Original Article

Role of *KRAS* Mutations in Patients with Metastatic Colorectal Cancer Who Receive Regorafenib Plus FOLFIRI as a Salvage Therapy

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Key Words
Regorafenib;
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Purpose. The aim of this study was to evaluate the role of *KRAS* status in patients with metastatic colorectal cancer (mCRC) who received regorafenib plus irinotecan dose-escalated folinic acid, fluorouracil, and irinotecan (FOLFIRI) as a salvage therapy.
Methods. Between October 2013 and June 2017, 21 patients with mCRC from a single institution were retrospectively reviewed for their clinical features and the efficacy of regorafenib plus irinotecan dose-escalated FOLFIRI as a salvage therapy. Patients' progression-free survival (PFS), overall survival (OS), and subgroup analysis results were compared among *KRAS* categories.
Results. The median follow-up period was 10.0 months (1.3-38.6 months), and the median PFS and OS of all patients were 7.0 and 10.0 months, respectively. The disease control rate (DCR) was 61.9%, comprising 9.5% of partial response and 52.4% of stable disease. Regarding outcomes, patients with wild-type *KRAS* tumors exhibited a trend toward a better median PFS (7.0 vs. 5.5 months, $p = 0.494$) and OS (13.0 vs. 9.5 months, $p = 0.249$) compared with those with mutant-type *KRAS* tumors, although this result was not statistically significant. The subgroup analysis conducted according to *KRAS* status also revealed no significant correlation with the patients' sex, age, *UGT1A1* status, irinotecan dosage, treatment response, DCR, and hand-foot syndrome occurrence rate.
Conclusions. The combination therapy of regorafenib plus FOLFIRI may yield a promising DCR and prominent median PFS and OS. The regorafenib plus irinotecan-based regimen had favorable clinical outcomes in patients with wild-type *KRAS* mCRC, although the result was not statistically significant.
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Colorectal cancer (CRC) is the third most common cancer worldwide, and approximately 20%-25% of patients have metastases at the time of diagnosis.[1] Although this disease is potentially curable with complete surgical resection, up to 50%-60% of patients eventually progress to metastatic CRC (mCRC)

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and require additional systemic therapies.[2] The present chemotherapy for mCRC, such as 5-fluorouracil (FU)/leucovorin (LV) combined with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI), yields a median overall survival (OS) of approximately 20 months, with the 5-year survival rate not exceeding 10%.[3] The recent introduction of biological therapies combined with chemotherapies has yielded improved oncological outcomes, with a median OS of approximately 30 months.[4]

Regorafenib, a novel oral multikinase inhibitor, targets stromal, angiogenic, and oncogenic receptor tyrosine kinases (RTKs) and inhibits intracellular and membrane-bound RTKs involved in angiogenesis, oncogenesis, and tumor proliferation.[5] The CORRECT and CONCUR trials have demonstrated that oral regorafenib monotherapy differed significantly from placebo treatment in terms of disease control rate (DCR; 41% vs. 51%), progression-free survival (PFS; 1.9 vs. 3.2 months), and OS (6.4 vs. 8.4 months) for previously treated mCRC.[6,7]

The active form of irinotecan (7-ethyl-10-hydroxycamptothecin, SN-38) is metabolized by the polymorphic enzyme UGT1A1, and individuals who are homozygous for the *UGT1A1**28 allele have decreased enzymatic activity and an increased risk of gastrointestinal and hematologic toxicity when receiving an irinotecan-based regimen.[8] The US Food and Drug Administration-approved label recommends testing for the presence of the *UGT1A1**28 allele and reducing the initial irinotecan dose in individuals who are homozygous for this allele in order to reduce the associated toxicity.

KRAS mutations are observed in approximately 46% of patients with mCRC and have a negative prognostic role in CRC.[9] Studies have reported that active *KRAS* mutations result in resistance to epidermal growth factor receptor (EGFR) inhibitors.[10-22] In such patients, vascular endothelial growth factor (VEGF) inhibitors, such as bevacizumab, are another beneficial biological therapy. Moreover, the efficacy of the antiangiogenic agent bevacizumab alone or in combination with chemotherapy appears to not be influenced by *KRAS* status.[23] A retrospective exploratory analysis performed in the CORRECT trial revealed beneficial effects of regorafenib monotherapy on OS and PFS across all patient subgroups, irrespective of *KRAS* status.[24] Our previous study revealed a favorable efficacy of regorafenib plus irinotecan dose-escalated FOLFIRI as a salvage therapy for patients with mCRC.[25] According to our review of the relevant literature, the influence of *KRAS* status on patients with mCRC who received regorafenib plus FOLFIRI remains unknown; therefore, the objective of this study was to determine this influence.

