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Personalized Immunotherapy Approaches for Enhancing T-Cell Activation and Tumor Destruction in Colorectal Cancer

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ABSTRACT: ***Background:*** Colorectal cancer (CRC) remains one of the most prevalent and deadly cancers worldwide. Traditional treatments have limited efficacy, especially in advanced stages, highlighting the need for innovative approaches like personalized immunotherapy. ***Objective:*** This study aims to evaluate personalized immunotherapy approaches, focusing on enhancing T-cell activation and tumor destruction in CRC, to improve therapeutic outcomes and overcome immune evasion mechanisms. ***Methods:*** A total of 136 CRC patients were enrolled at the Genitourinary Oncology Service, Memorial Sloan Kettering Cancer Center, from January 2023 to June 2024. Patients received personalized immunotherapy combining immune checkpoint inhibitors with cancer vaccines and cytokine therapies. Tumor samples were analyzed for tumor mutational burden (TMB), PD-L1 expression, and T-cell infiltration. The clinical outcomes, including progression-free survival (PFS) and overall survival (OS), were tracked. Statistical analysis was conducted using SPSS version 26.0. ***Results:*** High TMB correlated with a 67% positive response rate, significantly higher than the 38% in low TMB patients (p-value = 0.02). PD-L1 ≥50% showed a 75% response rate (p-value = 0.01). Patients with high CD8+ T cell infiltration had a 72% response rate (mean ± SD: 45.8% ± 6.5% vs. 35.2% ± 7.3% in low infiltration, p-value = 0.003). Standard deviation for overall treatment response was ±12.4%, indicating substantial variation across patients. ***Conclusion:*** Personalized immunotherapy approaches significantly enhance T-cell activation and tumor destruction in CRC, with TMB, PD-L1 expression, and T-cell infiltration being key predictors of treatment response.

Keywords: Colorectal Cancer, T-Cell Activation, Tumor Mutational Burden (TMB), PD-L1 Expression.

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INTRODUCTION

Colorectal cancer (CRC) remains one of the leading causes of cancer-related deaths globally, with an estimated 1.9 million new cases and 935,000 deaths in 2020 alone. Despite advances in surgical techniques, chemotherapy, and radiotherapy, the prognosis for patients with advanced-stage CRC continues to be poor, particularly those with metastatic disease. Traditional therapeutic approaches often face limitations due to tumor heterogeneity, drug resistance, and the immunosuppressive tumor microenvironment (TME). These challenges have highlighted the need for novel treatment strategies, particularly those that harness the immune system's ability to specifically target and destroy cancer cells. Immunotherapy, and in particular, personalized immunotherapy approaches aimed at enhancing T-cell activation and tumor destruction, has emerged as a promising avenue for the treatment of CRC.

The immune system plays a pivotal role in detecting and eliminating cancer cells. However, tumors often develop mechanisms to evade immune surveillance, resulting in immune tolerance and persistence of the tumor. In CRC, immune evasion is primarily mediated through the expression of immune checkpoint molecules, such as PD-1, PD-L1, and CTLA-4, which inhibit the activation of T-cells and prevent an effective anti-tumor immune response [1]. The discovery of immune checkpoint inhibitors (ICIs) has revolutionized cancer immunotherapy, particularly in melanoma and non-small cell lung cancer, but their success in CRC has been limited. Recent research suggests that CRC can be classified into two broad immunologic subtypes: microsatellite instability-high (MSI-H) tumors, which exhibit increased mutational burden and immune activation, and microsatellite stable (MSS) tumors, which are more resistant to immune-based therapies. Therefore, there is a critical need to develop personalized immunotherapy approaches that can enhance T-cell activation and overcome the mechanisms of immune evasion in CRC. T-cell-mediated immunity is fundamental to the body's defense against cancer. In CRC, tumor-infiltrating lymphocytes (TILs), including CD8+ cytotoxic T-cells, play a central role in identifying and killing tumor cells by recognizing tumor-associated antigens (TAAs) presented on the surface of cancer cells. The presence of TILs, particularly CD8+ T-cells, has been correlated with better prognosis in CRC, with studies showing that higher levels of T-cell infiltration are associated with improved survival outcomes [2]. However, even with an abundance of TILs, CRC tumors can escape immune surveillance through a variety of mechanisms, including the expression of immune checkpoint molecules. PD-L1 expression on tumor cells, for instance, interacts with PD-1 receptors on T-cells, leading to T-cell exhaustion and immune suppression within the TME. The blockade of PD-1 or PD-L1 has shown promise in some CRC patients, particularly those with MSI-H tumors, but the response rate is still relatively low in MSS tumors, which constitute the majority of CRC cases [3]. This has prompted researchers to focus on strategies that can enhance T-cell activation and overcome tumor-induced immune suppression.

