RESEARCH ARTICLE

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Towards Precision Oncology: A Predictive Nomogram Incorporating DPD and *MTHFR* for CapeOX Neoadjuvant Chemotherapy in Colorectal Cancer

Elvida Christy Imelda Tahiya, Ronald Erasio Lusikooy, Ilhamjaya Pattelongi, Warsinggih Raharjo, Julianus Aboyaman Uwuratuw, Erwin Syarifuddin, Citra Aryanti*

Abstract

Background: Colorectal cancer (CRC) is one of the most prevalent malignancies worldwide. Variability in patient response to fluoropyrimidine-based neoadjuvant chemotherapy remains a critical challenge. We aimed to develop a nomogram that integrated dihydropyrimidine dehydrogenase (*DPD*) and methylenetetrahydrofolate reductase (*MTHFR*) expression to predict CapeOX (Capecitabine-Oxaliplatin) neoadjuvant chemotherapy outcomes in colorectal cancer. **Methods:** A prospective cohort of 36 advanced-stage CRC patients who received CapeOX neoadjuvant chemotherapy at Wahidin Sudirohusodo Hospital from 2024 to 2025 was analyzed. mRNA expression levels of *TS*, *DPD*, and *MTHFR* were measured in tissue and blood using quantitative RT-PCR. The chemotherapy response was evaluated by RECIST 1.1. Statistical analysis was performed to identify predictors of response, which were incorporated into a nomogram with bootstrap validation. **Results:** Among the 36 patients with advanced colorectal cancer, response to CapeOX chemotherapy was observed in 50%. Blood-based gene profiling revealed that responders had significantly lower *DPD* and *MTHFR* expression compared with non-responders (both $p<0.001$), while *TS* showed no predictive relevance. A nomogram that integrated only blood *DPD* and *MTHFR* achieved outstanding discrimination (AUC 0.932, C-index 0.78) and demonstrated strong calibration, accurately predicting treatment response across probability ranges. These results established circulating *DPD* and *MTHFR* as powerful non-invasive biomarkers and validated the nomogram as a robust tool for individualized response prediction. **Conclusion:** A predictive nomogram that incorporated *DPD* and *MTHFR* has improved individualized estimation of CapeOX neoadjuvant chemotherapy response in CRC, supporting precision oncology strategies.

Keywords: Colorectal cancer- chemotherapy- *DPD*- *MTHFR*- nomogram

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Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and the second leading cause of cancer-related death, accounting for nearly 1.9 million new cases and 881,000 deaths globally in 2020 [1]. Indonesia, CRC ranked fourth among all cancers, with a rising incidence particularly in urban populations [2]. CapeOX, a combination of capecitabine and oxaliplatin, was widely used as the first-line neoadjuvant chemotherapy regimen for advanced CRC. However, marked heterogeneity existed in patient response. Genetic variability in drug-metabolizing enzymes had been implicated as a determinant of chemotherapy outcomes [3].

Thymidylate synthase (*TS*), the primary target of 5-FU, played a central role in DNA synthesis, and its overexpression had been linked to reduced treatment sensitivity [4]. Dihydropyrimidine dehydrogenase (*DPD*) was the rate-limiting enzyme in 5-FU catabolism, where deficiency led to increased toxicity, while elevated expression could reduce efficacy [5]. Methylenetetrahydrofolate reductase (*MTHFR*) regulated folate metabolism and influenced 5-FU–*TS* binding efficiency, thus impacting tumor sensitivity [6]. Together, these biomarkers held promise as predictive indicators.

Nomograms had gained traction as clinical prediction tools, translating complex regression models into intuitive, individualized probability assessments [7]. While prior studies had evaluated *TS, DPD*, and *MTHFR* separately, few had developed integrative predictive nomograms in the CRC neoadjuvant setting. This study aimed to analyze the association of *TS*, *DPD*, and *MTHFR* expression in tissue and blood with chemotherapy response and to construct and validate a predictive nomogram model to

*Division of Digestive Surgery, Department of Surgery, Wahidin Sudirohusodo Hospital, Makassar, Indonesia. *For Correspondence: citraary91@gmail.com*

guide clinical decision-making in CRC.

