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BROADENING THE SCOPE OF RISK FACTORS IN PREDICTING STAGE II COLON CANCER OUTCOMES

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Abstract
In this editorial, we examine the article by Wu et al., offering a critical assessment of their viewpoint and evaluating the significance of the findings from Liu et al.'s original clinical research. We believe that several newly identified factors related to colon cancer progression, highlighted in recent clinical studies, should be incorporated into the analysis to improve the accuracy of prognosis. These additional factors — including inflammation, gut microbiota diversity, immune system function, and nutritional status — play important roles in influencing the survival outcomes of patients with stage II colorectal cancer after surgery. Furthermore, we explore the practical application and potential limitations of these expanded analyses in clinical settings. A comprehensive evaluation of each patient's overall health context is crucial for determining the most effective therapeutic approach.

Keywords: Risk factor, prognosis, colon cancer, inflammation markers, tumor location.

Introduction

Colon cancer ranks as the third most common oncological condition globally[1]. The majority of cases (70%-80%) are sporadic intestinal tumors, while hereditary forms account for 20%-30%[2]. Dysbiosis and chronic inflammation, leading to compromised intestinal barrier function, have been implicated in the development of these tumors[3,4]. Additionally, the variability in histological features, tumor location, and molecular marker expression contributes to the diverse clinical presentation, progression, and prognosis of colon cancer[5]. Thus, evaluating key relapse factors such as gut microbiota composition, nutritional status, and immune system health — all of which significantly impact the tumor microenvironment (TME) — can enhance clinical understanding. According to the Union for International Cancer Control and the American Joint Committee on Cancer, using the tumor-node-metastasis (TNM) classification system, stage II colon cancer (T4N0M0) is characterized by early-stage tumors that penetrate the bowel wall without lymph node involvement or distant metastasis[6]. In these patients, surgical resection alone leads to a high cure rate (approximately 80%). Consequently, the decision to use adjuvant chemotherapy remains controversial, particularly when weighing its cost-effectiveness[7,8]. Current clinical

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guidelines recommend adjuvant chemotherapy for stage II patients presenting with high-risk pathological features[7]. Therefore, identifying patients who would genuinely benefit from chemotherapy based on individualized relapse risk is crucial. This editorial aims to emphasize and explore the various risk factors associated with colon cancer and review the emerging models designed to assess and predict disease progression.

Insights into colon cancer risk factors and evolution. Recent studies have emphasized the importance of a comprehensive assessment of oncologic patients' conditions for accurate prognosis and treatment planning. In this context, research on molecular markers, gut microbiota, immune cell interactions, and intestinal tissue dynamics has gained significant attention[3,9]. Within our research group, we have identified factors within the tumor microenvironment — such as parathyroid hormone-related peptide (PTHrP), Secreted Protein Acidic and Cysteine Rich (SPARC), and other tumor-promoting molecules — as being associated with more aggressive colon cancer phenotypes[1,10]. Furthermore, we investigated the expression of molecular markers linked to malignancy in colon cancer tissues, notably mesenchymal-epithelial transition receptor and parathyroid hormone receptor type 1, both of which showed a direct correlation with PTHrP levels. Our findings suggest that PTHrP plays a critical role in the early stages of tumor progression by activating molecular pathways associated with poor outcomes[11]. These observations, supported by other researchers advocating for the evaluation of circulating tumor DNA (ctDNA) and markers of stemness, migration, and invasion[7,12,13], point to the necessity of broadening the scope of molecular marker assessment in tissue and blood samples for colon cancer.Moreover, physiological and pathological conditions are heavily influenced by alterations in intestinal barrier integrity, which are regulated by changes in microbial populations and their metabolic byproducts[3]. Although the diagnostic and prognostic potential of gut microbiota profiles is still under investigation, studies have demonstrated links between specific microbial species and the onset and advancement of colon cancer. For example, a higher abundance of Fusobacterium nucleatum (F. nucleatum) has been correlated with faster recurrence rates[14,15]. Other species such as Bacteroides fragilis, Escherichia coli, and Helicobacter pylori are also found at elevated levels in the intestinal tracts of colon cancer patients[3,16]. Combining traditional fecal tests, like fecal occult blood and immunochemical testing, with microbiome analysis could significantly improve diagnostic accuracy for colon cancer[15]. Fecal microbiome profiling is emerging as a promising diagnostic strategy, offering a non-invasive, cost-effective way to detect disease-specific microbial signatures that correspond with tumor development and progression, thereby enabling earlier detection and better management of colon cancer[17]. As noted by Liu et al[26] in their original research, enterostomy surgery — identified as an independent risk factor for overall survival (OS) — can significantly impact a patient's hydration and nutritional status. Although temporary or permanent surgical interventions are often employed to enhance intestinal function, particularly in obstructive colon cancer or severe inflammation, evidence suggests that such procedures may also negatively affect patient outcomes. These adverse effects are primarily linked to anatomical alterations that disrupt the gut microbiota, potentially leading to dysbiosis — a risk factor previously discussed — and contributing to postoperative complications[27].Wu et al[28] analyzed various risk factors in their study to develop a prognostic nomogram for patients with stage II colon cancer, aiming to predict outcomes based on standard clinical management.

