year disease free survival (Fig. 8), but improved the overall survival (with UFT vs. without UFT: 93.8% vs. 81.8%, log-rank $p = 0.038$) (Fig. 9).

Discussion

Currently, the radical resection of non-metastatic

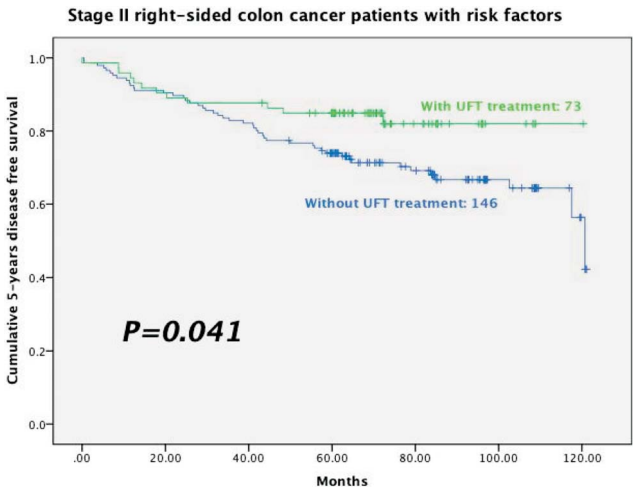

Fig. 2. The 5 years disease free survival in high risk stage II right-side colon cancer patients under UFT treatment or not.

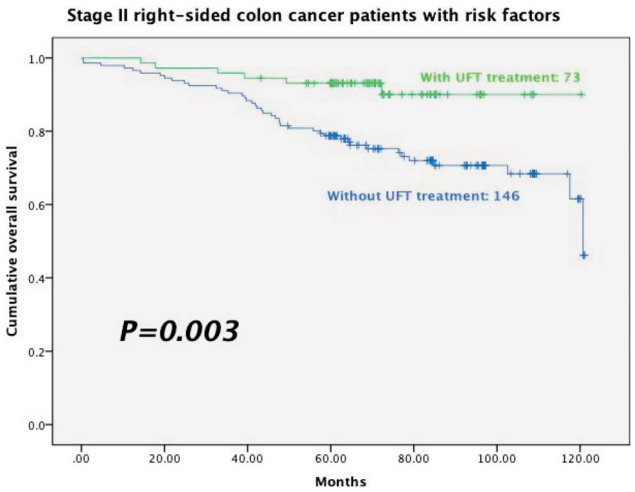

Fig. 3. The overall survival in high risk stage II right-side colon cancer patients under UFT treatment or not.

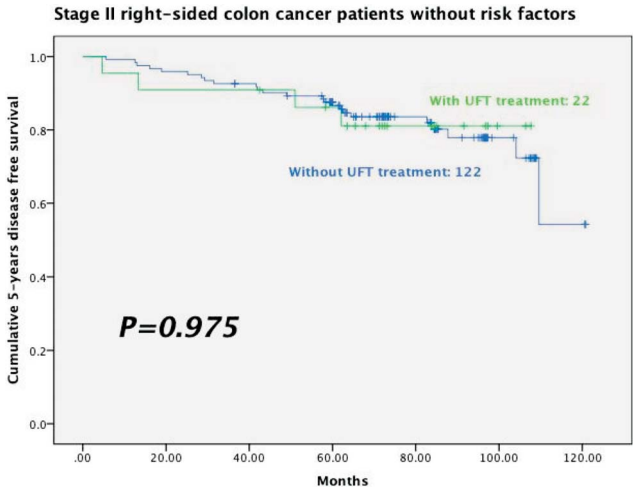

Fig. 4. The 5 years disease free survival in low risk stage II right-sided colon cancer patients under UFT treatment or not.

