FACTORS ASSOCIATED WITH SYNCHRONOUS METASTATIC PRESENTATION AND 24-MONTH PROGRESSION-FREE SURVIVAL IN COLORECTAL CANCER

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FACTORS ASSOCIATED WITH SYNCHRONOUS METASTATIC PRESENTATION AND 24-MONTH PROGRESSION-FREE SURVIVAL IN COLORECTAL CANCER (Abstract): Early identification of patients presenting with synchronous metastatic colorectal cancer (mCRC) is essential for optimizing staging and treatment. This study **aimed** to identify preoperative MRI-derived tumor characteristics independently associated with synchronous metastatic presentation and to develop an internally validated preoperative clinical–imaging prediction model. **Materials and methods:** We prospectively enrolled 161 patients with colorectal cancer, including 23 (14.3%) with synchronous metastatic disease. Univariable and multivariable Firth penalized logistic regression identified independent preoperative predictors of metastatic presentation. Model performance was assessed using the area under the receiver operating characteristic curve (ROC-AUC) and internally validated by leave-one-out cross-validation (LOOCV). Secondary analyses evaluated pathological and perioperative characteristics associated with metastatic disease, while progression-free survival (PFS) was estimated using the Kaplan–Meier method. (3) **Results:** Patients with synchronous mCRC more frequently presented with positive MRI circumferential resection margins (mCRM), MRI-detected extramural venous invasion (mrEMVI), anterior tumor location, and tumors located <4 cm from the anal verge (all $p < 0.001$). In multivariable analysis, mrEMVI (adjusted OR 16.11, 95% CI 3.09–83.97; $p < 0.001$) and positive mCRM (adjusted OR 7.56, 95% CI 1.57–36.31; $P = 0.012$) remained independently associated with synchronous metastatic presentation. The parsimonious preoperative model demonstrated an apparent ROC-AUC of 0.904 and a cross-validated ROC-AUC of 0.846 (95% CI 0.706–0.961), with a Brier score of 0.063. Metastatic patients also exhibited higher rates of positive pathological circumferential resection margins, incomplete total mesorectal excision, perioperative blood transfusion, and extensive nodal involvement. Estimated PFS was 75.0% at 24 months and 41.7% at 36 months. **Conclusions:** Preoperative mrEMVI and positive mCRM are independent MRI biomarkers of synchronous metastatic colorectal cancer. **Keywords:** COLORECTAL CANCER; SYNCHRONOUS METASTASES; MAGNETIC RESONANCE IMAGING; EXTRA-MURAL VENOUS INVASION; CIRCUMFERENTIAL RESECTION MARGIN; RISK STRATIFICATION.

INTRODUCTION

Colorectal cancer (CRC) remains one of the leading causes of cancer-related morbidity and mortality worldwide, with distant metastasis representing the principal determinant of long-term survival and therapeutic strategy. Despite major advances in screening, molecular characterization, and systemic treatment, approximately 20–25% of patients present with synchronous metastatic disease at the time of diagnosis, reflecting the biological heterogeneity of CRC and emphasizing the need for accurate risk stratification at initial presentation (1, 2) Early identification of patients at increased risk for synchronous metastases is clinically relevant because metastatic status directly influences treatment sequencing, the feasibility of curative surgery, selection of neoadjuvant or conversion therapies, and overall prognosis.

Current diagnostic evaluation relies primarily on contrast-enhanced computed tomography (CECT) for staging, complemented by clinicopathological and laboratory data. Although conventional imaging remains the cornerstone of metastatic assessment, occult metastatic disease may still be missed during initial staging, particularly in patients with early peritoneal dissemination or small-volume liver and lung metastases. Consequently, considerable research efforts have focused on developing predictive models capable of identifying patients with a high probability of synchronous metastatic disease before definitive treatment. These models integrate clinical, imaging, pathological, and increasingly molecular variables, achieving moderate-to-high discriminative performance, with reported areas under the receiver operating characteristic curve (AUCs) ranging from approximately 0.73 to 0.88. Nevertheless, external validation remains limited, preventing widespread implementation in routine clinical practice (3-5).

