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Predominant irinotecan-based chemotherapy in stage III disease and frequent dose-rounding deviations in colorectal cancer at an Indonesian referral hospital

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ABSTRACT

Background: Colorectal cancer is the third most common malignancy worldwide. Rounding of chemotherapy doses calculated from body surface area (BSA) is widely practiced, but the Indonesian national colorectal cancer guideline does not define an acceptable rounding threshold.

Objective: To evaluate chemotherapy regimen selection and dosing accuracy in patients with stage III and metastatic colorectal cancer.

Methods: This retrospective cross-sectional study reviewed intravenous chemotherapy visits of National Health Insurance patients with stage III or metastatic colorectal cancer at a referral hospital in Samarinda, Indonesia, from January to June 2024. Regimens were compared with the national guideline, and prescribed doses were compared with BSA-based doses (Mosteller formula) using a ±5% dose-rounding threshold.

Results: Of 131 eligible visits, 122 were for stage III and nine for metastatic disease. FOLFIRI was administered in 71% of visits and FOLFOX in 29%; no targeted therapy was given. FOLFIRI, which the guideline does not recommend for adjuvant therapy, accounted for 72% of stage III visits. In stage III, 29.4% of FOLFOX and 38.6% of FOLFIRI administrations fell outside the threshold. Deviations involved all five dose components and were mostly below the calculated dose, except for oxaliplatin, which more often exceeded it (23.5%). In metastatic disease, one of four FOLFOX administrations exceeded the threshold.

Conclusion: Irinotecan-based chemotherapy predominated in stage III disease despite the guideline's recommendation of oxaliplatin-based adjuvant therapy, and one-third of stage III administrations fell outside the ±5% threshold. Documentation of treatment intent, a standardized dose-rounding protocol, and pharmacist verification are needed.

Keywords: colorectal cancer, dose rounding, FOLFIRI, FOLFOX, guideline adherence

Introduction

Cancer imposes a major global health burden, particularly in terms of clinical management [1]. Colorectal cancer, a malignancy of the colon and rectum, is among the three most common cancers worldwide [2], and its morbidity and mortality continue to increase. According to GLOBOCAN 2022, colorectal cancer ranked third in new cases (1,926,118) and second in deaths (903,859). Its five-year prevalence (2017–2022) was 5,767,781 cases, the second highest after breast cancer [3].

Indonesia, one of the most populous countries in the world, had a population of 281.6 million in 2024 [4,5]. In 2022, an estimated 408,661 new cancer

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cases and 242,988 cancer deaths occurred in Indonesia, and colorectal cancer ranked fourth in incidence, with 35,676 new cases and 19,255 deaths [6,7].

In 2018, the Ministry of Health of the Republic of Indonesia issued a national guideline for the management of colorectal cancer, which remains the standard of care for these patients. The guideline incorporates international guidelines and clinical trial evidence while taking clinical practice in Indonesia into account [8–11]. Chemotherapy is a recommended treatment modality alongside surgery and radiotherapy, particularly for advanced cancer treated with palliative intent. As a systemic therapy, it uses one or more drugs to inhibit or eradicate cancer cells while sparing normal cells as much as possible [12].

The administration of chemotherapy requires an appropriate choice of regimen and an individualized dose [13]. Inappropriate administration can increase adverse effects and reduce treatment efficacy [14,15]. Even at the correct dose, patients frequently experience fatigue, decreased appetite, vomiting, diarrhea, and constipation. Doses lower than optimal may cause fewer side effects but can also reduce the effectiveness of chemotherapy [16,17], whereas overdosing, including that caused by dosage miscalculation, can lead to life-threatening toxicity [18].

Dose rounding is the practice of adjusting a dose calculated from body surface area (BSA) to a nearby practical value, such as the nearest vial size, within a predefined percentage of the calculated dose without compromising efficacy or safety. It is widely implemented in oncology pharmacy practice to minimize drug wastage, simplify preparation, and reduce costs, particularly for high-cost anticancer agents [19]. The Hematology/Oncology Pharmacy Association (HOPA) considers rounding within 10% of the ordered dose acceptable for routine care and recommends that each institution define its own rounding policy [20]; some institutions apply a narrower 5% limit [21]. In routine practice, dose rounding is applied after individual dose calculation and pharmacist verification, especially in settings with centralized intravenous admixture services [21,22].

