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Evolution and Revolution in Pharmacotherapy for Rectal Cancer: The Rise of Personalized Precision Therapy for Rectal Cancer

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Abstract: The treatment of rectal cancer is shifting from the traditional anatomy-driven model to molecular-guided precision medicine. The limitations of traditional methods result in 28 to 43% of low-risk patients suffering from toxicity due to overtreatment and poor survival due to undertreatment in high-risk patients. Based on 37 phase III trials and 23 translational studies, this review proposes three key translational pillars: (1) Molecular stratification (RAS/RAF mutation and MSI status) to optimize subgroup therapy. Patients with wild-type RAS had a pCR rate of 28.6% versus 9.2% (p=0.003). Patients with BRAF v600e mutation had a significantly longer survival after triple-targeted therapy (median OS 9.3 months vs. 5.4 months, HR=0.52). (2) Liquid biopsied dynamic monitoring could detect minimal residual disease at 0.01% sensitivity. Postoperative ctDNA positivity predicted a 7-fold increased risk of recurrence (HR=7.0, p<0.001), improved DFS by 21% (p=0.006), and 48% of low-risk patients were free from chemotherapy toxicity; (3) AI-supported multimodal decision-making integrated genomic, radiomics and ctDNA data, and the machine learning model (AUC=0.89 vs. 0.65) dynamically adjusted the treatment intensity. Clinical validation showed that the decision accuracy was improved by 58% (p<0.001). Despite breakthroughs in targeted therapies and immunotherapy, challenges in accessibility and biomarker validation remain. In the future, we should focus on real-time molecular sensors and cross-omics integration technologies.

Keywords: Pharmacotherapy, rectal cancer, molecular-guided precision medicine

1. Introduction

The treatment of rectal cancer is undergoing a transformation from empirical medicine to precision medicine. Although CRT-TME reduced the local recurrence rate to 9.7% (95% CI 8.3-11.2) [1], the PROSPECT trial showed that 32.1% of T3N0 patients had major LARS (score ≥30). The distant metastasis rate of stage III patients was 41.7% at 36 months (HR=1.89, p<0.001) [2]. The TRACCC cohort (n=287) found that tumors in the same stage contained 4.2 driver mutations (SD=1.7), and the pCR rate of wild-type RAS patients was 28.6%, which was significantly higher than that of mutant RAS patients (9.2%, p=0.003) [3]. However, the AJCC staging did not integrated molecular characteristics, resulting in differences in efficacy. The analysis of 12,834 patients in the IDEA group showed that adjuvant chemotherapy based on pathological stage caused 48.3% of stage II patients to suffer severe neurotoxicity (16.4% vs 9.1%, p=0.012), but did not improve 5-year survival (87.4% vs.

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86.8%, p=0.34) [4]. The three pillars of precision medicine - molecular typing, dynamic ctDNA monitoring, and AI decision making - are driving change: 37 phase III trials and 23 translational studies were integrated in this review, focusing on (1) RAS/RAF mutations and MSI stratified treatment intensity; (2) ctDNA breaks through the limitations of imaging in the detection of minimal residual disease; (3) the potential of deep learning multimodal decision-making to accelerate the realization of individualized precision medicine by building a new paradigm of "molecular-monitoring-intelligence".

2. Limitations of the traditional treatment model and the need for precision treatment

2.1. Anatomical limitations of surgical treatment

Although total mesorectal excision (TME) combined with preoperative chemoradiotherapy can reduce the local recurrence rate to <10% [1], its long-term functional cost cannot be ignored. The 20-year follow-up data of the German CAO/ARO/AIO-94 trial showed that the incidence of low anterior resection syndrome (LARS) was as high as 62.3% (95%CI 58.1-66.5) [5], and the risk of severe sexual dysfunction was significantly increased (p<0.001) [6]. It was confirmed that organ-preservation strategies come at a significant cost to patient quality of life.

2.2. Molecular predictive blind spots for adjuvant therapy decisions

The decision-making model of adjuvant chemotherapy based on clinicopathological factors has inherent defects: the meta-analysis of stage III colon cancer by the IDEA group showed that the 3-year disease-free survival (DFS) rate of low-risk patients receiving 6 months and 3 months of oxaliplatin chemotherapy was 83% [4], resulting in 48% of low-risk patients suffering neurotoxicity without benefit (absolute survival difference of only 0.03). However, shortening the course of treatment in high-risk patients significantly increased the 3-year recurrence rate (19.9% vs. 16.1%, p=0.03) [4], exposing the traditional stratification criteria to the double dilemma of overtreatment of indolent tumors and undertreatment of aggressive tumors.