Among clinical predictors, serum tumor markers remain the most consistently validated biomarkers. Elevated carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) concentrations have repeatedly been identified as independent predictors of synchronous distant metastases, reflecting increased tumor burden and biologically aggressive disease ((3, 4). Patient-related characteristics also appear to influence metastatic behavior. Younger age at diagnosis has been associated with a higher likelihood of de novo metastatic disease, particularly in early-onset colorectal cancer (EOCRC), a rapidly increasing clinical entity characterized by distinct molecular and pathological features (4, 6). Emerging epidemiological evidence further suggests that dietary habits, including high dietary sugar intake, may contribute to the development of de novo metastatic EOCRC, while racial and ethnic disparities have been associated with different metastatic patterns, with non-Hispanic Black patients demonstrating an increased propensity for combined hepatic and pulmonary synchronous metastases (6, 7).

Imaging-derived biomarkers have substantially expanded the predictive landscape of synchronous metastasis. Recent studies combining CECT-derived features with clinical variables have reported excellent discrimination for overall synchronous metastatic disease (AUC approximately 0.85) and even higher performance for synchronous peritoneal metastases (AUC approximately 0.87), outperforming conventional staging alone (3). Independent imaging predictors include tumor necrosis,

arterial-to-venous phase attenuation differences, tumor length-to-thickness ratio, and lymph node necrosis, all of which reflect aggressive tumor biology and increased metastatic potential. Likewise, the presence of ascites on staging CT has emerged as a significant indicator of synchronous peritoneal dissemination (3, 8). Parallel advances in radiomics have enabled quantitative extraction of imaging biomarkers invisible to the human eye. A recent meta-analysis demonstrated pooled diagnostic performance approaching an AUC of 0.85 for preoperative radiomics models predicting synchronous liver metastases, although publication bias and methodological heterogeneity may partially overestimate these results (9). Similar radiomics-based nomograms have also shown promising performance for predicting peritoneal metastatic disease before surgery (4).

Histopathological characteristics remain among the strongest indicators of metastatic potential. Vascular invasion, high-grade tumor budding (BD3), and an invasive tumor component exceeding 8 mm have consistently demonstrated independent associations with metastatic spread in early invasive colorectal carcinoma (10). Likewise, perineural invasion has emerged as an independent predictor of synchronous distant metastases, highlighting the role of local invasive pathways in systemic dissemination (4, 11). Increasing evidence also indicates that de novo colorectal cancers differ biologically from carcinomas arising through the conventional adenoma-carcinoma sequence. These tumors exhibit greater tumor budding, reduced E-cadherin expression, increased vimentin expression, and a more aggressive epithelial-to-mesenchymal transition phenotype, all consistent with enhanced metastatic capability (12). In patients with EOCRC, synchronous metastatic disease has additionally been associated with a higher prevalence of RAS mutations compared with localized tumors, whereas de novo cancers appear predominantly microsatellite stable (MSS), suggesting distinct molecular mechanisms underlying metastatic dissemination (12, 13). A five-variable logistic model incorporating vascular invasion, BD3, invasive width greater than 8 mm, invasive depth greater than 1.5 mm, and expansive desmoplasia demonstrated excellent predictive performance for metastatic disease in pT1 colorectal carcinoma, illustrating the value of integrated pathological risk assessment (10).

Perioperative factors also contribute to patient outcomes and treatment planning. Primary tumor resection has been associated with improved survival among selected patients with metastatic CRC, while emergency surgery occurs more frequently in patients presenting with synchronous metastatic EOCRC (11, 13). For colorectal peritoneal metastases, delayed surgery and intestinal obstruction have been identified as predictors of incomplete cytoreduction, emphasizing the importance of early identification and appropriate patient selection (8).

However, despite increasing interest in advanced biomarkers, including CT perfusion parameters, immunohistochemical markers, and genomic profiling, these novel approaches have not consistently demonstrated incremental predictive value beyond established clinicopathological models incorporating age, sex, tumor stage, tumor location, size, and venous invasion (14).

Although numerous prognostic models have been proposed, several limitations continue to hinder their clinical translation.

