

**“VICTOR BABES” UNIVERSITY OF MEDICINE AND PHARMACY
TIMISOARA
FACULTY OF GENERAL MEDICINE
DISCIPLINE OF GENERAL SURGERY**

BRAICU VLAD



DOCTORAL THESIS

**ADVANCEMENTS AND OUTCOMES IN RECTAL CANCER
MANAGEMENT POST-COVID-19**

- SUMMARY -

Scientific Coordinator
PROF. UNIV. DR. HABIL. PANTEA STELIAN

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STUDY 1: THREE-YEAR ANALYSIS OF THE RECTAL CANCER CARE TRAJECTORY AFTER THE COVID-19 PANDEMIC.

CONTEXT

Rectal cancer, a major malignancy of the lower gastrointestinal tract, remains a significant global health challenge. Managing rectal cancer requires a comprehensive approach that typically includes surgery, radiation therapy, and systemic treatments. In advanced stages, complex surgical techniques such as total mesorectal excision are crucial for reducing local recurrence and improving overall survival. Additionally, advancements in molecular research have enabled more personalized treatments, as different molecular subtypes of rectal cancer require specific therapeutic strategies.

The onset of the COVID-19 pandemic in early 2020 brought unprecedented challenges to healthcare systems worldwide, necessitating a significant reorganization of resources and care delivery strategies. Oncology services were particularly affected, as healthcare institutions shifted priorities to address pandemic-related care demands.

The COVID-19 pandemic highlighted the vulnerability of cancer care pathways to external health crises, emphasizing the urgent need for resilient healthcare infrastructures that can adapt to unforeseen challenges. Oncology services, already dealing with the complexities of managing aggressive diseases like rectal cancer, faced additional pressures as resources were diverted to address the pandemic. The long-term implications of delayed diagnoses and altered treatment timelines are under ongoing scrutiny within the oncology community, underscoring the importance of restoring and strengthening cancer care pathways during global health crises.

This study posits that by 2022, the management and surgical outcomes of rectal cancer patients had potentially reverted to pre-pandemic norms, following the disruptions experienced during the restrictive measures of 2020 and 2021. The primary aim of this research was to conduct a comparative analysis of patient outcomes across the years 2020, 2021, and 2022, focusing on treatment delays, surgical outcomes, and survival rates, and comparing these findings with the pre-pandemic period in 2019. This analysis seeks to shed light on how healthcare systems adapted and patients fared during the pandemic era, offering insights into the resilience and adaptability of oncologic care amidst unprecedented global health challenges.

SUMMARY OF FINDINGS

A retrospective analysis identified a total of 131 patients diagnosed with rectal cancer during the three-year pandemic period eligible for inclusion, alongside 33 patients identified in the year 2019, prior to the COVID-19 pandemic. Despite the absence of statistically significant differences between the three pandemic years, there was an approximate 10% annual increase in the total number of surgical interventions, from 1709 in 2020 to 2118 in 2022. However, there was a significant overall reduction in total interventions compared to the pre-pandemic year of 2019.

Statistical analysis indicated no significant variations in patient baseline characteristics during the study period

A significant variation was noted in the American Society of Anesthesiology (ASA) scores. Data revealed a notable shift from a larger percentage of patients having an ASA score of II in 2020 (62.5%) to an increased prevalence of scores III and IV in subsequent years, indicating a possible rise in case complexity over the period. TNM staging also showed significant changes over the pandemic years, with a decrease in stage II cases and an increase in stages III and IV, suggesting a trend towards diagnosing more advanced stages of rectal cancer as the years progressed.

The analysis indicated a slight but non-significant increase in both local and distant metastases, as well as local invasions, throughout the study period

The patient presentation data revealed significant changes over the three-year period. Emergency interventions remained stable in 2020 and 2021, accounting for 37.5% and 42.5% of cases, respectively, but saw a marked decline in 2022, with only 20.3% of cases requiring emergency attention. Conversely, elective interventions became more common in 2022, reaching 79.7%, compared to 62.5% in 2020 and 57.5% in 2021. The uptake of neoadjuvant therapy significantly increased in 2022, with 35.6% of patients undergoing this therapy, compared to 18.8% and 15.0% in 2020 and 2021, respectively ($p = 0.043$).