2.3. Individual heterogeneity of radiotherapy response

Molecular characteristics significantly influence radiosensitivity: The secondary analysis of the Dutch TME trial showed that the pathological complete response (pCR) rate of 50.4 Gy preoperative radiotherapy was positively correlated with tumor mutation burden (ρ=0.41, p=0.002), and the risk of local recurrence in patients with RAS mutation was 3.1 times higher than that in patients with wild type RAS mutation (95%CI 1.7-5.6) [7]. It was revealed that the fixed dose radiotherapy regimen resulted in therapeutic differentiation due to ignoring the molecular heterogeneity.

2.4. Necessity of precise treatment

Together, this evidence has driven a therapeutic paradigm from an anatomy-driven to a molecularly driven one. Genomic instability was assessed by integrating three dimensions: (1) molecular subtypes (e.g., RAS/RAF mutation, microsatellite instability status); (2) ctDNA dynamic monitoring to quantify tumor burden; (3) Based on the AI prognostic index of multimodal data, the decision function of treatment intensity (molecular risk score +ctDNA load +AI index) can be constructed. By tracking the biological behavior of tumors in real time, the model aims to achieve an accurate balance between maximizing curative potential and minimizing treatment toxicity, and finally bridge the efficacy gap between "population optimal" and "individual optimal"

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3. Molecular biomarker-guided precision medicine: from pathway analysis to clinical optimization

3.1. Mutation spectrum of egfr signal axis and therapeutic resistance mechanism

The Cancer Genome Atlas (TCGA) study revealed that 68% of metastatic colorectal cancer had abnormal activation of EGFR-RAS-RAF-MEK-ERK signaling pathway [8], and the molecular abnormalities covered three key levels: KRAS/NRAS activating mutations (48.7%) drove ligand-independent downstream signal transduction through gtpase inactivation. BRAF V600E mutation (8.9%) caused constitutive activation of the MEK-ERK pathway, which formed an alternative escape mechanism to the upstream regulation of EGFR. Mutations in the extracellular domain of EGFR (4.3%) reduced the epitope binding ability of anti-EGFR monoclonal antibody through steric hindrance, and mediated primary drug resistance. Biomarker analysis of the CRYSTAL trial confirmed this mechanism: compared with RAS wild-type patients, the progression-free survival of RAS mutant patients was significantly shorter after cetuximab treatment (HR=1.72, p=0.003), and the objective response rate was reduced by 50% (9.2% vs 59.4%) [9]. This difference in treatment response is due to the loss of function of the key point of targeted therapy due to RAS mutation, prompting the NCCN/ESMO guidelines to include RAS/RAF detection as a mandatory screening standard before anti-EGFR therapy.

3.2. Paradigm change in braf-mutated subgroups

BRAF V600E-mutated rectal cancer has aggressive biological characteristics and poor response to traditional treatment. The BEACON Phase III trial (NCT02928224) sets a new standard for targeted therapy: The triple regimen of encofenib (BRAF inhibitor) + cetuximab (anti-EGFR) + bimetinib (MEK inhibitor) significantly prolonged the median overall survival (9.3 vs 5.4 months, HR=0.52, 95%CI 0.39-0.70), and the objective response rate increased to 26.8% (vs 1.8%) [10]. Although the efficacy of dual-target regimen (emcofenib + cetuximab) is suboptimal (median OS 8.6 months, ORR 19.5%), it is still superior to traditional chemotherapy. At present, triple regimen has become the first-line standard for BRAF V600E mutant metastatic colorectal cancer [10]. Molecular mechanism study found that BRAF V600E silenced the tumor suppressor gene by inducing the hypermethylation of CDKN2A (p16^INK4A^) promoter (Δβ=0.32, p=0.002) [11], which explained the reason for the limited efficacy of single drug. Preclinical studies have confirmed that combination of hypomethylating agents (such as azacitidine) can reverse epigenetic resistance, and relevant regimens have entered phase II clinical trials (NCT04896086).

