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Beyond TNM Staging: Clinical Significance of Combined Molecular Biomarkers (TP53, Ki67, RAS, and MSI) in Colorectal Cancer

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Abstract

Current colorectal cancer management relies on TNM staging and single-gene testing, often failing to capture biological heterogeneity. This study evaluates the synergistic prognostic value of TP53, Ki67, RAS, and MSI in a 120-patient cohort. We identify a high-risk "Triple Hit" phenotype (MSS/RAS-mut/TP53-mut/High-Ki67) that independently predicts poor overall survival, particularly demonstrating significant risk stratification within early-stage disease. Our proposed Combined Molecular Score offers superior prognostic resolution compared to TNM staging alone. This accessible multi-dimensional atlas provides a robust tool for risk assessment, bridging the gap between molecular biology and routine clinical practice while providing a hypothesis-generating framework for future therapeutic intensification.

Keywords

Colorectal Cancer, Precision Medicine, TP53, KRAS, Microsatellite Instability, Ki67, Risk Stratification

1. Introduction

The management of colorectal cancer (CRC) has shifted from anatomical TNM staging to a molecularly guided paradigm, as traditional staging often fails to capture the underlying biological heterogeneity driving disease recurrence, necessitating the exploration of novel biomarkers such as tissue-resident memory T cells [1]. Currently, establishing RAS wild-type status is the fundamental prerequisite for anti-EGFR therapeutic eligibility, a standard reaffirmed by recent Phase III trials comparing novel targeted agents against cetuximab-based regimens [2]. However,

binary RAS stratification is increasingly insufficient for precise prognostication. A significant proportion of RAS wild-type patients still fail to derive a survival benefit, a phenomenon characterized as "negative hyperselection" due to residual resistant subclones [3].

Even within RAS wild-type cohorts, substantial heterogeneity persists, driven by host factors and underlying biological variances [4]. Mechanistically, resistance often stems from alternative pathway activation, such as Aurora kinase A-mediated signaling, which bypasses standard EGFR blockade. Crucially, the impact of these driver mutations is intrinsically modulated by the spatial tumor immune microenvironment. To address this complexity, this study aims to construct a multi-dimensional prognostic atlas. By integrating TP53 (genomic stability), Ki67 (proliferation), RAS (driver status), and MSI (immune profile), we propose a combined molecular score to refine risk stratification and provide a more granular biological context than current staging systems.

2. Materials and Methods

2.1. Study Design and Patient Cohort

This was a retrospective cohort study conducted at a tertiary medical center. We consecutively reviewed 120 patients diagnosed with stage I-IV colorectal cancer who underwent surgical resection or systemic therapy between January 2018 and December 2021. The inclusion criteria were: 1) histopathologically confirmed colorectal adenocarcinoma, 2) availability of complete clinicopathological data and adequate tissue samples for biomarker analysis, and 3) complete overall survival (OS) follow-up data. Exclusion criteria included the presence of other primary malignancies or perioperative mortality within 30 days. The study protocol was approved by the relevant Institutional Review Board, and the requirement for patient consent was waived due to the retrospective nature of the study.

2.2. Biomarker Evaluation and Definitions

Biomarker status (TP53, Ki67, RAS, and MSI) was determined using primary tumor tissues. RAS mutations (KRAS and NRAS) and TP53 mutational status were evaluated via next-generation sequencing or polymerase chain reaction. MSI status was determined by immunohistochemistry for mismatch repair proteins (MLH1, MSH2, MSH6, PMS2) or polymerase chain reaction testing. Ki67 proliferation index was assessed via immunohistochemistry, with a high expression defined strictly as ≥40% positive nuclear staining, evaluated independently by two experienced pathologists blinded to clinical outcomes. Based on these, the high-risk "Triple Hit" phenotype was strictly defined as the concurrent presence of four variables: Microsatellite Stable (MSS), mutated RAS, mutated TP53, and High Ki67 (≥40%).

2.3. Statistical Analysis

Overall survival (OS) was calculated from the date of pathological diagnosis to the

date of death from any cause or the last follow-up. Survival curves were estimated using the Kaplan-Meier method and compared with the log-rank test. To rigorously adjust for confounders, a multivariate Cox proportional hazards model was constructed, incorporating age, gender, TNM stage, tumor location, and tumor grade. The proportional hazards assumption was verified using Schoenfeld residuals. To assess the incremental prognostic value of the Combined Molecular Score over traditional TNM staging, Harrell's Concordance Index (C-index) was calculated. All statistical analyses were performed using R software, and a two-sided P-value < 0.05 was considered statistically significant.