Traditional open surgery declined from 68.8% in 2020 to 40.7% in 2022, while laparoscopic procedures nearly doubled, reaching 47.5% in 2022 from 25.0% in 2020. Robotic techniques saw a slight increase but remained less common. The surgical methods displayed a significant difference over the period, with amputations increasing from 15.6% in 2020 to 42.4% in 2022, and a corresponding decrease in resections from 62.5% to 39.0%. Anastomosis strategies showed consistency in terms of types and methods used ($p = 0.656$), indicating stability in surgical outcomes. The number of positive lymph nodes identified showed an increasing trend but without statistical significance, underscoring the need for vigilant lymph node assessments.

This three-year observational study detailing the recovery trajectory of rectal cancer care post-COVID-19 pandemic identified several statistically significant changes. One area requiring further exploration is the alterations in laboratory data over the years, particularly regarding albumin levels. Significant fluctuations in albumin levels observed in our study necessitate deeper investigation to understand their underlying causes and potential associations with surgical outcomes. It is hypothesized that complications such as wound healing, scar formation, and the development of fistulas may be influenced by albumin and total protein levels [66].

During the COVID-19 pandemic period, significant changes were also observed in the ASA score ($p = 0.043$) and TNM staging ($p = 0.039$), indicating an increase in the severity of cases and a higher proportion of patients presenting with advanced stages of the disease. This shift towards more advanced disease presentations may be attributed to delayed diagnoses and treatments due to healthcare disruptions during the pandemic. Management strategies adapted significantly, as evidenced by the increase in neoadjuvant therapy ($p = 0.043$) and laparoscopic surgeries ($p = 0.004$), reflecting a shift towards more conservative and minimally invasive approaches.

CONCLUSIONS

This study identified significant changes in rectal cancer management during the COVID-19 pandemic years of 2020 to 2022 compared to the pre-pandemic year of 2019. These changes were marked by substantial transformations in surgical interventions, diagnostic stages, and clinical complexities. The number of surgical interventions increased, with a notable doubling in laparoscopic procedures, reflecting a shift towards planned and elective surgeries, particularly evident in 2022. This shift was further supported by an increase in the application of neoadjuvant therapies during the same year, indicating a strategic move towards more preoperative treatments to manage rectal cancer more effectively before surgery.

Another concerning trend observed during this period was the rise in diagnoses of advanced stages of rectal cancer. This increase in late-stage diagnoses was accompanied by a significant rise in case complexity, as demonstrated by higher ASA (American Society of Anesthesiologists) scores.

Despite these challenges, it is noteworthy that ICU admission and mortality rates remained relatively stable throughout the study period. This stability suggests that, despite the increased complexity and severity of cases, the healthcare system was able to maintain consistent levels of critical care and patient survival.

STUDY 2: IMPACT OF SYSTEMIC TREATMENTS ON OUTCOMES AND QUALITY OF LIFE IN PATIENTS WITH RAS-POSITIVE STAGE IV COLORECTAL CANCER: A SYSTEMATIC REVIEW.

Colorectal cancer (CRC) ranks as the third most commonly diagnosed cancer and the second leading cause of cancer-related deaths globally. The prognosis for stage IV CRC, which involves distant metastases, remains poor, with a five-year survival rate of around 14%. Among the molecular anomalies driving CRC progression, mutations in the RAS oncogene family, including KRAS and NRAS, are particularly significant. These mutations, found in up to 50% of CRC cases, are critical in determining tumor behavior, therapeutic response, and overall patient prognosis.

The advent of systemic treatments, including chemotherapy, targeted therapy, and immunotherapy, has revolutionized the management of advanced-stage cancers. The effectiveness of anti-epidermal growth factor receptor (EGFR) therapies, such as cetuximab and panitumumab, is particularly influenced by the RAS mutation status in stage IV CRC. Patients with RAS mutations often show resistance to certain therapeutic agents, underscoring the necessity of a personalized treatment approach based on genetic profiling. Consequently, identifying RAS mutations has become essential for selecting the most appropriate systemic treatments.

Despite advancements in treatment modalities, the impact of systemic therapies and surgery on the outcomes and quality of life (QoL) of cancer patients remains a critical area of study, especially in the context of disease staging and treatment resistance. Quality of life, a crucial aspect of cancer care, can be evaluated using various standardized scales that assess the physical, psychological, and social effects of the disease and its treatments. Given the aggressive nature of stage IV CRC and the challenges in managing RAS-mutant tumors, it is essential to explore the outcomes and QoL in this patient population.

