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Original Article

Clinical and cost-effectiveness analysis of mFOLOFX6 with or without a targeted drug among patients with metastatic colorectal cancer: inverse probability of treatment weighting

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Abstract: This study investigated the cost-effectiveness and quality of life (QoL) within 1 year of receiving mFOLOFX6 with or without a targeted drug (bevacizumab or ramucirumab) as second-line treatment among patients with metastatic colorectal cancer (mCRC) following the failure of FOLFIRI + bevacizumab as first-line treatment. This prospective cohort study included patients who received a diagnosis of mCRC between March 2015 and May 2020. QoL was evaluated before treatment and at 6 months and 1 year posttreatment. All related variables were controlled using the inverse probability of treatment weighting method. Generalized estimating equations with the difference-in-difference method was used to explore changes in QoL. The incremental cost-utility ratio (ICUR) of the two groups was simulated using the annual-cycle Markov decision tree model. Finally, 39 and 76 patients were included in the targeted and nontargeted agent groups, respectively. At 6 months after treatment, QoL of the two groups improved significantly, but the targeted agent group had significantly better QoL than did the nontargeted agent group at 1 year posttreatment ($P < 0.05$). When the time frame was set to 20 years, the ICUR of the targeted agent group compared with the nontargeted agent group was US$32,052 per quality-adjusted life years. Addition of a targeted drug to the second-line mFOLOFX6 regimen not only improved the patients' QoL but was also more cost effective when the willingness-to-pay threshold was set at US$33,004 (the per capita gross domestic product of Taiwan). These patients should be reimbursed for these targeted agents by the National Health Insurance scheme in Taiwan.

Keywords: Metastatic colorectal cancer (mCRC), mFOLFOX6, quality of life (QoL), cost-effective, Markov model

Introduction

The International Agency for Research on Cancer reported 19.3 million new cancer cases and 10 million cancer-related deaths worldwide in 2020 [1]. Globally, cancer ranks third and second in terms of incidence and mortality, respectively. In Taiwan, cancer has been among the top 10 causes of death since 1982, with colorectal cancer (CRC) being the third leading cause of deaths [2]. Moreover, the incidence of CRC has been the highest among cancers for 14 consecutive years.

Currently, surgical resection is the primary treatment for CRC, and radiotherapy, chemotherapy, and targeted therapy are also frequently used. Patients with stage I-III CRC mainly undergo resection, and the need for adjuvant chemotherapy is determined on the basis of postoperative evaluation on the basis of the patient's pathological report and clinical status [3-5]. For patients with stage IV CRC who present with liver or lung metastases at the initial diagnosis, metastasectomy may be considered if metastatic lesions are easily resectable. If not, chemotherapy or targeted drugs are initially administered, followed by metastasectomy depending on treatment outcomes [6-8]. Chemotherapy and targeted drugs are the primary line of intervention, with surgery being the secondary option in such a situation. The combination of 5-fluorouracil and leucovorin with either irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) is the most commonly used chemotherapeutic regimen for metastatic CRC (mCRC) [9-12]. mCRC treatment often involves a combination of chemotherapy and targeted therapy, which is effective in prolonging patient survival. The most commonly employed targeted anti-vascular endothelial growth factor (anti-VEGF) agents include bevacizumab (Avastin) and ramucirumab (Cyramza) [13, 14].

Advances in medical technology have led to an increase in the available range of cancer treatment options. The combination of targeted therapy with a FOLFOX or FOLFIRI regimen is effective in prolonging the survival of patients with mCRC [9-12]. However, this combination may worsen the patient's quality of life and increase overall medical costs because the targeted agents are expensive [15, 16]. In this study, we evaluated whether this treatment approach can provide survival benefits without compromising cost-effectiveness and patient quality of life. Although many studies conducted in Taiwan have focused on first-line treatments for mCRC, no studies have examined the cost-effectiveness of second-line treatments. Therefore, this study examined changes in the quality of life of patients with mCRC receiving the FOLFOX regimen as second-line treatment with or without targeted drugs within a year of deterioration in their condition following first-line treatment with FOLFIRI and bevacizumab. In addition, we analyzed the cost-effectiveness of this treatment approach.

Materials and methods

Research samples and study design

This study employed a prospective cohort research design. From a teaching hospital in southern Taiwan, we recruited patients who received a diagnosis of mCRC between March 2015 and May 2020, had received first-line treatment with FOLFIRI plus bevacizumab, and were eligible for second-line treatment with mFOLFOX6 with or without a targeted drug (bevacizumab or ramucirumab). The exclusion criteria were as follows: (1) receiving first-line treatment other than FOLFIRI plus bevacizumab, (2) being aged < 20 or > 80 years, (3) having an ongoing pregnancy or breastfeeding status, (4) having any major disease, and (5) being unwilling to sign the consent form. Finally, 39 and 76 patients were included in the targeted agent and nontargeted agent groups, respectively. This study was approved by the institutional review board of our hospital (KMUHIRB-(EI)-20150147), and the patients provided their written informed consent.

Research instruments

A chart review was performed to collect the data on the following: age, sex, body mass index, educational level, marital status, drinking status, and smoking status.

We employed two quality of life (QoL) questionnaires to collect data on the patients' QoL: the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) for CRC, and the 36-Item Short Form Survey (SF-36). In-person interviews were conducted by a trained research assistant at the follow-up to evaluate changes

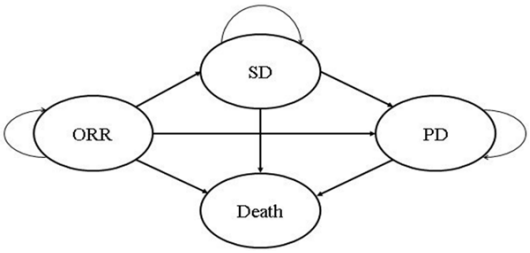

Figure 1. Schematic overview of the Markov model. Abbreviations: ORR, objective response rate; SD, stable disease; PD, progression disease.

in the patients' FACT-C and SF-36 scores before treatment, in the sixth month after treatment, and in first year after treatment.

Cost-utility analysis

We performed a cost-utility analysis to determine the need for the addition of a targeted drug to the second-line chemotherapy regimen. In particular, we analyzed the perspective of the payer and determined whether integrating mFOLFOX6 with or without a targeted drug in the second-line treatment for CRC is a more cost-effective option. We constructed a Markov model on the basis of domestic clinical experience and previous studies' findings (**Figure 1**) [17]. The model categorizes patient outcomes following the second-line treatment into four states: overall response rate (ORR), stable disease (SD), progressive disease (PD), and death. On the basis of domestic clinical experience, we set one cycle as 1 year, with the research time horizon spanning 20 years. Assuming that all the patients with mCRC began in a survival and responding state, after evaluation, we transferred them to their original state based on their outcomes. In each cycle, a patient's state might transition directly to death state. However, once patients are transitioned to the death state, they remain there without further changes.