Materials and Methods

Study Design and Population

This research was designed as a prospective cohort study and was carried out at RSUP Wahidin Sudirohusodo together with several affiliated hospitals. A total of thirty-six patients who had been newly diagnosed with stage III–IV colorectal adenocarcinoma and who were scheduled to receive fluoropyrimidine-based neoadjuvant chemotherapy were consecutively enrolledfrom Dec 2024 to Jun 2025. Patients were included after histopathological confirmation of adenocarcinoma and multidisciplinary team evaluation for chemotherapy eligibility. Subjects were excluded if they presented with signet-ring cell carcinoma or mucinous histology, if their tumor samples were damaged or inadequate for molecular analysis, or if they had incomplete follow-up during the study period. All patients provided written informed consent, and the study was approved by the institutional ethics committee in accordance with the Declaration of Helsinki. The number of samples were calculated accordingly using the minimum sample formula, which resulted in 36 minimal samples.

Sample Collection and Biomarker Analysis

Prior to the initiation of chemotherapy, both tumor tissue biopsies and peripheral blood samples were obtained from all participants. Total RNA was extracted from these specimens using Boom's silica-based method, which ensured high-quality nucleic acid isolation. The extracted RNA was then quantified and reverse-transcribed, and gene expression levels were determined using quantitative real-time polymerase chain reaction (qRT-PCR). The relative expression of thymidylate synthase (*TS*), dihydropyrimidine dehydrogenase (*DPD*), and methylenetetrahydrofolate reductase (*MTHFR*) was normalized against β-actin as a housekeeping gene to control for variation in RNA input.

Treatment and Response Evaluation

All patients received the CapeOX chemotherapy regimen as the neoadjuvant treatment of choice. The protocol consisted of capecitabine administered orally at a dose of 1000 mg/m² twice daily from days 1 to 14, in combination with oxaliplatin at a dose of 130 mg/m² delivered via intravenous infusion on day 1 of each cycle. The regimen was repeated every three weeks, with a total of four cycles planned per patient. Treatment adherence and toxicity profiles were closely monitored throughout the chemotherapy period. Tumor response was evaluated after the completion of four cycles using computed tomography (CT) scans. The Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was employed for standardized assessment. Patients who achieved complete response (CR) or partial response (PR) were categorized as responders, while those with stable disease (SD) or progressive disease (PD) were classified as non-responders.

Statistical Analysis

All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY) and R version 4.3 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were summarized as mean ± standard deviation (SD), whereas categorical variables were presented as frequencies and percentages. The relationship between biomarker expression levels and treatment response was explored using the Mann–Whitney U test for continuous data, chi-square test for categorical comparisons, and Spearman's rank correlation for non-parametric association. The discriminatory ability of biomarkers was assessed by constructing ROC curves, and the area under the curve (AUC) was calculated for each parameter. Biomarkers that demonstrated statistical significance were subsequently integrated into a predictive nomogram constructed with the "rms" package in R. Internal validation of the nomogram was carried out using 1,000 bootstrap resampling procedures to minimize overfitting. The performance of the model was further evaluated in terms of discrimination, measured by the concordance index (C-index), and calibration, assessed by plotting predicted versus observed probabilities of response.

Results

Patient Characteristics

A total of 36 patients with advanced colorectal cancer were enrolled in the study. The majority of participants were male (66.7%) with a median age of 45.6 years (range 34–62 years). Most tumors were located in the rectum (66.7%) and were histologically classified as well-differentiated adenocarcinomas (63.9%). After completion of four cycles of neoadjuvant chemotherapy, 18 patients (50%) were categorized as responders, achieving either complete response (CR) or partial response (PR), while the remaining 18 patients (50%) were identified as non-responders, presenting with either stable disease (SD) or progressive disease (PD). The median tumor reduction in the responder group reached 38.2%, whereas the non-responder group demonstrated a median tumor increase of 6.5%, a difference that was statistically significant ($p < 0.001$). Baseline demographic and clinical characteristics did not significantly differ between responders and non-responders ($p > 0.05$), indicating that treatment response was not attributable to initial patient characteristics (Table 1).

