Objective: Patients with metastatic colorectal cancer (mCRC) had oncological benefits with irinotecan dose escalation of FOLFIRI regimen combined with bevacizumab according to UGT1A1 genotypes in our previous study. In the current study, we performed a quality of life (QOL) outcome evaluation and cost-utility analysis of different irinotecan dose regimens in patients with mCRC.

Materials and Methods: With inverse probability-of-treatment weighting (IPTW) matching on all covariates, 75 patients with dose escalation of irinotecan (study group) and 121 patients with the recommended dose of irinotecan (control group) were recruited between October 2015 and December 2019. The QOL outcome measures were Functional Assessment of Cancer Therapy-Colorectal, Beck Anxiety Inventory, Beck Depression Inventory, and SF-36; cost-utility outcome measures were medical direct costs, quality-adjusted life-years (QALYs), and incremental cost-utility ratios (ICURs).

Results: All mCRC patients exhibited a significant decrease in both emotional wellbeing and depression from pretherapeutic period to posttherapeutic 6th month ($P < 0.05$); however, from the posttherapeutic 1st year to the 2nd year, improvement in most QOL measures was significantly better in the study group than in the control group ($P < 0.05$).
INTRODUCTION

With the recent advances in pharmacogenomic era, patients undergo genetic testing to determine their genotype before treatment, based on which a suitable medication or dosage is administered (1-3). For metastatic colorectal cancer (mCRC) patients, the standard chemotherapy regimens are 5-fluorouracil (5-FU), leucovorin, and oxaliplatin (FOLFOX); oxaliplatin with capecitabine (CAPOX); or 5-FU, leucovorin, and irinotecan (FOLFIRI). Bevacizumab is a recombinant humanized monoclonal antibody targeting the vascular endothelial growth factor and is usually added to these standard regimens to enhance the efficacy. Our previous multicenter, randomized, controlled, open-label trial study revealed that exceeding the recommended irinotecan dose is safe and effective when a regimen of FOLFIRI plus bevacizumab increased the total per-patient cost by 108 million IDR, it increased QALYs by 0.17 (9).

Roncato et al. estimated the per-patient cost of treating irinotecan-related toxicity associated with the UGT1A1*28 patient genotype. Mean per-patient cost was €812 for UGT1A1*1/*1 patients, €1,119 for UGT1A1*1/*28 patients, and €4,886 for UGT1A1*28/*28 patients (8). Notably, the incremental treatment cost per patient was €4,074 higher in UGT1A1*28/*28 patients compared to UGT1A1*1/*1 patients and €307 higher in UGT1A1*28/*28 patients compared to UGT1A1*1/*28 patients. Kristin et al. also found that the total per-patient cost of a FOLFOX or FOLFIRI chemotherapy regimen was 359 million Indonesian Rupiah ( IDR) with a mean average of 1.90 quality-adjusted life-years (QALYs) over a life-time horizon. Additionally, although FOLFOX or FOLFIRI plus bevacizumab increased the total per-patient cost by 108 million IDR, it increased QALYs by 0.17 (9).

Although irinotecan dose escalation demonstrates a more optimal treatment effect in patients with mCRC undergoing UGT1A1 genotyping and receiving FOLFIRI, the cost utility of different doses of irinotecan plus bevacizumab has not been comprehensively investigated. Additionally, most studies on the economic and cost-effectiveness of this treatment have analyzed the short-term results; however, few studies have analyzed the long-term results. Therefore, the objective of this prospective, long-term follow-up study was to perform a quality of life (QOL) outcome evaluation and a cost-utility analysis of different doses of irinotecan plus bevacizumab in patients with mCRC in the first-line setting.

METHODS

Study Design and Study Population

The study population included patients with mCRC at a medical center between October 2015 and December 2019. The inclusion criteria were as follows: (a) patients who underwent UGT1A1 genotyping before treatment; (b) mCRC patients with histologically diagnosed adenocarcinoma, and (c) patients aged 20-80 years. The exclusion criteria were as follows: (a) no receipt of bevacizumab plus FOLFIRI, (b) the UGT1A1 genotype 7TA/7TA (UGT1A1*28*28); (c) <20 or >80 years of age; (d) no dose escalation due to discomfort experienced by those in the dose escalation group; (e) being pregnant or breastfeeding; (f) a major comorbidity; and (g) having not signed the consent form. The recommended irinotecan dose in the FOLFIRI regimen is 180 mg/m² based on a dose-finding study (2, 4, 10). The detailed treatment regimen on irinotecan dose escalation including patient withdrawal was described in our previous study protocol (11). According to the above criteria, mCRC patients were divided into two groups: 75 patients were categorized into the dose escalation group (>180 mg/m², study group) and 121 patients into the recommended dose group (180 mg/m², control group). The patients in the recommended dose group received irinotecan at a dose of 180 mg/m². Figure 1 shows a flow diagram of the current study illustrating the enrollment, allocation, and matching analysis processes. Before study initiation, approval was obtained from the Institutional Review Board of our hospital (KMUHIRB-(EI)-20150147). The patients/participants provided their written informed consent to participate in this study.

