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THERAPEUTIC MANAGEMENT OF COLORECTAL CANCER IN THE ELDERLY: BALANCING EFFICACY AND TOLERABILITY

MANEJO TERAPÊUTICO DO CÂNCER COLORRETAL NO IDOSO: EQUILIBRANDO EFICÁCIA E TOLERABILIDADE

MANEJO TERAPÉUTICO DEL CÁNCER COLORRECTAL EN EL ADULTO MAYOR: EQUILIBRANDO EFICACIA Y TOLERABILIDAD

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ABSTRACT

Colorectal cancer (CRC) is the third leading cause of malignant neoplasia and the second leading cause of global cancer mortality (Sun et al., 2024). Due to the epidemiological aspects of this neoplasm, being more prevalent at older ages, this article focuses on this population group. Considering the physiological and pathological changes of aging (senescence and frailty), the elderly population has gained prominence in the search for better methods to ensure earlier diagnosis, improved screening strategies, and innovative targeted therapies that provide greater tolerability for this age group during oncological treatment. It is known that this group is more vulnerable and presents a higher prevalence of comorbidities compared to others. This study aims to conduct a review of current evidence on improvements in diagnostic protocols, such as the incorporation of proteomic analysis combined with non-genetic and genetic risk factors (Elez et al., 2025), and in oncological targeted therapies, such as cetuximab, bevacizumab, and FOLFOX for CRCs with KRAS mCR and BRAF mutations (H. Ahn et al., 2024; Elez et al., 2025). The analysis of the results shows that when individualized beyond chronological age, there is a positive association between research and techno-pharmacological innovation, targeted therapies focusing on oncopathogenesis, new diagnostic predictors, and improvement in prognostic indicators for the studied population.

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Keywords: Colorectal Cancer. Elderly. Targeted Therapies. BRAF Mutations. KRAS Mutations. Geriatric Oncology.

RESUMO

O câncer colorretal (CCR) é a terceira maior causa de neoplasia maligna e a segunda causa de mortalidade global por câncer (Sun et al., 2024). Devido aos aspectos epidemiológicos dessa neoplasia, sendo mais prevalente em idades mais avançadas, esse artigo tem enfoque nesse grupo populacional. Perante as alterações fisiológicos e patológicos (senescência e senilidade) do envelhecimento, observa-se a população idosa ganhar destaque na busca por melhores métodos para garantir um diagnóstico cada vez mais precoce, melhores métodos de rastreamento, terapias alvos inovadoras que garantirão maior tolerabilidade dessa faixa etária perante o tratamento oncológico. Sabe-se da fragilidade maior nesse grupo que apresenta maior prevalência de comorbidades quando comparado aos demais. O presente estudo tem como objetivo realizar uma revisão de todas as evidências atuais em melhorias nos protocolos de diagnóstico, como a incorporação da análise proteômica combinada com fatores de risco não genéticos e genéticos (Elez et al., 2025), em terapias alvos oncologicas, como cetuximabe, bevacizumabe e FOLFOX para CCRs com mutações KRAS mCR e BRAF (H. Ahn et al., 2024; Elez et al., 2025). Na análise dos resultados obtidos, observa-se, que quando individualizada para além da idade cronológica, existe uma associação positiva entre a pesquisa e inovação tecno-farmacológica, quando focada em terapias alvo direciona+ das a onco patogênese + novos preditores diagnósticos, e a melhoria nos indicadores prognósticos da população estudada.

Palavras-chave: Câncer Colorretal. Idoso. Terapias Alvo. Mutações BRAF. Mutações KRAS. Oncologia Geriátrica.

RESUMEN

El cáncer colorrectal (CCR) es la tercera causa de neoplasia maligna y la segunda causa de mortalidad global por cáncer (Sun et al., 2024). Debido a los aspectos epidemiológicos de esta neoplasia, siendo más prevalente en edades avanzadas, este artículo se centra en este grupo poblacional. Ante los cambios fisiológicos y patológicos del envejecimiento (senescencia y fragilidad), la población adulta mayor ha adquirido relevancia en la búsqueda de mejores métodos para garantizar un diagnóstico cada vez más temprano, estrategias de cribado mejoradas y terapias dirigidas innovadoras que aseguren una mayor tolerabilidad en este grupo etario durante el tratamiento oncológico. Se sabe que este grupo es más vulnerable y presenta una mayor prevalencia de comorbilidades en comparación con otros. El presente estudio tiene como objetivo realizar una revisión de la evidencia actual sobre mejoras en los protocolos de diagnóstico, como la incorporación del análisis proteómico combinado con factores de riesgo no genéticos y genéticos (Elez et al., 2025), y en terapias dirigidas oncológicas, como cetuximab, bevacizumab y FOLFOX para CCR con mutaciones KRAS mCR y BRAF (H. Ahn et al., 2024; Elez et al., 2025). El análisis de los resultados muestra que, cuando se individualiza más allá de la edad cronológica, existe una asociación positiva entre la investigación y la innovación tecno-farmacológica, terapias dirigidas enfocadas en la oncopatogénesis, nuevos predictores diagnósticos y la mejora de los indicadores pronósticos de la población estudiada.