The median (interquartile range, IQR) gene expression values for *TS*, *DPD*, and *MTHFR* in tumor tissue samples were 8.985 (0.563), 7.879 (0.711), and 9.408 (0.954), respectively. In peripheral blood samples, the corresponding median (IQR) values were 10.010 (0.853) for *TS*, 9.009 (0.555) for *DPD*, and 8.057 (0.844) for *MTHFR*. Spearman's rank correlation analysis demonstrated strong positive correlations between tissue and blood expression levels for all three biomarkers: *TS* ($r = 0.820$, $p < 0.001$), *DPD* ($r = 0.658$, $p < 0.001$), and *MTHFR* ($r = 0.623$, $p < 0.001$). These findings indicated that blood-based assays closely reflected tumor expression patterns, suggesting that minimally invasive blood

Table 1. Characteristic of the Subjects

Variables	Non-responders		Responders		Total		p
	n	%	n	%	n	%	
Gender							
Male	11	30.6	13	36.1	24	66.7	0.362
Female	7	19.4	5	13.9	12	33.3	
Location							
Right colon	4	11.1	4	11.1	8	22.2	1.000
Left colon	2	5.6	2	5.6	4	11.1	
Rectum	12	33.3	12	33.3	24	66.7	
Histological grade							
Well	13	36.1	10	27.8	23	63.9	0.567
Moderate	4	11.1	6	16.7	10	27.8	
Poor	1	2.8	2	5.6	3	8.3	
	Mean	SD	Mean	SD	Mean	SD	
Age	46.11	8.78	45.17	7.51	45.64	8.02	0.673

TS, DPD, MTHFR gene expression in tissue and blood

sampling could potentially serve as a surrogate for tumor biopsy in the prediction of chemotherapy response.

Further subgroup analysis revealed significant differences in biomarker expression between responders and non-responders. As summarized in Table 2, patients classified as responders exhibited markedly lower *DPD* expression in blood samples compared with non-responders (7.637 vs. 8.288; $p < 0.001$). A similar trend was observed for *MTHFR* expression, which was also significantly reduced among responders compared with non-responders (9.112 vs. 9.699; $p < 0.001$). In contrast, *TS* expression in blood did not significantly differ between the two groups ($p > 0.05$), suggesting that *TS* was not a reliable discriminator of treatment response in this cohort.

Nomogram Development

Among all evaluated variables, only *DPD* and *MTHFR* gene expression levels in peripheral blood were found to significantly differentiate between responders and non-responders. Gene expression measured in tumor tissue was not included in the final analysis. Based on these findings, a predictive nomogram was successfully developed. The model demonstrated excellent discriminatory ability, achieving an area under the receiver operating characteristic curve (AUC) of 0.932 and a concordance index (C-index) of 0.78, indicating robust predictive performance and good calibration. In the construction of the nomogram, each gene expression value was translated into a corresponding point score. Lower gene expression levels were assigned higher point values, reflecting the observed negative correlation between expression and treatment response. For *DPD* expression values ranging from 10.5 to 7.5 and *MTHFR* expression values ranging from 12.0 to 6.0, progressively lower levels were associated with higher scores. These individual scores were then summed on the "Total Points" axis to generate an estimated probability of treatment response. For instance, a patient with a *DPD* expression of 8.0 and

Table 2. *TS, DPD, MTHFR* Gene Expression in Tissue and Blood

Gene expression	Non responders		Responders		Total		p
	Median	IQR	Median	IQR	Median	IQR	
TS							
Tissue	8.949	0.495	9.002	0.634	8.985	0.563	0.584
Blood	10.01	0.824	10.037	0.757	10.01	0.853	0.339
r = 0.820 (p<0.001*)							
DPD							
Tissue	8.288	0.963	7.637	0.693	7.879	0.711	<0.001*
Blood	9.27	0.59	8.835	0.362	9.009	0.555	<0.001*
r = 0.658 (p<0.001*)							
MTHFR							
Tissue	9.699	0.871	9.112	2.433	9.408	0.954	0.010*
Blood	8.469	1.075	7.675	0.765	8.057	0.844	<0.001*
r = 0.623 (p<0.001*)							