Quality of Life Measures

The QOL measures included the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) (12), Beck Depression Inventory (BDI) (13), Beck Anxiety Inventory (BAI) (14), and SF-36 (15). Higher FACT-C and SF-36 scores indicated better outcomes, but higher BDI and BAI scores exhibited worse outcomes. All enrolled patients were scheduled to complete all
the above assessments at four time points: pretherapeutic and therapy at posttherapeutic 6th month, 1st year, and 2nd year.

**Economic Evaluation**

**Cost Estimation**

In accordance with the reimbursement criteria established by the National Health Insurance Administration, medical cost structure included total medical direct costs during therapy and total inpatient costs, total outpatient costs, and total medical emergency costs at posttherapeutic 2 years after discharge. All medical direct costs included expenses for physicians, ward, pharmacy, laboratory, inspection, medical materials, etc. All cost inputs were adjusted to US$ 2019 according to the consumer price index (CPI) and discounted annually by 3%.

**Estimation of Utility**

To estimate QALYs, cost-utility analysis often uses “utility scores” (health state valuations) anchored by 0 and 1, where 0 indicates death and 1 indicates full health. This study used the time trade-off valuation procedure to convert EuroQol-5D (EQ-5D) total scores to utility scores (16). The utilities reported by each patient were multiplied by the assumed duration of sustained benefit after intervention (summed up to the end of 2 years) to estimate QALYs. To maintain consistency with QALYs calculation, this study assumed that the only resources used by patients were those captured during the 2 years of follow-up. That is, the analysis assumed that patients did not incur any other healthcare costs during the remainder of the year.

**Statistical Analysis**

In the main patient-level analysis, we used inverse probability-of-treatment weighting (IPTW) based on propensity score to construct a weighted cohort of patients with different doses of irinotecan plus bevacizumab but similar with respect to other study characteristics. IPTW based on propensity scores was used to account for differences in study characteristics between the two regimens (17). The resulting differences between the weighted groups of interest reflected the average treatment effect (Table 1). The distribution of FACT-C scores at each time point was analyzed in terms of median, range and interquartile range and visualized by box-and-whisker plots.

A common limitation of longitudinal studies is the absence of an appropriate statistical methodology that can control for censoring and intercorrelations that occur when measures are repeatedly obtained for the same pool of subjects. To address this limitation, this study used a generalized estimating equation (GEE) model to

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**Table 1**

| Cost Component                  | Pretherapeutic | Therapy at 6th month | Therapy at 1st year | Therapy at 2nd year |
|--------------------------------|---------------|----------------------|---------------------|---------------------|
| Total Medical Direct Costs     | $X            | $Y                   | $Z                  | $W                  |
| Inpatient Costs                | $A            | $B                   | $C                  | $D                  |
| Outpatient Costs               | $E            | $F                   | $G                  | $H                  |
| Medical Emergency Costs        | $I            | $J                   | $K                  | $L                  |
Table 1: Study characteristics before and after IPTW.

| Variables       | Total (N=196) | Before IPTW matching | After IPTW matching | P value |
|-----------------|---------------|----------------------|---------------------|---------|
|                 | Study group (n=75) | Control group (n=121) | Study group (n=75) | Control group (n=121) |       |
| Gender          |               |                      |                     |                     |       |
| Male            | 125 (63.8%)   | 54 (72.0%)           | 71 (58.7%)          | 0.083†             |       |
| Female          | 71 (36.2%)    | 21 (28.0%)           | 50 (41.3%)          |                     |       |
| Age, years      |               |                      |                     |                     |       |
| 58.74 ± 12.06   | 56.11 ± 13.21 | 60.74 ± 10.77        | 0.021†              |                     |       |
| Education, years| 10.67 ± 3.68  | 11.22 ± 3.04         | 10.34 ± 3.40        | 0.064‡              |       |
| Body mass index, kg/m² | 22.96 ± 3.46 | 22.37 ± 3.43         | 23.90 ± 3.43        | 0.070†              |       |
| Marital status  |               |                      |                     |                     |       |
| Married         | 158 (80.6%)   | 63 (84.0%)           | 95 (78.5%)          | 0.448†              |       |
| Unmarried       | 38 (19.4%)    | 12 (16.0%)           | 26 (21.5%)          |                     |       |
| Smoking         |               |                      |                     |                     |       |
| Yes             | 36 (18.4%)    | 18 (24.0%)           | 18 (14.9%)          | 0.157†              |       |
| No              | 160 (81.6%)   | 57 (76.0%)           | 103 (85.1%)         |                     |       |
| Drinking        |               |                      |                     |                     |       |
| Yes             | 50 (25.5%)    | 21 (28.0%)           | 29 (24.0%)          | 0.645†              |       |
| No              | 146 (74.5%)   | 54 (72.0%)           | 92 (76.0%)          |                     |       |
| Die             |               |                      |                     |                     |       |
| Yes             | 69 (35.2%)    | 35 (46.7%)           | 34 (28.1%)          | 0.013†              |       |
| No              | 127 (64.8%)   | 40 (53.3%)           | 87 (71.9%)          |                     |       |

IPTW, inverse probability of treatment weighting.
†The values are presented as mean ± standard deviation or n (%).
‡P-values calculated by Student’s t-test.
§P-values calculated by chi-square test.