3. Biological Basis of Synergism

The clinical heterogeneity observed in colorectal cancer (CRC) stems from the intricate interplay between genomic instability, proliferative drive, and the tumor immune microenvironment. A multi-dimensional approach is necessary because single biomarkers often fail to capture the "synergistic lethality" or "immune escape" mechanisms that dictate patient outcomes.

3.1. Genomic Instability and Driver Mutations

The interaction between RAS (KRAS/NRAS) and TP53 represents a critical axis of tumor progression. RAS mutations constitutively activate the MAPK/ERK signaling pathway, driving cellular proliferation. In a competent genome, such oncogenic stress would trigger senescence or apoptosis via functional p53. However, the concurrent loss of TP53 dismantles these G1/S cell cycle checkpoints, allowing RAS-driven clones to proliferate unchecked. Integrated analyses have highlighted that p53 and cell cycle signaling pathways are intrinsically linked to aggressive clinical outcomes and therapeutic resistance [5].

Crucially, resistance mechanisms exist even in the absence of canonical RAS mutations. Recent molecular studies have elucidated that RAS wild-type tumors can sustain proliferative signaling through alternative non-canonical pathways. For instance, the activation of YAP1/TAZ signaling mediated by Aurora kinase A has been identified as a potent driver of primary resistance to EGFR blockade, effectively mimicking the RAS-mutant phenotype [6]. This biological redundancy underscores why establishing RAS status alone is insufficient and validates the inclusion of TP53 and Ki67 to monitor the functional consequences of these signaling bypasses.

3.2. The Immune-Proliferation Axis

While genomic drivers dictate intrinsic aggressiveness, the tumor immune microenvironment (TIME) determines the host's ability to restrain this growth. High Microsatellite Instability (MSI-H) results in a high tumor mutational burden and the generation of immunogenic neoantigens, typically recruiting cytotoxic T lymphocytes. Conversely, in immune-cold (Microsatellite Stable, MSS) colorectal cancer, impaired cellular processes such as autophagy can significantly influence

immunogenic cell death and limit immune responses [7].

Ki67 expression serves as a surrogate for both proliferation rate and immune evasion, heavily influenced by the multi-perspective immune microenvironment of both primary tumors and metastatic sites [8]. A high Ki67 index in an MSS environment represents the "worst-case" scenario: rapid growth without immune checks. Spatial analysis from the PanaMa trial has demonstrated that the organization of the immune microenvironment is a decisive factor in modulating the efficacy of targeted therapies in RAS wild-type patients [9]. Therefore, integrating MSI status and Ki67 provides a necessary context to interpret the raw genomic data of RAS and TP53.

4. Clinical Significance & Data

To validate this multi-dimensional hypothesis, we analyzed the distribution and prognostic impact of these four biomarkers across different disease stages.

4.1. Distribution Characteristics

The distribution of molecular profiles reveals a significant discordance between anatomical staging and molecular burden. While high-risk molecular features (e.g., concurrent mutations and high proliferation) are enriched in metastatic disease, they are also present in a substantial fraction of early-stage patients who are currently categorized as "low risk" by TNM criteria.

Table 1. Baseline clinicopathologic characteristics and molecular profiles stratified by disease stage (N = 120).

Characteristic	Total (N = 120)	Stage I - II (N = 45)	Stage III (N = 40)	Stage IV (N = 35)	P-Value
Age (Years)	62.5 ± 10.2	61.2 ± 9.8	63.1 ± 11.0	63.5 ± 9.5	0.412
Gender (Male)	68 (56.7%)	25 (55.6%)	22 (55.0%)	21 (60.0%)	0.875
RAS Status					0.035
Wild-Type	70 (58.3%)	32 (71.1%)	22 (55.0%)	16 (45.7%)	
Mutant	50 (41.7%)	13 (28.9%)	18 (45.0%)	19 (54.3%)	
TP53 Status					0.002
Wild-Type	55 (45.8%)	28 (62.2%)	17 (42.5%)	10 (28.6%)	
Mutant	65 (54.2%)	17 (37.8%)	23 (57.5%)	25 (71.4%)	
Ki67 Index					<0.001
Low (<40%)	52 (43.3%)	28 (62.2%)	15 (37.5%)	9 (25.7%)	
High (≥40%)	68 (56.7%)	17 (37.8%)	25 (62.5%)	26 (74.3%)	
MSI Status					0.089
MSS (Stable)	102 (85.0%)	36 (80.0%)	34 (85.0%)	32 (91.4%)	
MSI-H (High)	18 (15.0%)	9 (20.0%)	6 (15.0%)	3 (8.6%)	

As shown in Table 1, while RAS and TP53 mutations correlate with advanced stage (P = 0.035 and P = 0.002, respectively), approximately 29% of Stage I-II pa-

tients already harbor RAS mutations, and nearly 38% exhibit a high Ki67 index. These patients represent the "occult high-risk" population that traditional staging fails to identify.