*significant

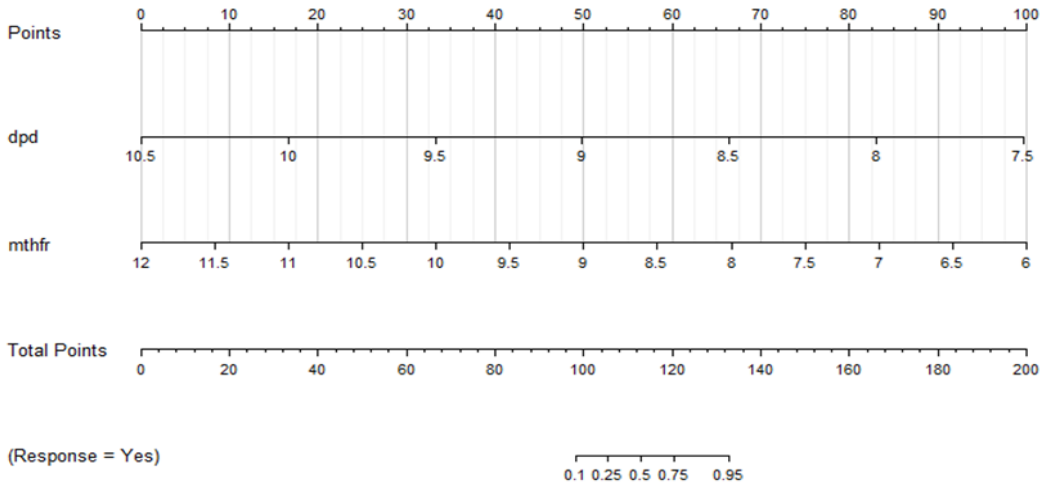

Figure 1. Nomogram Predicting the Probability of Response to Neoadjuvant CapeOX Chemotherapy in Patients with Colorectal Cancer. The nomogram incorporated peripheral blood expression levels of DPD and MTHFR as predictive variables. Each gene expression value was assigned a point score, with lower expression contributing to higher scores. The total score corresponded to the estimated probability of achieving a treatment response (complete or partial response).

an *MTHFR* expression of 7.0 achieved a high cumulative score, corresponding to a predicted probability of response exceeding 95%. This example underscored the practical value of the nomogram as a personalized clinical tool to guide therapeutic decision-making in colorectal cancer management (Figure 1).

Calibration plot evaluating the agreement between predicted and observed probabilities of response to CapeOX chemotherapy. The dashed diagonal line (y = x) indicated perfect prediction, whereas the solid calibration curve illustrated the actual performance of the nomogram. Across most probability ranges (0.3–0.9), the calibration curve closely approximated the ideal line, suggesting good predictive accuracy. A slight tendency toward underfitting was observed at lower predicted probabilities (<0.3). The surrounding dashed lines represented the 95% confidence intervals, within which the model's performance remained consistent and stable. Overall, the calibration plot demonstrated that the nomogram incorporating *DPD* and *MTHFR* blood expression was well-calibrated and reliable for estimating the probability of treatment response in patients receiving neoadjuvant CapeOX chemotherapy (Figure 2).

Discussion

This study demonstrated the feasibility and potential clinical utility of incorporating pharmacogenomic biomarkers into predictive models for neoadjuvant chemotherapy response in colorectal cancer (CRC). With CapeOX (capecitabine plus oxaliplatin) being widely adopted as a first-line regimen in Indonesia and globally,