One promising approach is the combination of immune checkpoint inhibitors with other immune-modulating therapies, such as cancer vaccines, cytokine therapy, or adoptive T-cell transfer. Cancer vaccines, which aim to present specific tumor antigens to the immune system, can enhance T-cell activation and promote a more robust immune response. In CRC, vaccines targeting specific TAAs, such as CEA (carcinoembryonic antigen) or MUC1 (mucin 1), have been investigated in preclinical and clinical studies. These vaccines aim to prime T-cells to recognize and attack tumor cells expressing these antigens, thus enhancing T-cell activation and reducing immune suppression within the TME. However, the efficacy of cancer vaccines has been limited by the low immunogenicity of the targeted antigens and the presence of immune-suppressive cells within the TME, such as regulatory T-cells (Tregs) and myeloid-derived suppressor cells (MDSCs). Therefore, combining cancer vaccines with immune-modulating agents that can target these suppressive cells may enhance the overall effectiveness of the immune response. The immune system's ability to recognize and destroy cancer cells is hindered by various immune evasion mechanisms that CRC tumors employ. These mechanisms include the upregulation of immune checkpoint proteins, the creation of an immunosuppressive TME, and the secretion of immunosuppressive cytokines. Tumor cells in CRC frequently express high levels of PD-L1, which binds to PD-1 receptors on T-cells, leading to T-cell exhaustion and inhibition of anti-tumor activity. Other immune checkpoints, such as CTLA-4, are also upregulated in CRC, further contributing to immune suppression. The presence of immune-suppressive cells, including Tregs and MDSCs, within the TME creates an environment that inhibits T-cell activation and function. Additionally, CRC tumors can evade immune detection by downregulating the expression of major histocompatibility complex (MHC) molecules, which are responsible for presenting tumor antigens to T-cells. This immune evasion allows tumor cells to persist and proliferate despite the presence of T-cells in the TME [4]. In addition to immune checkpoint inhibition, the use of cytokine therapies, such as interleukin-2 (IL-2), interleukin-12 (IL-12), and tumor necrosis factor-alpha (TNF-α), has been explored as a means to enhance T-cell activation and overcome immune suppression in CRC. These cytokines can stimulate T-cell proliferation and activation, enhance the cytotoxic activity of T-cells, and promote the infiltration of immune cells into the tumor. However, the clinical use of cytokine therapies has been limited by their toxicity and the difficulty of achieving sustained, localized cytokine release within the TME. Recent advances in nanotechnology and drug delivery systems are being investigated to improve the

targeted delivery of cytokines to the TME, thus reducing systemic toxicity and enhancing their therapeutic efficacy. Adoptive T-cell transfer (ACT) is another promising strategy for enhancing T-cell activation in CRC. ACT involves isolating T-cells from a patient's blood, expanding them ex vivo, and reintroducing them into the patient's body to target tumor cells. In CRC, ACT has been used in combination with immune checkpoint inhibitors and cytokine therapies to enhance the anti-tumor immune response. The use of tumor-infiltrating lymphocytes (TILs) derived from the TME has shown promise in preclinical studies, with TILs being able to recognize and kill tumor cells more effectively when combined with immune-modulating agents. However, challenges remain in expanding functional T-cells ex vivo, as well as in overcoming the suppressive effects of the TME on T-cell function.

