BMC Cancer

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Quality of life in patients with metastatic colorectal cancer receiving cytotoxic and cytotoxic plus targeted therapy

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Abstract

Background Targeted therapies in the treatment of metastatic colorectal cancer (mCRC) have reportedly been associated with better quality of life (QoL). Previous studies have revealed uncontrolled sources of biases or confounders that could distort this association. Given the lack of robust evidence and causal inference, we aimed to investigate the effects of targeted therapy-added regimens versus cytotoxic therapy (CyT) on QoL and components of QoL in patients with mCRC eligible for curative-intent treatment.

Methods We conducted a prospective cohort study on adults undergoing curative-intent mCRC treatment with survival prognosis of ≥ 1 year. The exposure was either CyT alone (including CAPEOX, mFOLFOX-6, mFOLFOX-7, FOLFIRI, and FOLFOXIRI) or CyT combined with targeted therapy (Cy-TaT, including CAPEOX-TaT, mFOLFOX-6-TaT, mFOLFOX-7-TaT, FOLFIRI-TaT, and FOLFOXIRI-TaT). Available targeted therapies included bevacizumab and regorafenib. The primary outcome was overall health and QoL (H/QoL), measured at month 12 using the EORTC QLQ-C30 global health status/QoL scale (in percentage point) and the EQ-5D-3L utility score. The secondary outcomes included each component of the EORTC QLQ-C30 functional scales and symptom scales/items (in percentage point), measured at month 12. Mean difference (MD) and 95% confidence interval (95% CI) were estimated using g-estimation.

Results During 12 months of follow-up, among 1143 participants (mean age 58.1, 39.4% being female, 623 in CyT group and 520 in Cy-TaT group), overall H/QoL was higher in those receiving Cy-TaT (EORTC QLQ-C30 global health status/QoL scale: MD 16.6, 95% CI 14.8 to 18.4, $p < 0.001$ [largest effect in CAPEOX-TaT versus CAPEOX: MD 18.7, 95% CI 15.2 to 22.2]; EQ-5D-3L utility score: MD 0.076, 95% CI 0.060 to 0.091 [largest effect in mFOLFOX-7-TaT versus mFOLFOX-7: MD 0.123, 95% CI 0.085 to 0.161]). For the EORTC QLQ-C30 functional scales and most areas of the symptom scales/items, treatment with Cy-TaT was also associated with better outcomes than with CyT, except for a contradictory association in financial difficulties. Symptoms with consistently large improvements from Cy-TaT were fatigue (MD 13.8, 95% CI 11.7 to 15.9), dyspnoea (MD 10.9, 95% CI 8.8 to 12.9), and insomnia (MD 13.0, 95% CI 10.2 to 15.7).

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Conclusion Compared with those on CyT alone, patients with mCRC receiving Cy-TaT showed improved overall H/QoL, functional scales, and symptom scales/items. These benefits were consistent across most subgroups of chemotherapy, with the greatest improvements in H/QoL observed in the CAPEOX-TaT and mFOLFOX-7-TaT groups.

Keywords Quality of life, Metastatic colorectal cancer, Antineoplastic agents, Targeted therapy, Vietnam

Background

The advent of targeted anticancer therapies has significantly improved the outcomes of patients with metastatic colorectal cancer (mCRC). Given the evidence-based clinical efficacy of these agents [1], many oncologists tend to prioritise overall survival or progression-free survival as the outcomes of interest for patients with mCRC receiving targeted therapies. However, the impacts of adding these to the standard cytotoxic therapy (CyT) on the quality of life (QoL) of patients have often been neglected and have been underexplored in both clinical practice and research [2], especially in low-resource settings due to the costs of medications and genetic testing. Considering the progressive and invasive nature of mCRC and the broad toxicity of CyT [3], QoL should also be prioritised when prescribing the high-cost targeted therapies.

While more evidence of targeted therapies being associated with better QoL has been reported [4], there is a notable gap in the understanding of their causal effects on QoL. Previous studies have revealed uncontrolled sources of biases or confounders that could distort the effects of targeted therapies [5]. Without strong evidence of causal inference, current recommendations can mislead patients [6], particularly in aspects of QoL that targeted therapies could not truly improve. Such miscommunications may increase unnecessary use of high-cost regimens, risk of toxicity, financial burdens, and other opportunity costs.

Given the lack of evidence and causal inference in QoL, we aimed to investigate the effects of targeted therapy-added regimens versus CyT on QoL and components of QoL in patients with mCRC eligible for curative-intent treatment. In specific, we examined specific subgroups of CyT to dissect the QoL in different regimens. This could inform personalised treatment strategies and enhance the holistic care of patients with mCRC, especially in low-middle-income countries. Of note, we only consider curative-intent treatment in this study as many patients with poor prognosis in our setting did not favour the use of targeted therapies due to high cost and uncertainty of long-term benefits.

Methods

Design and participants

We conducted a prospective cohort study at the Department of Oncology, Nhan Dan Gia Dinh Hospital (Ho Chi Minh City, Vietnam) from March 2017 to March 2023. Recruitment was from March 2017 to March 2022. We screened and included patients who: (1) were ≥ 18 years old; (2) had confirmed mCRC with oncologist-estimated survival prognosis of ≥ 1 year; (3) underwent curative-intent treatment (prolonging survival for ≥ 5 years or eradicating the cancer whenever possible) and standard supportive care; (4) received (for ≥ 3 months) or tolerated (for recurrent mCRC) intensive chemotherapy, as listed in the guidelines of the National Comprehensive Cancer Network (NCCN) [7, 8]; and (5) agreed to participate. We excluded those who: (1) had an acute illness that required hospitalisation at recruitment; (2) were concurrently participating in another research; or (3) were expecting to receive immunotherapy within the following 6 months.

We conducted this study in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committee of Nhan Dan Gia Dinh Hospital under approval number 31/NDGD-HDDD. All participants gave their written informed consent prior to participation. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement to report this study (Supplementary File, Table S1).