Most published studies are retrospective, single-center investigations with relatively small sample sizes, substantial methodological heterogeneity, and limited external validation (3). While integrated clinical-imaging models frequently achieve AUCs between 0.85 and 0.88 in derivation cohorts, predictive performance often decreases during independent validation, with reported AUCs around 0.78, raising concerns regarding generalizability and real-world applicability (4). Furthermore, recent evidence suggests that although comprehensive clinicopathological models outperform conventional TN staging alone, incorporation of novel biomarkers has yet to provide clinically meaningful improvements in predictive accuracy (14).

Given these considerations, a comprehensive evaluation of established and emerging predictors of synchronous metastatic disease is warranted. Integrating clinical characteristics, laboratory biomarkers, imaging features, pathological parameters, and perioperative factors may facilitate earlier identification of high-risk patients, optimize individualized staging strategies, and improve multidisciplinary therapeutic decision-making.

This study aimed to determine which preoperative MRI-derived tumor characteristics are independently associated with synchronous metastatic presentation in rectal cancer and to develop and internally validate a parsimonious preoperative clinical–imaging model for metastatic risk stratification.

Secondary analyses compared pathological and perioperative characteristics between metastatic and non-metastatic patients and described progression - free survival in patients presenting with synchronous metastatic disease.

MATERIALS AND METHODS

We performed a prospective observational study at the Oncology Center Euroclinic, Iasi, Romania, between October 2023 to July 2026 that included patients with patients diagnosed with colorectal cancer (CRC). Ethical approval for this study was obtained from the Institutional Ethics Committees of the Grigore T. Popa University of Medicine and Pharmacy (No. 672/ 12.11.2025) and of the Oncology Center Euroclinic (No. 2855/15.02.2025).

The present analysis was specifically designed to investigate prognostic heterogeneity among patients presenting with synchronous metastatic colorectal cancer (mCRC), defined as the presence of distant metastatic disease at the time of diagnosis of the primary tumor.

The final database comprised 162 patient records, out of which 24 patients have been diagnosed with synchronous metastatic CRC. All variables included in the primary analyses were complete, and no missing data were observed among either the candidate predictors or study outcomes.

Candidate variables were prespecified according to clinical relevance and data availability. Demographic characteristics included age and sex, whereas clinicopathological and perioperative variables comprised mesorectal circumferential resection margin (mCRM_r), extramural vascular invasion (EMVI_r), anterior tumor location (anterior_r), tumor distance from the anal verge (distance_r), pathological circumferential resection margin (pCRM_r), incomplete total mesorectal excision (incomplete_TME_r), lymph node yield below five (5_LN_r), and perioperative blood transfusion (transfusion_r).

Continuous variables were summarized as mean ± standard deviation (SD) or me-

dian with interquartile range (IQR), as appropriate, whereas categorical variables were reported as frequencies and percentages. Baseline characteristics were compared between patients with non-metastatic colorectal cancer (CRC) and those presenting with synchronous metastatic colorectal cancer (mCRC). Continuous variables were compared using the Wilcoxon rank-sum test, while categorical variables were analyzed using Fisher's exact test. Standardized mean differences (SMDs) were additionally calculated to quantify the magnitude of between-group imbalances independently of sample size.

The primary objective of the statistical analysis was to identify preoperative factors associated with synchronous metastatic presentation. Univariable associations between each preoperative clinical or MRI-derived variable (age, sex, MRI circumferential resection margin [mCRM], MRI-detected extramural venous invasion [mrEMVI], anterior tumor location, and tumor distance from the anal verge) and synchronous metastatic status were evaluated using Firth penalized logistic regression. Odds ratios (ORs), 95% Wald confidence intervals (CIs), and two-sided P values were reported. Firth penalization was selected to reduce small-sample bias and to account for sparse data and quasi-complete separation resulting from the relatively small number of metastatic cases.

A parsimonious multivariable Firth logistic regression model was subsequently constructed to identify factors independently associated with synchronous metastatic presentation. To minimize overfitting, only age together with the two MRI-derived variables demonstrating the strongest clinical relevance (mCRM and mrEMVI) were retained in the final model. Adjusted odds ratios (aORs) with 95% Wald confidence intervals were reported.