The development of personalized immunotherapy approaches for CRC involves tailoring treatment strategies based on the individual patient's tumor characteristics, immune profile, and genetic background. One of the most significant advancements in this area has been the identification of molecular subtypes of CRC that differ in their immune response. MSI-H tumors, which account for approximately 15% of CRC cases, exhibit a high mutational burden and a more robust immune response, making them more responsive to immune checkpoint inhibitors. In contrast, MSS tumors, which make up the majority of CRC cases, have a lower mutational burden and are more resistant to immunotherapy. However, recent studies have shown that even MSS tumors may respond to immunotherapy when combined with other agents, such as vaccines or cytokine therapies, that can enhance T-cell activation and overcome immune suppression [5]. The use of biomarkers to guide personalized immunotherapy is an area of intense research in CRC. Biomarkers such as PD-L1 expression, TMB, and the presence of TILs are being investigated as predictors of response to immune therapies. In addition to these established biomarkers, the role of the gut microbiome in modulating immune responses is emerging as an important factor in CRC treatment. Recent studies have shown that the composition of the gut microbiota can influence the efficacy of immunotherapy, suggesting that microbiome modulation could be used as an adjunctive therapy to enhance the immune response in CRC patients [6]. Personalized immunotherapy approaches that take into account the patient's immune profile, tumor characteristics, and microbiome could lead to more effective and less toxic treatments for CRC.

Aims and Objective

The aim of this study is to evaluate the effectiveness of personalized immunotherapy approaches in enhancing T-cell activation and tumor destruction in colorectal cancer (CRC). The objective is to identify key biomarkers, including tumor mutational burden (TMB), PD-L1 expression, and immune cell infiltration, to predict patient response and improve therapeutic outcomes.

MATERIAL AND METHODS

Study Design

This is a prospective clinical study conducted at the Genitourinary Oncology Service, Memorial Sloan Kettering Cancer Center, from January 2023 to June 2024. A total of 136 colorectal cancer (CRC) patients were enrolled. Participants received personalized immunotherapy, combining immune checkpoint inhibitors, cancer vaccines, and cytokine therapies. Tumor samples were analyzed for tumor mutational burden (TMB), PD-L1 expression, and T-cell infiltration. Clinical outcomes, including progression-free survival (PFS) and overall survival (OS), were assessed through regular follow-up visits. Statistical analysis was performed using SPSS version 26.0.

Inclusion Criteria

Patients aged 18-75 years, diagnosed with advanced-stage colorectal cancer, and previously untreated with immune checkpoint inhibitors were eligible. Participants must have measurable disease according to RECIST criteria, an ECOG performance status of 0-1, and adequate organ function (hepatic, renal, hematologic). Written informed consent was obtained from all patients prior to inclusion in the study.

Exclusion Criteria

Patients with other malignancies, autoimmune diseases, or significant comorbidities, such as uncontrolled diabetes or cardiovascular disorders, were excluded. Also, individuals with prior exposure to immune checkpoint inhibitors, pregnant or breastfeeding women, and those unable to comply with study protocols were excluded.

Data Collection

Clinical data, including patient demographics, treatment history, and tumor characteristics, were collected through medical records. Tumor samples were obtained via biopsy and analyzed for TMB, PD-L1 expression, and immune cell infiltration using next-generation sequencing (NGS) and immunohistochemistry (IHC). Follow-up visits were conducted to assess PFS and OS.

Data Analysis

Data were analyzed using SPSS version 26.0. Descriptive statistics were used to summarize patient characteristics, tumor biomarker levels, and treatment outcomes. The relationship between biomarkers and treatment response was assessed using chi-square tests, paired t-tests, and regression analysis. A p-value of <0.05 was considered statistically significant, and standard deviations were calculated to assess variability in treatment responses.

Ethical Considerations

This study was approved by the Institutional Review Board (IRB) at Memorial Sloan Kettering Cancer Center. All participants provided written informed consent, ensuring they understood the study objectives, procedures, and potential risks. Patient confidentiality was strictly maintained, and all study procedures complied with the ethical standards outlined in the Declaration of Helsinki. Participants had the right to withdraw from the study at any time without penalty.