This systematic review aims to critically assess the existing literature on the outcomes and quality of life of patients with RAS-positive stage IV colorectal cancer following systemic treatment. By integrating data from clinical trials, observational studies, and real-world evidence, this review seeks to provide a thorough understanding of the efficacy and impact of systemic therapies in this specific patient group, ultimately guiding future research and clinical practices to enhance both survival and quality of life for patients with advanced RAS-mutant colorectal cancer.

SUMMARY OF FINDINGS

This systematic review assessed the impact of systemic treatments on outcomes and quality of life in patients with RAS-positive stage IV colorectal cancer, focusing on 11 distinct studies conducted between 2011 and 2023. These studies were carried out in various countries. Predominantly, these investigations were randomized trials, underscoring the rigorous methodology applied in assessing the efficacy and safety of systemic treatments for this patient population.

This geographical and methodological diversity offers a broad spectrum of insights into the nuanced effects of systemic treatments on patients with RAS-positive stage IV colorectal cancer.

The reviewed studies consistently highlighted the advanced stage of colorectal cancer in patients with RAS mutations, focusing on a subgroup with significant therapeutic challenges. The specifics of RAS mutations were uniformly reported, with several studies documenting 100% KRAS wild-type cases.

The studies presented detailed findings on baseline results, quality of life (QoL) follow-up results, complications, dropout rates, survival, and study conclusions. Bennett et al. [121] reported baseline EQ-5D Health Status Index (HSI) mean scores ranging from 0.76 to 0.78 and EQ-5D Visual Analogue Scale (VAS) mean scores from 70.1 to 74.1, noting that improvements in EQ-5D scores were not clinically meaningful. This study also highlighted a late dropout/completer rate varying between 29.8 and 70.2% across different treatment arms, concluding that the addition of panitumumab to chemotherapy did not significantly compromise QoL while notably improving disease-free survival (DFS).

Similarly, Odom et al. presented Functional Assessment of Cancer Therapy-Colorectal (FACT-C) score mean ranges from 72.27 to 73.21 for the panitumumab plus Best Supportive Care (BSC) arm, and 71.84 to 71.91 for the BSC alone arm, with EQ-5D Index mean scores between 0.68 and 0.73. This study observed improvements in FCSI and EQ-5D Index scores, particularly favoring the panitumumab + BSC in wild-type KRAS metastatic colorectal cancer, with early

dropout rates of 38–42% for panitumumab + BSC and 68% for BSC alone. The study concluded that patients treated with panitumumab maintained better control of CRC symptoms and QoL compared with BSC alone.

Láng et al. did not report baseline QoL scores but noted worsened nausea and vomiting at week 16 and a worse change from baseline score for dyspnea in the FOLFIRI + cetuximab arm. With a median survival of 25.7 months for cetuximab + FOLFIRI versus 16.4 months for FOLFIRI alone, the study concluded that adding cetuximab to FOLFIRI did not significantly impact global health status/QoL or social functioning, despite improved response rates and survival.

CONCLUSION

This review underscores the efficacy of various systemic therapies, particularly the integration of targeted therapies such as panitumumab and cetuximab with chemotherapy regimens like FOLFOX4 and FOLFIRI. The findings indicate that these combinations do not significantly detract from patients' quality of life (QoL) while providing substantial benefits in terms of disease-free survival

STUDY 3: ASSESSING THE PROGNOSTIC VALUE OF NLR, PLR, APRI, SII, AND LIVER FUNCTION TESTS FOR FISTULA FORMATION AFTER COLORECTAL CANCER SURGERY.

BACKGROUND

Colorectal cancer remains one of the most prevalent malignancies worldwide, contributing significantly to morbidity and mortality. Surgical resection is the cornerstone of treatment for localized disease, aiming to achieve a cure or substantial disease control. However, postoperative complications can greatly impact patient outcomes and healthcare resources. Among these complications, the formation of anastomotic fistulas is particularly concerning due to its high rates of morbidity and potential mortality.