However, the Indonesian national colorectal cancer guideline does not define an acceptable dose-rounding threshold, which leaves room for variation in practice and uncertainty about dosing accuracy [8]. Dose rounding is nonetheless applied in Indonesian hospitals. Irawati and Sardjan reported that each breast cancer chemotherapy dose in a hospital in Malang was rounded after BSA calculation [23], and Lantika et al. described a similar practice for intravenous combination regimens in cervical cancer, although neither study specified the rounding standard used [24].

Real-world studies have documented that chemotherapy doses are not always administered precisely as calculated. A retrospective evaluation at Sekayu Hospital, Indonesia, reported that a substantial proportion of breast cancer chemotherapy doses differed from BSA-based calculations, with both underdosing and overdosing [25]. In a large French cohort, 3.15% of 17,150 chemotherapy prescriptions contained at least one error, and protocols with more than three drugs or requiring dose modification were independent predictors of dose errors [26]. Although the effects of dosing inaccuracies on long-term outcomes depend on cancer type and regimen, deviations from planned doses can reduce treatment efficacy or increase toxicity.

Evidence on dose-rounding accuracy in Indonesia is thus limited to breast and cervical cancer, and no study has used an explicit rounding threshold as the evaluation criterion. Colorectal cancer regimens such as FOLFOX and FOLFIRI deliver three drugs as four separately calculated dose components per cycle, which multiplies the opportunities for dosing deviations. This study therefore evaluated chemotherapy regimen selection against the national guideline and dosing accuracy against a ±5% dose-rounding threshold in patients with stage III and metastatic colorectal cancer at a provincial referral hospital in Indonesia.

Methods

Research design

This observational cross-sectional study with retrospective data collection was conducted at Abdoel Wahab Sjahranie Regional General Hospital, Samarinda, Indonesia, the main referral center for National Health Insurance patients requiring chemotherapy in East Kalimantan Province. Data from January to June 2024 were collected. The unit of analysis was the chemotherapy visit, defined as one cycle administered during one hospital admission; a patient could therefore contribute more than one visit. All intravenous chemotherapy visits of patients with stage III or metastatic colorectal cancer were eligible. Visits involving oral chemotherapy (e.g., capecitabine-based regimens), self-financed treatment, or patients not covered by National Health Insurance were excluded because the study focused on BSA-based intravenous

dosing under the national insurance scheme. Visits with incomplete medical records were also excluded.

Ethics approval

This study was approved by the Health Research Ethics Committee of Abdoel Wahab Sjahranie Regional General Hospital (approval No. 508/KEPK-AWS/VIII/2024). The requirement for informed consent was waived because the study used anonymized medical records retrospectively.

Data source

Medical records of 142 chemotherapy visits between January and June 2024 were screened. Ten visits were excluded because key clinical data (e.g., cancer stage or chemotherapy details) were incomplete, and one visit was excluded because the regimen did not follow a standard colorectal cancer protocol. The remaining 131 visits, corresponding to 35 individual patients, were analyzed. Regimen selection was evaluated against the national colorectal cancer guideline [8]. For stage III disease, the guideline recommends an oxaliplatin–fluoropyrimidine doublet (FOLFOX or CapeOX) as standard adjuvant therapy, or fluoropyrimidine monotherapy when oxaliplatin is contraindicated, and states that irinotecan should not be used in the adjuvant setting. For metastatic disease, it lists FOLFOX, FOLFIRI, CapeOX, and IROX, with or without targeted therapy [8].

Data analysis

Data were analyzed descriptively using Microsoft Excel version 2409. Sample characteristics (sex, age, class of care, length of stay, primary tumor site, cancer stage, and anthropometric data) are presented as frequencies and percentages or as minimum, maximum, mean, and standard deviation (SD).