Cluster mCRC patients; the GEE model was also useful for generating propensity scores. Moreover, total scores for each QOL measure were compared between the study group and control group by using the differences-in-differences (DID) methodology (i.e., a pre-post study design with a comparison group) (18). Standard errors in DID in the predicted values were estimated using the bootstrap technique (1,000 replications and sample sizes equal to the original sample size) (19). Additionally, effect size was obtained using Cohen’s d statistics (i.e., the difference between the mean posttherapeutic QOL value and the mean pretherapeutic QOL value divided by the pooled standard deviation) (20).

After converting EQ-5D scores into utility scores, the number of QALYs over a period of 2 years was calculated for each patient by using the area under the curve approach after controlling for imbalances in baseline utility scores (21). The incremental cost-utility ratio (ICUR) was calculated as the ratio of the difference in mean cost per patient to the difference in mean QALYs per patient between the study and control groups. A willingness-to-pay (WTP) threshold of gross domestic product (GDP) US$ 26,263.5 per QALY was used to assess cost-effectiveness. A regimen is termed dominant when it is both less costly and more effective. To derive cost-effectiveness acceptability curve, this study performed nonparametric bootstrapping on the incremental cost and effectiveness acceptability frontier. All P values reported were two-sided, and P values of <0.05 were considered statistically significant. The software package used to perform GEE in all statistical analyses was xtgee in Stata version 13.0 (Stata Corp LP, College Station, TX, USA), and a decision tree model was built using the TreeAge Pro 2017 (Tree-Age Software Inc. Williamstown, MA, USA).

Results
To unify the study characteristics of the two groups and reinforce the subsequent research results, IPTW was used to match all study characteristics; thus, no variables were significantly different between the groups (Table 1).

Changing Trends of QOL in the Two Groups After IPTW
Figure 2 shows box plots illustrating the FACT-C score distributions in the study and control groups at different time points. From pretherapeutic to posttherapeutic 6th month after discharge, mCRC patients exhibited a significant decrease in FACT-C functional wellbeing (ES = −0.05 in the study group and ES = −0.35 in the control group), SF-36 physical functioning (ES = −0.39 in the study group and ES = −0.37 in the control group), and depression function (ES = 0.28 in the study group and ES = 0.13 in the control group; Tables 2, 3). At the remaining follow-up time points, different changing trends in QOL values in the two groups were noted.

Differences in the QOL Between the Two Groups After IPTW
Table 4 presents a comparison of the differences in QOL measures between the two groups at four time points: pretherapeutic (T0), posttherapeutic 6th month (T1), posttherapeutic 1st year (T2), and posttherapeutic 2nd year (T3). Compared with the control group, at T0, the study group had a significantly better function in FACT-C social/family wellbeing (P = 0.024) and BAI (P = 0.039); at T1, the study group had a significantly better function in FACT-C functional wellbeing (P = 0.025), BAI (P = 0.003), SF-36 physical functioning (P = 0.008), vitality (P = 0.031), and role limitation due to emotional problems (P = 0.033); at T2, the study group had a significantly better function in FACT-C physical wellbeing (P = 0.025), FACT-C emotional wellbeing (P = 0.002), and SF-36 role limitation due to physical problems (P = 0.033); at T3, the study group had a significantly better function in FACT-C colorectal cancer-specific wellbeing (P = 0.017), BAI (P = 0.009), SF-36 physical functioning (P = 0.002), role limitation due to physical problems (P = 0.004), and role limitation due to emotional problems (P = 0.017). Overall, from posttherapeutic 1st year to the 2nd year, improvements in most QOL

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FIGURE 2 | Box and whisker plots of the FACT-C scores [(A) FACT-C PWB; (B) FACT-C SWB; (C) FACT-C EWB; (D) FACT-C EWB; (E) FACT-C CCS] at each time-point, with study and control groups presented side by side. The box contains 50% of all values (the 25th to 75th percentile) and is divided by the horizontal bar which is the median value (50th percentile). FACT-C, functional assessment of cancer therapy-colorectal; PWB, physical wellbeing; SWB, social/family wellbeing; EWB, emotional wellbeing; FWB, functional wellbeing; CCS, colorectal cancer specific wellbeing; T0, pretherapeutic; T1, posttherapeutic 6th month; T2, posttherapeutic 1st year; T3, posttherapeutic 2nd year.
Paired t test was employed to evaluate trends of the FACT-C, BDI, BAI, and SF-36 in the study group in patients with metastatic colorectal cancer at different time points (n=121).