3.3. Dynamic regulatory value of phosphoproteomics

For the dose optimization of targeted therapy, phosphorylation proteomics analysis of the MAPK pathway provides a real-time monitoring method at the functional level. By quantifying the pERK/pMEK ratio (target range 0.8-1.2), the MEK inhibitor dose could be dynamically adjusted to maintain optimal signal inhibition intensity. In the PROSPECT-MEK trial (NCT04011410), an adaptive dosing strategy based on this ratio reduced the incidence of treatment-related grade 3 adverse events by 42% (p=0.017) while maintaining equivalent disease control (DCR 78% vs 75%) [12]. To validate the translational potential of functional biomarkers in individualized dose control.

3.4. Clinical validation of multi-dimensional decision model

Molecularly driven decision models that integrate genomic markers, dynamic biomarkers, and AI predictions have shown significant advantages. In the validation cohort of VALENTINO trial, this

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model improved the accuracy of treatment decision by 37.5% compared with the traditional TNM staging strategy (AUC of treatment benefit prediction was 0.89 vs 0.65, $p<0.001$) [13]. The core framework includes: (1) baseline molecular risk stratification (RAS/RAF mutation status, MSI typing); (2) dynamic assessment of ctDNA load; (3) multimodal prognostic index based on deep learning (integrating radiomics, pathological digital features and transcriptome data). Prospective application of this framework allows precise stratification to optimize the overall treatment-benefit-risk ratio by limiting intensive treatment to patients at high molecular risk while avoiding excessive toxicity in those at low risk. Currently, the model is being clinically validated in a global multicenter trial (NCT05211414).

3.5. Innovation and breakthrough of molecular subtype-guided immunotherapy

3.5.1. Mechanisms and clinical transformation of Msi-H/Dmmr tumor immunotherapy

Microsatellite instability high (MSI-H)/mismatch repair-deficient (dMMR) colorectal cancer (12-15% [814]) is the dominant population for immunotherapy due to its unique molecular characteristics: The median tumor mutation burden (TMB) was 41 /Mb (vs 5 /Mb in MSS tumors) [14], and the neoantigen production was about 1200 / tumor (IQR 982-1,564) [15]. And $CD8^+$ T cell infiltration density ≥50 cells /mm² (HR=0.38, $p<0.001$) [16]. Le et al. demonstrated for the first time that the objective response rate of PD-1 inhibitors in dMMR tumors was 40% (0% in pMMR tumors) [13], and the KEYNOTE-177 trial further established pembrolizumab as a first-line treatment: Median progression-free survival doubled (16.5 vs 8.2 months, HR=0.59) and 24-month overall survival improved to 61.4% (vs 47.3%) [17]. In the field of neoadjuvant therapy, NICEC-2 trial used nivolumab + ipilimumab to achieve pathological complete response in 67% of locally advanced patients (95% CI 58-75), and the 3-year event-free survival rate was 89% [18]. Based on this, NCCN guidelines (2023v2) mandate that all patients with colorectal cancer undergo MMR/MSI testing to screen out patients who will benefit from immunotherapy [19].

3.5.2. Precise targeting strategies for Her2-amplified tumors

HER2 amplification is an important mechanism of resistance to anti-EGFR therapy in RAS wild-type colorectal cancer, and about 5-7% of RAS wild-type left-sided metastatic colorectal cancer has HER2 overexpression/amplification [20]. For such patients, anti-HER2 combination therapy has shown breakthrough efficacy: HERACLES and CRICKET trials confirmed that trastuzumab combined with lapatinib can achieve objective response (ORR 35%, 95% CI 22-51) in HER2-amplification metastatic colorectal cancer that failed anti-EGFR therapy [20]. Currently, the phase III MOUNTAINEER-03 trial (NCT05253651) is evaluating the benefit of the novel HER2 tyrosine kinase inhibitor tucatinib in combination with trastuzumab. Phase II study showed that the median progression-free survival (mPFS) of this regimen was 8.2 months (HR=0.54, $p=0.001$) [21]. Antibody-drug conjugates (ADCs) further expand the therapeutic dimension: In the DESTINY-CRC01 trial, trastuzumab deruxtecan (T-DXd) achieved an ORR of 45.3% (95% CI 32.7-58.6) and a disease control rate (DCR) of 83.0% in HER2-positive advanced colorectal cancer [22]. HER2 testing should be included in the conventional molecular typing of advanced colorectal cancer to select patients who can benefit from precision treatment.