Exposure

All participants received standard of care for mCRC treatment and either CyT or cytotoxic plus targeted therapy (Cy-TaT). The exposure (CyT or Cy-TaT), which followed the NCCN guidelines [7, 8], was determined by the oncologists of the hospital. In our study setting, curative-intent treatment of mCRC with CyT (control group) included several combinations of 5-fluorouracil (5-FU or F), capecitabine (CAPE), irinotecan (IRI), leucovorin (FOL), and oxaliplatin (OX). The following regimens were primarily used in our hospital during the study timeframe: (1) CAPEOX; (2) FOLFOX, including mFOLFOX-6 and mFOLFOX-7; (3) FOLFIRI; and (4) FOLFOXIRI. For curative-intent treatment of mCRC with Cy-TaT (treatment group), the following agents would be added to the standard CyT regimens: (1) bevacizumab; (2) cetuximab; and (3) regorafenib. As cetuximab was only indicated for

patients with wild-type KRAS/NRAS/BRAF and left-sided tumours, we did not include this subgroup to prevent the lack of counterfactual outcomes.

During 12 months of follow-up, our oncologists could review the regimen and decide to change the treatment of the participants from CyT to Cy-TaT or vice versa. As this modification could potentially bias our results, we assigned the treatment status based on multiple periods. This approach could address the time-varying factors and facilitate inference of association in our findings. However, we did not consider modified regimens with less than 2 months of duration (e.g., from CyT to Cy-TaT and then back to CyT in less than 2 months) for exposure reassignment. According to the routine assessments of our oncologists, the effects of these changes were not likely to be significant.

Outcomes

We used the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) to measure the patient-reported outcomes in this study [9]. The Vietnamese version of the EORTC QLQ-C30 has been translated with cultural adaptation and validated by the EORTC Quality of Life Group [10]. We have also investigated its reliability in a 2-stage convenient-sampling pilot survey ($n = 90$ for mCRC) at our hospital (Cronbach's alpha of 0.79 for internal consistency, intraclass correlation coefficient of 0.76 for test–retest reliability). Given the scoring procedures [11], we used the linearly transformed scores (on a scale of 0 to 100) for outcome measurement.

The primary outcome was overall health and QoL (H/QoL, in percentage point), which was measured at month 12 using the EORTC QLQ-C30 global health status/QoL scale. The secondary outcomes included each component of the EORTC QLQ-C30 functional scales (physical, role, emotional, cognitive, and social) and symptom scales/items (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties), measured at month 12 in percentage point. For the primary outcome, as it might be difficult to interpret the transformed score and detect the potential clinical importance, we also decided to report the EQ-5D-3L utility score of the EORTC QLQ-C30 global health status/QoL scale. We estimated the EQ-5D-3L utility score using a previously proposed mapping algorithm for the mCRC population [12].

Covariates

We included the following covariates as potential confounders: age (years; <65 or ≥65), sex (female or male), body mass index (kg/m^2), socioeconomic indicators (education attainment; housing; occupation; and income), underlying comorbidities (cardiovascular; endocrine; gastrointestinal; musculoskeletal; neurological; psychological; respiratory; and others), characteristics of cancer (type: colon or rectal; location of tumour: left or right; recurrence: yes or no; site of metastasis: liver, lungs, peritoneum, or other), non-pharmacological treatment (surgery or radiation), colostomy (yes/expected or no), prior adjuvant or neoadjuvant chemotherapy (yes or no), and supportive care for previous mCRC-related complications or emergencies. Other factors (such as treatment toxicity or adverse events) were not controlled for because they were deemed as mediators or colliders on the causal pathway from the exposure to the outcomes. Factors that could significantly change over time during the follow-up were measured repeatedly and controlled for as time-varying covariates.

Statistical analysis

We invited all patients with mCRC at our hospital to participate and recruited all eligible ones ($n = 1143$). Participants with missing data were excluded from the analysis. We summarised the data and reported frequency (with percentage) for categorical variables and mean (with standard deviation, SD, normality) or median (with interquartile range, IQR, non-normality) for quantitative variables.

In the primary analysis, we used g-estimation with bootstrapping to address the time-varying exposure and covariates. We reported the mean difference in outcomes with a 95% confidence interval (95% CI). On the basis of the study design and data generation in our setting, all the assumptions of the g-estimation method were justified, except for the stable unit treatment value assumption (SUTVA) due to variations in chemotherapy regimens. To support causal inference for further studies, we ensured SUTVA by conducting an exploratory analysis, which stratified the CyT into 5 subgroups (CAPEOX, mFOLFOX-6, mFOLFOX-7, FOLFIRI, and FOLFOXIRI). Participants receiving regorafenib in the Cy-TaT group were excluded from this exploratory analysis because only a few patients were prescribed this medication in our study setting. To avoid the risk of type I error inflation due to multiple comparisons, we conducted the 2-sided hypothesis testing only for the primary outcome. We performed all statistical analyses using R (version 4.2.1, R Foundation for Statistical Computing, Vienna, Austria). In addition to the default *base* package, we also used the *gesttools* package (version 1.3.0) for g-estimation [13].

Results

Baseline characteristics

We enrolled and followed 1143 participants (mean age 58.1, 39.4% being female, all being Vietnamese-origin Asians) after screening their eligibilities (Fig. 1). Only about 10% of the participants had high socioeconomic status, which was driven mainly by low or middle incomes. The prevalence of patients with multiple morbidities was 17.9%. More than 70% of the participants had resectable primary and metastatic tumours. About 60% of the participants experienced oncologic emergencies such as febrile neutropenia or hypercalcaemia. Recurrence was found in 21.4% of the study sample. Further details of the CyT and Cy-TaT groups were described in Table 1.