| Measures | Pretherapeutic (T₀) | Posttherapeutic 6th month (T₁) | Posttherapeutic 1st year (T₂) | Posttherapeutic 2nd year (T₃) |
|----------|---------------------|---------------------------------|-----------------------------|-----------------------------|
|          | Mean ± SD           | Mean ± SD                       | Mean ± SD                   | Mean ± SD                   |
| FACT-C   | 24.83 ± 4.27        | 22.28 ± 5.10                    | 23.47 ± 4.88                | 24.62 ± 4.91                |
| PWB      | ¶                     | §                               | †                            |                               |
| FACT-C   | 21.59 ± 3.96        | 21.37 ± 3.99                    | 21.20 ± 2.94                | 21.75 ± 3.05                |
| SWB      | ¶                     | §                               | †                            |                               |
| FACT-C   | 21.63 ± 4.70        | 17.55 ± 3.35                    | 21.10 ± 3.75                | 18.76 ± 3.12                |
| EBW      | ¶                     | §                               | †                            |                               |
| FACT-C   | 17.50 ± 6.17        | 15.47 ± 7.06                    | 15.02 ± 3.19                | 15.64 ± 3.53                |
| FWB      | ¶                     | §                               | †                            |                               |
| FACT-C   | 19.96 ± 4.08        | 19.60 ± 4.07                    | 16.48 ± 4.07                | 18.30 ± 5.07                |
| CCS      | ¶                     | §                               | †                            |                               |

SF36 PF  87.01 ± 17.32  80.20 ± 20.98  83.41 ± 6.53  93.08 ± 8.96  1.48 <0.001
SF36 RP  59.59 ± 49.94  44.92 ± 48.65  56.33 ± 45.99  62.09 ± 47.31  1.30 <0.027
SF36 BP  78.54 ± 23.93  80.25 ± 27.49  86.25 ± 18.33  87.14 ± 18.80  0.05 0.085
SF36 GH  56.02 ± 21.13  54.01 ± 20.78  59.26 ± 18.56  66.06 ± 22.48  0.37 <0.001
SF36 VT  66.65 ± 19.73  64.19 ± 19.39  65.38 ± 20.44  68.79 ± 19.84  0.17 0.193
SF36 SF  70.73 ± 25.36  68.82 ± 30.49  73.23 ± 22.86  74.33 ± 21.20  0.05 0.697
SF36 RE  72.06 ± 43.97  73.50 ± 43.21  75.91 ± 32.63  85.75 ± 32.38  0.30 0.532
SF36 MH  72.65 ± 19.03  71.59 ± 20.01  72.35 ± 15.86  76.04 ± 15.25  0.23 0.038

BDI  2.88 ± 4.23  4.05 ± 6.65  0.70 ± 2.25  0.41 ± 1.38  0.13 0.298
BAI  0.11 ± 0.77  0.07 ± 0.42  0.05 ± 0.37  0.01 ± 0.52  0.11 0.055

FACT-C, functional assessment of cancer therapy-colorectal; PWB, physical wellbeing; SWB, social/family wellbeing; EWB, emotional wellbeing; FWB, functional wellbeing; CCS, colorectal cancer specific wellbeing; PF, physical functioning; RP, role limitation due to physical problems; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role limitation due to emotional problems; MH, mental health; BDI, Beck depression inventory; BAI, Beck anxiety inventory; SD, standard deviation; ES, effect size.

°P-values calculated by paired t-test.

Cost-Utility Analysis of the Study Group

The mean total medical direct costs per patient over a 2-year time period included the mean total medical direct costs during therapy and the mean total medical direct costs at posttherapeutic 2 years after discharge. The mean total medical direct cost of the study group was US$ 54,742 (standard deviation, SD, US$ 14,013) compared with US$ 54,608 (SD US$ 9,673) for the control group, resulting in mean incremental costs of US$ 134 (Table 5). Treatment in the study group led to a decrease in the mean utility score from 0.97 (SD 0.09) at the pretherapeutic time point to 0.95 (SD 0.09) at posttherapeutic 2nd year compared with the control group, which had a mean of 0.94 (SD 0.16) at the pretherapeutic time point to 0.86 (SD 0.24) at

Cost-Utility Analysis of the Study Group Compared With the Control Group

The mean total medical direct costs per patient over a 2-year time period included the mean total medical direct costs during therapy and the mean total medical direct costs at posttherapeutic 2 years after discharge. The mean total medical direct cost of the study group was US$ 54,742 (standard deviation, SD, US$ 14,013) compared with US$ 54,608 (SD US$ 9,673) for the control group, resulting in mean incremental costs of US$ 134 (Table 5). Treatment in the study group led to a decrease in the mean utility score from 0.97 (SD 0.09) at the pretherapeutic time point to 0.95 (SD 0.09) at posttherapeutic 2nd year compared with the control group, which had a mean of 0.94 (SD 0.16) at the pretherapeutic time point to 0.86 (SD 0.24) at
After adjusting for pretherapeutic utility, the mean QALYs per patient in the study group was 1.88, whereas the mean QALYs per patient in the control group was 1.65. This resulted in an ICUR of US$ 583 per QALY over the first 2 years for patients in the study group.