Materials and Methods

Patient selection

In this retrospective study, 21 patients with progressive mCRC who were previously treated with FOLFOX, FOLFIRI, monoclonal anti-VEGF antibodies, and monoclonal anti-EGFR antibodies if *KRAS* wild-type tumors were identified were recruited from a single institution between October 2013 and June 2017. The genomic DNA of these patients was extracted from the peripheral blood and subjected to polymerase chain reaction sequencing for genotyping the promoter region of *UGT1A1*, as described elsewhere.[26] The study protocol was approved by the institutional ethics committees [KMUHIRB-2014-03-16(II)] and was conducted in accordance with the 1964 Declaration of Helsinki (2008 revision). Written informed consent was obtained from all patients.

Regimen of chemotherapy and target therapy

For each patient, regorafenib plus irinotecan dose-escalated FOLFIRI according to *UGT1A1* genotyping was administered. All the patients began with the combination therapy with regorafenib plus FOLFIRI not the monotherapy with regorafenib until the patient was unable to tolerate the AEs or declined to receive the FOLFIRI regimen. Because severe hand-foot syndrome developed frequently in patients receiving oral regorafenib at 160 mg/day (for 21 days at a 7-day interval), the dosage was adjusted to 120 mg/day daily. If severe regorafenib-related adverse events (AEs)

such as hand-foot syndrome persisted, regorafenib was discontinued until the AEs subsided. Furthermore, according to our previous clinical results,[15] patients with *UGT1A1**1/*1 and *UGT1A1**1/*28 genotypes were initially administered a standard irinotecan dose of 180 mg/m^2 and those with the *UGT1A1**28/*28 genotype were administered an irinotecan dose of 120 mg/m^2. Irinotecan was administered for over 2 hours on day 1, followed by 5-FU (2,800 mg/m^2 intravenously infused for over 46 hours in a 2-week cycle). For all patients, the irinotecan dose was increased by 30 mg/m^2 every 2 cycles until ≥ grade 3 AEs or severe irinotecan-related AEs developed (mainly diarrhea and neutropenia), following which the dose was reverted to and maintained at the previously tolerated level.

Clinicopathological features and response evaluation

The clinicopathological features analyzed in this investigation included the patients' sex, age, *UGT1A1* status, irinotecan dosage, treatment response, DCR, and hand-foot syndrome occurrence rate. The treatment response was radiologically assessed every 8 weeks through computed tomography, magnetic resonance imaging, or positron emission tomography. Objective responses were classified according to the Response Evaluation Criteria in Solid Tumors,[27] and optimal treatment responses were recorded. The National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0) were used for evaluating the treatment-associated AEs. The regorafenib plus irinotecan dose-escalated FOLFIRI regimen was stopped if progressive disease occurred.

DNA extraction and *KRAS* direct sequencing

Genomic DNA was isolated from frozen primary CRC tissues through proteinase-K (Stratagene, La Jolla, CA, USA) digestion and phenol/chloroform extraction, as described previously by Sambrook et al.[28] The designed sequences of the oligonucleotide primers for *KRAS* exons 2-4 and the operational procedure of direct sequencing were based on those reported in our previous studies.[29,30]

PFS and OS

The correlations between PFS and OS were estimated. PFS was defined as the period after primary surgery during which a patient survives with no disease progression. OS was defined as the time elapsed between the primary surgery and death of a patient due to any cause.

Statistical analysis

Continuous variables are presented as means ± standard deviations, and dichotomous variables are presented as numbers and percentage values. All statistical analyses were performed using the Statistical Package for Sciences (version 19.0, SPSS, Inc., Chicago, IL, USA). According to *KRAS* status, patients were categorized into awild- or mutant-type *KRAS* group. The clinicopathological characteristics of the wild- and mutant-type *KRAS* groups were compared using the Pearson chi-squared test, and the survival rates were estimated using the Kaplan-Meier method. The log rank test was used to determine the differences. A p value of < 0.05 was considered statistically significant.