The discriminative ability of the parsimonious preoperative model was evaluated using the area under the receiver operating characteristic curve (ROC-AUC). Internal validation was performed using leave-one-out cross-validation (LOOCV), whereby each patient served once as an independent validation case. Cross-validated discrimination was summarized by the ROC-AUC with bootstrap-derived 95% confidence intervals, and overall predictive accuracy was quantified using the out-of-fold Brier score.

As secondary analyses, pathological and perioperative characteristics, including pathological circumferential resection margin (pCRM), incomplete total mesorectal excision (TME), perioperative blood transfusion, and the presence of more than five metastatic lymph nodes, were evaluated for their association with synchronous metastatic presentation using univariable Firth logistic regression. Because these variables become available only during or after surgery, they were analyzed separately from the preoperative prediction model and were interpreted as markers associated with metastatic disease rather than preoperative predictors.

Among patients with synchronous metastatic colorectal cancer, progression-free survival (PFS) was estimated using the Kaplan–Meier method. PFS was defined as the interval from diagnosis to the first documented disease progression or recurrence. Patients without progression were censored at the date of their last clinical follow-up. Estimated progression-free survival probabilities with corresponding 95% confidence intervals were reported at predefined time points.

All analyses were performed according to a prespecified statistical analysis plan using *R software version 4.2.2* (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two-sided, and a nominal significance threshold of $p < 0.05$ was adopted.

RESULTS

Population characteristics were summarized in first table. The mean age was 63.6±9.4 years and 65/161 patients (40.4%) were female. Age and sex were similar between groups. Marked imbalances were observed for mCRM (78.3% *vs.* 8.0%), mrEMVI (73.9% *vs.* 2.9%), anterior location (73.9% *vs.* 8.0%), tumor <4 cm from the anal verge (78.3% *vs.* 25.4%), incomplete TME (34.8% *vs.* 8.0%), transfusion (30.4% *vs.* 9.4%), >5 positive nodes (73.9% *vs.* 2.2%), and pCRM (56.5% *vs.* 2.2%)

TABLE I.
Characteristics of the study population.

Characteristic	CRC (n=138)	Synchronous mCRC (n=24)	SMD	p
Age	63.2 ± 9.4; median 64.0 [56.0–71.0]	66.2 ± 9.3; median 64.0 [62.5–74.5]	0.33	0.191
Female sex	56/138 (40.6%)	9/23 (39.1%)	-0.03	1.000
Positive circumferential resection margin on MRI (mCRM)	11/138 (8.0%)	18/23 (78.3%)	2.01	<0.001
Extramural venous invasion on MRI (mrEMVI)	4/138 (2.9%)	17/23 (73.9%)	2.14	<0.001
Anterior tumor location	11/138 (8.0%)	17/23 (73.9%)	1.81	<0.001
Tumor <4 cm from the anal verge	35/138 (25.4%)	18/23 (78.3%)	1.25	<0.001
Incomplete total mesorectal excision	11/138 (8.0%)	8/23 (34.8%)	0.69	0.001
Need for perioperative blood transfusion	13/138 (9.4%)	7/23 (30.4%)	0.55	0.011
More than 5 positive lymph nodes	3/138 (2.2%)	17/23 (73.9%)	2.19	<0.001
Positive pathological circumferential resection margin (pCRM)	3/138 (2.2%)	13/23 (56.5%)	1.49	<0.001

pCRM- pathological (positive) circumferential resection margin; mCRM- positive circumferential resection margin on MRI; mrEMVI- extramural venous invasion on MRI; SD- standard deviation.

The univariable Firth logistic regression analysis identified several preoperative MRI-derived and anatomical tumor characteristics that were significantly associated with synchronous metastatic presentation (tab. II). Neither age (OR per 10-year increase, 1.42; 95% CI, 0.87–2.31; $p = 0.163$) nor sex (OR, 0.96; 95% CI, 0.39–2.32; $p = 0.922$) was associated with metastatic status at diagnosis.

Among imaging variables, the presence of extramural venous invasion on MRI (mrEMVI) demonstrated the strongest association with synchronous metastatic disease (OR, 18.47; 95% CI, 7.91–25.59; $p < 0.001$). Similarly, a positive circumferential resection margin on MRI (mCRM) was associated with substantially increased

odds of metastatic presentation (OR, 37.29; 95% CI, 12.08–115.11; p < 0.001).