### Sensitivity Analysis

#### Probabilistic Sensitivity Analysis (PSA)

The ICURs for the 1,000 samples in the PSA are shown in the scatter plot (Figure 4). All points were under the US$ 26,263.5-per-QALY level, and 100% of the tested ICURs were in the

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TABLE 5 | Comparisons of means and standard deviations of medical direct costs between the two groups in patients with metastatic colorectal.

| Items                              | Total (n=196)   | Study group (n=75) | Control group (n=121) | P value* |
|------------------------------------|-----------------|--------------------|-----------------------|----------|
| Total medical direct costs during therapy | 2,289 ± 747     | 2,330 ± 896        | 2,250 ± 567           | 0.035    |
| Total numbers of inpatient during the study period | 17.9 ± 8.8      | 17.7 ± 9.2        | 18.1 ± 8.4           | 0.355    |
| Posttherapeutic 6 months after discharge | Total inpatient costs | 17,543 ± 5,620    | 18,493 ± 5,965       | 16,614 ± 5,096 | <0.001 |
|                                    | Total outpatient costs | 1,304 ± 1,742     | 1,119 ± 1,701        | 1,489 ± 1,763 | <0.001 |
|                                    | Health insurance reimbursement expenses | 1,105 ± 1,336     | 891 ± 1,162          | 1,314 ± 1,461 | <0.001 |
|                                    | Self-paid (out of pocket) expenses | 199 ± 628         | 227 ± 714            | 171 ± 532   | 0.078   |
|                                    | Total medical emergency costs | 59 ± 136          | 58 ± 162             | 60 ± 103   | 0.236   |
|                                    | Health insurance reimbursement expenses | 57 ± 129         | 57 ± 154             | 58 ± 99    | 0.855   |
|                                    | Self-paid (out of pocket) expenses | 2 ± 1             | 2 ± 12               | 2 ± 8      | 0.411   |
| Posttherapeutic 1 year after discharge | Total inpatient costs | 31,014 ± 7,501    | 32,360 ± 8,304       | 29,697 ± 6,391 | <0.001 |
|                                    | Total outpatient costs | 2,164 ± 2,338     | 1,998 ± 2,044        | 2,326 ± 2,592 | 0.006   |
|                                    | Health insurance reimbursement expenses | 1,879 ± 2,123     | 1,648 ± 1,620        | 2,106 ± 2,507 | <0.001 |
|                                    | Self-paid (out of pocket) expenses | 286 ± 698        | 350 ± 793            | 220 ± 586   | <0.001 |
|                                    | Total medical emergency costs | 125 ± 235        | 97 ± 174             | 153 ± 281   | <0.001 |
|                                    | Health insurance reimbursement expenses | 124 ± 231        | 95 ± 166             | 151 ± 279   | <0.001 |
|                                    | Self-paid (out of pocket) expenses | 2 ± 10           | 2 ± 12               | 2 ± 6      | 0.715   |
| Posttherapeutic 2 years after discharge | Total inpatient costs | 49,161 ± 11,522   | 48,859 ± 13,459      | 49,456 ± 9,242 | 0.308   |
|                                    | Total outpatient costs | 3,085 ± 3,562     | 3,425 ± 4,402        | 2,753 ± 2,438 | <0.001 |
|                                    | Health insurance reimbursement expenses | 2,819 ± 3,221    | 3,051 ± 3,902        | 2,592 ± 2,371 | 0.005   |
|                                    | Self-paid (out of pocket) expenses | 266 ± 680        | 374 ± 889            | 160 ± 351   | <0.001 |
|                                    | Total medical emergency costs | 138 ± 232        | 128 ± 227            | 149 ± 236   | 0.066   |
|                                    | Health insurance reimbursement expenses | 135 ± 228        | 124 ± 223            | 148 ± 232   | 0.057   |
|                                    | Self-paid (out of pocket) expenses | 3 ± 19           | 4 ± 26               | 3 ± 9      | 0.731   |

*P-values calculated by Student’s t-test.

northeastern quadrant. The cost-effectiveness acceptability curve is also shown in Figure 5 for varying values of WTP per QALY.

Univariable Sensitivity Analysis (USA)
The results of the USA are shown in the tornado diagram (Figure 6). The parameters with the greatest influence on the ICUR were total costs in the study group with improved QOL, followed by total costs in the study group with maintained QOL, and total costs in the control group with maintained QOL. Even with a broad variation in range for each parameter, the ICUR remained below US$ 26,263.5 per QALY.

DISCUSSION
In both groups of patients with mCRC, physiological functions and emotional wellbeing significantly worsened at posttherapeutic 6th month compared with the pretherapeutic status. This can probably be attributed to the adverse effect of the chemotherapy. The study group exhibited significant improvement in physiological functions and emotional wellbeing from posttherapeutic 6th month to posttherapeutic 1st year. However, the control group exhibited worse emotional wellbeing, possibly because their physiological functions had not fully recovered. From posttherapeutic 1st year to posttherapeutic 2nd year, the study group gradually improved in most QOL measures. By contrast, the control group exhibited slow improvement in physiological functions, and their moods were still affected. These results were consistent with previous reports that compared patient conditions before chemotherapy and radiotherapy; the physiological functions, social functions, and nausea and vomit symptoms of cancer patients worsened during the 6-month treatment, leading to negative emotional functions (22–24). However, most QOL outcomes improved but they still were inferior to the initial status at 1–2 years after chemotherapy and radiotherapy. These results emphasized that baseline characterization of symptom status should be incorporated into clinical trials as they may affect symptom burden.