Inflammation plays a pivotal role in the body's response to surgical interventions, serving dual functions in both the healing process and the development of complications. Markers of inflammation are often elevated following colorectal surgeries and can be predictive of the patient's recovery trajectory. Elevated levels of these markers are frequently associated with poor outcomes, such as impaired wound healing and an increased risk of postoperative complications, including infections and fistula formation. The complexities of postoperative recovery in colorectal cancer surgeries are further magnified by systemic inflammation, which can adversely affect multiple organ systems

Emerging as valuable tools in the clinical assessment of postoperative patients are various hematological markers, such as the Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR). These markers are studied for their ability to predict systemic inflammation and, by extension, the likelihood of recovery or complications following surgery. Similarly, the Aspartate Aminotransferase-to-Platelet Ratio Index (APRI) and the Systemic Immune-Inflammation Index (SII) are being explored for their potential to provide insights into a patient's inflammatory and immunological status, which could correlate with the occurrence of adverse postoperative events.

This study focuses on the predictive capabilities of these inflammatory markers, including NLR, PLR, APRI, and SII, as well as routine liver function tests, in determining the risk of fistula development following colorectal cancer surgery. The hypothesis being tested posits that higher preoperative values of these markers may indicate a greater risk of developing a fistula, suggesting their utility in preoperative risk assessment and management.

SUMMARY OF FINDINGS

The study evaluated a total of 219 patients who underwent colorectal cancer surgery, segregating them into two groups based on the postoperative development of fistulas. Specifically, 38 patients developed fistulas, while 181 did not experience this complication.

Among the various markers studied, the Systemic Immune-Inflammation Index (SII) stood out for its predictive accuracy. The SII demonstrated a cutoff value greater than 460.5, which was found to have the highest sensitivity at 75.6% and specificity at 71.3% among all markers evaluated. The area under the curve (AUC) for SII was 0.774, indicating a good predictive performance with a statistically significant P-value of 0.001. This suggests that SII is a robust marker for assessing the risk of fistula formation in patients undergoing colorectal cancer surgery.

Albumin levels also showed strong predictive significance, with a cutoff value set at less than 2.9 g/dL. The sensitivity of albumin levels reached 77.3%, the highest among the markers, and a specificity of 73.8%. The corresponding AUC was 0.788, which not only reflects a high level of predictive accuracy but also confirms the statistical significance with a P-value of less than 0.001. This indicates that lower albumin levels might be a critical factor in predicting post-surgical complications such as fistulas.

Other inflammatory and liver function markers were also evaluated for their ability to predict fistula formation. The Neutrophil to Lymphocyte Ratio (NLR) was another key marker, with a cutoff value of more than 3.95, showing a sensitivity of 71.2% and a specificity of 67.9%. The AUC for NLR was 0.732, indicating its useful predictive capacity, and the associated P-value was less than 0.001, underscoring its statistical relevance in the study.

Similarly, the Platelet to Lymphocyte Ratio (PLR) was identified as a significant predictive marker. With a cutoff value of more than 191.6, PLR achieved a sensitivity of 73.5% and a specificity of 69.4%. The AUC for PLR stood at 0.746, which is indicative of a strong predictive ability, and a P-value of 0.001 further established its significance in assessing the risk of developing fistulas post-operation.

The Derived Neutrophil to Lymphocyte Ratio (dNLR), along with other composite ratios such as the Neutrophil, Lymphocyte, and Platelet Ratio (NLPR), and the Aspartate Aminotransferase to Platelet Ratio Index (APRI) also demonstrated considerable predictive values. These markers, each with their respective sensitivity and specificity metrics, provided a broad spectrum of data supporting their potential utility in predicting postoperative outcomes. Their significant P-values reaffirmed the robustness of these biomarkers as tools for clinical assessment and decision-making in the management of colorectal cancer surgery patients.

CONCLUSIONS

This study makes a significant contribution to the field of colorectal surgery by demonstrating that elevated preoperative levels of specific inflammatory markers and liver function tests correlate with an increased risk of developing fistulas post-surgery. These biomarkers, which include the Systemic Inflammation Index (SII), Neutrophil to Lymphocyte Ratio (NLR), Platelet to Lymphocyte Ratio (PLR), Aspartate Aminotransferase to Platelet Ratio Index (APRI), and albumin levels, are critical for assessing patient risk before undergoing surgical procedures.