We initially conducted our evaluation from the payer's perspective. Details regarding the direct cost component were obtained from the Kaohsiung Medical University Hospital Research Database. Outpatient costs included consultation, examination, and pharmaceutical service fees. Inpatient costs included charges for ward stay, tube feeding, laboratory examination, radiotherapy, therapeutic procedures, rehabilitation, blood/plasma, surgery, anesthesia, special material, chemotherapy drugs, pharmaceutical services, injection techniques, and self-funded targeted drugs. Indirect societal costs were calculated as the following formula: period × average man-hours × production cost × average participation rate × percentage of patients aged < 65 years [18, 19]. The health-related quality of life scale (EQ-5D-3L) scores were converted to utility values by using the time trade-off formula with the Taiwan Coefficient [20]. Finally, each cost structure was converted to the present value in 2021 in accordance with Taiwan's consumer price index (CPI), and both costs and quality-adjusted survival years (QALYs) in the decision-making model were discounted at a rate of 2% [18, 19].

Statistical analysis

Continuous data are presented as the mean ± standard deviation (standard deviation), and categorical data are presented as the frequency (*n*) and percentage (%). The chi-square and independent samples t tests were used to analyze between-group differences in demographic characteristics. We used the effect size (ES) to examine the direction and magnitude of changes in the QoL scale at two time points to represent the intensity of treatment efficacy and compare between scales and constructs, with an ES of 0-0.2 indicating a very small difference, 0.2-0.5 indicating a small difference, 0.5-0.8 indicating a medium difference, and > 0.8 indicating a large difference [21]. Moreover, we combined the generalized estimating equation with the difference in differences method to investigate changes in QoL before and within 1 year after treatment [22].

To avoid selection bias resulting from the use of a nonrandomized sampling technique, we used propensity scores (PSs) to reduce the interference of demographic characteristics [23]. A PS is a probability value between 0 and 1, which can be obtained by converting all interfering factors through conditional logistic regression. In this study, the inverse probability of treatment weighting (IPTW) method was used to balance observable study characteristics between the groups [24]. The weight value was used as the inverse of PSs, and the weighting principle was used to assign higher (> 1) or lower (< 1) weights to some cases. However, in general, IPTW is susceptible to extreme weights, leading

to large variability in the obtained estimates. Therefore, we used stabilized weights to mitigate the aforementioned problem. The weight of each group was calculated as follows: The targeted agent group (mFOLFOX6 plus bevacizumab or ramucirumab): [(the sample size of the targeted agent group)/(total sample size)]/(PS). The nontargeted agent group (mFOLFOX6): [(the sample size of the nontargeted agent group)/(total sample size)]/(1 - PS).

For cost-utility analysis, the between-group difference in total costs and QALYs are expressed as the incremental cost-utility ratio (ICUR). We built a Markov decision model by predetermining the utility value, transfer rate value, cost, and benefit of each state, simulating the patients' state transition during treatment, summing up the results of each stage, and finally using decision tree results to determine the more cost-effective option. We performed single-factor sensitivity analysis to determine the variable exerting the highest effect on the ICUR value by varying the cost, treatment outcome, and odds ratio by ±20%, and the results are presented using tornado diagrams. For a probabilistic sensitivity analysis, 1,000 Monte Carlo simulations were conducted to extract cost and benefit values from the respective parameter assignments and to calculate 1,000 ICUR values. The results are presented using a cost-utility acceptability curve (CUAC) and an incremental cost-utility scatter plot (ICS).

We used SPSS v23.0 (SPSS, Chicago, IL, USA) for descriptive and inferential statistics and TreeAge Pro 2017 version (Tree-Age Software, Williamstown, MA, USA) for cost-utility analysis.

Results

Descriptive statistics

Because of the use of the IPTW method, no differences in any of the relevant variables were observed between the targeted and nontargeted agent groups (**Table 1**).

Changing trend of QoL

The targeted agent group had significantly poorer SF-36 RP (P = 0.042) and GH (P = 0.004) scores at 6 months after treatment than before treatment. The nontargeted agent group had significantly poorer FACT-C PWB (P = 0.047) and FWB (P < 0.001) and SF-36 PF (P = 0.009), RP (P = 0.050), GH (P = 0.017), and SF (P = 0.023) scores at 6 months after treatment than before treatment (**Tables 2** and **3**). The targeted agent group exhibited significant improvements in the FACT-C FWB (P = 0.019) and SF-36 RP (P = 0.002), GH (Both P = 0.004) and VT (P < 0.001) scores at 1 year after treatment than at 6 months after treatment. However, the nontargeted agent group displayed significantly worsened FACT-C FWB scores (P < 0.001) at 1 year after treatment than at 6 months after treatment.

The targeted agent group had significantly better FACT-C FWB (P = 0.001) and SF-36 RE scores (P = 0.001) than did the nontargeted agent group at 6 months after treatment (**Tables 4** and **5**). Furthermore, the targeted agent group had significantly better FACT-C EWB (P = 0.032) and FWB (P = 0.001) and SF-36 PF (P = 0.012), RP (P = 0.002), GH (P = 0.001), and VT (P = 0.001) scores than did the nontargeted agent group at 1 year after treatment.

Cost-utility analysis

In addition to various costs, the Markov Model in this study included the clinical transition probability between states and the utility value for each state. All these values were collected from the research, and the cost, probability, and utility values are listed in **Table 6**. The constructed Markov decision-making model is presented in **Figure 2**. The optimal path for decision analysis was determined using the Rollback method, which is used to backtrack the cumulative cost and treatment outcomes associated with the selected strategies. The results of cost-effectiveness analysis for both the targeted and nontargeted agent groups are listed in **Table 7**. Over 20 years, the total cost and total utility were $90,336 and 3.719 QALYs, respectively, for the targeted agent group and $50,749 and 2.483 QALYs, respectively, for the nontargeted agent group; the incremental cost-effectiveness ratio was $32,052/QALYs. When the willingness-to-pay price (WTP) was set at US$33,004, which was the gross domestic product (GDP) per capita in Taiwan in 2021, the addition of a targeted drug to the mFOLFOX6 regimen was more cost-effective than not adding a targeted drug.