Compared with the control group, the study group had higher mean total medical direct costs, possibly because of the dose difference. The study group had higher hospitalization expenses during therapy and subsequent hospitalization expenses
compared with the control group. From pretherapeutic to posttherapeutic 6th month, patients with mCRC in both groups had significantly reduced utility, possibly because they both initially received accumulated doses of irinotecan and had substantial adverse effects. However, at posttherapeutic 1st year, the study group exhibited gradual recovery and a significant increase in their utility, whereas the control group showed a significant decline from posttherapeutic 6th month to posttherapeutic 1st year, only showing a gradual increase at the posttherapeutic 2nd year. This may be because the study group patients undergo UGT1A1 genotyping before treatment, and better oncological outcomes were verified by our previous study (2). In addition, Shulman et al. and Li et al. revealed that in treating mCRC using FOLFIRI combined with bevacizumab, patients with genotypes UGT1A1*28/*28 had significantly increased grades III or IV hematological toxicity.

**FIGURE 3** | Utilities of the two groups in patients with metastatic colorectal cancer at different time points (N = 196).

**FIGURE 4** | Incremental cost-effectiveness (study group vs. control group). Scatter plots of incremental effectiveness (quality-adjusted life-years) versus incremental costs from 1,000 resamplings in the probabilistic sensitivity analysis with variation limited to cost and effectiveness assumptions and with transition-probabilities constant. This probabilistic sensitivity analysis demonstrated that the study group had a 100% probability of achieving cost-effectiveness relative to the control group in patients with metastatic colorectal cancer. Each plotted point is the result of an incremental cost divided by incremental quality-adjusted life-years. The elliptic circle represents the 95% confidence interval.
FIGURE 5 | Cost-effectiveness acceptability curves for the probabilistic sensitivity analysis. Results from 1,000 resamplings in the probabilistic sensitivity analysis created synthetic populations of patients from the trial using bootstrapping. The lines represent the fraction of simulation iterations in which the study group achieved more cost-effectiveness than the control group (y-axis) at various levels of willingness to pay for quality-adjusted life-year (QALYs) gains (x-axis).

FIGURE 6 | Tornado diagram showing one-way sensitivity analysis results. Costs are expressed in US$ 2020. ICUR, incremental cost-utility ratio; QOL, quality of life.
than those with UGT1A1*1/*28 and UGT1A1*1/*1 (10, 25). Gradual irinotecan dose escalation according to UGT1A1 genotypes can yield better treatment outcomes and more easily prevent adverse effects.

The present study indicated that escalated irinotecan dose can help achieve the optimal values for cost-effective incremental costs of care in Taiwan. Few studies have analyzed treatment with different irinotecan doses combined with bevacizumab. Obradovic et al. divided patients with mCRC into those with or without specific UGT1A1 genotypes (26); however, they did not compare patients who did not undergo genotyping (administered the fixed-dose regimen) and patients who underwent UGT1A1 genotyping (administered escalated-dose regimen). If patients with UGT1A1*1/*28 and UGT1A1*1/*1 were administered an escalated dose of irinotecan and those with UGT1A1*28/*28 were given a reduced irinotecan dose, the overall total medical direct costs may be reduced. Butzke et al. performed a sensitivity analysis and discovered that a UGT1A1 test before irinotecan chemotherapy and medical expenses were critical factors determining costs (27). Gold et al. conducted a sensitivity analysis and revealed that only when irinotecan dose adjustment achieved 98.4% of the effectiveness of the full dose, the DNA test can be continued (28). When ICUR was US$ 100,073 per QALY and WTP was US$ 100,000, UGT1A1 genotyping test remained the most optimal choice before administering irinotecan. Therefore, treatment in the study group resulted in fewer disease recurrences, and thus, an ICUR decline when additional costs after disease recurrences increased. Given this, the escalated dose of irinotecan will be cost-effective compared with the recommended dose of irinotecan when combined with other costlier treatment strategies in mCRC patients. To enable decision making for tailored therapy, before administering irinotecan, different doses should be determined according to the UGT1A1 genotype, thereby achieving more favorable cost-utility.

The following limitations of this study must be acknowledged. First, this was not a randomized study. At baseline, the study group (escalated dose group) had higher mean scores for FACT-C social/family wellbeing and BAI than the control group (recommended dose group). Therefore, the magnitude of QOL improvements obtained by different doses of irinotecan plus bevacizumab may have been underestimated. Nonetheless, the potential bias would not have changed our result that the study group seemed to achieve more cost-effectiveness than the control dose group. Second, we did not include costs involved in the nonhealthcare sector or from the societal perspective, including productivity loss and out-of-pocket expenses. Third, repeated measures of QOL outcomes were limited to 2 years. Basic symptoms of pain, neuropathic pain, and chemicals were not assessed, which is a noted limitation of the quality of life assessment in this study. Further randomized clinical trials are needed to corroborate the benefit on clinical outcomes, additional costs other than healthcare costs including survival, and overall societal impact.