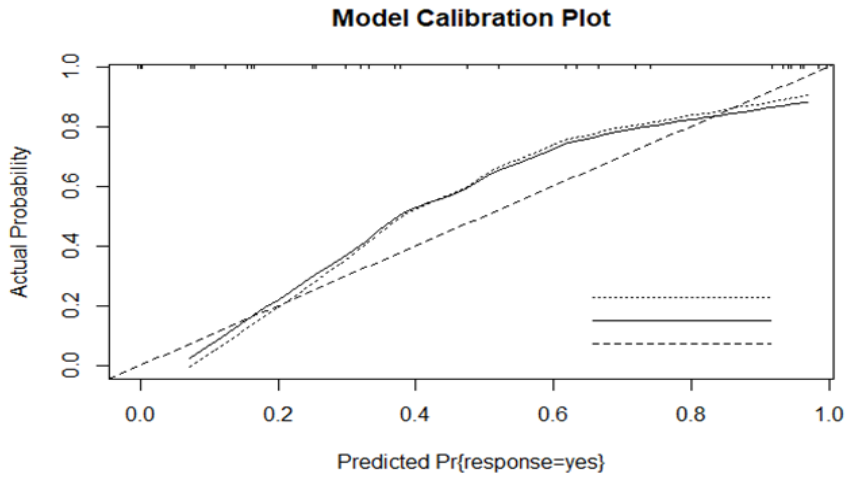

Figure 2. Calibration Plot of the Nomogram Model Developed in This Study. The dashed diagonal line (y = x) represented perfect agreement between predicted and observed probabilities of response, while the solid line showed the actual calibration of the model. Across most probability ranges, the calibration curve closely followed the ideal line, indicating good concordance. Slight deviations were observed at lower predicted probabilities, but the 95% confidence intervals demonstrated that the model maintained stable and reliable performance.

the ability to identify patients who were most likely to benefit from treatment was crucial for optimizing outcomes while minimizing unnecessary toxicity. By focusing on *DPD* and *MTHFR*, two enzymes central to fluoropyrimidine metabolism, the study provided compelling evidence that pre-treatment biomarker assessment could offer actionable insights, enabling clinicians to tailor therapy, avoid overtreatment, and preserve patient quality of life.

DPD emerged as an independent and biologically relevant predictor of response to CapeOX. As the primary enzyme responsible for catabolizing over 80% of administered 5-fluorouracil (5-FU), variability in *DPD* activity strongly influenced systemic drug exposure. Patients with reduced *DPD* activity exhibited higher circulating levels of 5-FU, which enhanced cytotoxic effects against tumor cells but simultaneously increased the risk of severe, sometimes life-threatening toxicity [8]. This duality highlighted the clinical challenge of using CapeOX in unselected populations. Incorporating *DPD* testing before chemotherapy initiation enabled oncologists to balance efficacy with safety. Patients with low *DPD* activity often required dose adjustments or alternative regimens, while those with normal activity tolerated standard dosing. Thus, including *DPD* in predictive models informed treatment selection and safeguarded against overtreatment [9].

In parallel, *MTHFR* was identified as another key biomarker affecting response to CapeOX [10]. Through its role in folate metabolism, *MTHFR* contributed to the stability of the 5-FU–thymidylate synthase (*TS*)–folate ternary complex, a crucial determinant of fluoropyrimidine activity [6].. Our findings aligned with studies reporting a positive association between *MTHFR* variants and chemotherapy response, particularly in gastrointestinal cancers. Importantly, these results could be applied prospectively to identify patients most likely to benefit from CapeOX, while sparing those with less favorable biomarker profiles from ineffective treatment and unnecessary toxicity [11].

The predictive nomogram developed in this study integrated *DPD* and *MTHFR* expression to estimate individualized probabilities of neoadjuvant chemotherapy response. With a concordance index of 0.78 and satisfactory calibration, the model showed strong discriminatory power. Bootstrap resampling mitigated overfitting and enhanced reliability. Clinically, the nomogram enabled stratification of patients: those with low predicted response could be considered for intensified or alternative therapies, while those with high predicted response proceeded with standard regimens, helping prevent overtreatment.

The majority of existing nomograms in colorectal cancer focus on prognosis (overall survival, disease-free survival) or on predicting pathological complete response after chemoradiotherapy, and they usually combine demographic, pathological and radiologic features for example, survival nomograms from major centers and registry-based models typically include age, TNM stage, grade, lymphovascular invasion and treatment variables and report C-indices commonly in the 0.70–0.85 range [12]. Existing nomograms that specifically predict response to neoadjuvant therapy in rectal cancer tend to rely on imaging (MRI features), clinical stage, and routine labs rather than pharmacogenomic biomarkers [13]. Against this background, our model differs in three clinically important ways. First, it uses blood (circulating) molecular markers that showed strong correlation with tumor expression in our cohort, permitting a minimally invasive assay that avoids repeated or difficult tissue sampling.