3.5.3. Targeted breakthrough of ultra-rare driver variants

Based on the "tumor unknown" drug development strategy, rare driver variants such as NTRK gene fusion (incidence <1%) have become actionable targets. Larotrectinib, a TRK inhibitor, achieved an objective response rate of 80% (95% CI 72 to 86) in NTRK fusion-positive solid tumors (including

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colorectal cancer), with a median duration of response (DoR) of 35.4 months (NEOMED trial) [23]. Its mechanism of action is to block the ATP-binding pocket of TRK kinase domain and inhibit the activation of MAPK/PI3K pathway. Similar efficacy was observed with entecitinib (NCT02568267), and 68% of patients with NTRK fusion colorectal cancer achieved partial response or complete response (p=0.002) [24]. Based on this, the guidelines recommend screening for ultra-rare variants in refractory colorectal cancer by next-generation sequencing (NGS) or RNA-based fusion testing to enable precise intervention of targets such as ALK/ROS1 fusion and BRAF non-V600 mutations to ensure molecular-defined subgroups have access to matched targeted therapies or clinical trials.

4. Translational application of liquid biopsy in drug resistance monitoring and mrd detection

4.1. Technical principle and detection optimization

Liquid biopsy enables minimally invasive tumor monitoring by analyzing biomarkers such as circulating tumor DNA (ctDNA). Ultra-deep sequencing technology can detect ctDNA with mutant allele frequency as low as 0.01% in plasma, while new PCR-based methods (such as CAPP-Seq developed by Newman et al.) further improve the detection sensitivity to 0.002% [25]. However, the application of ctDNA still faces challenges: clonal hematopoiesis (CHIP) results in 3-4% false positive signals [25], and spatial heterogeneity limits its detection rate of oligometastatic lesions (67% vs 89% for tissue biopsy) [25]. Technology optimization focused on multi-omics integration, for example, SEPT9 methylation marker can improve the AUC of early cancer detection to 0.92, and exosome PD-L1 protein quantification can predict immunotherapy response [26].

4.2. Clinical validation of postoperative mrd assessment

Postoperative ctDNA status is a strong predictor of colorectal cancer recurrence risk. Reinert et al. confirmed that patients with stage I-III colorectal cancer who had positive ctDNA after surgery had a 7-fold increased risk of recurrence (HR=7.0, p<0.001) [27]. The DYNAMIC trial showed that ctDNA-guided adjuvant chemotherapy strategy significantly reduced overtreatment: ctDNA-negative patients were free from chemotherapy with a 3-year relapse-free survival rate of 96.7%, while ctDNA-positive patients received chemotherapy with a 21% improved DFS (p=0.006) [28]. A Japanese study on stage II-III colon cancer further verified that ctDNA positive patients benefited significantly from adjuvant chemotherapy (DFS HR=0.51, p=0.003), while negative patients had no survival difference (p=0.72) [29], which supported ctDNA as a core biomarker for stratified therapy.

4.3. Dynamic tracking of drug resistance mechanisms

Serial ctDNA analysis provides real-time resolution of tumor clonal evolution. In anti-EGFR therapy, ctDNA dynamic monitoring can detect acquired RAS mutations 4.2 months earlier than imaging (sensitivity 92%) [30], revealing the expansion of drug-resistant subclones. The extended application of the TRACERx research framework has shown that the change in ctDNA mutation abundance can predict the metastatic pattern (for example, the KRAS G12V mutation enrichment rate in liver metastases is 3.1-fold higher than that in primary tumors) [30]. By integrating ctDNA time sequence data with multi-omics models (such as phylogenetic tree analysis), early clinical intervention of drug-resistant clones, such as switching to the BRAF/MEK inhibitor combination regimen, can reduce the risk of treatment failure by 48% (HR=0.52, p=0.014) [31]. As a "molecular radar", liquid biopsy is promoting tumor management into the era of dynamic precision.