Table 1. Study characteristics before and after IPTW matching[†]

Variable	Total (N = 115)	Before IPTW matching			After IPTW matching		
		mFOLFOX6 plus Ramucirumab or Bevacizumab (n = 39)	mFOLFOX6 (n = 76)	*P* value	mFOLFOX6 plus Ramucirumab or Bevacizumab	mFOLFOX6	*P* value
Gender							
Male	72 (62.6%)	20 (51.3%)	52 (68.4%)	0.111	(64.2%)	(64.6%)	1.000
Female	43 (37.4%)	19 (48.7%)	24 (31.6%)		(35.8%)	(35.4%)	
Age, years	57.50±11.91	54.82±12.05	58.88±11.68	0.083	56.55±12.58	57.50±11.75	0.562
BMI, kg/m^2	23.92±4.14	23.55±5.50	24.11±3.25	0.491	23.75±5.83	24.04±3.26	0.644
Education, years	10.69±4.11	12.59±2.88	9.71±4.32	< 0.001	11.40±3.06	10.57±4.11	0.088
Marital status							
Married	101 (87.8%)	31 (79.5%)	70 (92.1%)	0.097	(88.1%)	(89.4%)	0.924
Unmarried/others	14 (12.2%)	8 (20.5%)	6 (7.9%)		(11.9%)	(10.6%)	
Drink habit							
Yes	17 (14.8%)	2 (5.1%)	15 (19.7%)	0.070	(10.2%)	(15.0%)	0.377
No	98 (85.2%)	37 (94.9%)	61 (80.3%)		(89.8%)	(85.0%)	
Smoke							
Yes	20 (17.4%)	4 (10.3%)	16 (21.1%)	0.236	(13.9%)	(17.5%)	0.574
No	95 (82.6%)	35 (89.7%)	60 (78.9%)		(86.1%)	(82.5%)	

IPTW, inverse probability of treatment weighting; BMI, body mass index. [†]Values are presented as the mean ± standard deviation or n (%).

Table 2. Changing trend of quality of life of modified FOLFOX-6 plus ramucirumab or bevacizumab as second-line therapy for metastatic colorectal cancer (*n = 39*)

Subscale	Before the treatment (T0)	6th month after the treatment (T1)			1st year after the treatment (T2)		
	Mean ± standard error	Mean ± standard error	Effect size (T1 vs. T0)	*P* value	Mean ± standard error	Effect size (T2 vs. T1)	*P* value
Functional Assessment of Cancer Therapy-Colorectal (FACT-C)							
PWB	24.83±0.64	23.95±0.70	-1.38	0.097	25.04±0.61	-1.56	0.055
SWB	21.19±0.57	20.43±0.68	-1.33	0.354	20.35±0.61	-0.12	0.924
EWB	21.84±0.44	21.87±0.48	0.07	0.960	22.65±0.24	1.63	0.108
FWB	17.13±1.21	16.47±1.19	-0.55	0.433	18.99±1.15	2.12	0.019
CCS	19.88±0.65	20.39±0.70	0.78	0.465	21.17±0.53	1.11	0.267
36-Item Short Form Survey (SF-36)							
PF	84.40±2.98	78.42±2.80	-2.01	0.152	83.08±3.11	1.66	0.184
RP	64.37±8.53	40.25±10.14	-2.83	0.042	75.76±6.08	3.50	0.002
BP	85.39±2.96	79.60±3.37	-1.96	0.178	83.36±3.08	1.12	0.291
GH	58.72±3.51	53.55±3.05	-1.47	0.004	59.28±3.13	1.88	0.004
VT	62.42±4.39	61.69±3.09	-0.17	0.849	73.57±3.05	3.84	< 0.001
SF	75.61±4.18	74.77±3.77	-0.20	0.853	79.97±3.66	1.38	0.129
RE	60.70±9.04	77.15±7.67	1.82	0.097	72.32±10.54	-0.63	0.474
MH	71.93±2.75	75.70±2.39	1.37	0.055	76.36±1.96	0.28	0.071

PWB, physical well-being; SWB, social/family well-being; EWB, emotional well-being; FWB, functional well-being; CCS, additional concerns of colorectal cancer subscale; PF, physical functioning; RP, role limitations due to physical problems; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role limitations due to emotional problems; MH, mental health; PCS, physical component summary; MCS, mental component summary.

Table 3. Changing trend of quality of life of modified FOLFOX-6 as second-line therapy for metastatic colorectal cancer (*n* = 76)

Subscale	Before treatment (T0)	After treatment 6th month (T1)			After treatment 1st year (T2)		
	Mean ± standard error	Mean ± standard error	Effect size (T1 vs. T0)	*P* value	Mean ± standard error	Effect size (T2 vs. T1)	*P* value
Functional Assessment of Cancer Therapy-Colorectal (FACT-C)							
PWB	24.05±0.55	22.76±0.56	-2.35	0.047	22.17±0.73	-1.05	0.402
SWB	21.18±0.57	20.54±0.49	-1.12	0.331	20.59±0.53	0.10	0.929
EWB	21.24±0.40	21.63±0.32	0.98	0.342	20.94±0.47	-2.16	0.162
FWB	16.59±0.74	13.20±0.63	-4.58	< 0.001	11.59±0.98	-2.56	< 0.001
CCS	20.01±0.46	19.03±0.46	-2.13	0.057	20.00±0.53	2.11	0.071
36-Item Short Form Survey (SF-36)							
PF	83.29±2.60	75.09±2.71	-3.15	0.009	67.76±4.64	2.70	0.112
RP	62.53±5.65	48.44±5.52	-2.49	0.050	47.26±7.62	-0.21	0.878
BP	82.97±2.57	78.10±2.95	-1.89	0.191	75.33±4.69	-0.94	0.585
GH	58.26±2.26	50.67±2.33	-3.36	0.017	51.73±2.88	0.45	0.728
VT	64.52±2.50	62.71±2.46	-0.72	0.542	57.94±3.67	-1.94	0.202
SF	77.14±2.81	69.75±3.18	-2.63	0.023	66.80±6.61	-0.93	0.643
RE	76.01±4.99	64.62±6.02	-2.28	0.131	65.84±7.42	0.20	0.859
MH	73.81±1.83	73.07±1.65	-0.40	0.730	68.33±3.01	-2.87	0.082

PWB, physical well-being; SWB, social/family well-being; EWB, emotional well-being; FWB, functional well-being; CCS, additional concerns of colorectal cancer subscale; PF, physical functioning; RP, role limitations due to physical problems; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role limitations due to emotional problems; MH, mental health; PCS, physical component summary; MCS, mental component summary.