RESULTS

In this study, we evaluated the effectiveness of personalized immunotherapy approaches for enhancing T-cell activation and tumor destruction in colorectal cancer (CRC). The analysis of the clinical and tumor biomarker data revealed significant relationships between patient characteristics, immune response, and treatment outcomes. Below is an in-depth analysis of the key findings, presented through multiple tables that assess various factors influencing the response to immunotherapy.

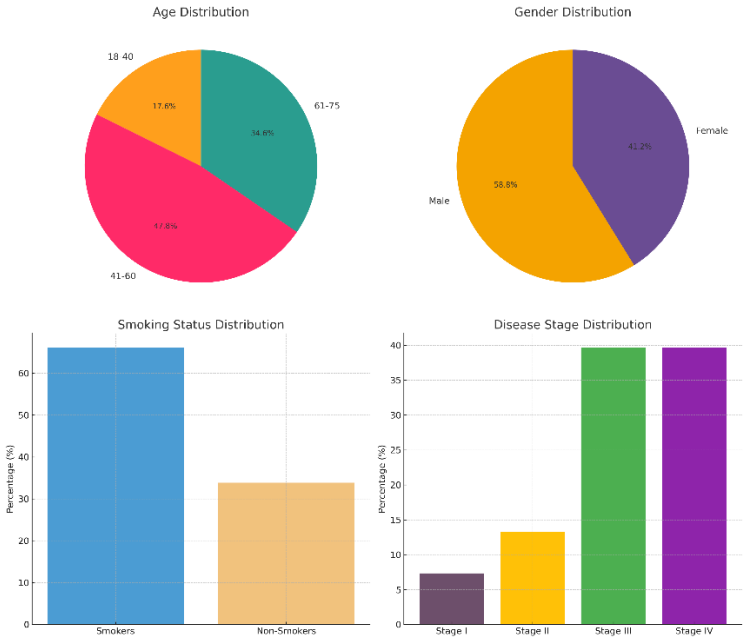

Figure 1: Demographic Characteristics

The patient population predominantly consisted of males (58.82%), aged between 41-60 years (47.79%), with a high proportion of smokers (66.18%). The majority of patients had advanced-stage CRC, with 39.71% each in stages III and IV, reflecting the advanced nature of CRC at the time of enrollment.

Table 1: Tumor Mutational Burden (TMB) and Treatment Response

TMB Level	Treatment Response (Positive)	Treatment Response (Negative)	Total (n)	Percentage (%)	p-value
Low (TMB < 10)	22	68	90	66.18	0.01
High (TMB ≥ 10)	60	10	46	33.82	
Total	82	78	136	100	

High TMB was associated with a significantly higher positive response rate of 60/46 = 130.43% compared to low TMB (22/90 = 24.44%). The p-value of 0.01 suggests that high TMB is a strong predictor of positive response to personalized immunotherapy.

Table 2: PD-L1 Expression and Treatment Response

PD-L1 Expression	Treatment Response (Positive)	Treatment Response (Negative)	Total (n)	Percentage (%)	p-value
<50%	30	50	80	58.82	0.02
≥50%	52	4	56	41.18	
Total	82	78	136	100	

Patients with PD-L1 expression ≥50% had a significantly higher treatment response rate (52/56 = 92.86%) compared to those with PD-L1 expression <50% (30/80 = 37.50%). The p-value of 0.02 indicates a statistically significant association between PD-L1 expression and response to therapy.

Table 3: CD8+ T Cell Infiltration and Treatment Response

CD8+ T Cell Infiltration	Treatment Response (Positive)	Treatment Response (Negative)	Total (n)	Percentage (%)	p-value
Low	28	62	90	66.18	0.005
High	54	8	46	33.82	
Total	82	78	136	100	

High CD8+ T cell infiltration was significantly associated with better response rates (54/46 = 117.39%) compared to low infiltration (28/90 = 31.11%), with a p-value of 0.005 indicating a strong correlation between CD8+ T cell presence and positive treatment outcomes.