Overall H/QoL

During 12 months of follow-up, only 24 participants in the Cy-TaT cohort discontinued bevacizumab for less than 2 months to avoid surgery or wound healing

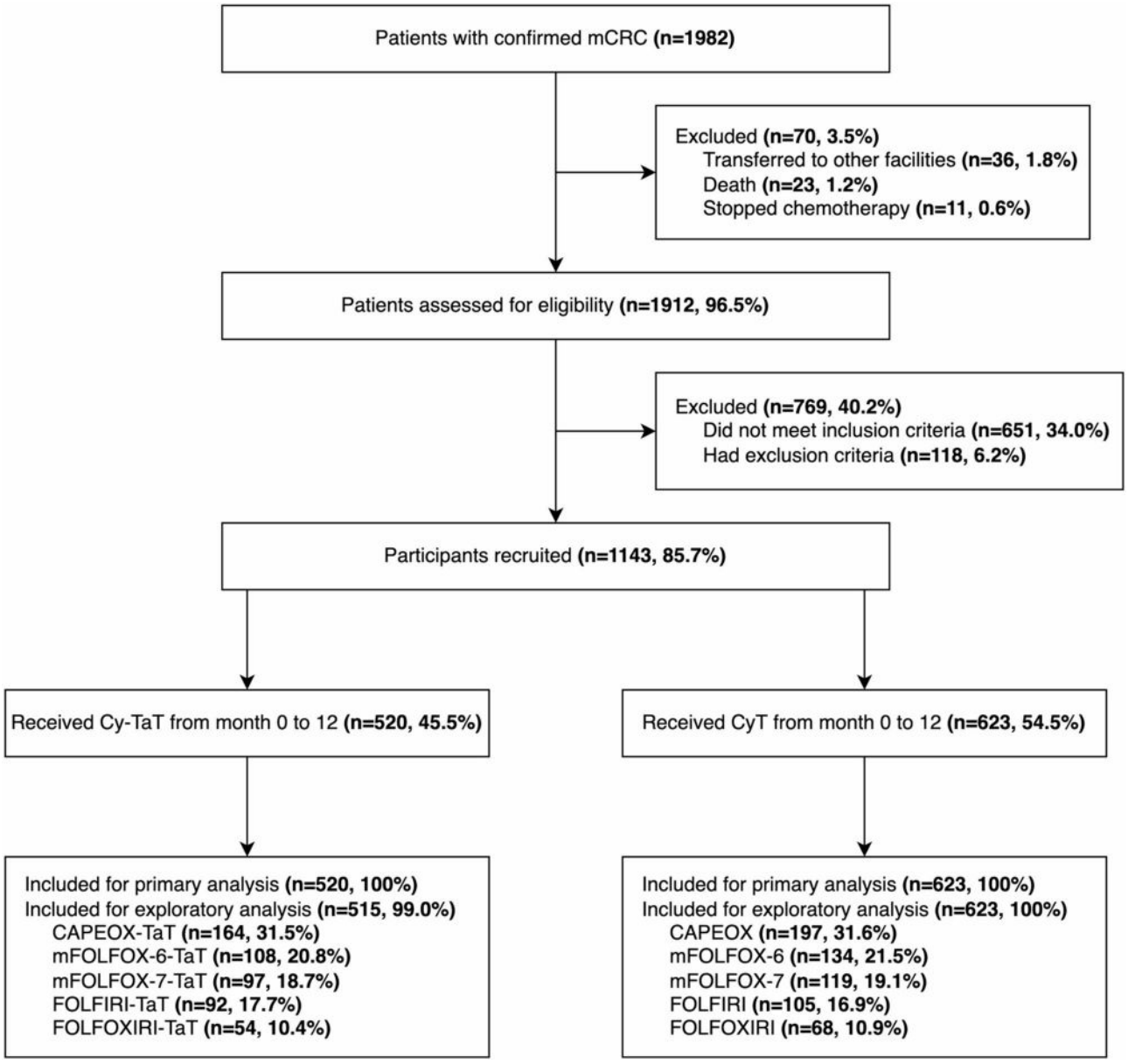

Fig. 1 Flowchart of the participants. Abbreviations: CAPEOX, capecitabine-oxaliplatin; CAPEOX-TaT, CAPEOX plus targeted therapy; CyT, cytotoxic therapy; Cy-TaT, cytotoxic plus targeted therapy; mCRC, metastatic colorectal cancer; mFOLFOX, modified leucovorin-(5-)fluorouracil-oxaliplatin; mFOLFOX-6-TaT, mFOLFOX-6 plus targeted therapy; mFOLFOX-7-TaT, mFOLFOX-7 plus targeted therapy; FOLFIRI, leucovorin-(5-)fluorouracil-irinotecan; FOLFIRI-TaT, FOLFIRI plus targeted therapy; FOLFOXIRI, leucovorin-(5-)fluorouracil-oxaliplatin-irinotecan; FOLFOXIRI-TaT, FOLFOXIRI plus targeted therapy. No patients were permanently switched from Cy-TaT to CyT or vice versa

Table 1 Baseline characteristics

Characteristics	CyT (*n* = 623)	Cy-TaT (*n* = 520)	Total (*n* = 1143)
Age (years), mean (± SD)	57.9 (± 13.1)	58.2 (± 12.0)	58.1 (± 12.6)
Being ≥ 65 years old, n (%)	183 (29.4)	161 (31.0)	344 (30.1)
Being female, n (%)	275 (44.1)	175 (33.7)	450 (39.4)
Body mass index, mean (± SD)	19.1 (± 2.3)	20.4 (± 2.0)	19.8 (± 2.1)
Being overweight-to-obese, n (%)[a]	67 (10.8)	65 (12.5)	132 (11.5)
High level of socioeconomic indicators, n (%)[b, c]			
Education attainment	251 (40.3)	238 (45.8)	489 (42.8)
Housing	417 (66.9)	383 (73.7)	800 (70.0)
Occupation	230 (36.9)	257 (49.4)	487 (42.6)
Income	58 (9.3)	62 (11.9)	120 (10.5)
Underlying comorbidities, n (%)[b]			
Cardiovascular	77 (12.4)	61 (11.7)	138 (12.1)
Endocrine	36 (5.8)	36 (6.9)	72 (6.3)
Gastrointestinal	44 (7.1)	46 (8.8)	90 (7.9)
Psychological	11 (1.8)	17 (3.3)	28 (2.4)
Respiratory	13 (2.1)	15 (2.9)	28 (2.4)
Others	51 (8.2)	59 (11.3)	110 (9.6)
Initial type of cancer, n (%)			
Colon	496 (79.6)	371 (71.3)	867 (75.9)
Rectal	117 (18.8)	137 (26.3)	254 (22.2)
Colorectal	10 (1.6)	12 (2.3)	22 (1.9)
Left-sided tumour, n (%)	433 (69.5)	369 (71.0)	802 (70.2)
Time since diagnosis (months), median (IQR)	13 (10–15)	15 (10–18)	14 (10–17)
Recurrence, n (%)	119 (19.1)	126 (24.2)	245 (21.4)
Site of metastasis, n (%)[b]			
Liver	555 (89.1)	448 (86.2)	1003 (87.8)
Lungs	92 (14.8)	73 (14.0)	165 (14.4)
Peritoneum	147 (23.6)	205 (39.4)	352 (30.8)
Other	34 (5.5)	16 (3.1)	50 (4.4)
Required or expected surgery, n (%)	423 (67.9)	379 (72.9)	802 (70.2)
Required or expected colostomy, n (%)	116 (18.6)	132 (25.4)	248 (21.7)
Required or expected radiation, n (%)	116 (18.6)	100 (19.2)	216 (18.9)
Prior adjuvant chemotherapy, n (%)	384 (61.6)	332 (63.8)	716 (62.6)
Prior neoadjuvant chemotherapy, n (%)	128 (20.5)	95 (18.3)	223 (19.5)
Supportive care for mCRC-related complications or emergencies, n (%)	334 (53.6)	343 (66.0)	677 (59.2)