The improved effectiveness in the study group was corroborated by evidence of significant improvements in QOL outcomes from posttherapeutic 6th month to posttherapeutic 2nd year. Nevertheless, we suggest that before the introduction of irinotecan treatment, patients with mCRC undergo UGT1A1 genotyping to help determine the appropriate irinotecan dose, thereby achieving higher cost-utility and better medical resource allocation. Further scientific research is needed to determine what doses achieve the most desirable therapeutic effects in different UGT1A1 genotypes, which would translate into improved QOL after such a burdensome treatment of the underlying disease. Our results may serve as potential references for health departments, academic units, and medical supply units to treat mCRC.

**DATA AVAILABILITY STATEMENT**

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

**ETHICS STATEMENT**

The studies involving human participants were reviewed and approved by the institutional ethics committee of our hospital (KMUHIRB-(EI)-20150147). The patients/participants provided their written informed consent to participate in this study.

**AUTHOR CONTRIBUTIONS**

H-YS, H-LT, and J-YW had full access to all the data in the study take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: H-YS, H-LT, and J-YW. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: H-YS, H-LT, and J-YW. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: H-YS. Obtained funding: JYW. Supervision: H-YS, H-LT, and J-YW. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Zhu J, Liu A, Sun X, Liu L, Zhu Y, Zhang T, et al. Multicenter, Randomized, Phase III Trial of Neoadjuvant Chemoradiation With Capcitabine and Irinotecan Guided by UGT1A1 Status in Patients With Locally Advanced Rectal Cancer. J Clin Oncol (2020) 38:2431–9. doi: 10.1200/JCO.20.01932

2. Tsai HL, Huang CW, Lin YW, Wang IH, Wu CC, Sung YC, et al. Determination of the UGT1A1 Polymorphism as Guidance for Irinotecan Dose Escalation in Metastatic Colorectal Cancer Treated With First-Line Bevacizumab and FOLFIRI (PURE FIST). Eur J Cancer (2010) 46:189–96. doi: 10.1016/j.ejca.2009.05.031

3. Glimelius B, Stintzing S, Marshall J, Yoshino T, De Gramont A. Metastatic Colorectal Cancer: Advances in the Folate-Fluoropyrimidine Chemotherapy Backbone. Cancer Treat Rev (2021) 98:102218. doi: 10.1016/j.ctrv.2021.102218

4. Qiu J, Shi K, Sun J, Zhang Q, Xu T, Zhao H, et al. Fluorouracil Combined With Oxaliplatin or Irinotecan for Solid Tumors: Indications From Clinical Characteristics and Health Outcomes of Patients. Front Oncol (2020) 10:542. doi: 10.3389/fonc.2020.00542

5. Toffoli G, Cecchin E, Gasparini G, D’Andrea M, Azzarello G, Basso U. Genotype-Driven Phase I Study of Irinotecan Administered in Combination With Fluorouracil/Leucovorin in Patients With Metastatic Colorectal Cancer. J Clin Oncol (2010) 28:8668–71. doi: 10.1200/JCO.2009.23.6125

6. Innocenti F, Sliski RL, Ramirez J, Janisch L, Undevia S, House LK, et al. Dose-Finding and Pharmacokinetic Study to Optimize the Dosing of Irinotecan According to the UGT1A1 Genotype of Patients With Cancer. J Clin Oncol (2014) 32:2328–34. doi: 10.1200/JCO.2014.55.2307

7. Cremolini C, Antoniotti C, Rossini D, Loupakis F, Pietrantonio F, et al. Quality of Life Instrument. Validity of the Functional Assessment of Cancer Therapy-Colorectal (FACT-COL) in Patients Treated With Irinotecan From the Perspective of the German Statutory Health Insurance. J Am Stat Assoc (2016) 111:939–52. doi: 10.1080/01621459.2015.1053983

8. Butzke B, Oduncu FS, Severin F, Pfeufer A, Heinemann V, Giessen-Jung C, et al. Cost Evaluation of Irinotecan-Related Toxicities Associated With the UGT1A1*28 Genotype Testing in Colorectal Cancer Patients. Cancer Treat Rev (2021) 98:102218. doi: 10.1016/j.ctrv.2021.102218

9. Schluchter MD. Flexible Approaches to Computing Mediated Effects in Generalized Linear Models: Generalized Estimating Equations and Bootstrapping. Multivariate Behav Res (2008) 43:268–88. doi: 10.1080/10822864.2015.1053983

10. Shiu et al. CUA of Different Irinotecan Doses

11. Van Der Weijst I, Lieveyn S, Schrauwen V, Surmont V. Health-Related Quality of Life in Advanced Non-Small Cell Lung Cancer: A Methodological Appraisal Based on a Systematic Literature Review. Front Oncol (2019) 9:775. doi: 10.3389/fonc.2019.00715