Table 4. Comparison of each functional assessment of cancer therapy-colorectal (FACT-C) subscale score between the modified FOLFOX6 plus ramucirumab or bevacizumab and modified FOLFOX6 as second-line therapy for metastatic colorectal cancer at different time points†

Subscale	Before treatment	After treatment		T1 - T0			T2 - T0		
	Baseline (T0)	6th month (T1)	1st year (T2)	Difference§	SE	*P* value	Difference§	SE	*P* value
FACT-C PWB									
mFOLFOX6 plus target drug	24.83±0.64	23.95±0.70	25.04±0.61	-0.88	0.11	0.097	0.21	0.01	0.741
mFOLFOX6	24.05±0.55	22.76±0.56	22.17±0.73	-1.29	0.10	0.047	-1.88	0.19	0.012
Difference§	0.82±0.71	1.19±0.72	2.87±0.69	0.37	0.11	0.901	2.05	0.10	0.063
FACT-C SWB									
mFOLFOX6 plus target drug	21.19±0.57	20.43±0.68	20.35±0.61	-0.76	0.25	0.354	-0.84	0.01	0.154
mFOLFOX6	21.18±0.57	20.54±0.49	20.59±0.53	-0.64	0.09	0.331	-0.59	0.25	0.471
Difference§	0.01±0.60	-0.11±0.59	-0.24±0.60	0.12	0.17	0.731	-0.25	0.13	0.670
FACT-C EWB									
mFOLFOX6 plus target drug	21.84±0.44	21.87±0.48	22.65±0.24	0.03	0.15	0.960	0.81	0.02	0.083
mFOLFOX6	21.24±0.40	21.63±0.32	20.94±0.47	0.39	0.01	0.342	-0.30	0.10	0.542
Difference§	0.60±0.47	0.24±0.53	1.71±0.49	-0.36	0.08	0.585	1.11	0.06	0.032
FACT-C FWB									
mFOLFOX6 plus target drug	17.13±1.21	16.47±1.19	18.99±1.15	-0.66	0.37	0.433	1.86	0.09	0.096
mFOLFOX6	16.59±0.74	13.20±0.63	11.59±0.98	-3.39	0.01	< 0.001	-5.00	0.23	< 0.001
Difference§	0.54±1.87	3.27±1.20	7.40±1.08	2.73	0.19	0.010	6.86	0.16	0.001
FACT-C CCS									
mFOLFOX6 plus target drug	19.88±0.65	20.39±0.70	21.17±0.53	0.51	0.04	0.465	1.29	0.06	0.072
mFOLFOX6	20.01±0.46	19.03±0.46	20.00±0.53	-0.98	0.05	0.057	-0.01	0.12	0.983
Difference§	-0.13±0.67	1.36±0.82	1.17±0.78	1.49	0.04	0.264	1.30	0.09	0.227

PWB, physical well-being; SWB, social/family well-being; EWB, emotional well-being; FWB, functional well-being; CCS, additional concerns of colorectal cancer subscale; SE, bootstrap standard error. †Predicted values obtained by generalized estimating equation model with gamma distribution. §Difference: mFOLFOX6 plus target drug - mFOLFOX6.

Table 5. Comparison of each SF-36 subscale score between modified FOLFOX6 plus ramucirumab or bevacizumab and modified FOLFOX6 as second-line therapy for metastatic colorectal cancer at different time points†

Subscale	Before treatment	After treatment		T1 - T0			T2 - T0		
	Baseline (T0)	6th month (T1)	1st year (T2)	Difference	SE	*P* value	Difference	SE	*P* value
SF-36 PF									
mFOLFOX6 plus target drug	84.40±2.98	78.42±2.80	83.08±3.11	-5.98	1.19	0.152	-1.32	1.28	0.758
mFOLFOX6	83.29±2.60	75.09±2.71	67.76±4.64	-8.20	0.54	0.009	-15.53	1.79	< 0.001
Difference§	1.11±2.10	3.33±2.54	15.32±5.57	4.44	0.87	0.857	14.21	1.54	0.012
SF-36 RP									
mFOLFOX6 plus target drug	64.37±8.53	40.25±10.14	75.76±6.08	-24.12	3.36	0.042	11.39	1.41	0.109
mFOLFOX6	62.53±5.65	48.44±5.52	47.26±7.62	-14.09	1.56	0.050	-15.27	3.13	0.082
Difference§	1.84±2.78	-8.19±8.97	28.50±9.74	-10.03	2.46	0.128	26.66	2.27	0.002
SF-36 BP									
mFOLFOX6 plus target drug	85.39±2.96	79.60±3.37	83.36±3.08	-5.79	1.34	0.178	-2.03	1.21	0.626
mFOLFOX6	82.97±2.57	78.10±2.95	75.33±4.69	-4.87	1.16	0.191	-7.64	2.06	0.099
Difference§	2.42±2.23	1.50±2.87	8.03±4.89	-0.92	1.25	0.879	5.61	1.64	0.263
SF-36 GH									
mFOLFOX6 plus target drug	58.72±3.51	53.55±3.05	59.28±3.13	-5.17	1.70	0.004	0.56	1.11	0.816
mFOLFOX6	58.26±2.26	50.67±2.33	51.73±2.88	-7.59	0.91	0.170	-6.53	0.94	0.041
Difference§	0.46±1.17	2.88±3.32	7.55±3.57	2.42	1.30	0.290	7.09	1.03	0.001
SF-36 VT									
mFOLFOX6 plus target drug	62.42±4.39	61.69±3.09	73.57±3.05	-0.73	0.58	0.849	11.15	0.31	0.018
mFOLFOX6	64.52±2.50	62.71±2.46	57.94±3.67	-1.81	0.46	0.542	-6.58	1.47	0.098
Difference§	-2.10±3.10	-1.02±3.68	15.63±4.01	1.08	0.52	0.300	17.73	0.89	0.001
SF-36 SF									
mFOLFOX6 plus target drug	75.61±4.18	74.77±3.77	79.97±3.66	-0.84	0.32	0.853	4.36	0.78	0.380
mFOLFOX6	77.14±2.81	69.75±3.18	66.80±6.61	-7.39	0.44	0.023	-10.34	3.73	0.114
Difference§	-1.53±3.89	5.02±4.32	13.17±7.65	6.55	0.38	0.178	14.70	2.26	0.440
SF-36 RE									
mFOLFOX6 plus target drug	60.70±9.04	77.15±7.67	72.32±10.54	16.45	0.86	0.097	11.62	7.17	0.474
mFOLFOX6	76.01±4.99	64.62±6.02	65.84±7.42	-11.39	2.55	0.131	-10.17	3.72	0.243
Difference§	-15.31±9.87	12.53±8.07	6.48±11.01	27.84	1.71	0.001	21.79	1.72	0.494
SF-36 MH									
mFOLFOX6 plus target drug	71.93±2.75	75.70±2.39	76.36±1.96	3.77	0.78	0.055	4.43	0.18	0.071
mFOLFOX6	73.81±1.83	73.07±1.65	68.33±3.01	-0.74	0.29	0.730	-5.48	1.42	0.093
Difference§	-1.88±2.23	2.63±2.43	8.03±3.67	4.51	0.54	0.089	9.91	0.80	0.072

PF, physical functioning; RP, role limitations due to physical problems; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role limitations due to emotional problems; MH, mental health; SE, bootstrap standard error. †Predicted values obtained by generalized estimating equation model with gamma distribution. §Difference: mFOLFOX6 plus target drug - mFOLFOX6.