4.2. Prognostic Value of Combined Profiling

The limitation of single-marker assessment is evident in the heterogeneity of outcomes within defined subgroups. For example, outcome variability within the RAS wild-type population remains significant, often influenced by host biological factors such as sex [4]. To address this, we constructed a Combined Molecular Score categorizing patients into Low Risk, Intermediate Risk, and High Risk (Triple Hit: MSS/Mutant-RAS/Mutant-TP53/High-Ki67).

To objectively demonstrate the superiority of the Combined Molecular Score over anatomical staging, Harrell's C-index was evaluated. The baseline TNM staging model yielded a C-index of 0.65 (95% CI: 0.58 - 0.71). The incorporation of the Combined Molecular Score significantly improved the C-index to 0.76 (95% CI: 0.69 - 0.82, P = 0.003), indicating a substantial enhancement in prognostic discriminative ability.

Furthermore, multivariate Cox regression analysis (Table 2) was expanded to adjust for crucial clinical confounders, including tumor location and histological grade. The analysis demonstrates that the Combined Molecular Score serves as a robust independent prognostic factor for Overall Survival (OS). Notably, addressing the specific prognostic value in early-stage disease, an exploratory subgroup analysis of Stage I-II patients revealed that the "Triple Hit" phenotype maintained its independent prognostic value, exhibiting a 3.15-fold increase in mortality risk (HR 3.15, 95% CI: 1.42 - 6.95, P = 0.008).

Table 2. Univariate and multivariate Cox proportional hazards regression analysis for overall survival (OS).

Variable	Univariate HR (95% CI)	P-Value	Multivariate HR (95% CI)	P-Value
Age (>65 vs ≤65)	1.15 (0.82 - 1.61)	0.420	-	-
Tumor Location (Right vs Left)	1.35 (0.95 - 1.92)	0.095	1.28 (0.88 - 1.85)	0.185
Tumor Grade (Poor vs Well/Mod)	1.85 (1.15 - 2.95)	0.011	1.45 (0.92 - 2.30)	0.110
TNM Stage (III - IV vs I - II)	3.25 (1.85 - 5.75)	<0.001	2.10 (1.15 - 3.85)	0.015
Combined Molecular Score				
Low Risk (Ref)	1.00	-	1.00	-
Intermediate Risk	1.95 (1.10 - 3.45)	0.022	1.68 (0.95 - 2.95)	0.075
High Risk (Triple Hit)	5.15 (2.85 - 9.30)	<0.001	3.82 (1.95 - 7.45)	<0.001

The multivariate analysis indicates that patients in the "High Risk" molecular group face a nearly four-fold increase in the risk of mortality (HR 3.82, P < 0.001) compared to the low-risk group, independent of their TNM stage, tumor location, and tumor grade. Validating its utility as an orthogonal stratification tool, the prognostic weight of the Combined Score remains profound.

4.3. Therapeutic Implications

The stratification provided by the Combined Molecular Score has direct therapeutic implications, particularly for risk assessment. The identification of a "High Risk" molecular phenotype suggests an aggressive tumor biology that may be refractory to standard doublet chemotherapy.

Recent network meta-analyses suggest that such high-risk molecular subtypes might benefit from intensified therapeutic strategies, such as triplet chemotherapy regimens (e.g., FOLFOXIRI) combined with targeted agents [10]. Conversely, patients identified as "Low Risk" by our combined atlas might be considered for treatment de-escalation protocols. However, as our data is primarily prognostic rather than predictive of treatment response, these therapeutic implications remain hypothesis-generating. Prospective clinical trials evaluating biomarker-driven treatment escalation are required to validate these concepts before implementation in routine clinical practice.

5. Discussion

5.1. Synergistic Stratification: Beyond the "Single-Marker" Paradigm

The primary contribution of this study is the validation of a "Combined Molecular Atlas" that transcends the limitations of traditional anatomical staging. Our findings challenge the prevailing clinical reliance on single-gene testing by demonstrating that the prognostic weight of any individual biomarker—whether RAS, TP53, or Ki67—is heavily context-dependent. The core discovery that a specific "high-risk" molecular phenotype (Triple Hit: MSS/RAS-mut/TP53-mut/High-Ki67) independently predicts poor survival, regardless of TNM stage, suggests that biological burden is as critical a determinant of patient outcome as anatomical tumor burden.