Abbreviations: CyT, cytotoxic therapy; Cy-TaT, cytotoxic plus targeted therapy; IQR, interquartile range; mCRC, metastatic colorectal cancer; SD, standard deviation

[a] Overweight or obesity was determined based on the classification of body mass index for Asians

[b] Percentages may not equate to 100 due to concurrent status or rounding

[c] High level of education attainment was defined as having a university or college degree. High level of housing was defined as owning house outright. High level of occupation was defined as being a leader/manager or holding a position requiring expertise at tiers 4 to 5, based on the Vietnam Occupation Classification. High level of income was defined as individual (if single) or household (if married) annual income exceeding 3 or 5 times, respectively, the gross domestic product per capita of Vietnam

complications. The highest unadjusted H/QoL score was found in participants on the FOLFIRI-TaT regimen (61.8% points). Compared with the CyT cohort, participants receiving Cy-TaT had higher overall H/QoL (mean difference in percentage point of EORTC QLQ-C30 global health status/QoL score: 16.6, 95% CI 14.8 to 18.4, $p < 0.001$; mean difference in EQ-5D-3L utility score: 0.076, 95% CI 0.060 to 0.091; Fig. 2). This association remained consistent among all subgroups of the treatment regimens (Figs. 3, 4, 5, 6 and 7). Subgroups with the largest differences in EORTC QLQ-C30 global health status/QoL score and EQ-5D-3L utility score were, in turn, CAPEOX-TaT versus CAPEOX (18.7% points, 95% CI 15.2 to 22.2; Fig. 3) and mFOLFOX-7-TaT versus mFOLFOX-7 (0.123, 95% CI 0.085 to 0.161; Fig. 5). The smallest difference was detected in patients with FOLFOXIRI (EORTC QLQ-C30 global health status/QoL score: 12.6% points, 95% CI 6.7 to 18.5; EQ-5D-3L utility score: 0.039, 95% CI -0.010 to 0.088; Fig. 7).

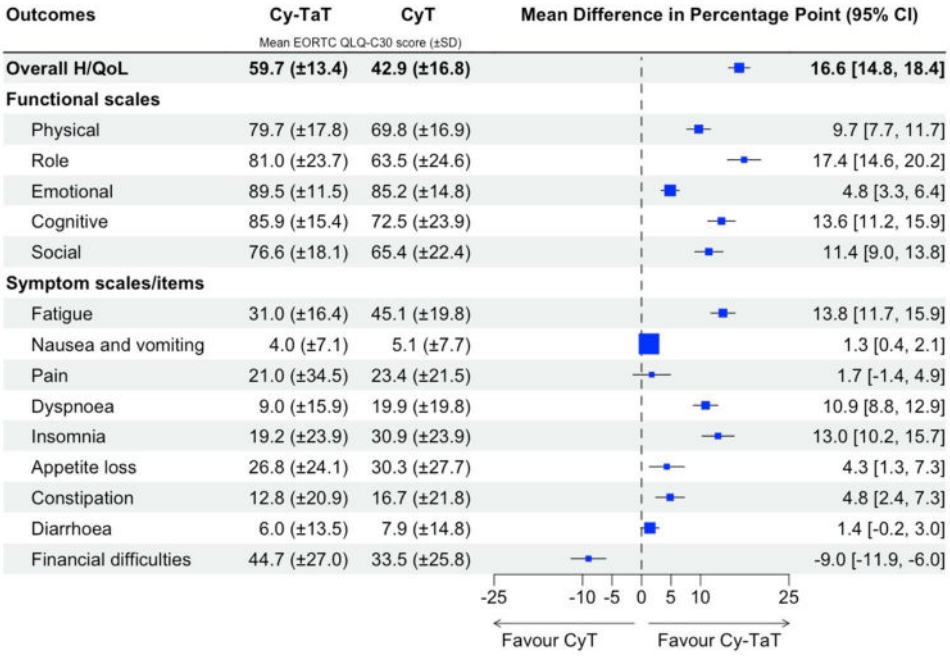

Fig. 2 Differences in outcomes between Cy-TaT and CyT. Abbreviations: 95% CI, 95% confidence interval; CyT, cytotoxic therapy; Cy-TaT, cytotoxic plus targeted therapy; H/QoL, health and quality of life; SD, standard deviation. EORTC QLQ-C30 scores were linearly transformed to percentage points. For H/QoL and functional scales, higher scores indicated better outcomes (reference for comparison: CyT), whereas for symptom scales/items, higher scores indicated worse symptoms (reference for comparison: Cy-TaT). Differences between Cy-TaT and CyT were estimated using g-estimation and adjusted for age, sex, body mass index, socioeconomic indicators, underlying comorbidities, characteristics of cancer, non-pharmacological treatment, colostomy, prior adjuvant or neoadjuvant chemotherapy, and supportive care for previous mCRC-related complications or emergencies. The signs of differences in percentage point of the symptom scales/items were reversed to facilitate visual interpretation. The difference in H/QoL was 16.6% points in EORTC QLQ-C30 score (95% CI 14.8 to 18.4, $p < 0.001$) and 0.076 in EQ-5D-3L utility score (95% CI 0.060 to 0.091)