Table 6. Outcome and survival probability, treatment costs, and health-state utilities

Variable	Value	Minimum	Maximum	Distribution	Reference
Probability					
mFOLFOX6				Beta	Real data
From ORR to SD	0.3261	0.240	0.411		
From ORR to PD	0.2990	0.215	0.383		
From SD to PD	0.3399	0.253	0.426		
Mortality rate	0.2897	0.207	0.373		
mFOLFOX6 plus bevacizumab					
From ORR to SD	0.1898	0.118	0.261		
From ORR to PD	0.1898	0.118	0.261		
From SD to PD	0.2485	0.170	0.327		
Mortality rate	0.2708	0.190	0.352		
mFOLFOX6 plus ramucirumab					
From ORR to SD	0.2592	0.179	0.339		
From ORR to PD	0.1813	0.111	0.252		
From SD to PD	0.2097	0.135	0.284		
Mortality rate	0.1813	0.111	0.252		
Cost (per cycle 1 year)†					
mFOLFOX6				Gamma	Real data
ORR - direct medical	18,610	14,888	22,332		
ORR - indirect societal	4,472	3,578	5,366		
SD - direct medical	15,266	12,213	18,319		
SD - indirect societal	5,183	4,146	6,220		
PD - direct medical	15,426	12,341	18,511		
PD - indirect societal	5,962	4,770	7,154		
Mean subtotal costs	21,640	17,312	25,968		
mFOLFOX6 plus bevacizumab				Gamma	Real data
ORR - direct medical	16,014	12,811	19,217		
ORR - indirect societal	6,108	4,886	7,330		
SD - direct medical	8,088	6,470	9,706		
SD - indirect societal	6,003	4,802	7204		
PD - direct medical	20,101	16,081	24,121		
PD - indirect societal	7,354	5,883	8,825		
Mean subtotal costs	21,223	16,978	25,468		
mFOLFOX6 plus ramucirumab				Gamma	Real data
ORR - direct medical	16,792	13,434	20,150		
ORR - indirect societal	6,035	4,828	7,242		
SD - direct medical	17,968	14,374	21,562		
SD - indirect societal	5,469	4,375	6,563		
PD - direct medical	17,267	13,814	20,720		
PD - indirect societal	5,193	4,154	6,232		
Mean subtotal costs	22,908	18,326	27,490		
Cost for bevacizumab	11,584	9,267	13,901	Gamma	Real data
Cost for Ramucirumab	44,342	35,474	53,210		

Utility					
ORR				Beta	Real data
mFOLFOX6	0.80	0.64	0.96		
mFOLFOX6 plus bevacizumab	0.94	0.75	1.00		
mFOLFOX6 plus ramucirumab	1.00	0.80	1.00		
SD					
mFOLFOX6	0.77	0.62	0.92		
mFOLFOX6 plus bevacizumab	0.90	0.72	1.00		
mFOLFOX6 plus ramucirumab	0.90	0.72	1.00		
PD					
mFOLFOX6	0.72	0.58	0.86		
mFOLFOX6 plus bevacizumab	0.81	0.65	0.97		
mFOLFOX6 plus ramucirumab	0.76	0.61	0.91		

ORR, objective response rate; SD, stable disease; PD, progression disease. †Indirect societal cost = (friction period) × (mean working hours) × (production costs) × (mean participation) × (percentage of patients aged <65 years).

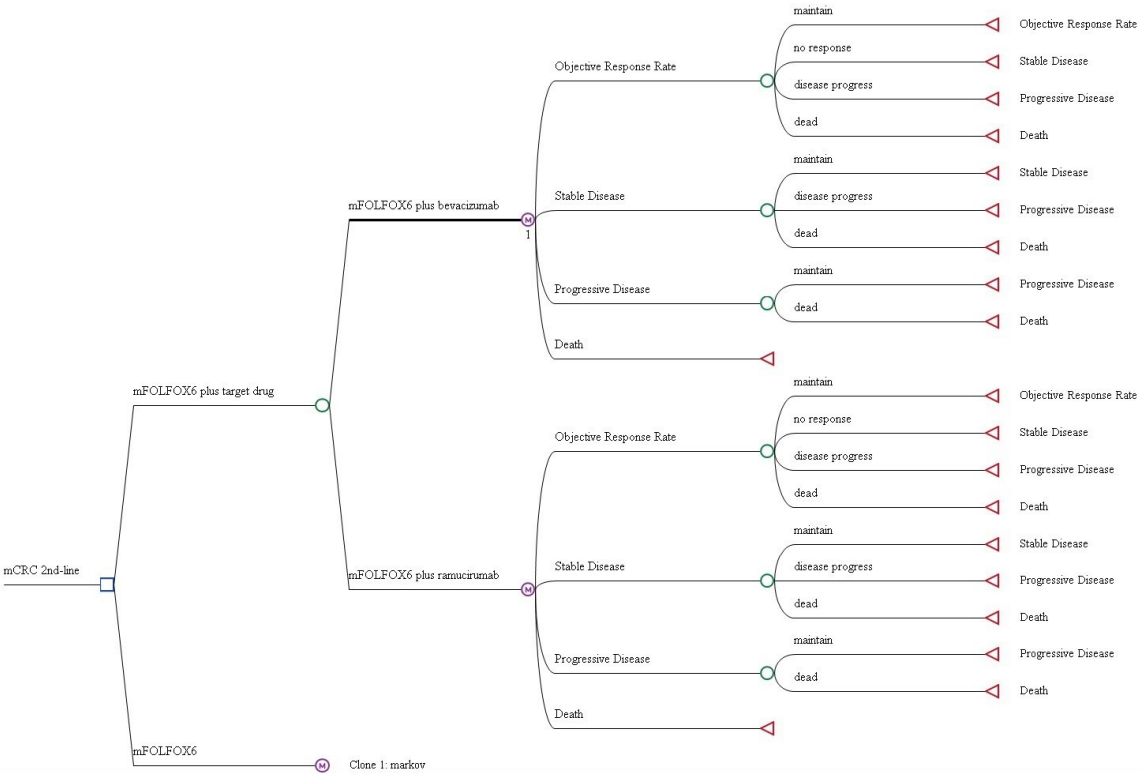

Figure 2. Markov decision model for cost-utility analysis of modified FOLFOX6 plus ramucirumab or bevacizumab and modified FOLFOX6 as second-line therapy for metastatic colorectal cancer.