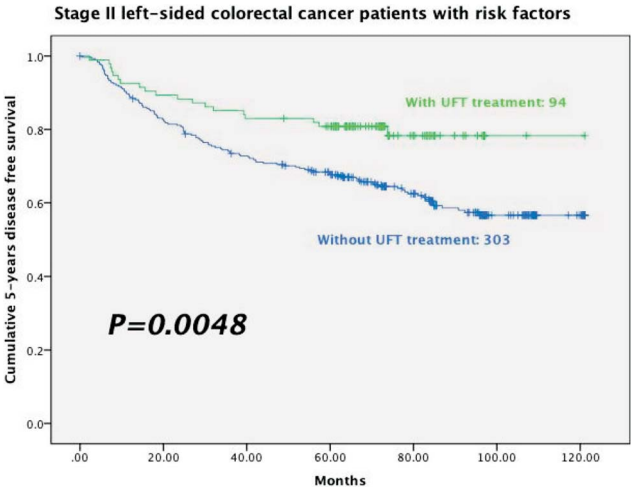

Fig. 6. The 5 years disease free survival in high risk stage II left-sided colorectal cancer patients under UFT treatment or not.

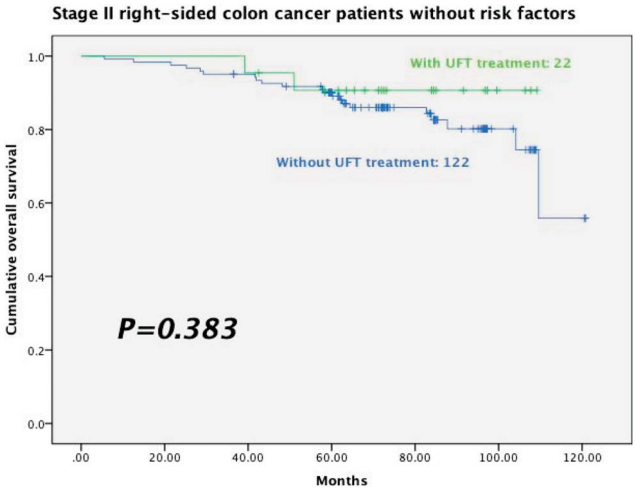

Fig. 5. The overall survival in low risk stage II right-sided colon cancer patients under UFT treatment or not.

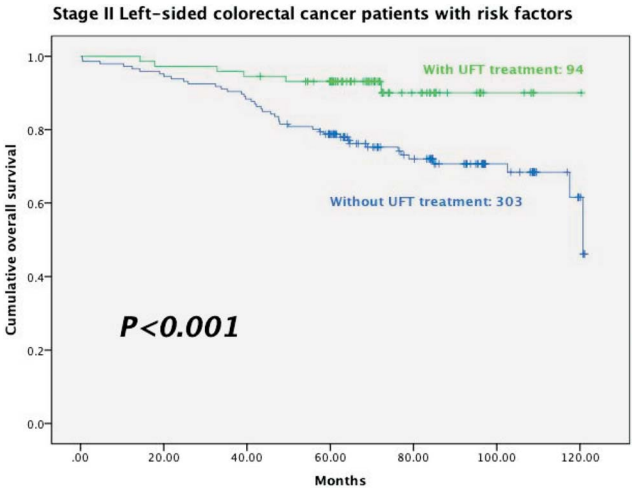

Fig. 7. The overall survival in high risk stage II left-sided colorectal cancer patients under UFT treatment or not.

colorectal cancer (stage I-III) remains the most common option for right-sided colon cancer and left-sided colorectal cancer.[9] Radical resection includes complete removal of the tumor and associated major lymphovascular pedicles of the affected colorectal segment. The specimen from the surgical procedures can be used to distinguish between right-sided colon cancer and left-sided colorectal cancer. The right-sided colon cancer is typically bulky, exophytic, with polypoid lesions projecting into the lumen, and causing significant anemia while the left-sided colorectal cancer has infiltrating and constricting lesions encircling the lumen, and often leading to obstruction.[10]

According to NCCN guidelines, adjuvant chemotherapy is recommended for stage II colorectal cancer patients with high-risk factors.[7] The UFT and leucovorin used as adjuvant chemotherapy is one of the treatment choices.[11] UFT was first prescribed in Japan and it was a combination of tegafur and uracil at a molar ratio of 1:4. Tegafur is a precursor of 5-fluorouracil (5-FU) and it can be metabolized into the active 5-FU form in the human body. Uracil can inhibit dihydropyrimidine dehydrogenase, which can degrade 5-FU, and prolong the action time of 5-FU in human body.