Results

Table 1 present the patients' demographic patient data. This study included 21 patients (14 men and 7 women), with a median age of 62.0 years (33-77 years). Of the 21 patients, 13 had liver metastasis, 11 had lung metastasis, 4 had peritoneal metastasis, 1 had neck lymph node metastasis, and 8 had two metastatic sites. Moreover, 10 and 11 patients had mutant- and wild-type *KRAS* CRC, respectively. Furthermore, 20 patients had the *UGT1A1**1/*1 genotype, and for these patients, the highest prescribed irinotecan dose was 290 mg/m^2 (180-290 mg/m^2); for the one patient who had the *UGT1A1**1/*28 genotype, the irinotecan dose was maintained at 180 mg/m^2. The present regimen was administered to 10 and 11 patients as the third-

Table 1. Demographic data of the study patients

Clinical characteristics	Number of case
Gender	
Male	14 (66.7%)
Female	7 (33.3%)
Median age (year)	62.0 (33-77)
Site of metastasis	
Liver	13 (61.9%)
Lung	11 (52.4%)
Peritoneum	4 (19.0%)
Neck lymph nodes	1 (4.8%)
Number of sites of metastasis	
1	13 (61.9%)
2	8 (38.1%)
KRAS status	
Wild type	11 (52.4%)
Mutant type	10 (47.6%)
UGT1A1 status	
TA6/TA6	20 (95.2%)
TA6/TA7	1 (4.8%)
Dose escalation of irinotecan (mg/m^2)	
180	9 (42.9%)
210	1 (4.8%)
240	4 (19.0%)
260	4 (19.0%)
290	3 (14.3%)
Lines of systemic therapy	
3rd	10 (47.6%)
4th	10 (47.6%)
5th	1 (4.8%)
≥ Grade 3 AEs	
Hand-foot syndrome	12 (57.1%)
Mucositis	6 (28.6%)
Diarrhea	5 (23.8%)
Neutropenia	4 (19.0%)
Fatigue	3 (14.3%)
Best objective response	
CR (complete response)	0
PR (partial response)	2 (9.5%)
SD (stable disease)	11 (52.4%)
PD (progressive disease)	8 (38.1%)

and fourth-line treatments, respectively. Patients in the mutant-type *KRAS* group were first treated with bevacizumab and FOLFIRI (irinotecan dose: 180 mg/m^2), followed by FOLFOX6 if disease progression occurred, and they were administered regorafenib plus irinotecan dose-escalated FOLFIRI as the third-line treatment after FOLFOX6 failure. For the wild-type *KRAS* group, the first-line treatment was cetuximab plus FOLFIRI without dose escalation and the second-line treatment was FOLFOX6 followed by bevacizumab plus FOLFIRI without dose escalation. Furthermore, FOLFOXIRI was administered to two of nine patients as the fourth-line treatment before regorafenib treatment was accepted for reimbursement in the Taiwan National Health Insurance program. All treatments were substituted only if disease progression occurred. The occurrence rates of previously encountered neutropenia and diarrhea were 15%-20% and 18%-22%, respectively, with an irinotecan dose of 180 mg/m^2. The median length of a previous salvage therapy was 13.4 months. The most commonly encountered ≥ grade 3 AE was hand-foot syndrome (n = 12, 57.1%), followed by mucositis (n = 6, 28.6%), diarrhea (n = 5, 23.8%), neutropenia (n = 4, 19.0%), and fatigue (n = 3, 14.3%).

The median follow-up periods were 10.0 (1.3-38.6 months) and 12.7 months (8.5-38.6 months) for all patients and surviving patients, respectively. All patients were followed until June 2017 or their death. Of the 21 patients, 2 (9.5%) had a partial response (PR), 11 (52.4%) had a stable disease, and 8 (38.1%) had a progressive disease, yielding an overall DCR of 61.9%. The efficacy outcome of all patients yielded a median PFS and OS of 7.0 and 13.0 months, respectively [95% confidence interval (CI): 1.69-12.31 and 6.41-19.59, respectively; Fig. 1]. The wild- and mutant-type *KRAS* groups exhibited no significant differences in terms of the median PFS (7.0 vs. 5.5 months, $p = 0.494$) and median OS (13.0 vs. 9.5 months, $p = 0.249$; Fig. 2). The subgroup analysis conducted according to *KRAS* status revealed no significant differences in the patients' sex, age, *UGT1A1* status, irinotecan dosage, treatment response, DCR, and hand-foot syndrome occurrence rate (Table 2). Besides the irinotecan escalating dose had no statistically significant influence on patient's PFS and OS.