Table 7. Cost-utility analysis between modified FOLFOX6 plus ramucirumab or bevacizumab and modified FOLFOX6 as second-line therapy for metastatic colorectal cancer

	Costs (US$)	Incremental costs (US$)	QALYs	Incremental QALYs	ICERs
mFOLFOX6 plus Ramucirumab or Bevacizumab	90,336		3.719		
mFOLFOX6	50,749	39,587	2.483	1.235	32,052

QALYs, quality-adjusted life years; ICER, incremental cost effectiveness ratio.

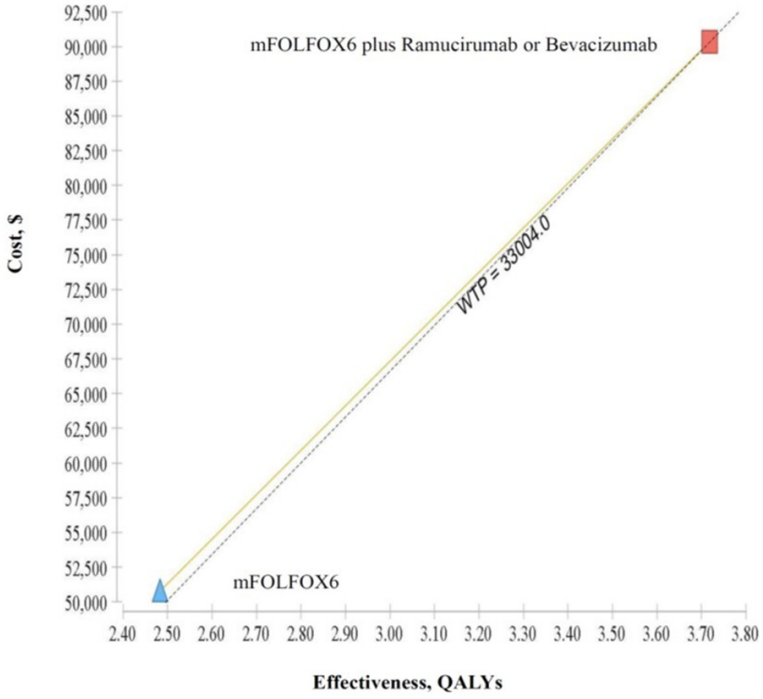

Figure 3. Cost-effectiveness acceptability curve of modified FOLFOX6 plus ramucirumab or bevacizumab and modified FOLFOX6 as second-line therapy for metastatic colorectal cancer.

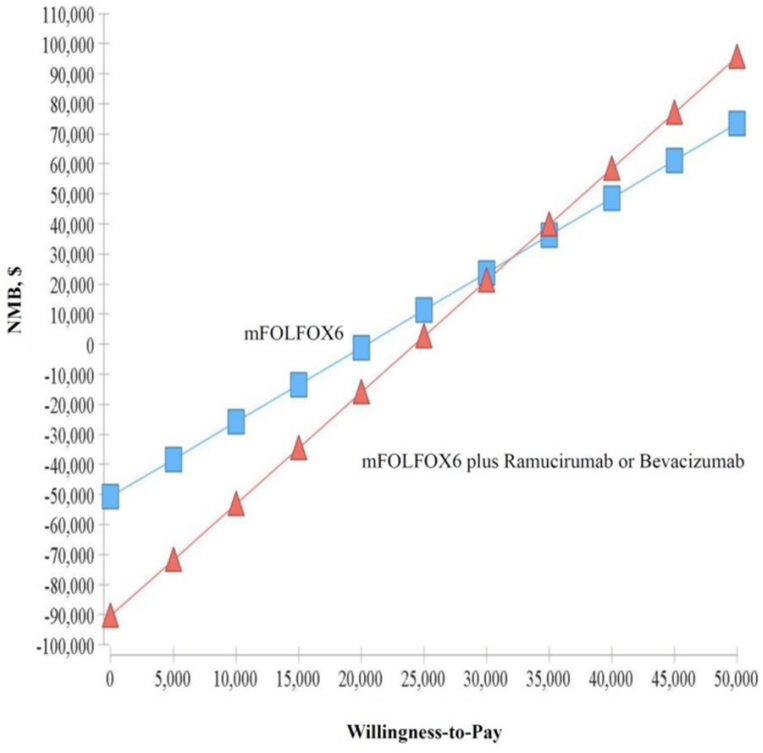

Figure 4. Net money benefit (NMB) of modified FOLFOX6 plus ramucirumab or bevacizumab and modified FOLFOX6 as second-line therapy for metastatic colorectal cancer.

Figure 3 presents the findings of the cost-utility analysis for the targeted and nontargeted agent groups for comparison. The results revealed that neither of the two drug treatment strategies had a clear advantage or disadvantage in both groups. As illustrated in **Figure 4**, with an increase in the WTP, the net monetary benefit of both treatment strategies increased, and when the WTP reached $32,052 (ICUR value), the net monetary benefit for the targeted agent group was better than that for the nontargeted agent group. **Figure 5** displays the CUAC for varying WTP values per QALY.

The sensitivity analysis revealed that when the WTP was $33,004, the targeted and nontargeted agent groups had an 83% and 17% chance of being more cost-effective, respectively (**Figure 6**). This figure, presenting a scatter diagram of the incremental cost-effectiveness from 1,000 random samples, was located in the first quadrant. This finding indicated that when the marginal total costs increased in the targeted agent group than in the nontargeted agent group, the marginal treatment effects (QALYs) also tended to increase. When the WTP was $33,004, 83% of the targeted agent group was more cost-effective compared with the nontargeted agent group. The utility value of the PD state for the nontargeted agent group was the most influential parameter (**Figure 7**), followed by the initial cost of the ORR state for the RAM group, the rate of transition to death in the PD state for the nontargeted agent group, the utility value of the PD state for the