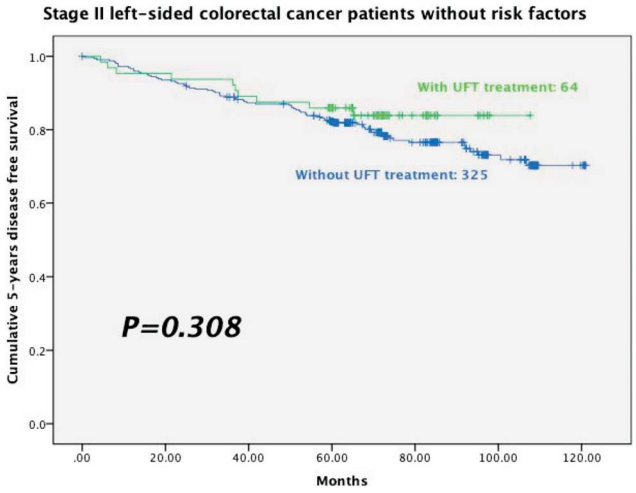

Fig. 8. The 5 years disease free survival in low risk stage II left-sided colorectal cancer patients under UFT treatment or not.

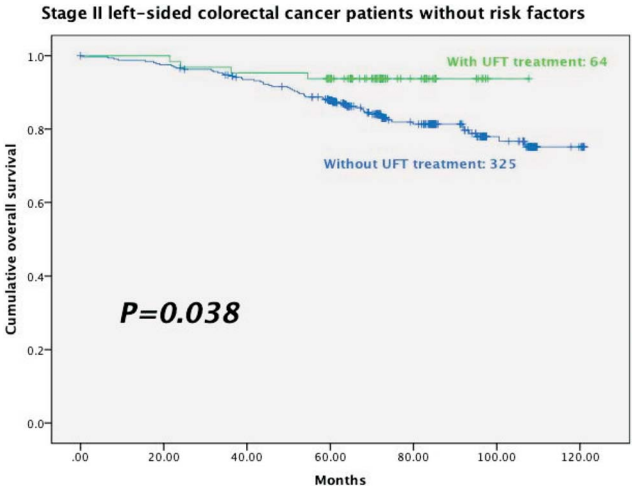

Fig. 9. The overall survival in low risk stage II left-sided colorectal cancer patients under UFT treatment or not.

UFT can be used in several cancer diseases. Kato et al. suggested that administration of UFT was an effective and safe postoperative adjuvant chemotherapy for stage II and stage III colorectal cancer patients.[12] Lembersky et al. also showed that UFT plus leucovorin had similar effects as intravenously administered 5-FU based chemotherapy after primary surgery in stage II and stage III colorectal cancer patients.[13] With the emergence of cancer biology, the existence of cancer micrometastasis is coexistent when cancer is been diagnosed.[14] The goal of introducing postoperative adjuvant chemotherapy is to eradicate micrometastasis and reduce the risk of recurrence.[15]

In our study, we had the same results from the recommendations of the NCCN guidelines. We revealed that the tegafur/uracil and leucovorin adjuvant chemotherapy for the treatment of high-risk stage II colorectal cancer can improve the 5-year disease free survival and overall survival for both right-sided and left-sided colorectal cancer. For the low-risk stage II colorectal cancer patients, we found that the tegafur/uracil and leucovorin adjuvant chemotherapy for the treatment of left-sided colorectal cancer has improved statistically significant overall survival (with UFT vs. without UFT = 93.8%: 81.8%, $p = 0.038$). However, our study did not show any improvement in the five-year disease free survival (with UFT vs. without UFT = 81.8%: 80.3%, $p = 0.975$) or overall survival (with UFT vs. without UFT = 90.9%: 82.8%, $p = 0.383$), in patients with low-risk stage II right-sided colon cancer who received the UFT treatment.