Palabras clave: Cáncer Colorrectal. Adulto Mayor. Terapias Dirigidas. Mutaciones BRAF. Mutaciones KRAS. Oncología Geriátrica.

1 INTRODUCTION

Colorectal cancer (CRC) is one of the most prevalent neoplasms worldwide, with an incidence that increases significantly with advancing age. In the context of population aging, the clinical management of elderly patients presents unique challenges, requiring a delicate balance between oncological efficacy and tolerability to treatments, due to the higher prevalence of comorbidities and reduced physiological reserve (Huang et al., 2023). The biological heterogeneity of CRC, characterized by distinct molecular subtypes, such as BRAF and KRAS mutations, demands increasingly personalized therapeutic strategies to avoid excessive toxicity and overtreatment (Kopetz et al., 2025; Yaeger et al., 2024).

Recently, advances in plasma biomarkers and artificial intelligence tools have improved risk stratification, allowing for more accurate and less invasive diagnoses, which is particularly beneficial for the geriatric population (Sun et al., 2024). In addition, the introduction of targeted therapies such as KRAS and BRAF inhibitors offers alternatives that may be more convenient and less toxic than conventional chemotherapy regimens (Ahn et al., 2023; Elez et al., 2025). The aim of this article is to review the current evidence on the diagnosis and treatment of CRC in the elderly, focusing on the integration of new technologies and targeted therapies to optimize clinical care.

2 METHODOLOGY

The present study is characterized as a narrative literature review, with a qualitative approach, whose objective was to analyze and synthesize the available scientific evidence about the therapeutic strategies employed in the treatment of colorectal cancer in elderly patients. The review sought to emphasize aspects related to the efficacy, safety, and clinical applicability of the therapeutic modalities described in the recent literature.

The search for articles was performed in the PubMed database, using the controlled descriptors "Colorectal Cancer", "Elderly" and "Treatment", combined with each other using the Boolean operators AND and OR, according to the standardization of the Medical Subject Headings (MeSH). The search strategy was structured in order to ensure a broad retrieval of studies relevant to the proposed theme.

Scientific articles published in the last five years were included, available in full, written in English and directly addressing the treatment of colorectal cancer, focusing on

elderly populations or on therapeutic aspects applicable to this age group. Original studies and clinical trials that presented methodological consistency and clinical relevance were considered.

Duplicate publications, studies that did not have a direct relationship with the research objective, brief communications, editorials, letters to the editor, and narrative reviews with low methodological rigor were excluded. The selection of articles occurred in two stages: initially, the titles and abstracts were read for preliminary screening; Subsequently, the selected texts were read in full, in order to confirm their adequacy to the established inclusion criteria.

The data extracted from the selected studies were organized in a descriptive manner, allowing for an integrated analysis of the findings and a critical discussion of the evidence related to the therapeutic options currently available for the management of colorectal cancer in the elderly.

3 RESULTS AND DISCUSSION

3.1 ADVANCES IN RISK DIAGNOSIS AND STRATIFICATION

The diagnosis of CRC in elderly patients has benefited from less invasive methods, which reduce the need for repetitive and stressful procedures. Plasma proteomic profiling and polygenic risk scores (PRS) have demonstrated high sensitivity in early disease identification and risk stratification, allowing personalization of age of onset and screening frequency (Sun et al., 2024). In addition, plasma and fecal metabolomics have identified specific signatures, such as oleic acid enrichment and allocholic acid depletion, which function as robust biomarkers for progression from adenoma to carcinoma (Sun et al., 2024).

For stage II patients, where the decision on adjuvant chemotherapy is often controversial due to fragility, the use of deep learning computed tomography (CT)-based classifiers has been shown to be superior to traditional pathological markers. This technology makes it possible to identify patients at low risk of recurrence who could avoid the unnecessary toxicity of chemotherapy, thus balancing the effectiveness of the treatment with the quality of life of the elderly (Huang et al., 2025).

3.2 TARGETED THERAPIES AND TOLERABILITY IN THE MANAGEMENT OF MCRC

In metastatic colorectal cancer (mCRC), the treatment of elderly patients with specific mutations, such as BRAF V600E, has been transformed by regimens that combine targeted therapies and moderate chemotherapy. The BREAKWATER study demonstrated that the first-line combination of encorafenib, cetuximab, and mFOLFOX6 resulted in a significantly higher objective response rate (60.9%) compared to standard of care (40.0%) while maintaining a manageable safety profile (Kopetz et al., 2025; Elez et al., 2025). This approach allows for a higher rate of disease control in a group that has historically had a poor prognosis.