Tumor anatomical characteristics were also significantly associated with metastatic disease. Anterior tumor location was associated with an increase in the odds of synchronous metastases (OR, 9.85; 95% CI, 3.10–18.24; p < 0.001), while tumors located within 4 cm of the anal verge demonstrated nearly a tenfold higher odd of metastatic presentation (OR, 9.81; 95% CI, 3.52–17.34; p < 0.001).

TABLE II.

Univariable firth logistic regression for synchronous metastatic presentation

Preoperative Characteristic	Firth OR	95% Wald CI	p value
Age (per 10-year increase)	1.42	0.87–2.31	0.163
Female sex	0.96	0.39–2.32	0.922
Positive circumferential resection margin on MRI (mCRM)	37.29	12.08–115.11	<0.001
Extramural venous invasion on MRI (mrEMVI)	18.47	7.91–25.59	<0.001
Anterior tumor location	9.85	3.10–18.24	<0.001
Tumor <4 cm from the anal verge	9.81	3.52–17.34	<0.001

mCRM- positive circumferential resection margin on MRI; mrEMVI- extramural venous invasion on MRI; OR- odds ratio; CI- confidence interval.

In the parsimonious multivariable Firth logistic regression model, mrEMVI and mCRM remained independently associated with synchronous metastatic presentation after adjustment for age (tab. III).

The presence of mrEMVI was associated with a more than 16-fold increase in the odds of synchronous metastatic disease (adjusted OR, 16.11; 95% CI, 3.09–83.97; p < 0.001), representing the strongest independent association identified in the model. Likewise, a positive mCRM remained significantly associated with metastatic presentation, conferring approximately 7.5-fold higher adjusted odds (adjusted OR, 7.56; 95% CI, 1.57–36.31; p = 0.012).

TABLE III.

Parsimonious multivariable firth logistic regression model for synchronous metastatic presentation

Variable	Adjusted Firth OR	95% Wald CI	p value
Age (per 10-year increase)	1.19	0.57–2.47	0.648
Positive circumferential resection margin on MRI (mCRM)	7.56	1.57–36.31	0.012
Extramural venous invasion on MRI (mrEMVI)	16.11	3.09–83.97	<0.001

Legend: mCRM- positive circumferential resection margin on MRI; mrEMVI- extramural venous invasion on MRI; OR- odds ratio; CI- confidence interval.

Conversely, age was not independently associated with synchronous metastatic disease after adjustment for MRI-derived tumor characteristics (adjusted OR per 10-year increase, 1.19; 95% CI, 0.57–2.47; p = 0.648).

The apparent ROC-AUC was 0.904. LOOCV reduced the ROC-AUC to 0.846 (bootstrap 95% CI 0.706–0.961). The out-of-fold Brier score was 0.063. The decrease from apparent to cross-validated performance and the wide interval indicate optimism and limited precision (fig. 1).