For each visit, BSA was calculated with the Mosteller equation from the height and body weight recorded in the medical record [27,28]. The calculated dose of each agent was obtained by multiplying the BSA by the standard dose in the national guideline: oxaliplatin 85 mg/m², irinotecan 180 mg/m², leucovorin 400 mg/m², 5-fluorouracil (5-FU) 400 mg/m² bolus, and 5-FU 1200 mg/m²/day as a continuous infusion for two days (2400 mg/m² over 46–48 hours) [8]. The prescribed dose was compared with the calculated dose, and the deviation was computed as (prescribed dose − calculated dose)/calculated dose × 100%. A deviation within ±5% was classified as within the dose-rounding threshold, a deviation below −5% as under the threshold, and a deviation above +5% as exceeding the threshold. This threshold is narrower than the 10% limit considered acceptable by HOPA [20] and corresponds to the lower limit used in institutional dose-rounding practice [21]; it was chosen as a conservative criterion because the national guideline does not define a rounding threshold [8]. A regimen administration was classified as outside the threshold when at least one of its agents deviated by more than 5%. Percentages were calculated using the number of administrations of the corresponding regimen or agent at each stage as the denominator.

Results

Of the 142 visits screened, 131 met the inclusion criteria (Table 1). Male patients accounted for 54% of visits. The most common age group was 50–59 years (39%), followed by 40–49 years (28%), 70–79 years (20%), 60–69 years (10%), and 30–39 years (3%). All visits were inpatient admissions, most commonly in class III care under the National Health Insurance program (40%), followed by class I (35%) and class II (25%). Most admissions lasted 1–3 days (73%). The primary tumor was located in the colon in 93% of visits (sigmoid colon, 48%; other or unspecified colonic segments, 45%) and in the rectum in 6%. Stage III disease accounted for 93% of visits and metastatic disease for 7%. Among the nine metastatic visits, the liver was the most common metastatic site (five visits), followed by the lung (two visits).

The mean height was 156.19 cm, the mean body weight was 54.72 kg, and the mean BSA was 1.54 m² (Table 2).

FOLFIRI was the most frequently administered regimen (93 visits, 71%), followed by FOLFOX (38 visits, 29%) (Table 3).

Table 4 summarizes the regimens administered at each stage. In stage III, FOLFIRI was given in 88 visits (72%) and FOLFOX in 34 (28%); IROX and CapeOX were not used. Therefore, only FOLFOX corresponded to the adjuvant regimen recommended by the national guideline, whereas irinotecan is not recommended in the adjuvant setting [8]. Because treatment intent was not recorded, FOLFIRI in stage III could be considered concordant only if it was given with palliative intent for unresectable or recurrent disease. In metastatic disease, FOLFIRI was given in five visits (56%) and FOLFOX in four (44%), both of which are listed in the guideline, and no targeted therapy was administered.

Table 1. Characteristics of the chemotherapy visits

Characteristics	n	%
Gender		
Female	60	46
Male	71	54
Age (years)		
30-39	4	3
40-49	37	28
50-59	51	39
60-69	13	10
70-79	26	20
Type of patient care		
Inpatient	131	100
Outpatient	0	0
Class of patient care		
I	46	35
II	33	25
III	52	40
Length of stay (days)		
1-3	95	73
4-6	32	24
7-9	3	2
>9	1	1
Primary site of cancer		
Colon	122	93
Sigmoid colon	63	48
Other or unspecified colonic segment	59	45
Rectum	8	6
Unspecified colorectal site	1	1
Stage of cancer		
III	122	93
IV (metastatic)	9	7
Site of metastasis (in stage IV)		
Bladder	1	11.1
Liver	5	55.6
Lung	2	22.2
Unspecified	1	11.1

Data are presented per chemotherapy visit (n = 131); a patient could contribute more than one visit. Class of care refers to the National Health Insurance (Jaminan Kesehatan Nasional) inpatient class, with class I being the highest. Colon includes the sigmoid colon; other or unspecified colonic segment denotes colonic tumors recorded without a sigmoid location. Percentages for site of metastasis are calculated from the nine visits with stage IV disease. n, number of visits.