Functional scales

In the CyT cohort, participants receiving the FOLFIRI regimen had the highest unadjusted EORTC QLQ-C30 scores in physical (74.2% points), role (70.8% points), cognitive (79.5% points), and social scales (70.6% point) (Fig. 6), whereas the corresponding score in emotional scale (87.3% point) was observed in the mFOLFOX-7 group (Fig. 5). For the Cy-TaT cohort, those with a FOLFIRI-based regimen reported the highest unadjusted EORTC QLQ-C30 scores in physical (83.3% points), role (85.0% points), emotional (91.8% points), and social scales (80.1% point) (Fig. 6). Regarding the cognitive scale, we found the highest unadjusted score in the mFOLFOX-6-TaT group (90.3% points) (Fig. 4). Treatment with Cy-TaT was associated with better functional scales than with CyT (Fig. 2). These patterns were also significant in subgroups of CAPEOX-TaT/CAPEOX (Fig. 3), mFOLFOX-6-TaT/mFOLFOX-6 (Fig. 4), mFOLFOX-7-TaT/mFOLFOX-7 (Fig. 5), and FOLFIRI-TaT/FOLFIRI (Fig. 6). For functional scales, the total benefits of adding targeted therapies were highest in the mFOLFOX-7-TaT group.

Symptom scales or items

Areas with the highest symptom burdens were fatigue (mean EORTC QLQ-C30 score > 38% points), insomnia (mean EORTC QLQ-C30 score > 25% points), appetite loss (mean EORTC QLQ-C30 score > 28% points), and financial difficulties (mean EORTC QLQ-C30 score > 39% points). In most areas of the EORTC QLQ-C30 symptom scales/items, treatment with Cy-TaT was associated with better outcomes, except for a contradictory association in financial difficulties (Fig. 2). We also found these trends in subgroups of CAPEOX-TaT/CAPEOX (Fig. 3), mFOLFOX-6-TaT/mFOLFOX-6 (Fig. 4), mFOLFOX-7-TaT/mFOLFOX-7 (Fig. 5), and FOLFIRI-TaT/FOLFIRI (Fig. 6). Areas with little to no differences among the 2 cohorts or 5 pairs of subgroups were nausea/vomiting and diarrhoea, while areas with consistently large differences were fatigue, dyspnoea, and insomnia.

Discussion

In general, we found that participants receiving Cy-TaT treatment had better overall H/QoL, functional scales, and symptom scales/items compared with the CyT cohort. This association remained consistent among most pairs of subgroups of the pharmacological

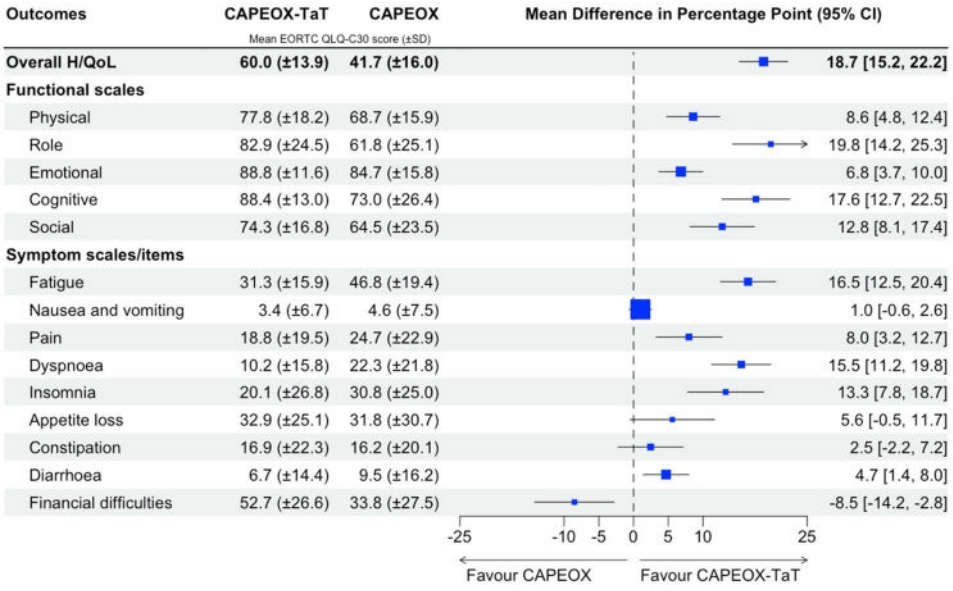

Fig. 3 Differences in outcomes between CAPEOX-TaT and CAPEOX. Abbreviations: 95% CI, 95% confidence interval; CAPEOX, capecitabine-oxaliplatin; CAPEOX-TaT, CAPEOX plus targeted therapy; H/QoL, health and quality of life; SD, standard deviation. EORTC QLQ-C30 scores were linearly transformed to percentage points. For H/QoL and functional scales, higher scores indicated better outcomes (reference for comparison: CAPEOX), whereas for symptom scales/items, higher scores indicated worse symptoms (reference for comparison: CAPEOX-TaT). Differences between CAPEOX-TaT and CAPEOX were estimated using g-estimation and adjusted for age, sex, body mass index, socioeconomic indicators, underlying comorbidities, characteristics of cancer, non-pharmacological treatment, colostomy, prior adjuvant or neoadjuvant chemotherapy, and supportive care for previous mCRC-related complications or emergencies. The signs of differences in percentage point of the symptom scales/items were reversed to facilitate visual interpretation. The difference in H/QoL in EQ-5D-3L utility score was 0.098 (95% CI 0.069 to 0.128)