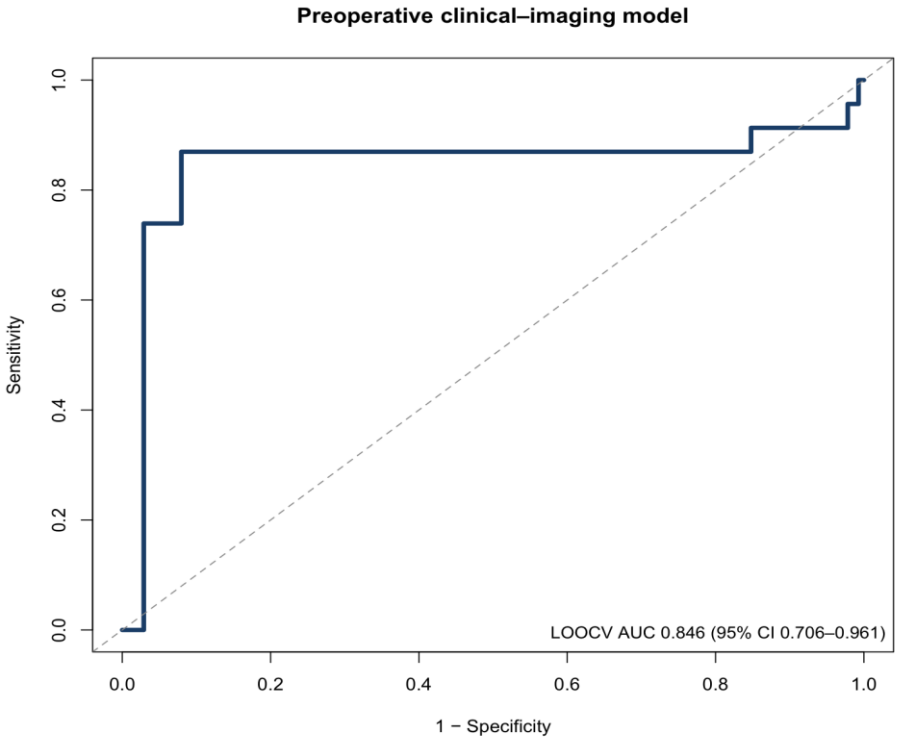

Fig. 1. Leave-one-out cross-validated ROC curve
for the parsimonious preoperative clinical–imaging model.

Patients with synchronous mCRC more frequently had incomplete TME (37.5% *vs.* 8.0%), required transfusion (54.2% *vs.* 9.4%), had more than five positive lymph nodes (75.0% *vs.* 2.2%), and had positive pCRM (58.3% *vs.* 2.2%) (tab. V).

TABLE V.
Pathological and perioperative characteristics associated with synchronous metastatic presentation

Characteristic	CRC (n=138)	Synchronous mCRC (n=23)	Univariable Firth OR	95% CI	p value
Incomplete total mesorectal excision	11/138 (8.0%)	9/24 (37.5%)	6.80	2.48–18.62	<0.001
Need for perioperative blood transfusion	13/138 (9.4%)	13/24 (54.2%)	10.91	4.15–28.68	<0.001
More than 5 positive lymph nodes	3/138 (2.2%)	18/24 (75.0%)	110.19	27.52–441.19	<0.001
Positive pathological circumferential resection margin (pCRM)	3/138 (2.2%)	14/24 (58.3%)	53.46	14.20–201.22	<0.001

pCRM- pathological (positive) circumferential resection margin; OR- odds ratio; CI- confidence interval.

Among the 24 patients with synchronous metastatic disease, 14 progression/recurrence events were recorded. Estimated progression-free survival was 100.0% at 12 months, 75.

0% at 24 months, and 41.7% at 36 months (36-month 95% CI 26.0–66.9%) (fig. 2).

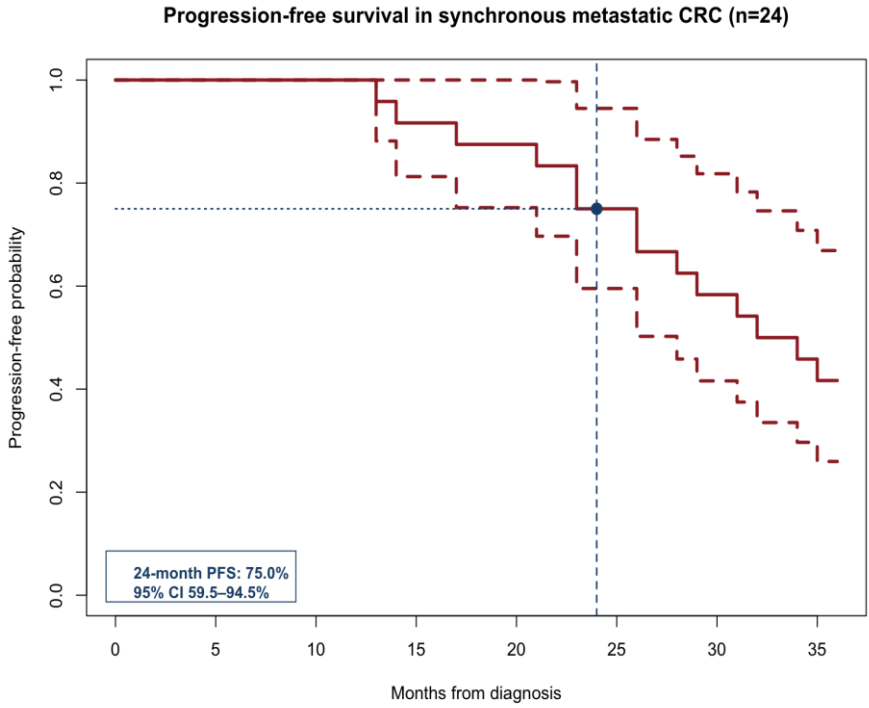

Fig. 2. Kaplan–Meier estimate of progression-free survival among all 24 patients with synchronous metastatic colorectal cancer.