Compared with current guidelines from NCCN and ESMO, our findings highlighted an important gap [14, 15]. While these guidelines recommended testing for molecular drivers such as RAS, BRAF, and MSI in advanced CRC, pharmacogenomic markers like *DPD* and *MTHFR* were not routinely integrated into neoadjuvant chemotherapy decisions. To address this, we proposed a workflow: (1) pre-treatment blood testing for *DPD* and *MTHFR*; (2) nomogram scoring to estimate individualized response probabilities and stratify risk high probability: standard CapeOX; intermediate: dose adjustment or added monitoring; low: consider alternative regimens or clinical trials; (3) treatment initiation with biomarker-informed adjustments and close toxicity monitoring.

A notable strength of our study was the dual evaluation of biomarker expression in both tumor tissue and circulating blood samples. The strong correlation observed between tissue-based and blood-based markers for *DPD* and *MTHFR* suggested that blood samples represented a non-invasive, practical, and widely accessible method for biomarker assessment. This was particularly relevant in real-world clinical settings, where tumor tissue was often difficult to obtain due to procedural risks, patient comorbidities, or insufficient sample size. On the other hand, these findings resonated with the broader paradigm shift in oncology from uniform treatment approaches to personalized, biomarker-guided strategies [16]. While predictive nomograms had been successfully developed and applied in other malignancies, such as breast and gastric cancers, their application in colorectal cancer remained relatively limited [17]. By integrating pharmacogenomic markers into a predictive model, this study provided an important contribution to the emerging evidence base for precision oncology in CRC.

Nevertheless, limitations had to be acknowledged. Our study was conducted at a single center, which may have limited generalizability. The modest cohort size reduced the statistical power for subgroup analyses, and important molecular drivers of CRC, such as KRAS, NRAS, BRAF, and MSI, were not included, despite their established roles in prognosis and treatment selection. Incorporating these variables in future models could have enhanced predictive accuracy and provided a more comprehensive tool for guiding clinical decision-making. External validation across larger, multi-center, and ethnically diverse cohorts would also have been essential to confirm the clinical utility of our nomogram.

In conclusion, this study provided strong evidence that *DPD* and *MTHFR* were valuable biomarkers for predicting response to neoadjuvant CapeOX chemotherapy in colorectal cancer. By integrating these biomarkers into a predictive nomogram, we demonstrated

the feasibility of transforming pharmacogenomic data into practical decision-support tools for clinicians. Such approaches helped optimize patient selection, reduced overtreatment, improved survival outcomes, and advanced the implementation of precision oncology in CRC management.

In conclusion, a predictive nomogram that incorporated *DPD* and *MTHFR* improved individualized estimation of CapeOX neoadjuvant chemotherapy response in CRC, supporting precision oncology strategies.

Author Contribution Statement

All authors contributed equally in this study.