Discussion

This study obtained a promising efficacy outcome for the regorafenib plus irinotecan dose-escalated FOLFIRI combination therapy compared with previ-

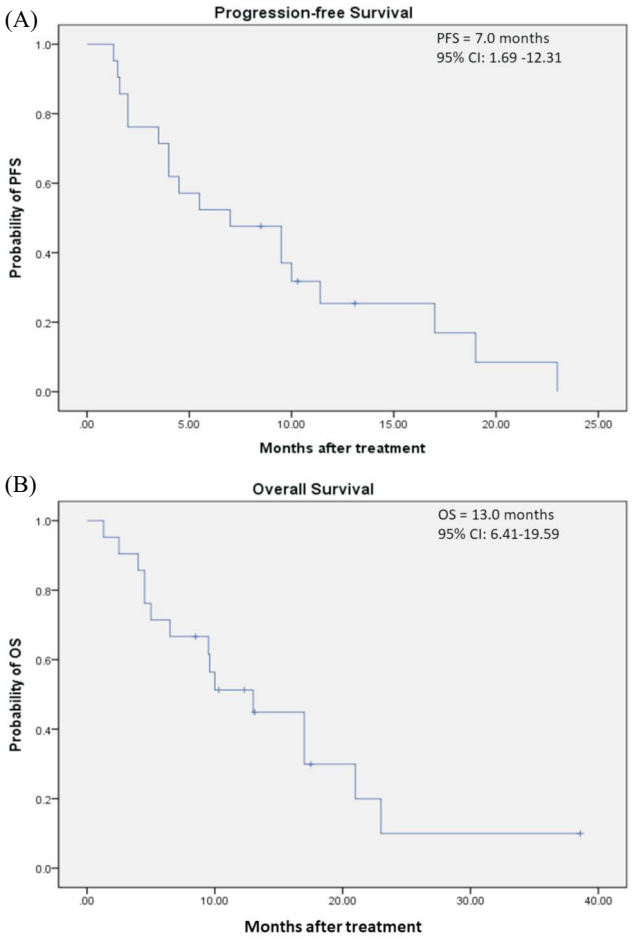

Fig. 1. Kaplan-Meier survival analysis of 21 patients with metastatic colon cancer, (A) progression-free survival and (B) overall survival.

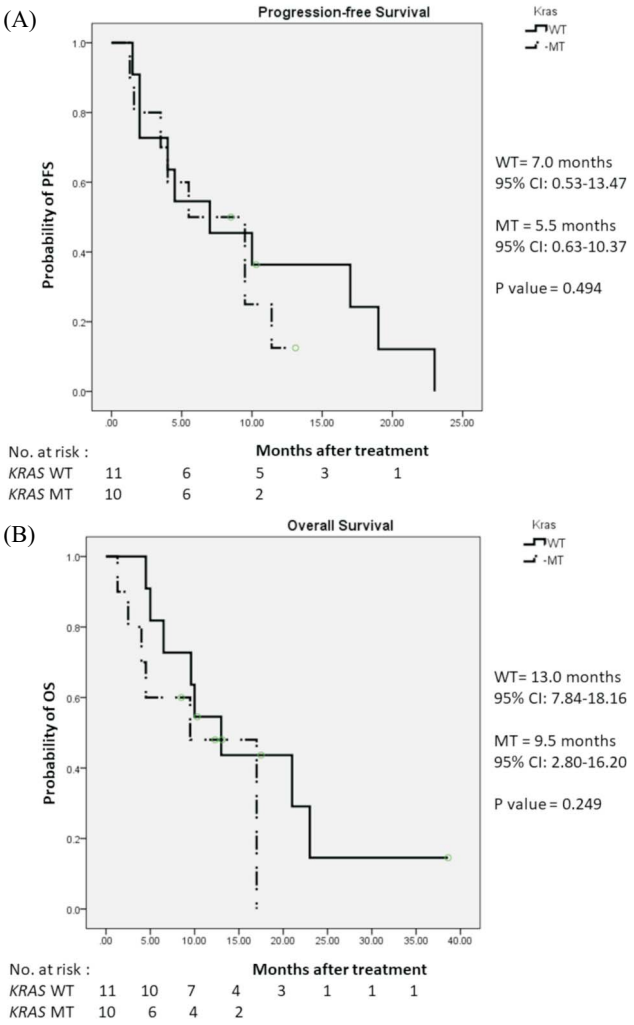

Fig. 2. Kaplan-Meier survival analysis according to *KRAS* status, (A) progression-free survival and (B) overall survival. WT: wild-type, MT: mutant-type.