DISCUSSION

The present study demonstrates that preoperative MRI-derived tumor characteristics are strongly associated with synchronous metastatic presentation in colorectal cancer. Among all evaluated variables, MRI-detected extramural venous invasion (mrEMVI) and a positive MRI circumferential resection margin (mCRM) remained independently associated with synchronous metastatic disease after multivariable adjustment, whereas age was not independently associated after accounting for

MRI-derived tumor characteristics. Furthermore, a parsimonious model incorporating only routinely available preoperative MRI variables achieved good discrimination after internal validation (cross-validated ROC-AUC 0.846), supporting the feasibility of MRI-based risk stratification before surgery.

Our findings are highly consistent with the current body of evidence supporting mrEMVI as one of the strongest imaging biomarkers of systemic tumor dissemination. Biologically, extramural venous invasion represents direct penetration of tumor cells into the extramural venous circulation, providing a plausible mechanism for early hematogenous spread, particularly to

the liver.

This biological rationale has been confirmed by two independent meta-analyses. Fournier *et al*. reported that pre-treatment mrEMVI positivity increased the risk of synchronous metastases more than fourfold (pooled RR 4.11) and was also associated with poorer disease-free and overall survival (15). Similarly, Siddiqui *et al*. demonstrated a pooled odds ratio of 5.68 for synchronous metastatic disease and an odds ratio of 3.91 for subsequent distant metastases, reinforcing the concept that mrEMVI reflects a biologically aggressive tumor phenotype rather than simply advanced local disease (16). The strong independent association observed in our cohort therefore corroborates these findings and further supports the incorporation of mrEMVI into routine preoperative risk stratification.

Evidence from large observational cohorts also strengthens this interpretation. Zhang *et al*. showed that both mrEMVI and mesorectal fascia involvement independently predicted metastasis-free survival and overall survival while demonstrating excellent interobserver reproducibility (κ = 0.80) for mrEMVI assessment (17). More recently, Geffen *et al*. reported a progressive increase in distant metastatic risk according to mrEMVI grade within the Dutch national cohort, with distant metastases occurring in approximately half of patients with grade 4 mrEMVI and nearly one-quarter developing metastatic disease within three months following surgery (18). These studies suggest that standardized MRI captures biological characteristics that extend well beyond anatomical staging and may identify patients with occult systemic disease at presentation.

The independent association between mCRM and synchronous metastatic presentation observed in our study is biologically plausible and broadly concordant with previous literature, although the available evidence is less robust than for mrEMVI. Positive or threatened mCRM has consistently been associated with locally advanced disease, incomplete surgical clearance, local recurrence, and inferior oncological outcomes (19-21). More recently, MRI-based predictive models and radiomics analyses developed by Yao *et al*. (22) and Yanqing *et al*. (23) demonstrated that mCRM remained an independent contributor to preoperative models predicting recurrence and distant metastases. Nevertheless, unlike mrEMVI, relatively few studies have specifically evaluated the relationship between mCRM and synchronous metastatic presentation. Consequently, our findings extend the existing evidence by suggesting that MRI-defined circumferential margin involvement may identify tumors with both extensive local invasion and increased metastatic potential.

Anterior tumor location and tumor distance from the anal verge were associated with metastatic presentation in the univariable analyses but were not retained in the final multivariable model after adjustment for MRI-derived tumor aggressiveness. This observation mirrors the heterogeneous literature regarding tumor location. Several population-based studies (24, 25) have reported associations between tumor location and specific metastatic patterns, whereas others have failed to demonstrate an independent effect after accounting for tumor stage and imaging characteristics. Our findings therefore support the hypothesis that tumor location may function primarily as a surrogate marker for aggressive local tumor biology rather than representing a universal independent determinant of metastatic dissemination.