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References

1. Rawla P, Sunkara T, Barsouk A. Epidemiology of colorectal cancer: Incidence, mortality, survival, and risk factors. Prz Gastroenterol . 2019;14(2):89-103. https://doi.org/10.5114/pg.2018.81072.
2. Purnomo HD, Permatadewi CO, Prasetyo A, Indiarso D, Hutami HT, Puspasari D, et al. Colorectal cancer screening in semarang, indonesia: A multicenter primary health care based study. PloS one. 2023;18(1):e0279570. https://doi.org/10.1371/journal.pone.0279570.
3. Liu F, Yang L, Wu Y, Li C, Zhao J, Keranmu A, et al. Capox as neoadjuvant chemotherapy for locally advanced operable colon cancer patients: A prospective single-arm phase ii trial. Chinese J Cancer Res . 2016;28(6):589-97. https://doi.org/10.21147/j.issn.1000-9604.2016.06.05.
4. Zhang N, Yin Y, Xu SJ, Chen WS. 5-fluorouracil: Mechanisms of resistance and reversal strategies. Molecules (Basel, Switzerland). 2008;13(8):1551-69. https://doi.org/10.3390/molecules13081551.
5. Latchman J, Guastella A, Tofthagen C. 5-fluorouracil toxicity and dihydropyrimidine dehydrogenase enzyme: Implications for practice. Clin J Oncol Nurs. 2014;18(5):581-5. https://doi.org/10.1188/14.Cjon.581-585.
6. Etienne MC, Ilc K, Formento JL, Laurent-Puig P, Formento P, Cheradame S, et al. Thymidylate synthase and methylenetetrahydrofolate reductase gene polymorphisms: Relationships with 5-fluorouracil sensitivity. Br J Cancer. 2004;90(2):526-34. https://doi.org/10.1038/sj.bjc.6601523.
7. Balachandran VP, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: More than meets the eye. Lancet Oncol. 2015;16(4):e173-80. https://doi.org/10.1016/s1470-2045(14)71116-7.
8. de Moraes FCA, de Almeida Barbosa AB, Sano VKT, Kelly FA, Burbano RMR. Pharmacogenetics of dpyd and treatment-related mortality on fluoropyrimidine chemotherapy for cancer patients: A meta-analysis and trial sequential analysis. BMC cancer. 2024;24(1):1210. https://doi.org/10.1186/s12885-024-12981-5.
9. Ho TT, Smith DM, Aquilante CL, Cicali EJ, El Rouby N, Hertz DL, et al. A guide for implementing dpyd genotyping for systemic fluoropyrimidines into clinical practice. Clin Pharmacol Ther . 2025;117(5):1194-208. https://doi.org/10.1002/cpt.3567.
10. Amirfallah A, Kocal GC, Unal OU, Ellidokuz H, Oztop I, Basbinar Y. Dpyd, tyms and *MTHFR* genes polymorphism frequencies in a series of turkish colorectal cancer patients. J Pers Med. 2018;8(4). https://doi.org/10.3390/jpm8040045.
11. Zintzaras E, Ziogas DC, Kitsios GD, Papathanasiou AA, Lau J, Raman G. *MTHFR* gene polymorphisms and response to chemotherapy in colorectal cancer: A meta-analysis. Pharmacogenomics. 2009;10(8):1285-94. https://doi.org/10.2217/pgs.09.59.
12. Wu H, Liu GJ, Zhang ZY, Wu W, Meng YF, Wang S, et al. Nomogram including chemotherapy response for prediction of intrahepatic progression-free survival in patients with colorectal liver metastasis through chemotherapy followed by radiofrequency ablation. Int J Hypertherm. 2021;38(1):633-9. https://doi.org/10.1080/02656736.2021.1912415.
13. Tang X, Jiang W, Li H, Xie F, Dong A, Liu L, et al. Predicting poor response to neoadjuvant chemoradiotherapy for locally advanced rectal cancer: Model constructed using pre-treatment mri features of structured report template. Radiother Oncol. 2020;148:97-106. https://doi.org/10.1016/j.radonc.2020.03.046.
14. Benson AB, Venook AP, Adam M, Chang G, Chen YJ, Ciombor KK, et al. Nccn guidelines® insights: Rectal cancer, version 3.2024. J Natl Compr Canc Netw. 2024;22(6):366-75. https://doi.org/10.6004/jnccn.2024.0041.
15. Hofheinz RD, Fokas E, Benhaim L, Price TJ, Arnold D, Beets-Tan R, et al. Localised rectal cancer: Esmo clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol. 2025;36(9):1007-24. https://doi.org/10.1016/j.annonc.2025.05.528.
16. Jørgensen JT. A paradigm shift in biomarker guided oncology drug development. Ann Transl Med. 2019;7(7):148. https://doi.org/10.21037/atm.2019.03.36.
17. Wang Q, Shen K, Fei B, Wei M, Ge X, Xie Z. Development and validation of a nomogram to predict cancer-specific survival of elderly patients with unresected gastric cancer who received chemotherapy. Sci rep. 2024;14(1):9008. https://doi.org/10.1038/s41598-024-59516-3.