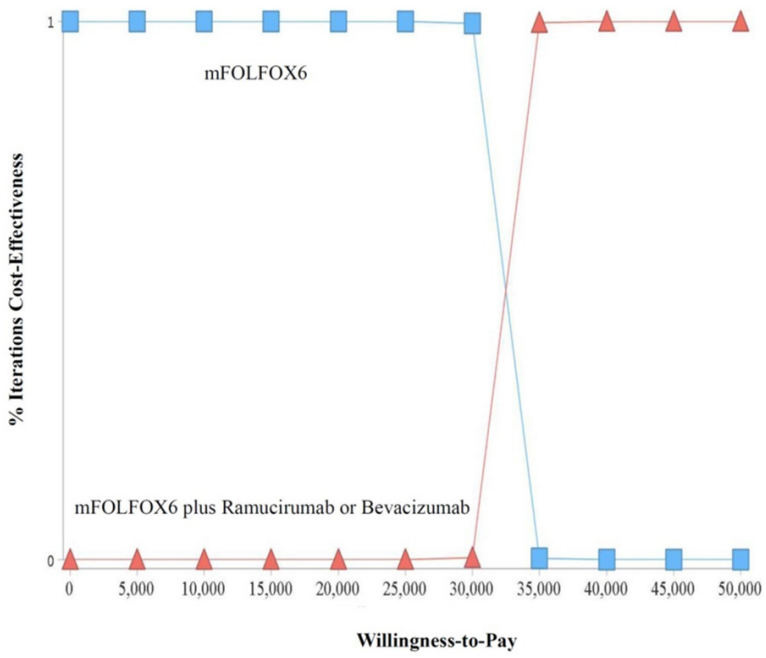

Figure 5. Cost effectiveness analysis of modified FOLFOX6 plus ramucirumab or bevacizumab and modified FOLFOX6 as second-line therapy for metastatic colorectal cancer. Abbreviations: WTP, willingness-to-pay; QALYs, quality-adjusted life years.

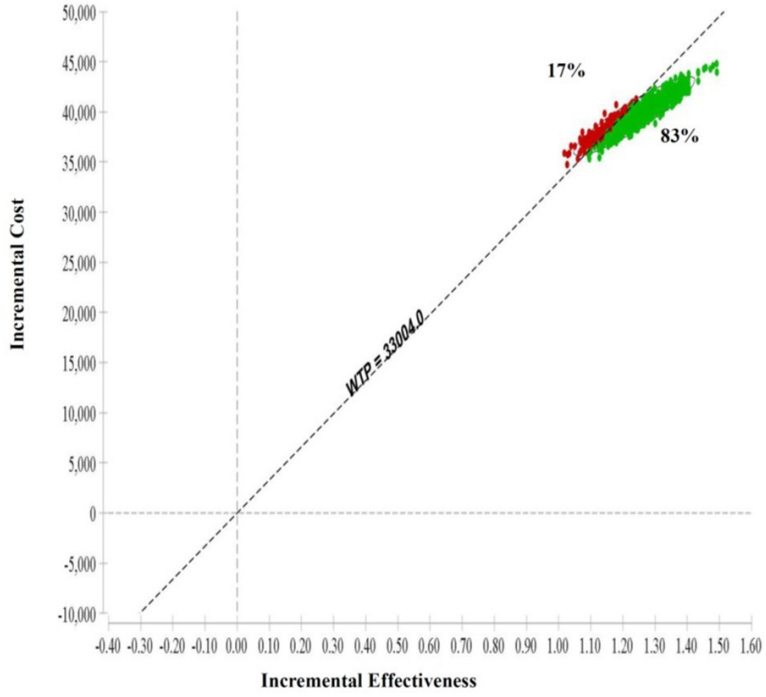

Figure 6. Incremental cost-effectiveness scatter plot of modified FOLFOX6 plus ramucirumab or bevacizumab and modified FOLFOX6 as second-line therapy for metastatic colorectal cancer. Abbreviations: WTP, willingness-to-pay.

RAM group, and the utility value of the ORR state for the nontargeted agent group.

Discussion

The findings of the current study revealed that the patients with mCRC who received second-line therapy had significantly poorer QoL at 6 months after treatment than before treatment, and both groups had significantly better QoL at 1 year after treatment than at 6 months after treatment. From before treatment to 6 months after treatment, the nontargeted agent group exhibited a significant improvement in QoL than did the targeted agent group. From 6 months to 1 year after treatment, the targeted agent group exhibited a significant improvement in QoL than did the nontargeted agent group. The average total medical costs of the targeted and nontargeted agent groups were US$90,336 and US$50,749, respectively. The higher cost for the targeted agent group primarily results from the usage of the targeted drugs bevacizumab and ramucirumab in the second-line treatment of mCRC; these drugs are expensive and self-funded, indicating that they are not covered under Taiwan's National Health Insurance. This cost difference is similar to that reported in previous studies [25-27]. A study reported that the use of bevacizumab and ramucirumab substantially varies among Japan, the United States, and European Union countries due to the different payment methods for targeted drugs in each country [28].

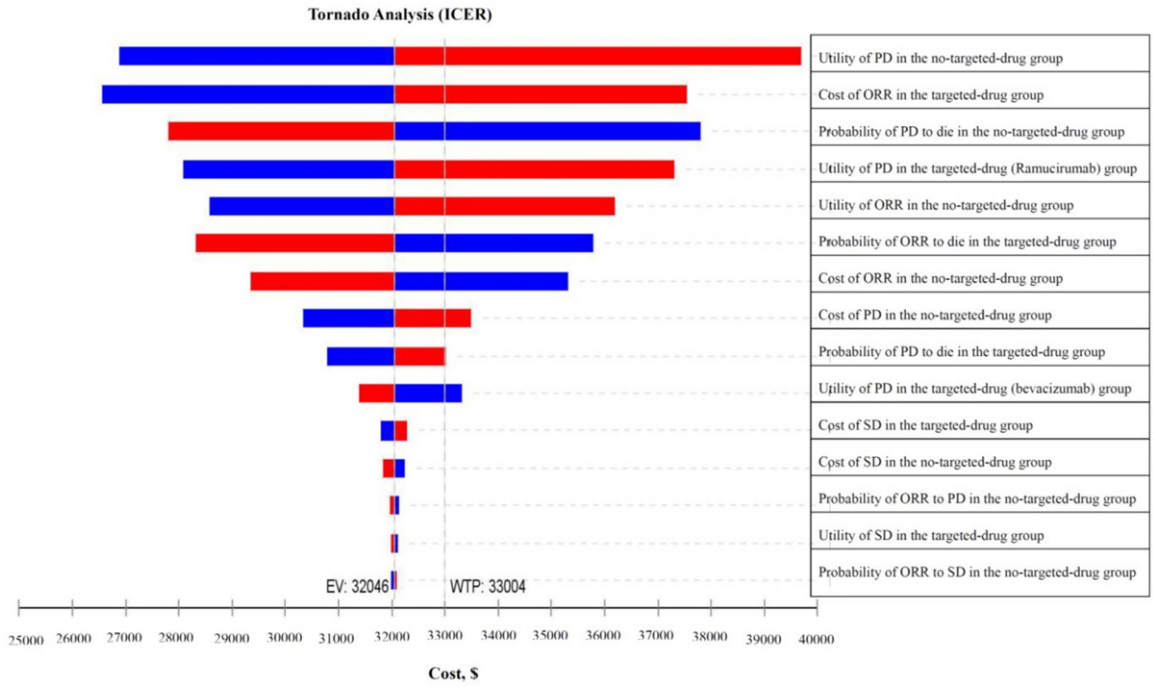

Figure 7. Tornado diagram showing one-way sensitivity analysis results. Bars indicate the effect of a ±20% variance of a variable on the incremental cost-effectiveness ratio (ICER). Costs are expressed in 2021 US$. Abbreviations: ORR, objective response rate; SD, stable disease; PD, progression disease.