Neither age nor sex was independently

associated with synchronous metastatic presentation in our cohort. These findings should be interpreted cautiously because the literature remains inconsistent. While several imaging-based studies similarly failed to identify independent demographic effects, large epidemiological analyses have reported a higher frequency of metastatic presentation among younger patients (24). Likewise, although sex appears to exert little influence on overall metastatic risk, female sex has been associated with an increased likelihood of synchronous peritoneal metastases in studies by Alexandrescu *et al*. (25) and Zhang *et al*. (17). Consequently, our results suggest that MRI-derived tumor biology contributes substantially more prognostic information than demographic variables.

The pathological and perioperative findings further characterize the phenotype of synchronous metastatic disease. Patients presenting with metastases exhibited markedly higher frequencies of positive pathological circumferential resection margins, extensive lymph node involvement, incomplete total mesorectal excision, and perioperative blood transfusion. These variables should not be interpreted as predictors of metastasis because they become available only during or after surgery. Rather, they most likely represent downstream manifestations of advanced tumor burden and technically more demanding resections, emphasizing the close relationship between systemic dissemination and locally advanced pelvic disease.

The parsimonious MRI-based prediction model demonstrated excellent apparent discrimination (ROC-AUC 0.904) and maintained good performance following leave-one-out cross-validation (ROC-AUC 0.846). However, the reduction in discrimination after internal validation and the relatively wide confidence interval indicate optimism and limited statistical precision, both expected consequences of the relatively small number of metastatic cases. Similar observations have been reported in MRI-based predictive studies by Yao *et al*. (22)and in multicenter modelling studies by Rumpold *et al*. (26), where internally validated performance remained encouraging but external validation consistently resulted in reduced discrimination. Therefore, our model should be considered an internally validated tool requiring independent external validation.

From a clinical perspective, one of the principal strengths of this approach is that both mrEMVI and mCRM are already included in standardized pelvic MRI assessment and require no additional imaging techniques, molecular analyses, or laboratory biomarkers. Consequently, systematic reporting of these features could facilitate earlier identification of patients at increased risk of synchronous metastatic disease, prompting more comprehensive systemic staging, multidisciplinary discussion, and individualized treatment planning. This concept is consistent with recent MRI-based prediction study by Geffen *et al*. (18), which advocates integrating imaging biomarkers into preoperative decision-making while emphasizing the need for standardized MRI interpretation.

Overall, our findings are consistent with the current literature indicating that mrEMVI represents the most robust MRI biomarker of synchronous metastatic disease, as demonstrated by Fournier *et al*. (15), Siddiqui *et al*. (16), Zhang *et al*. (17), and Geffen *et al*. (18), while mCRM provides complementary information regarding tumor aggressiveness and metastatic potential, as suggested by Yao *et al*. (22), Yanqing *et al*. (23), and Al-Sukhni *et al*.

(19). Together, these routinely available MRI features may improve preoperative biological risk stratification and support individualized multidisciplinary management of patients with colorectal cancer.

Several limitations should be acknowledged. First, this was a single-centre observational study with a relatively small number of patients presenting with synchronous metastatic disease, resulting in wide confidence intervals despite the use of Firth penalized regression.

Second, the model underwent internal validation only. Therefore, external validation in independent multicenter cohorts is required.

Third, molecular tumor characteristics, including RAS, BRAF, microsatellite instability, and circulating biomarkers, were not incorporated into the present analysis and may provide additional prognostic information beyond MRI findings.

CONCLUSIONS

In conclusion, preoperative MRI-derived markers of tumor aggressiveness, particularly mrEMVI and mCRM, were independently associated with synchronous metastatic presentation in colorectal cancer and enabled accurate preoperative discrimination after internal validation.

These findings support the potential role of standardized MRI assessment not only for local staging but also for identifying patients with biologically aggressive disease who may benefit from intensified preoperative evaluation and individualized multidisciplinary management.

CONFLICT OF INTEREST AND FUNDING

The authors declare that there is no conflict of interest, and they received no specific funding regarding this scientific research.

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