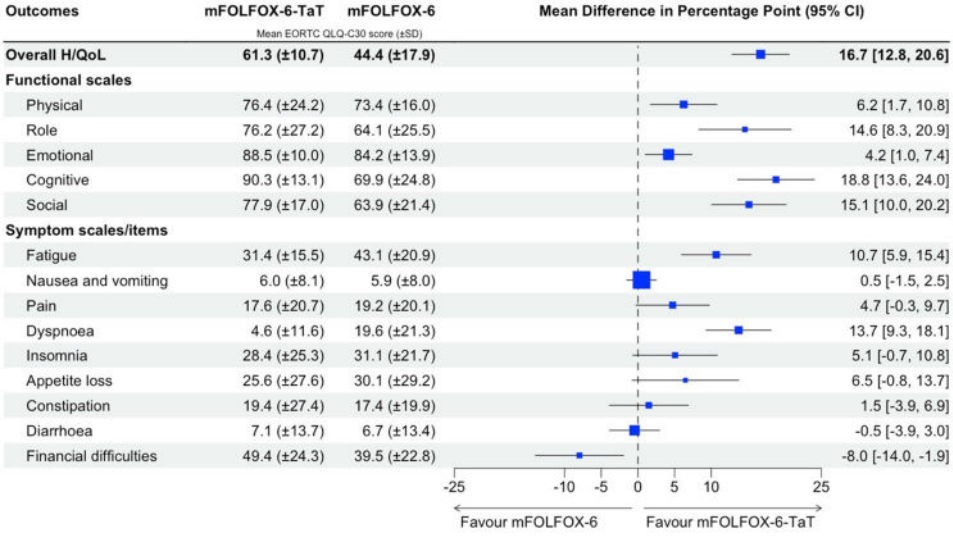

Fig. 4 Differences in outcomes between mFOLFOX-6-TaT and mFOLFOX-6. Abbreviations: 95% CI, 95% confidence interval; mFOLFOX, modified leucovorin-(5-)fluorouracil-oxaliplatin; mFOLFOX-6-TaT, mFOLFOX-6 plus targeted therapy; H/QoL, health and quality of life; SD, standard deviation. EORTC QLQ-C30 scores were linearly transformed to percentage points. For H/QoL and functional scales, higher scores indicated better outcomes (reference for comparison: mFOLFOX-6), whereas for symptom scales/items, higher scores indicated worse symptoms (reference for comparison: mFOLFOX-6-TaT). Differences between mFOLFOX-6-TaT and mFOLFOX-6 were estimated using g-estimation and adjusted for age, sex, body mass index, socioeconomic indicators, underlying comorbidities, characteristics of cancer, non-pharmacological treatment, colostomy, prior adjuvant or neoadjuvant chemotherapy, and supportive care for previous mCRC-related complications or emergencies. The signs of differences in percentage point of the symptom scales/items were reversed to facilitate visual interpretation. The difference in H/QoL in EQ-5D-3L utility score was 0.071 (95% CI 0.039 to 0.104)

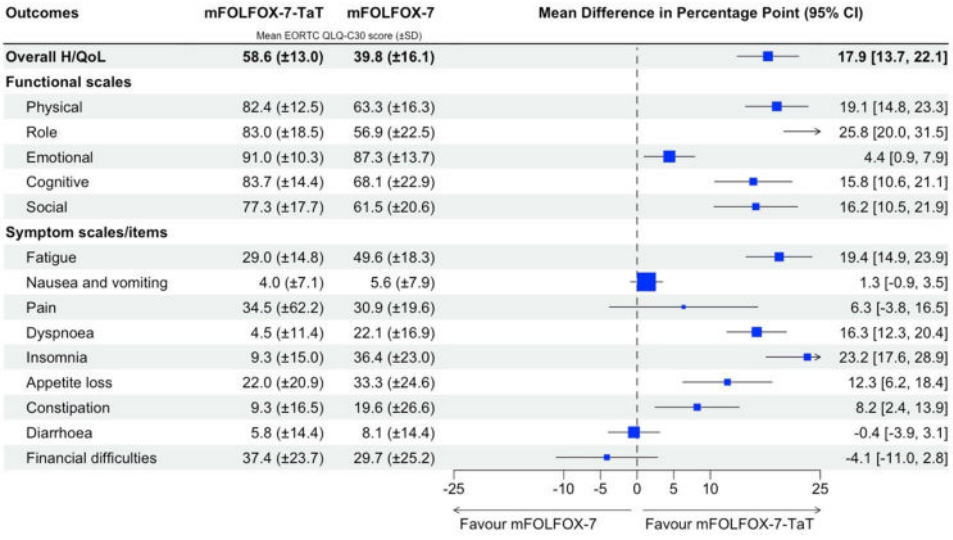

Fig. 5 Differences in outcomes between mFOLFOX-7-TaT and mFOLFOX-7. Abbreviations: 95% CI, 95% confidence interval; mFOLFOX, modified leucovorin-(5-)fluorouracil-oxaliplatin; mFOLFOX-7-TaT, mFOLFOX-7 plus targeted therapy; H/QoL, health and quality of life; SD, standard deviation. EORTC QLQ-C30 scores were linearly transformed to percentage points. For H/QoL and functional scales, higher scores indicated better outcomes (reference for comparison: mFOLFOX-7), whereas for symptom scales/items, higher scores indicated worse symptoms (reference for comparison: mFOLFOX-7-TaT). Differences between mFOLFOX-7-TaT and mFOLFOX-7 were estimated using g-estimation and adjusted for age, sex, body mass index, socioeconomic indicators, underlying comorbidities, characteristics of cancer, non-pharmacological treatment, colostomy, prior adjuvant or neoadjuvant chemotherapy, and supportive care for previous mCRC-related complications or emergencies. The signs of differences in percentage point of the symptom scales/items were reversed to facilitate visual interpretation. The difference in H/QoL in EQ-5D-3L utility score was 0.123 (95% CI 0.085 to 0.161)