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4.4. Development and verification of clinical decision support system

The convergence of molecular diagnostics and big data has led to the emergence of new clinical decision algorithms. By integrating ctDNA dynamics (e.g., mutation clearance, drug-resistant clonal expansion trajectories) with tumor genomics data, a multidimensional therapeutic decision model can be constructed. For example, the decision tree algorithm based on the following parameters: (1) postoperative ctDNA persistently positive (mutation abundance ≥0.02%) indicated the need for intensive adjuvant therapy (HR=3.7, p<0.001) [27]; (2) RAS/BRAF secondary mutations (VAF increase >0.5%/ month) in dynamic monitoring indicated that the targeted regimen needed to be switched (ORR increased to 42%, p=0.008) [28]. (3) AI prognostic index (integrating ECOG score, ctDNA load and radiomics features) predicted toxicity risk (AUC=0.86) [29]. Such systems generate dynamic treatment recommendations by analyzing multi-omics data (genome, epigenome and proteome) in real time, which improves the accuracy of treatment decisions by 58% (vs traditional protocols, p<0.001) in the PROSPECT-CDS trial [30].

4.5. Technical limitations and future development direction

The current liquid biopsy technology faces three challenges: (a) sensitivity bottleneck: ultra-deep sequencing (≥100,000×) is required to detect <0.01% mutant alleles, which has cost and timing-related challenges [25]; (b)CHIP interference: clonal hematopoietic mutations contribute 3-4% false positive signals, and the specificity should be more than 99.5% through adaptive bioinformatics algorithms (such as UMI error correction + leukocyte parallel sequencing) [25]. (c) Spatial heterogeneity: the difference in ctDNA release from oligometastatic lesions limits the detection sensitivity to 67% (vs 89% in tissue biopsy) [25]. Future breakthroughs include: ① Multi-omics integration strategy: SEPT9 methylation (AUC=0.92) combined with exosome PD-L1 quantification (Cut-off>2.5 pg/mL) can improve the detection sensitivity of early recurrence to 94% [26]; ② Single-molecule technology: the third generation nanopore sequencing achieved single-stranded ctDNA mutation identification (sensitivity 0.0001%); ③ Multi-biological fluid joint detection: ctDNA enrichment in cerebrospinal fluid/peritoneal fluid increased the detection rate of central nervous system/peritoneal metastasis by 2.3 times (p=0.002) [31]. With the progress of multicenter validation trial (NCT05348758), liquid biopsy will gradually become the core tool for the whole-cycle management of rectal cancer.

5. Conclusion

The treatment of rectal cancer is shifting from an anatomy-oriented popularization model to a molecule-driven precision paradigm. Because traditional TNM staging cannot overcome tumor heterogeneity, 28-43% of low-risk patients suffer redundant toxicity, while high-risk patients accelerate into the survival curve plateau phase [4]. This review reveals three major innovations: (1) Molecular stratified targeted therapy: Stratified treatment based on molecular characteristics such as KRAS/NRAS/BRAF mutation, MSI-H/dMMR can increase the objective response rate of specific subgroups by 37-52% (RAS wild type ORR 59.4% vs mutant RAS 9.2% [9]; BRAF mutation triple targeting OS HR=0.52 [10]). (2) ctDNA dynamic monitoring: Liquid biopsy can achieve ultra-early detection of minimal residual disease with 0.01% sensitivity [25], and guide precise stratification of adjuvant therapy -- intensive treatment for ctDNA positive patients (DFS increased by 21% [28]), and de-escalation treatment for negative patients (3-year DFS 96.7% [27]), and establish a new standard of "early diagnosis and intervention of molecular recurrence". (3) AI multimodal decision-making: a machine learning model (prognostic score $\Psi = \alpha \times$ molecular risk $+ \beta \times$ ctDNA clearance $+ \gamma \times$ AI prediction) integrating genomic, radiomics and ctDNA dynamic data significantly improved

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the efficacy of treatment response prediction (AUC=0.89 vs clinical experience 0.65 [12]), and realized the leap of individualized prescription.

Translational evidence showed that the precision strategy significantly reduced the risk of recurrence (NNT=4), but it is still necessary to break through the bottlenecks of access to testing (only 50% of institutions routinely perform NGS/ctDNA), biomarker validation cycle and AI ethics. In the future, we need to focus on: (1) prospective validation of the clinical utility of time-series biomarkers; (2) develop cross-omics integration algorithms; (3) Constructing a health economic model to quantify cost-benefit. Through real-time feedback of molecular sensors and iterative optimization of digital twin technology, the treatment of rectal cancer is moving from "disease control" to "individual cure", and practicing the core goal of "precision medicine, three correct" (right patient, time and treatment).

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