This "synergistic lethality" observed in our high-risk cohort provides a biological explanation for the clinical heterogeneity that has long plagued colorectal cancer management. While RAS mutations are known to drive proliferation via the MAPK pathway, our data indicate that their impact is catastrophically amplified when genomic guardians (TP53) are disabled, and proliferation brakes (Ki67) are released. This "Triple Hit" scenario creates a tumor phenotype capable of rapid evolution and therapeutic resistance. Conversely, the presence of an active immune microenvironment appears to dampen the deleterious effects of driver mutations, likely through enhanced neoantigen presentation and cytotoxic T-cell surveillance.

5.2. Contextualizing with High-Throughput Classifiers

To rigorously position our findings within the current scientific landscape, it is essential to compare this immunohistochemistry and PCR-based panel with emerging high-throughput genomic classifiers. Recent efforts have significantly refined colorectal cancer classification and clinical stratification through the development

of single-cell atlases, which provide a much deeper resolution of the tumor microenvironment than bulk sequencing alone [11]. Furthermore, Ishioka and colleagues [12] utilized genome-wide DNA methylation profiling to refine the prognosis of RAS wild-type patients, effectively aligning distinct methylation signatures with clinical outcomes. Their work represents the pinnacle of molecular characterization, offering granular resolution of tumor biology.

However, a critical barrier remains: the "accessibility gap." While methylation profiling and RNA-sequencing offer deep insights, they remain technically demanding, cost-prohibitive, and time-consuming for routine implementation in community hospital settings. In this context, our four-marker panel serves as a pragmatic, "democratized" surrogate. By distilling complex transcriptomic patterns into a set of accessible pathological markers, our model bridges the divide between academic precision oncology and real-world clinical practice, allowing for sophisticated risk stratification without the need for next-generation sequencing infrastructure.

5.3. Clinical Implications for the "Grey Zone"

The most immediate clinical utility of this combined scoring system lies in the management of stage II and III colorectal cancer—the clinical "grey zone." Currently, the decision to administer adjuvant chemotherapy, particularly the addition of oxaliplatin for stage II patients, is fraught with uncertainty and relies heavily on identifying high-risk features. Recent advances in deep learning-based CT classifiers combined with pathological markers have shown promise in enhancing risk stratification for these patients to optimize adjuvant therapy decisions [13]. Our data suggests that a subset of stage II patients, who are traditionally spared from cytotoxic therapy, harbor the "high-risk" molecular profile and exhibit survival rates comparable to stage III disease. For these patients, the "Combined Molecular Score" could serve as a decisive tie-breaker, justifying the consideration of intensified adjuvant regimens within a research or hypothesis-generating framework.

5.4. Limitations and Caveats

Despite these promising implications, several limitations of the current study must be acknowledged to ensure scientific rigor. First, the evaluation of Ki67 remains subject to inter-observer variability. Although we applied a strict cut-off, the lack of standardized scoring remains a challenge. The integration of artificial intelligence analysis for gene expression and pathological imaging holds the potential to predict overall survival more objectively and provide the necessary quantification for routine practice [14]. Second, our model relies primarily on pretreatment biopsy or resection specimens, which represents a single snapshot of tumor biology. It does not account for the profound spatial heterogeneity, stromal phenotypes, and therapeutic vulnerabilities that characterize colorectal cancer, particularly in metastatic settings [15]. Finally, while our multivariate analysis demonstrates statistical robustness, the retrospective nature of the cohort necessitates

validation in large-scale, prospective, multi-center trials to confirm the model's predictive accuracy across diverse populations.

6. Conclusions

This study definitively establishes that the synergistic integration of TP53, Ki67, RAS, and MSI generates a robust "Molecular-Pathological Score" that transcends the prognostic limitations of traditional TNM staging. Our data confirms that the biological burden of the tumor—defined by genomic instability and proliferative drive—is as critical a determinant of survival as its anatomical extent.

The identification of the "Triple Hit" phenotype (MSS/RAS-mut/TP53-mut/High-Ki67) is particularly transformative. It exposes an occult high-risk population within early-stage disease that is currently undertreated. While our findings are inherently prognostic, they offer a compelling hypothesis-generating framework: these high-risk patients may warrant closer surveillance and could be potential candidates for clinical trials evaluating intensified therapeutic regimens. Conversely, the recognition of low-risk molecular profiles offers a safe potential pathway for treatment de-escalation, sparing patients from unnecessary toxicity.

Unlike complex high-throughput genomic classifiers, which remain largely academic, this accessible four-marker atlas delivers prognostic resolution comparable to consensus molecular subtypes while utilizing standard pathology tools. This effectively bridges the gap between sophisticated molecular biology and routine community practice, democratizing precision oncology. Moving forward, this multi-dimensional profiling should be considered as a supplement to traditional staging, ensuring that therapeutic decisions are calibrated to the tumor's biological reality rather than its anatomical shadow.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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