The right-sided colon cancer has the lower incidence among all the colorectal cancer patients, but it has steadily increased over recent years.[16] Clinically, the right-sided colon cancer has higher TNM-stages, larger tumor size, higher vascular invasion rate, and higher mucinous types compare to left-side colorectal cancer.[17] The microbiota diversity in colorectal cancer is also been noted. The Helicobacter spp. are present and significantly higher in the right-sided colon cancer while the Fusobacteria is present and significantly higher in left-sided colorectal cancer.[18] Immunologically, the right-sided colon has more active immune cell infiltrations than the left-sided colorectum.[19,20] As reflected in the colorectal cancer microenvironment, the right-sided colon cancer would be exposed to increased immune activity compared to the left-sided colorectal cancer. The phenomenon of tumor infiltrating lymphocytes (TIL) is also more common in the proximal colon,[17] and is a characteristic of microsatellite instability (MSI) positive tumor.[21]

The heterogeneity of MSI is common in colorectal cancers and about 15% of colorectal cancer patients can be detected.[22] The defect of the DNA mismatch repair (dMMR) system induced the high number of mutational events during cell division and prone to

DNA polymerase slippage during DNA replication. This phenotype is called high-level of microsatellite instability (MSI-H).[23] The MSI-H phenotype has a higher incidence of early colorectal cancer as 20% in stage II compared to 12% in stage III and 4% in stage IV.[24] The right-sided colon cancer has higher MSI-H incident rate than the left-sided colorectal cancer, which is estimated at about 20~25%.[25] MSI-high tumors have a better prognosis and lower risk of metastasis.[26] Although the 5-fluorouracil-based (5-FU) chemotherapy is a standard adjuvant treatment for colorectal cancer, there are no overall survival or 5-year disease free survival benefits for MSI-H tumors who received the 5-fluorouracil-based (5-FU) adjuvant chemotherapy.[27] After summarizing the above study, the tumor location may affect the differential benefit of the adjuvant chemotherapy.

This study has some limitations. It is a retrospective study and not a randomized control trial. The administration of the uracil-tegafur (UFT) adjuvant chemotherapy and treatment period depended on the surgeons' experience and the patients' performance. The MSI test was not a routine examination in our cohort in the former days. In the future, it is imperative to develop a standard protocol for MSI examination and for the indication for administering an adjuvant therapy.

In conclusion, we predict that using uracil-tegafur (UFT) and leucovorin adjuvant chemotherapy in treating high-risk stage II colorectal cancer patients can improve the 5-year disease free survival and overall survival in both right-sided and left-sided colorectal cancer. In low-risk stage II colorectal cancer patients, our data showed that only the left-sided colon cancer patients had benefits from receiving the uracil-tegafur (UFT) and leucovorin adjuvant chemotherapy.

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原　著

輔助性口服化療藥物對於第二期大腸直腸癌病人治療的成效之以腫瘤位置為基礎

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目的　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。大腸直腸癌可以依照腫瘤所在的位置分成近端/右側大腸癌以及遠端/左側大腸直腸癌。而腫瘤的不同位置對化學治療在臨床上有著不同的反應。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不同腫瘤位置、不同風險的第二期大腸直腸癌治療成效進行評估。

方法　我們統計了從 2004 年 6 月到 2009 年 8 月共 1320 位在基隆長庚紀念醫院、林口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資料，排除了接受放射線治療、術後死亡個案、六個月內復發以及接受靜脈注射化學治療的病患後，共分析了 1149 位病患完整的臨床病歷。其中 363 位病患屬於右側第二期大腸癌患者 (36.1%)，786 位病患屬於左側第二期大腸直腸癌患者 (68.4%)，再進行近一步的研究分析。

結果　在我們的資料庫中，右側大腸癌的患者相較於左側大腸直腸癌的患者女性的比例較高；病理學上分化不良的比例較高；貧血、營養不良的比例較高；屬於高風險第二期大腸直腸癌及接受輔助性口服化療藥物治療的比例也較高。無論腫瘤是位在右側結腸還是左側結腸直腸，輔助性口服化療藥物都可改善高風險第二期大腸直腸癌的 5 年無病生存率及總體生存率。對於低風險第二期的大腸直腸癌患者而言，輔助性口服化療藥物的治療可以改善左側結直腸癌患者的總體生存率。

結論　我們的研究顯示，優富多的治療可以改善高風險左右側大腸直腸癌患者的 5 年無病生存率和總體生存率。右側大腸癌和左側大腸直腸癌具有不同的分子生成途徑和對化療反應。在低風險的第二期大腸直腸癌患者中，由於不同的腫瘤位置，優富多的治療似乎對左側大腸直腸癌有更好的效果。

關鍵詞　右側大腸癌、左側大腸直腸癌、高/低風險第二期大腸直腸癌、優富多、輔助性化療。