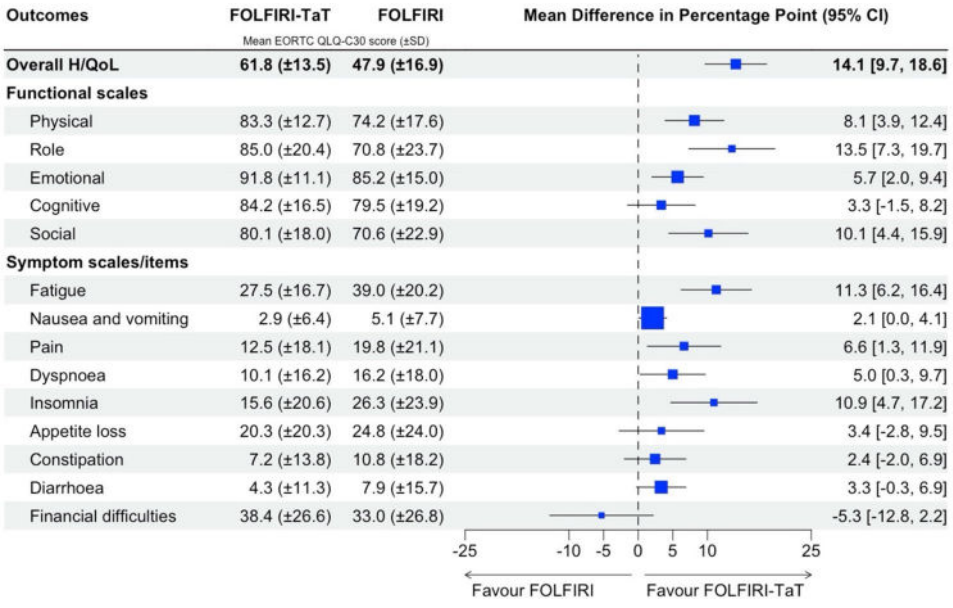

Fig. 6 Differences in outcomes between FOLFIRI-TaT and FOLFIRI. Abbreviations: 95% CI, 95% confidence interval; FOLFIRI, leucovorin-(5-)fluorouracil-irinotecan; FOLFIRI-TaT, FOLFIRI plus targeted therapy; H/QoL, health and quality of life; SD, standard deviation. EORTC QLQ-C30 scores were linearly transformed to percentage points. For H/QoL and functional scales, higher scores indicated better outcomes (reference for comparison: FOLFIRI), whereas for symptom scales/items, higher scores indicated worse symptoms (reference for comparison: FOLFIRI-TaT). Differences between FOLFIRI-TaT and FOLFIRI were estimated using g-estimation and adjusted for age, sex, body mass index, socioeconomic indicators, underlying comorbidities, characteristics of cancer, non-pharmacological treatment, colostomy, prior adjuvant or neoadjuvant chemotherapy, and supportive care for previous mCRC-related complications or emergencies. The signs of differences in percentage point of the symptom scales/items were reversed to facilitate visual interpretation. The difference in H/QoL in EQ-5D-3L utility score was 0.075 (95% CI 0.043 to 0.106)

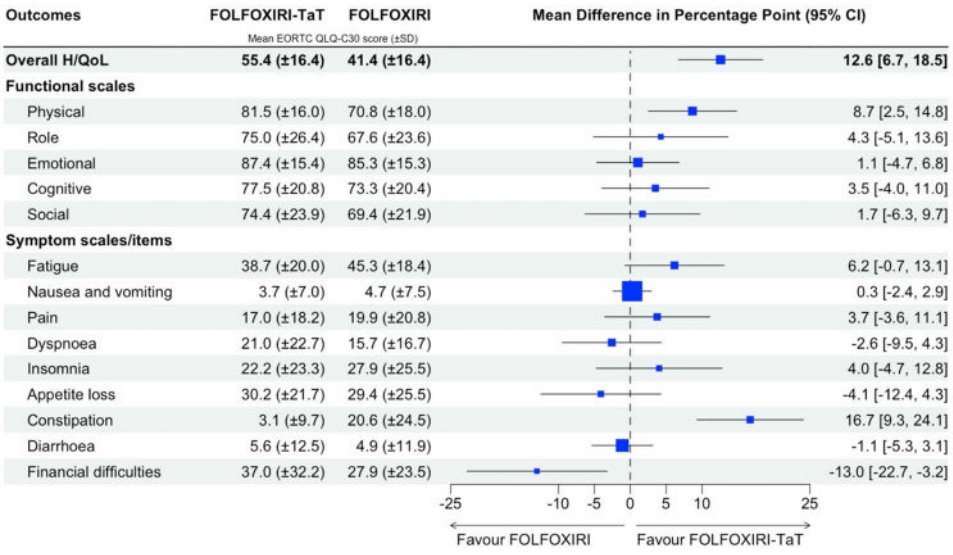

Fig. 7 Differences in outcomes between FOLFOXIRI-TaT and FOLFOXIRI. Abbreviations: 95% CI, 95% confidence interval; FOLFOXIRI, leucovorin-(5-)fluorouracil-oxaliplatin-irinotecan; FOLFOXIRI-TaT, FOLFOXIRI plus targeted therapy; H/QoL, health and quality of life; SD, standard deviation. EORTC QLQ-C30 scores were linearly transformed to percentage points. For H/QoL and functional scales, higher scores indicated better outcomes (reference for comparison: FOLFOXIRI), whereas for symptom scales/items, higher scores indicated worse symptoms (reference for comparison: FOLFOXIRI-TaT). Differences between FOLFOXIRI-TaT and FOLFOXIRI were estimated using g-estimation and adjusted for age, sex, body mass index, socioeconomic indicators, underlying comorbidities, characteristics of cancer, non-pharmacological treatment, colostomy, prior adjuvant or neoadjuvant chemotherapy, and supportive care for previous mCRC-related complications or emergencies. The signs of differences in percentage point of the symptom scales/items were reversed to facilitate visual interpretation. The difference in H/QoL in EQ-5D-3L utility score was 0.039 (95% CI -0.010 to 0.088)

regimens. For the overall H/QoL, the benefits of Cy-TaT were highest in the CAPEOX and mFOLFOX-7 groups. Participants with the mFOLFOX-7-TaT regimen also had the most benefits on functional scales from the targeted therapies. Regarding the symptom scales/items, areas with the most improvements from Cy-TaT regimens were fatigue, dyspnoea, and insomnia.