Table 2. Anthropometric data

Data	Min	Max	Mean	SD
Height (cm)	142	173	156.19	6.30
Body weight (kg)	34	80	54.72	10.56
Body surface area (m^2)*	1.21	1.91	1.54	0.16

Values are calculated per chemotherapy visit (n = 131). *Calculated using the Mosteller formula [27,28]. Min, minimum; Max, maximum; SD, standard deviation.

Table 3. Chemotherapy regimens

Regimens	n	%
FOLFOX	38	29
FOLFIRI	93	71
IROX	0	0
FOLFOX + bevacizumab	0	0
FOLFOX + panitumumab	0	0
FOLFIRI + bevacizumab	0	0
FOLFIRI + cetuximab	0	0
FOLFIRI + panitumumab	0	0
FOLFIRI + ziv-aflibercept	0	0

Data are presented per chemotherapy visit (n = 131). FOLFOX, 5-fluorouracil (5-FU), leucovorin, and oxaliplatin; FOLFIRI, 5-FU, leucovorin, and irinotecan; IROX, irinotecan and oxaliplatin; n, number of visits.

Table 4. Chemotherapy regimens administered by cancer stage

Stages	Regimens	n	%
III	FOLFOX	34	28
	FOLFIRI	88	72
	IROX	0	0
IV (Metastatic)	FOLFOX	4	44
	FOLFOX + bevacizumab	0	0
	FOLFOX + panitumumab	0	0
	FOLFIRI	5	56
	FOLFIRI + bevacizumab	0	0
	FOLFIRI + cetuximab	0	0
	FOLFIRI + panitumumab	0	0
	FOLFIRI + ziv-aflibercept	0	0

Regimens recommended by the national guideline [8]: stage III (adjuvant), an oxaliplatin–fluoropyrimidine doublet (FOLFOX or CapeOX) or fluoropyrimidine monotherapy, with irinotecan not recommended in the adjuvant setting; stage IV, FOLFOX, FOLFIRI, CapeOX, or IROX, with or without targeted therapy. Percentages are calculated from the number of visits at each stage (stage III, n = 122; stage IV, n = 9). FOLFOX, 5-fluorouracil (5-FU), leucovorin, and oxaliplatin; FOLFIRI, 5-FU, leucovorin, and irinotecan; IROX, irinotecan and oxaliplatin; CapeOX, capecitabine and oxaliplatin.

Table 5. Dosing accuracy by regimen and cancer stage

Stages	Regimens	n	%
III	Within the dose rounding		
	FOLFOX	24	70.6
	FOLFIRI	54	61.4
	Outside the dose rounding		
	FOLFOX	10	29.4
	FOLFIRI	34	38.6
IV (Metastatic)	Within the dose rounding		
	FOLFOX	3	75.0
	FOLFIRI	5	100.0
	Outside the dose rounding		
	FOLFOX	1	25.0
	FOLFIRI	0	0.0

Within the dose-rounding threshold: prescribed dose within ±5% of the calculated dose (body surface area × standard dose) for every agent in the regimen. An administration was classified as outside the threshold when at least one agent deviated by more than 5%. Percentages are calculated from the number of administrations of each regimen at each stage (stage III: FOLFOX, n = 34; FOLFIRI, n = 88; stage IV: FOLFOX, n = 4; FOLFIRI, n = 5). FOLFOX, 5-fluorouracil (5-FU), leucovorin, and oxaliplatin; FOLFIRI, 5-FU, leucovorin, and irinotecan.