12. Obradovic M, Mrhar A, Kos M. Cost-Effectiveness of UGT1A1 Genotyping in Patients Treated With First-Line, High-Dose, Once Every 3 Weeks Irinotecan Monotherapy Treatment of Colorectal Cancer. Pharmacogenomics (2008) 9:539–49. doi: 10.2217/14622416.9.5.539

13. Zeger SL, Liang KY. Longitudinal Data Analysis for Discrete and Continuous Outcomes. J Am Stat Assoc (1986) 81:671–85. doi: 10.1080/01621459.2015.1053983

14. Schluchter MD. Flexible Approaches to Computing Mediated Effects in Generalized Linear Models: Generalized Estimating Equations and Bootstrapping. Multivariate Behav Res (2008) 43:268–88. doi: 10.1080/10822864.2015.1053983

15. Butzke B, Oduncu FS, Severin F, Pfeufer A, Heinemann V, Giessen-Jung C, et al. Cost Evaluation of Irinotecan-Related Toxicities Associated With the UGT1A1*28 Genotype Testing in Colorectal Cancer Patients. Cancer Treat Rev (2021) 98:102218. doi: 10.1016/j.ctrv.2021.102218

16. Lee HY, Hung MC, Hu FC, Chang YY, Hsieh CL, Wang JD. Estimating Quality Weights for EQ-5d (EuroQol-5 Dimensions) Health States With the Time Trade-Off Method in Taiwan. J Formos Med Assoc (2013) 112:699–706. doi: 10.1016/j.jfma.2012.12.015

17. Zeger SL, Liang KY. Longitudinal Data Analysis for Discrete and Continuous Outcomes. Biometrics (1986) 42:121–30. doi: 10.2307/2531248

18. Schluchter MD. Flexible Approaches to Computing Mediated Effects in Generalized Linear Models: Generalized Estimating Equations and Bootstrapping. Multivariate Behav Res (2008) 43:268–88. doi: 10.1080/10822864.2015.1053983

19. Nakagawa S, Cuthill IC. Effect Size, Confidence Interval and Statistical Significance: A Practical Guide for Biologists. Biol Rev Camb Philos Soc (2007) 82:591–605. doi: 10.1111/j.1469-185X.2007.00027.x

20. Van Der Weijst I, Lieveyn S, Schrauwen V, Surmont V. Health-Related Quality of Life in Advanced Non-Small Cell Lung Cancer: A Methodological Appraisal Based on a Systematic Literature Review. Front Oncol (2019) 9:775. doi: 10.3389/fonc.2019.00715

21. Schluchter MD. Flexible Approaches to Computing Mediated Effects in Generalized Linear Models: Generalized Estimating Equations and Bootstrapping. Multivariate Behav Res (2008) 43:268–88. doi: 10.1080/10822864.2015.1053983

22. Obradovic M, Mrhar A, Kos M. Cost-Effectiveness of UGT1A1 Genotyping in Patients Treated With First-Line, High-Dose, Once Every 3 Weeks Irinotecan Monotherapy Treatment of Colorectal Cancer. Pharmacogenomics (2008) 9:539–49. doi: 10.2217/14622416.9.5.539

23. Zeger SL, Liang KY. Longitudinal Data Analysis for Discrete and Continuous Outcomes. J Am Stat Assoc (1986) 81:671–85. doi: 10.1080/01621459.2015.1053983

24. Butzke B, Oduncu FS, Severin F, Pfeufer A, Heinemann V, Giessen-Jung C, et al. Cost Evaluation of Irinotecan-Related Toxicities Associated With the UGT1A1*28 Genotype Testing in Colorectal Cancer Patients. Cancer Treat Rev (2021) 98:102218. doi: 10.1016/j.ctrv.2021.102218

25. Schluchter MD. Flexible Approaches to Computing Mediated Effects in Generalized Linear Models: Generalized Estimating Equations and Bootstrapping. Multivariate Behav Res (2008) 43:268–88. doi: 10.1080/10822864.2015.1053983

26. Obradovic M, Mrhar A, Kos M. Cost-Effectiveness of UGT1A1 Genotyping in Patients Treated With First-Line, High-Dose, Once Every 3 Weeks Irinotecan Monotherapy Treatment of Colorectal Cancer. Pharmacogenomics (2008) 9:539–49. doi: 10.2217/14622416.9.5.539

27. Zeger SL, Liang KY. Longitudinal Data Analysis for Discrete and Continuous Outcomes. J Am Stat Assoc (1986) 81:671–85. doi: 10.1080/01621459.2015.1053983

28. Gold HT, Hall MJ, Blinder V, Schackman BR. Cost Effectiveness of Pharmacogenetic Testing for Uracil Diphosphate Glucuronosyltransferase 1A1 Before Irinotecan Administration for Metastatic Colorectal Cancer. Cancer (2009) 115:3858–67. doi: 10.1002/cncr.24428

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