This study investigated the difference in QoL between the patients with CRC who were treated with a targeted drug (ramucirumab or bevacizumab) and those who were not treated with a targeted drug, and the results are summarized in **Table 8** [29-31].

Our results revealed that the ICUR was US$32,052. When the WTP threshold was set at the GDP per capita = US$33,004, the addition of a targeted drug to the mFOLFOX6 chemotherapy regimen was a more cost-effective strategy for the patients with mCRC receiving second-line therapy. Goldstein et al. developed the Markov Model to evaluate the cost-effectiveness of combining targeted drugs in the first- and second-line treatment of colorectal cancer [32]. They indicated that the cost per Markov cycle (2 weeks) for FOLFOX and bevacizumab was US$435.05 and US$2,649.42, respectively. In addition, they reported that the costs of FOLFOX and bevacizumab varied widely and demonstrated that the cost of drugs is a crucial variable in cost-benefit analysis. Unlike our results, Goldstein et al. indicated that not adding a targeted drug is more cost-effective. This discrepancy may be because the targeted drug is more expensive in the United States than in Taiwan.

Strengths of the study

This prospective cohort study examined changes in the QoL of the patients with mCRC. In addition, we performed a cost-utility analysis comparing the patients receiving mFOLFOX6 plus ramucirumab or bevacizumab with those receiving mFOLFOX6 only. A review of the literature in Taiwan and abroad revealed that few studies have compared both treatment strategies with respect to QoL and cost-effectiveness. This is the first study to compare QoL and conduct a cost-utility analysis for the two treatment strategies used for patients with mCRC. We employed a 20-year dynamic Markov decision-making model to simulate the current second-line treatment strategies for these patients, integrating actual direct medical costs and clinical health status odds ratios. The results are expressed in terms of ICUR. In addition, we used IPTW for matching to reduce selection bias. Furthermore, because the data collection period spanned the 2015 to 2020 period, we adjusted the monetary time value

Table 8. Comparison of quality of life between ramucirumab or bevacizumab and placebo in metastatic colorectal cancer reported in selected studies

Authors (country)	No. of patients	Measures	Findings
Shi et al., 2022 (Taiwan)	After inverse probability of treatment weighting (IPTW) matching, 39 patients with metastatic colorectal cancer (mCRC) received mFOLFOX6 plus ramucirumab or bevacizumab and 76 patients received mFOLFOX6.	Functional Assessment of Cancer Therapy-Colorectal (FACT-C) and 36-Item Short Form Survey (SF-36)	1. All patients with mCRC exhibited a significant decrease in most quality of life subscales from baseline to 6 months after treatment ($P < 0.05$). 2. All patients with mCRC displayed a significant improvement in most quality of life subscales from 6 months to 1 year after treatment ($P < 0.05$). However, patients receiving mFOLFOX6 plus ramucirumab or bevacizumab had significantly better quality of life than did those receiving mFOLFOX6 only ($P < 0.05$).
Avallone et al., 2021 (Italy) [29]	230 patients with mCRC were randomly assigned to the standard arm (n = 115) or the experimental arm (n = 115).	European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire 30 (EORTC QLQ-C30)	The sequential bevacizumab scheduling plus modified FOLFOX-6 chemotherapy compared with the traditional concomitant schedule was associated with a significant improved physical functioning (mean [standard deviation] change from baseline, 0.65 [1.96] vs. -7.41 [2.95] at 24 weeks; $P = 0.02$), and constipation scores (mean [standard deviation] change from baseline, -17.2 [3.73] vs. -0.62 [4.44]; $P = 0.003$).
Liu et al., 2020 (China) [30]	320 patients with mCRC were randomly assigned (1:1) to chemotherapy combined with chemotherapy and cetuximab (CET) or bevacizumab (BV) and placebo in a randomized clinical trial study.	EORTC QLQ-C30	1. In terms of functional subscales, the levels of role function (83.33±13.21 vs. 76.19±13.58) and social function (83.33±13.80 vs. 74.29±15.31) in the treatment group were significantly higher than those in the control group ($P < 0.05$). 2. In terms of symptom subscales, fatigue (27.47±14.42 vs. 34.92±16.42) and appetite loss (19.44±23.06 vs. 31.43±25.49) in the treatment group were significantly lower than those in the control group ($P < 0.05$).
Garcia-Carbonero et al., 2015 (24 counties) [31]	Randomized, double-blind phase III study of FOLFIRI plus ramucirumab or placebo in 1,072 patients with mCRC at 224 sites in 24 countries.	EORTC QLQ-C30	1. Rates of improved/stable scores were not significantly different between arms except for lower rates in the ramucirumab plus FOLFIRI arm before 6 weeks for global quality of life, physical functioning, role functioning, cognitive functioning, social functioning, pain, and dyspnea and during 6 weeks and 10 weeks for fatigue and appetite loss. 2. No significant differences in rates of improved/stable scores were observed for subsequent assessments.

using Taiwan's 2021 CPI when calculating medical costs. Given the 20-year simulation time, the follow-up medical costs were calculated and adjusted using a 2% discount rate, as suggested by Shiroiwa et al. [33].

Limitations of the study

We included only patients who received second-line mCRC treatment in a medical center in southern Taiwan. Therefore, the study findings may not be generalizable to other regions and countries. Furthermore, in Taiwan, the National Health Insurance does not cover the regimen of mFOLFOX6 plus VEGF inhibitors as second-line treatment. This factor would lead to substantial differences in the number of patients among different groups. To avoid selection bias, future studies should include patients from various regions of Taiwan. In addition to direct costs, we considered indirect costs. However, data on hospital medical costs did not contain details related to the cost of adverse events, causing difficulties in data processing. The inclusion of these costs can enhance the accuracy of study findings.

In conclusion, although targeted drugs are self-funded and expensive for second-line mCRC treatment, our findings demonstrated that the addition of a targeted drug in this context proved to be more cost-effective in the long term compared with the administration of mFOLFOX6 alone. With recent advancements in medical technology, techniques, and infrastructure, the combination of second-line chemotherapy with targeted drugs can prolong the survival of patients and enhance their QoL. On the basis of these positive outcomes, we recommend that the addition of targeted drugs in the treatment of patients with mCRC should be covered under Taiwan's National Health Insurance.

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Disclosure of conflict of interest

None.

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