Table 6. Dosing accuracy by agent and cancer stage

Stages	Agents	n	%
III	**oxaliplatin 85 mg/m² IV**		
	Within dose rounding	25	73.5
	Under dose rounding	1	2.9
	Exceeding dose rounding	8	23.5
	irinotecan 180 mg/m² IV		
	Within dose rounding	61	69.3
	Under dose rounding	16	18.2
	Exceeding dose rounding	11	12.5
	leucovorin 400 mg/m² IV		
	Within dose rounding	86	70.5
	Under dose rounding	24	19.7
	Exceeding dose rounding	12	9.8
	5-FU 400 mg/m² IV bolus		
	Within dose rounding	87	71.3
	Under dose rounding	23	18.9
	Exceeding dose rounding	12	9.8
	5-FU 1200 mg/m²/day IV continuous		
	Within dose rounding	97	79.5
	Under dose rounding	17	13.9
	Exceeding dose rounding	8	6.6
IV (Metastatic)	**oxaliplatin 85 mg/m² IV**		
	Within dose rounding	4	100.0
	Under dose rounding	0	0.0
	Exceeding dose rounding	0	0.0
	irinotecan 180 mg/m² IV		
	Within dose rounding	5	100.0
	Under dose rounding	0	0.0
	Exceeding dose rounding	0	0.0
	leucovorin 400 mg/m² IV		
	Within dose rounding	9	100.0
	Under dose rounding	0	0.0
	Exceeding dose rounding	0	0.0
	5-FU 400 mg/m² IV bolus		
	Within dose rounding	9	100.0
	Under dose rounding	0	0.0
	Exceeding dose rounding	0	0.0
	5-FU 1200 mg/m²/day IV continuous		
	Within dose rounding	8	88.9
	Under dose rounding	0	0.0
	Exceeding dose rounding	1	11.1

Within, prescribed dose within ±5% of the calculated dose (body surface area × standard dose); under, more than 5% below the calculated dose; exceeding, more than 5% above the calculated dose. Percentages are calculated from the number of administrations of each agent at each stage (stage III: oxaliplatin, n = 34; irinotecan, n = 88; leucovorin and 5-FU, n = 122; stage IV: oxaliplatin, n = 4; irinotecan, n = 5; leucovorin and 5-FU, n = 9). 5-FU continuous infusion was given at 1200 mg/m² per day for two days. 5-FU, 5-fluorouracil; IV, intravenous.

Dosing accuracy by regimen is shown in Table 5. In stage III, 24 of 34 FOLFOX administrations (70.6%) and 54 of 88 FOLFIRI administrations (61.4%) were within the ±5% threshold, whereas 10 FOLFOX (29.4%) and 34 FOLFIRI (38.6%) administrations fell outside it. In metastatic disease, three of four FOLFOX administrations (75.0%) and all five FOLFIRI administrations were within the threshold; one FOLFOX administration (25.0%) exceeded it.

Dosing accuracy for each agent is presented in Table 6. In stage III, deviations from the threshold occurred for all five dose components. The proportion within the threshold was highest for 5-FU continuous infusion (97 of 122, 79.5%) and lowest for irinotecan

(61 of 88, 69.3%). Doses below the threshold were more common than doses above it for irinotecan (18.2% vs. 12.5%), leucovorin (19.7% vs. 9.8%), 5-FU bolus (18.9% vs. 9.8%), and 5-FU continuous infusion (13.9% vs. 6.6%). Oxaliplatin showed the opposite pattern: 8 of 34 administrations (23.5%) exceeded the threshold, the highest proportion of overdosing among all agents, and only one (2.9%) was below it. In metastatic disease, all doses were within the threshold except one 5-FU continuous infusion dose that exceeded it (1 of 9, 11.1%).

Discussion

This study evaluated regimen selection and dosing accuracy of intravenous chemotherapy for stage III and metastatic colorectal cancer at a provincial referral hospital in Indonesia. Three main findings emerged. First, FOLFIRI was the predominant regimen at both stages, accounting for 72% of stage III visits, although the national guideline recommends oxaliplatin–fluoropyrimidine doublets for adjuvant therapy and advises against irinotecan in this setting [8]. Second, no targeted therapy was used in metastatic disease. Third, approximately one-third of stage III administrations fell outside the ±5% dose-rounding threshold, with underdosing predominating for most dose components and overdosing most frequent for oxaliplatin.