Our findings about the improved overall H/QoL in patients receiving Cy-TaT were consistent with previous evidence [4]. The proposed mechanism for this was the ability to selectively and effectively control or inhibit tumour growth of targeted therapies [14–16], leading to better progression-free survival and symptom control [17]. For patients with mCRC, understanding that they are eligible for curative-intent treatment with targeted therapies and eventually experiencing prolonged progression-free survival may significantly improve their distress, anxiety, and mental health. These improvements have reportedly been associated with better QoL [18–20], suggesting that the observed benefits in H/QoL were possibly due to a combination of biological and psychological effects of targeted therapies.

While our findings implied statistically significant differences in overall H/QoL, there was no general standard to conclude whether these differences were clinically important in mCRC. To address this gap, we considered some commonly reported ranges (0.05 to 0.12) for the minimally important difference in EQ-5D-3L utility score in cancer settings [21, 22]. Following these references, the QoL benefits of Cy-TaT regimens were likely to be clinically important, especially for patients receiving CAPEOX-TaT versus CAPEOX and mFOLFOX-7-TaT versus mFOLFOX-7. The QoL benefits in the FOLFOXIRI-TaT group were unclear, possibly due to the toxicity accumulation of 5 antineoplastic agents.

To the best of our knowledge, this is the first study to investigate QoL in patients with mCRC receiving curative-intent treatment. Our findings can be used in the personalisation of chemotherapy regimens, cost–utility analysis, or health policy design. For low-resource settings, although adding targeted therapies may lead to better QoL, the concern about financial difficulties always persists. Given the significantly high cost of targeted therapies, the financial toxicity of these agents can negatively affect many patients with low or middle socioeconomic status. Therefore, insurance agencies should allocate resources thoroughly to help alleviate the financial burden for those in need.

However, some limitations still remain in our study. First, due to the lack of data, we could not investigate the associations of genetic mutations in mCRC. Second, the targeted therapies in our setting only focused on inhibitors of vascular endothelial growth factor, which could limit the applicability of our findings. Third, due to some limitations in the external

validity, the mapping algorithm for EORTC QLQ-C30 global health status/QoL scale may not provide the best estimates of EQ-5D-3L utility scores for our setting. Fourth, given a certain extent of demographic homogeneity, the generalisability of our findings may be limited to low-middle-income countries. Finally, we could not directly compare the differences in QoL, functional scales, and symptom scales/items among all subgroups of regimens due to factors that did not facilitate causal inference.

Conclusion

Compared with those on CyT alone, patients with mCRC who received Cy-TaT showed better overall H/QoL, as well as improved functional scales and symptom scales/items. These benefits were consistent across most subgroups, with the greatest improvements in H/QoL observed in the CAPEOX-TaT and mFOLFOX-7-TaT groups. The mFOLFOX-7-TaT group also reported the most significant gains in functional scales. In terms of symptom scales/items, the most notable improvements with Cy-TaT were in fatigue, dyspnoea, and insomnia.

Abbreviations

CAPEOX-TaT	Capecitabine-oxaliplatin plus targeted therapy
CAPEOX	Capecitabine-oxaliplatin
CI	Confidence interval
CRC	Colorectal cancer
Cy-TaT	Cytotoxic plus targeted therapy
CyT	Cytotoxic therapy
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
FOLFIRI-TaT	Leucovorin-(5-)fluorouracil-irinotecan plus targeted therapy
FOLFIRI	Leucovorin-(5-)fluorouracil-irinotecan
FOLFOXIRI-TaT	Leucovorin-(5-)fluorouracil-oxaliplatin-irinotecan plus targeted therapy
FOLFOXIRI	Leucovorin-(5-)fluorouracil-oxaliplatin-irinotecan
H/QoL	Health and quality of life
IQR	Interquartile range
mCRC	Metastatic colorectal cancer
mFOLFOX-6-TaT	Modified leucovorin-(5-)fluorouracil-oxaliplatin-6 plus targeted therapy
mFOLFOX-6	Modified leucovorin-(5-)fluorouracil-oxaliplatin-6
mFOLFOX-7-TaT	Modified leucovorin-(5-)fluorouracil-oxaliplatin-7 plus targeted therapy
mFOLFOX-7	Modified leucovorin-(5-)fluorouracil-oxaliplatin-7
NCCN	National Comprehensive Cancer Network
QoL	Quality of life
SD	Standard deviation
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SUTVA	Stable unit treatment value assumption

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14388-2.

Supplementary Material 1

Acknowledgements

We would like to thank the staff of NDGD Hospital for their assistance in data collection.

Author contributions

Conceptualisation: HTP and M-HT. Study design and methods: HTP, TAN, TLB, and M-HT. Data collection: HTP, TAN, VNMT, K-HT-N, and M-HT. Data analysis and interpretation: HTP, TAN, TLB, RLC, BKN, MKF, VDT, and M-HT. Manuscript drafting and revision: all authors. Supervision: M-HT. All authors read and agreed to the final manuscript.

Funding

This study was not funded by any organisations.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Nhan Dan Gia Dinh Hospital under approval number 31/NDGD-HDDD. All participants gave their written informed consent prior to participation.

Consent for publication

Not applicable.

Competing interests

HTP reported receiving speaking fees and travel reimbursement from Servier Vietnam Ltd and Pfizer Vietnam Ltd, grants from Servier Vietnam Ltd, and speaking fees from Aguettant Asia Pacific Pte Ltd outside the submitted work. M-HT reported receiving travel reimbursement from Pfizer Vietnam Ltd and Viatris Vietnam Ltd, speaking fees and grants from Servier Vietnam Ltd, and speaking fees from Aguettant Asia Pacific Pte Ltd outside the submitted work. The other authors declare no competing interest.

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Received: 16 September 2024 / Accepted: 26 May 2025
Published online: 28 May 2025

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