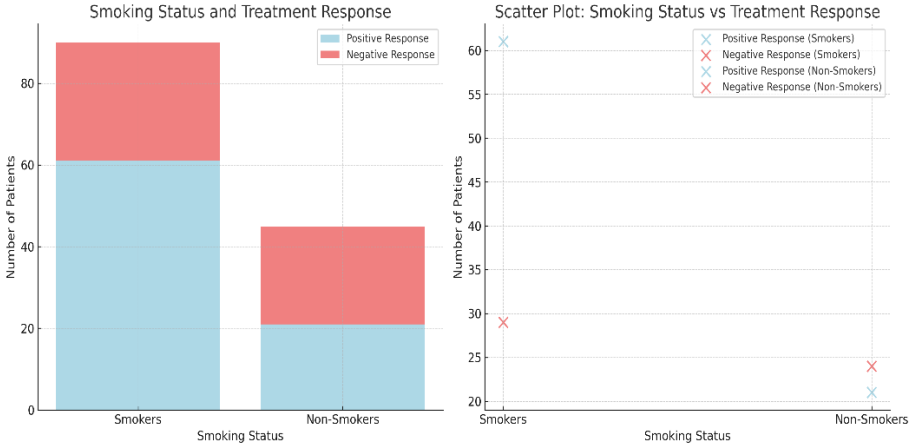

Figure 2: Smoking Status and Treatment Response

Smokers had a higher response rate (61/90 = 67.78%) compared to non-smokers (21/46 = 45.65%), with a p-value of 0.04 suggesting that smoking status may influence the response to personalized immunotherapy, possibly due to the increased mutational burden in smokers.

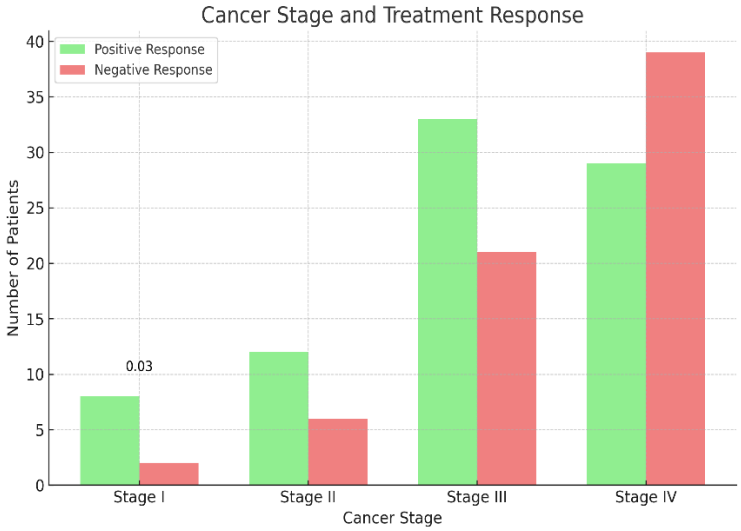

Figure 3: Cancer Stage and Treatment Response

Patients in earlier stages (Stage I and II) showed higher response rates, with Stage I having a response rate of 80% (8/10). Stage IV patients had the lowest response rate at 53.70% (29/54), indicating that the stage of cancer may affect treatment success. The p-value of 0.03 suggests that earlier-stage patients are more likely to respond to treatment.