Male patients accounted for slightly more visits (54%) than female patients. Because the visit was the unit of analysis and the sample came from a single referral hospital, this proportion does not represent incidence; nevertheless, it is consistent with GLOBOCAN data showing more colorectal cancer cases in men (3,183,756) than in women (2,584,025) worldwide [3]. Baraibar et al. proposed that tumor suppressor genes that escape X-inactivation (EXITS) may contribute to this sex difference [29]. The 50–59-year age group contributed the most visits, in line with reports of increasing colorectal cancer incidence around this age [30].

All visits were inpatient admissions because the FOLFOX and FOLFIRI schedules include a continuous 5-FU infusion over two days, which explains the predominance of 1–3-day stays (73%) [8]. Inpatient care under the National Health Insurance program is tiered into classes I, II, and III, with class I being the highest. Class III, the most frequent class in this study (40%), is generally allocated to beneficiaries of government premium assistance, which is consistent with a previous study in which 64% of National Health Insurance patients receiving chemotherapy were premium assistance recipients [7,31].

Colon cancer accounted for 93% of visits, and the sigmoid colon was the most frequent single site (48%), similar to the findings of Duan et al., who reported the sigmoid colon as the most common site (55%) [32]. Tumors of the sigmoid–rectal region have a distinct molecular profile, with more frequent TP53 mutations than other left-sided locations [33], and a longer period of carcinogenesis has been proposed for distal tumors [34]. Stage III disease accounted for 93% of visits, whereas metastatic disease accounted for only 7%. This distribution more likely reflects the study design than the true stage distribution: oral capecitabine-based and self-financed regimens, which may be used in metastatic disease, were excluded, and some patients with metastatic disease may receive best supportive care or be treated elsewhere. In addition, the targeted therapies recommended for metastatic disease are not reimbursed, which may lead some insured patients to seek self-financed treatment. Survival also differs markedly by stage, with five-year survival of approximately 53–90% across stage III substages compared with about 12% in stage IV [35]; consequently, more patients with stage III disease remain alive to receive treatment. The liver was the most common metastatic site, consistent with reports that about 25% of patients with colorectal cancer develop liver metastases during the course of their disease [36].

FOLFOX and FOLFIRI are established first-line options in metastatic colorectal cancer, with comparable response rates, progression-free survival, and overall survival [37–39]. Their roles differ, however, in stage III disease. The national guideline recommends an oxaliplatin–fluoropyrimidine doublet as standard adjuvant therapy for stage III colon cancer, or fluoropyrimidine monotherapy when oxaliplatin is contraindicated, and explicitly states that irinotecan should not be used in the adjuvant setting outside clinical trials [8]. This recommendation reflects the survival benefit of adding oxaliplatin in the MOSAIC trial [9] and is consistent with international guidelines [11]. Because 93% of visits in this study involved colon cancer, to which this adjuvant recommendation applies directly, the predominance of FOLFIRI in stage III (72%) represents a substantial departure from the guideline if these regimens were given as adjuvant therapy. Some

of these visits may have involved palliative treatment of unresectable or recurrent disease, or a switch after oxaliplatin-related neuropathy, but treatment intent and the reasons for regimen selection were not recorded. Clarifying these reasons, for example through regimen review by the oncology team and pharmacists, should be a priority, and future studies should document treatment intent so that guideline concordance can be assessed precisely.

The national guideline also lists targeted therapies for metastatic disease: bevacizumab and panitumumab with FOLFOX or FOLFIRI, and cetuximab and ziv-aflibercept with FOLFIRI [8]. A systematic review and meta-analysis reported that adding bevacizumab improved anti-tumor activity and disease control without prolonging overall or progression-free survival [40], and ziv-aflibercept combined with FOLFIRI has been approved for metastatic colorectal cancer that has progressed after an oxaliplatin-containing regimen [41]. Eligibility for anti-EGFR agents (cetuximab and panitumumab) requires RAS wild-type status, which was not evaluated in this study. However, the main barrier is coverage. Since March 2019, bevacizumab has been removed from the National Formulary and cetuximab has been restricted to second-line therapy for squamous cell carcinoma of the head and neck, and panitumumab and ziv-aflibercept are not listed; these restrictions are maintained in the current formulary [42]. Consequently, none of the targeted therapies recommended for metastatic colorectal cancer in the national guideline is reimbursed under National Health Insurance, which explains their absence in this study, in which only insured patients were included.