ous studies on regorafenib monotherapy. Recent studies have reported a mean PFS and OS of approximately 2.6 (1.9-3.2 months) and 6.9 months (5.5-8.8 months), respectively, and a DCR of approximately 46% (41%-51%) for regorafenib monotherapy.[6,7,31] In the present study, the combination therapy of regorafenib plus irinotecan dose-escalated FOLFIRI had a longer median PFS and OS (7.0 and 13.0 months, respectively) and a higher DCR (61.9%) than regorafenib monotherapy. The PFS and OS of the wild- and mutant-type *KRAS* groups did not differ significantly; however, the wild-type *KRAS* group exhibited a favorable trend toward higher PFS and OS rates.

Various clinical outcomes and AEs have been observed in patients receiving the recommended irinotecan dose of 180 mg/m^2 (biweekly) in combination with the FOLFIRI regimen. In patients with wild-type *UGT1A1* status, SN-38 is more efficiently metabolized and AEs are favorably tolerated. By contrast, patients with mutant-type *UGT1A1* status, particularly those homozygous for the *UGT1A1**28 allele, may experience severe AEs under the recommended irinotecan dose of 180 mg/m^2, necessitating irinotecan dose reduction or even complete withdrawal.[8,32-34] Therefore, the irinotecan dose should be adjusted according to *UGT1A1* status for reducing the number of AEs and achieving optimal oncological results. So far there was no large-scale randomized control trials confirmed the efficacy of escalating irinotecan dose. Lu et al. in 2014 reported irinotecan dose escalation plus

Table 2. *KRAS* status-based subgroup analysis of the clinical features of the study patients

	KRAS wild type	*KRAS* mutant type	*p*-value
Number of patients	11	10	
Gender			0.757
Male	7 (63.6%)	7 (70%)	
Female	4 (36.4%)	3 (30%)	
Age (y/o)			0.466
≥ 65	5 (45.5%)	3 (30%)	
< 65	6 (54.5%)	7 (70%)	
UTT1A1 status			0.283
TA6/TA6	11 (100%)	9 (90%)	
TA6/TA7	0	1 (10%)	
Dose escalation of irinotecan (mg/m^2)			0.367
180	3 (27.3%)	6 (60%)	
210	0	1 (10%)	
240	3 (27.3%)	1 (10%)	
260	3 (27.3%)	1 (10%)	
290	2 (18.1%)	1 (10%)	
Response			0.359
CR	0	0	
PR	2 (18.1%)	0 (0%)	
SD	5 (45.5%)	6 (60%)	
PD	4 (36.4%)	4 (40%)	
DCR (disease control rate)			0.864
CR + PR + SD	7 (63.6%)	6 (60%)	
PD	4 (36.4%)	4 (40%)	
Hand-foot syndrome			0.466
≥ grade 3	5 (45.5%)	3 (30%)	
< grade 3	6 (54.5%)	7 (70%)	

bevacizumab as first-line chemotherapy for metastatic colorectal cancer improved the median PFS with tolerable AEs.[26] Phelip et al. in 2016 reported high-dose FOLFIRI combined with cetuximab yielded high response rates and enabled complete resection of class II hepatic metastases in most patients. It seemed to be well-tolerated among healthy selected patients thanks to irinotecan dose adaptation according to UGT1A1 pharmacogenomics status.[35] Besides, in our previous study, 13 patients with mCRC were treated with regorafenib plus FOLFIRI (irinotecan dose escalation according to *UGT1A1* status) in 2016, which yielded a median PFS and OS of 9.5 and 13.0 months, respectively, and a DCR of 69.2%; this finding indicates that the regimen is a clinically effective therapy that yields favorable oncological results and acceptable toxicities in patients with mCRC who have previously received intensive treatments.[25]

KRAS mutations are observed in 35%-42% of patients with CRC, rendering it the most frequently observed genetic alteration in this patient population.[36] To date, the data from several clinical trials have shown that active *KRAS* mutations are negative predictors of the clinical benefit of anti-EGFR therapies in patients with mCRC.