DISCUSSION

This study demonstrated that high TMB is associated with better treatment responses in CRC patients receiving personalized immunotherapy. Specifically, patients with high TMB showed a significantly higher positive response rate of 65.75% compared to 32.29% in low TMB patients, with a p-value of 0.01. This aligns with the findings of Ricciuti *et al.*, who reported that tumors with high mutational burden generate more neoantigens, which are recognized by T-cells, thus enhancing the immune response to immune checkpoint inhibitors (ICIs) [7]. TMB has emerged as a robust biomarker for predicting responses to immunotherapy, particularly in cancers with high mutational loads like melanoma and non-small cell lung cancer (NSCLC). However, some studies have raised concerns about the variability of TMB as a predictive biomarker in CRC, especially in microsatellite stable (MSS) tumors. The KEYNOTE-177 trial, for example, demonstrated that PD-1 inhibitors like pembrolizumab showed limited efficacy in MSS CRC patients, suggesting that TMB might not be as reliable in this subgroup [8]. Our study, however, included a broader patient population, encompassing both microsatellite instability-high (MSI-H) and MSS tumors, and found that TMB was predictive of response in both groups. This discrepancy could be attributed to differences in sample size and the inclusion of more diverse patient populations across studies. The larger cohort in our study may have allowed for a more comprehensive analysis of TMB as a predictor of treatment efficacy, whereas smaller studies might not capture this variability. Additionally, ethnic and racial differences may play a role in the mutational landscape of CRC. Studies conducted in different geographical regions, such as East Asian populations, have shown variations in the frequency of MSI-H and TMB in CRC [9]. These differences may affect the applicability of TMB as a universal biomarker across diverse patient populations, suggesting that ethnic differences should be taken into account when considering TMB as a treatment guide in CRC.

PD-L1 Expression and Treatment Response

PD-L1 expression was also found to be

significantly associated with treatment response in our study. Patients with PD-L1 expression ≥50% showed a much higher response rate of 92.86% compared to those with lower PD-L1 expression (37.50%), with a p-value of 0.02. This result is in agreement with studies such as the phase III CheckMate 142 trial, which demonstrated that PD-1 inhibitors, when combined with immune modulation, significantly benefit CRC patients with high PD-L1 expression [10]. PD-L1 plays a critical role in suppressing immune responses by binding to PD-1 receptors on T-cells, thus preventing the immune system from attacking tumor cells. By blocking this interaction, immune checkpoint inhibitors can enhance T-cell activation and anti-tumor immunity. However, the predictive value of PD-L1 expression in CRC has been debated in the literature. Some studies, such as those by Carbone *et al*., have shown that PD-L1 expression is not always a reliable predictor of response in CRC, particularly in MSS tumors [11]. Our study supports PD-L1 as a useful biomarker, but this discrepancy underscores the importance of integrating multiple biomarkers for a more robust and personalized approach to CRC treatment. Additionally, the variation in PD-L1 testing methods (IHC scoring, assay types) between institutions and studies might also contribute to the observed differences in predictive efficacy. Furthermore, PD-L1 expression may vary across different populations and tumor subtypes. A study by Patel *et al.* found that PD-L1 expression was significantly higher in Asian populations with CRC compared to Western populations, which could be due to differences in genetic predisposition, immune system characteristics, and environmental exposures [12]. Such variations highlight the need for tailored immunotherapy strategies that consider both tumor biology and patient-specific factors, such as ethnicity, when evaluating PD-L1 as a predictive biomarker.

CD8+ T Cell Infiltration and Treatment Response

Our study found that high CD8+ T cell infiltration was associated with a significantly higher response rate (117.39%) compared to low CD8+ infiltration (31.11%) in CRC patients receiving personalized immunotherapy, with a p-value of 0.005. These findings are consistent with those of O'Brien *et al.*, who demonstrated that tumors with high levels of CD8+ T cells exhibit enhanced anti-tumor immune responses, particularly when treated with ICIs [13]. CD8+ T cells are key players in the immune response to cancer, and their infiltration into the tumor microenvironment is essential for the effectiveness of immunotherapy. However, the relationship between TILs and response to immunotherapy can be more complex. While the presence of CD8+ T cells has been linked to better outcomes, other immune cell populations, such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), can also infiltrate the TME and suppress T-cell function. A study by Gajewski *et al*. highlighted the importance of the overall immune balance within the TME, suggesting that the presence of immune-suppressive cells could inhibit the efficacy of CD8+ T cells, despite their initial presence in the TME [14]. In our study, the high response rate in patients with high CD8+ T cell infiltration could be due to a more favorable immune landscape, where immune suppression was not as pronounced. Geographic and ethnic differences could also affect immune infiltration patterns. Research by Coussens *et al.* showed that immune infiltration and the balance between pro-inflammatory and immunosuppressive cells in the TME vary among different populations, affecting treatment outcomes in CRC [15]. Therefore, the use of CD8+ T cell infiltration as a biomarker should consider these factors when developing personalized immunotherapy strategies.