For KRAS G12C mutations, the use of adagrasib in combination with cetuximab showed promising results, with a disease control rate of 85.1% and a median duration of response of 5.8 months (Yaeger et al., 2024). The tolerability of these new combinations is a determining factor for the geriatric population; onvansertib, a pole-like kinase 1 (PLK1) inhibitor, for example, has a half-life of 24 hours, which allows for flexible and well-regulated oral dosing regimens, reducing the treatment burden for the patient (Ahn et al., 2023).

A study conducted in the United States using onvansertib as a measure for the second-line treatment of metastatic colorectal cancer with mutation in *the KRAS* gene showed considerable performance. Therapy using onvansertib associated with chemotherapy and bevacizumab was well tolerated, showing better results than the conventional protocol (cytotoxic chemotherapy with fluoropyrimidines, combined with oxaliplatin or irinotecan and bevacizumab) reaching an objective response rate (ORT) of 26.4%, and median duration of response (DOR) was 11.7 months (standard treatment with ORT around 15% and a median progression-free survival of 6 to 7 months) (Ahn et al., 2025).

Also in this study, a post hoc analysis indicated that patients without previous treatment with bevacizumab revealed better results compared to those who had previous treatment with bevacizumab, with significantly higher ORT and longer progression-free survival (PFS): data were collected on ORT of 76.9% versus 10.0% and median PFS of 14.9 months versus 6.6 months (Ahn et al., 2025). This shows the importance of studies and experiments on this topic, so that patients, especially those of advanced age, have adequate therapeutic management with good tolerability from the beginning of treatment.

In recent years, promising results have emerged from the incorporation of targeted therapies based on specific molecular alterations, particularly in subgroups historically associated with a worse prognosis. The phase III BREAKWATER study demonstrated that the combination of encorafenib and cetuximab plus chemotherapy (mFOLFOX6) promoted clinically and statistically significant gains in progression-free survival and overall survival in patients with metastatic RCC carrying the BRAF V600E mutation, outperforming previously established standard of care (Elez et al., 2025; Kopetz et al., 2025.). These findings represent a milestone in establishing, for the first time, an effective first-line targeted therapy for this aggressive subtype of the disease.

In addition, relevant advances were also observed in tumors with KRAS G12C mutation, another molecular subgroup associated with low response to conventional therapies. Data from the KRYSTAL-1 study indicate that the combination of adagrasib and cetuximab showed significant rates of objective response, disease control, and overall survival in previously treated patients, reinforcing the role of simultaneous inhibition of KRAS and EGFR as a strategy to overcome adaptive resistance mechanisms (Yaeger et al., 2024; Kopetz et al., 2025).

3.3 PERSONALIZATION AND CLINICAL DECISION

The therapeutic decision in the elderly should transcend chronological age, incorporating tumor biology and the pharmacokinetics of the new agents. The use of circulating tumor DNA (ctDNA) has emerged as a vital tool for monitoring treatment response in real-time, allowing for rapid adjustments in doses or regimens to mitigate side effects without compromising antitumor efficacy (Ahn et al., 2023; Yaeger et al., 2024). The integration of AI technologies and molecular biomarkers offers the path to precision oncology that respects the physiological limitations of the elderly patient, ensuring that the treatment is as effective as it is tolerable.

4 CONCLUSION

The therapeutic management of Colorectal Cancer (CRC) in elderly patients represents a unique challenge, marked by the need to balance oncological aggressiveness with tolerability and quality of life, given the higher prevalence of comorbidities and reduced physiological reserve in this population.

As evidenced in this review, geriatric oncology has been transformed by significant advances in both diagnosis and treatment strategies. The incorporation of less invasive risk stratification methods, such as plasma proteomic profiling, polygenic risk scores, and computed tomography-based deep learning-based classifiers, allows for more accurate personalization of screening and decision on adjuvant chemotherapy at early stages, minimizing unnecessary toxicity.

In the setting of metastatic RCC (mCRC), the introduction of targeted therapies targeting specific molecular mutations, such as BRAF V600E and KRAS G12C, has demonstrated clinically relevant gains. The BREAKWATER study, for example, set a new standard for the BRAF-mutant subtype, and the promising results with adagrasib and cetuximab for KRAS G12C tumors reinforce the efficacy of simultaneous inhibition of signaling pathways. In addition, the good tolerability of new agents, such as onvansertib, in second-line regimens for KRAS-mutated RCC points to more elderly patient-friendly therapeutic options.

Ultimately, the therapeutic decision must go beyond chronological age, being based on tumor biology and the integration of real-time monitoring tools, such as circulating tumor DNA (ctDNA) and artificial intelligence. This precision approach is crucial to optimize clinical care, ensuring that treatment is as effective as possible, while respecting the physiological limitations inherent in the aging process.

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