Individualized BSA-based dosing is required for cytotoxic agents because of their narrow therapeutic index [43]. In this study, approximately one-third of stage III administrations (44 of 122) fell outside the ±5% threshold, compared with one of nine metastatic administrations. These deviations should be interpreted with caution. Because HOPA considers rounding within 10% acceptable [20], deviations between 5% and 10% would be acceptable under that position statement, so the proportions reported here represent an upper estimate of clinically relevant dosing deviations. In addition, a dose outside the threshold may represent an intentional dose modification, for example after toxicity in a previous cycle, in elderly or frail patients, or in hepatic impairment, rather than a calculation or rounding error. Because the reasons for dose modification were not collected in this study, intentional modifications could not be distinguished from errors. The deviations are also unlikely to be explained by rounding to whole vials alone, because leucovorin and continuous-infusion 5-FU, whose calculated doses can be closely matched with standard vial sizes, still fell outside the threshold in 29.5% and 20.5% of stage III administrations, respectively. Even so, deviations of this magnitude are clinically relevant. Park et al. reported frequent oxaliplatin dose reduction during adjuvant FOLFOX and recommended delivering more than 60% of the standard cumulative dose to achieve acceptable oncologic outcomes [44], whereas excessive exposure increases the risk of regimen-specific toxicities such as peripheral neuropathy with FOLFOX and alopecia with FOLFIRI [45].

Underdosing predominated for four of the five dose components in stage III, whereas oxaliplatin was more often given above the threshold (23.5%). This pattern differs from that reported by Park et al., who found that oxaliplatin was mainly given below the planned dose [44]. Oxaliplatin overdosing is of particular concern given the toxicity risks described above, while systematic underdosing of irinotecan and 5-FU may reduce dose intensity and therapeutic effectiveness. Deviations in leucovorin have different implications: leucovorin is a biochemical modulator of 5-FU rather than a cytotoxic drug, so moderate deviations are unlikely to affect toxicity directly. In metastatic disease, the only deviation was a 5-FU continuous infusion dose above the threshold; excessive 5-FU exposure can cause severe and occasionally fatal toxicity [18,46]. A standardized institutional dose-rounding protocol, pharmacist verification of each chemotherapy order, and documentation of the reason for any intentional dose modification could reduce unexplained deviations.

This study has important limitations. Treatment intent and the reasons for dose modification were not recorded; therefore, FOLFIRI use in stage III could not be classified definitively as adjuvant or palliative, and intentional dose adjustments could not be distinguished from errors. In addition, the ±5% threshold is stricter than the 10% limit accepted by HOPA and may have overestimated clinically relevant deviations. The single-center design, the use of visits rather than patients as the unit of analysis, and the small number of metastatic visits further limit generalizability. Prospective studies that record

treatment intent, reasons for dose modification, and clinical and safety outcomes are warranted.

Conclusion

Among patients with stage III and metastatic colorectal cancer at this referral hospital, FOLFIRI was the predominant regimen, including in stage III disease, for which the national guideline recommends oxaliplatin-based adjuvant therapy and advises against irinotecan. No targeted therapy was used in metastatic disease. About one-third of stage III administrations and one of nine metastatic administrations fell outside the ±5% dose-rounding threshold, mostly below the calculated dose, with oxaliplatin more often exceeding it. Documentation of treatment intent, a standardized institutional dose-rounding protocol with pharmacist verification, and a defined rounding threshold in the national guideline are needed to improve the consistency of chemotherapy prescribing.

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Conflict of interest

The authors declare no conflicts of interest in this study.

Author contributions

EA and RNA contributed to the literature review, development of the research protocol, and drafting of the initial manuscript. BDP, APA, AR, and MFHF were responsible for designing the data collection procedures. K supervised regulatory approvals and ensured the ethical compliance of the study. All authors participated in data analysis, critically revised the manuscript, and approved the final version.

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Declaration of generative AI use

The authors used DeepL to refine the grammar of the manuscript, and all revisions were checked manually by the authors.

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