Regorafenib is an orally administered multikinase inhibitor that blocks a series of protein kinases involved in angiogenesis (VEGF receptors 1-3 and tyrosine receptor kinase-2), oncogenesis (*KIT*, *RET*, *RAF1*, *BRAF*, and *BRAF* V600E), and the tumor microenvironment (platelet-derived growth factor receptor and fibroblast growth factor receptor). Camaj et al. reported that *KRAS* exon 2 mutations may reduce the antitumor effects of regorafenibin the SW48 CRC cell line.[37] Ohta et al. reported the successful treatment of patients with mutant-type *KRAS* colon cancer by using regorafenib.[38] In the CORRECT trial, 57% of patients had *KRAS* mutations. The subgroup analysis of

the CORRECT trial revealed a survival benefit across all subgroups, regardless of their *KRAS* status [wild-type: hazard ratio (HR) = 0.65, 95% CI: 0.48-0.80; mutant-type: HR = 0.87, 95% CI: 0.67-1.12)]. However, *KRAS* status was not a predictor of OS or PFS associated with regorafenib.[6] In the CONCUR trial, 70% of patients were assessed for *KRAS* status and 21% were analyzed for *BRAF* mutation status. Neither *KRAS* nor *BRAF* was found to be a predictor of treatment response to regorafenib. The *KRAS* status of patients with mCRC treated with regorafenib appears to be a modest predictor of treatment response, but the results remain controversial. According to our review of the relevant literature, until now, no study has reported the influence of *KRAS* status on patients with mCRC who received the regorafenib plus irinotecan-based combination therapy. Our study results indicate that *KRAS* status is not a predictive factor in patients with mCRC treated with the regorafenib plus irinotecan-based regimen. The limitations of the present study its relatively small sample size and its retrospective and nonrandomized design. Therefore, a prospective, randomized large-scale study is warranted to validate the present findings.

Conclusions

The combination therapy of regorafenib plus FOLFIRI may yield a promising DCR and prominent median PFS and OS. The clinical outcomes of the wild- and mutant-type *KRAS* groups who received the regorafenib plus irinotecan-based therapy did not exhibit significant differences.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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原　著

KRAS 基因突變於接受 regorafenib 及 FOLFIRI 為救援治療的轉移性大腸直腸癌病人

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目的　本研究的目的在於評估 *KRAS* 基因的角色在接受 regorafenib 及 irinotecan 劑量調整過的 FOLFIRI 當作救援治療的轉移性大腸直腸癌病人。

方法　以單一醫學中心，從 2013 年 10 月至 2017 年 6 月，總共收錄了 21 位病人。回顧性的記錄其臨床特徵及以 regorafenib 及 irinotecan 劑量調整過的 FOLFIRI 當作救援治療的療效。其無進展生存期、總生存期依據 *KRAS* 基因做出分組分析。

結果　經過 10.0 個月 (1.3-38.6 個月) 中位數追蹤時間，全部病人的中位數無進展生存期及總生存期分別為 7.0 及 10.0 個月。疾病控制率為 61.9%，其中包含有 9.5%的病人疾病程度為部分改善及 52.4%為穩定疾病。在 *KRAS* 基因野生型及突變型之間，兩個族群的中位數無進展生存期 (野生型 7.0 個月對比突變型 5.5 個月，*p* 值等於 0.494) 及中位數總生存期 (野生型 13.0 個月對比突變型 9.5 個月，*p* 值等於 0.249)。兩組病人的性別、年齡、*UGT1A1* 基因型、irinotecan 劑量、治療反應、疾病控制率及手足症候群發生率亦均無統計學上的顯著差異。

結論　針對轉移性大腸直腸癌病人以 regorafenib 及 irinotecan 劑量調整過的 FOLFIRI 的合併治療可以得到較好的疾病控制率及較長的無進展生存期及總生存期。而 *KRAS* 基因野生型的轉移性大腸直腸癌病人在接受此合併療法後顯示出無統計學上差異但仍有較好的治療趨勢。

關鍵詞　regorafenib、FOLFIRI、*KRAS*、轉移性大腸直腸癌。