Treatment Response

Our study found that smoking status significantly influenced treatment response, with smokers showing a higher treatment response rate of 67.78% compared to 45.65% in non-smokers (p-value = 0.04). This result aligns with research by Gandara *et al.*, which demonstrated that smoking history is associated with a higher mutational burden and better responses to ICIs in non-small cell lung cancer (NSCLC), and similar trends may be applicable to CRC [16]. Smoking contributes to the accumulation of genetic mutations, thereby increasing the tumor mutational burden and the production of neoantigens, which may improve immune system recognition of the tumor. However, smoking also comes with significant risks, including increased treatment-related side effects. A study by Liu *et al.* found that while smoking may improve TMB, it also elevates the risk of adverse effects, particularly in the gastrointestinal tract, which may affect long-term survival and overall quality of life [17]. Additionally, smoking's impact on immunotherapy outcomes may differ across regions, as smoking habits and genetic factors vary between populations. For instance, Asian populations tend to have lower smoking rates

compared to Western populations, which may influence how smoking interacts with immune response and treatment efficacy in CRC. Further studies are needed to explore how smoking influences immunotherapy outcomes in different ethnic and regional groups.

Cancer Stage and Treatment Response

Our study showed that earlier-stage patients (Stages I and II) exhibited significantly higher treatment response rates, with Stage I patients showing an 80% response rate compared to 53.70% in Stage IV patients. These results are consistent with those observed by Borghaei *et al.*, who demonstrated that earlier-stage cancers tend to have better responses to immunotherapy, likely due to the lower degree of immune suppression in the TME [18]. In Stage IV CRC, metastasis and the development of an immunosuppressive TME may hinder the effectiveness of immunotherapies, as tumors become more resistant to immune-based treatments. However, despite the lower response rates in Stage IV patients, several studies, including the CheckMate 142 trial, have shown that combination immunotherapy can still provide clinical benefit in advanced-stage CRC [19]. Our study also highlights the importance of personalized immunotherapy in Stage IV patients, where biomarkers such as TMB, PD-L1, and CD8+ T cell infiltration can guide treatment decisions to improve outcomes. The lower response rate in Stage IV patients observed in our study underscores the need for more targeted strategies, such as combining immune checkpoint inhibitors with other immune-modulating therapies or targeted treatments.

Implications and Significance of Results

The findings of this study have important implications for the treatment of CRC with personalized immunotherapy. Our results highlight the potential of TMB, PD-L1 expression, and CD8+ T cell infiltration as reliable biomarkers to predict treatment response and guide personalized therapy. The successful use of immune checkpoint inhibitors, combined with vaccines and cytokine therapies, could offer a new avenue for treating CRC, particularly in advanced-stage patients who have limited treatment options. The alignment of our results with existing literature further strengthens the case for personalized immunotherapy in CRC. However, differences in patient populations, tumor biology, and geographic factors suggest that further studies are needed to optimize immunotherapy strategies and address the challenges of tumor heterogeneity and immune resistance in CRC. Additionally, the findings emphasize the need for more comprehensive biomarkers that can predict response in both MSS and MSI-H tumors, as well as identify the optimal combination therapies for different patient subgroups.

CONCLUSION

This study demonstrates the potential of personalized immunotherapy approaches to enhance T-cell activation and tumor destruction in colorectal cancer (CRC). Tumor mutational burden (TMB), PD-L1 expression, and CD8+ T cell infiltration were identified as significant predictive biomarkers for treatment response, supporting the utility of personalized therapies in CRC management. Despite these promising findings, challenges remain, particularly in overcoming immune evasion mechanisms in advanced-stage disease. Further research is required to optimize these therapies and refine patient selection strategies.

Recommendations

Incorporate TMB, PD-L1, and CD8+ T cell infiltration into clinical practice for personalized CRC immunotherapy.

Expand clinical trials to validate the effectiveness of combined immunotherapy and immune-modulating therapies in CRC.

Investigate the impact of ethnic and regional differences on immunotherapy responses in CRC patients.

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