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Their editorial correspondence emphasized the good consistency of the nomogram model[28]. However, we believe that the analysis should be further refined by focusing specifically on patients with T4N0M0 classification and risk factors particularly relevant to this subgroup.In clinical practice, certain high-risk features — such as a high T stage, lymphovascular invasion, bowel obstruction or perforation, and poor histological differentiation — have been used to establish a 20% cut-off point to guide decisions regarding adjuvant chemotherapy[6]. Nevertheless, many patients are classified as having intermediate risk, complicating therapeutic decisions[6].Recent work by Tie and colleagues underlined the importance of detecting circulating tumor DNA (ctDNA) in stage II colon cancer patients. Their study demonstrated that ctDNA analysis post-surgery enables the identification of patients most likely to benefit from adjuvant chemotherapy[7]. This approach introduces a promising, minimally invasive, real-time monitoring tool through blood sample analysis[6,7,29].Clinical validation studies, such as that by Jin et al[30], using multiplex ctDNA assays in a cohort of 179 colon cancer patients and healthy individuals, have shown sensitivity and specificity rates exceeding 80%. Importantly, ctDNA detection proved effective for early diagnosis of stage I and II tumors as well as for prognosis evaluation[30]. Furthermore, recent research indicates that incorporating ctDNA testing could have a favorable economic impact by reducing unnecessary chemotherapy administration without compromising patient survival outcomes[31]. Recent advances in single-cell RNA sequencing techniques now enable the determination of individual tumor cell contributions to the overall tumor response and the identification of early transcriptomic changes associated with tumor cell differentiation. This approach facilitates the discovery of new genes and epigenetic mechanisms, as well as the identification of cell populations that play a role in tumor progression and the spatiotemporal features of the preinvasive niche at various stages of primary colorectal cancer[42]. The ability to analyze at single-cell resolution, combined with progress in multi-omic analyses, has generated a vast amount of data, contributing to initiatives like the Human Tumor Atlas Network. This network is expected to provide valuable insights that can inform clinical decision-making.

In terms of integrating non-conventional parameters into colon cancer prognosis models, Mazaki et al[23] developed innovative nomograms to predict disease-free survival (DFS) in stage II and III colon cancer patients, utilizing nutritional and inflammatory markers observed during the postoperative period, spanning 1 to 5 years. Wang et al[43] also highlighted the significance of these risk factors. In their recent work, they focused on constructing prospective/predictive nomograms using artificial intelligence. Machine learning was employed to integrate pathophysiological data, radiomic features, immunoscore, and clinical factors to predict postoperative outcomes in colon cancer patients[43]. The implementation of these models, particularly those incorporating non-invasive techniques, holds the potential to enhance prognostic accuracy, particularly for stage II patients.

DISCUSSION

The analysis of inflammatory and nutritional markers has been shown to predict cancer recurrence after curative surgery in patients with stage II colon cancer[23]. The original research by Liu et al[26] evaluates, through a retrospective analysis, the clinical outcomes and prognostic factors in T4N0M0 colon cancer patients (stage II) after resection surgery without microscopic or macroscopic residual tumors. Several risk factors associated with this oncological disease were

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investigated in a training cohort (n = 127) and a validation cohort (n = 88) applying statistical techniques of univariate and multivariate analysis concerning 3 years OS. A nomogram model was constructed with these data[26]. It is highlighted that this article analyzes risk factors like sex, age, and relevant molecular markers in colon cancer such as carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), pathological type, status, tumor size and location; but in addition includes the study of variables such as the type of surgery achieved (laparotomy/laparoscopy), whether anastomosis/enterostomy was performed, preoperative or postoperative complications and patients/clinicians compromised with regular reviews. These aspects, which only a few studies consider, are extremely relevant when evaluating OS and DFS in patients with colon cancer. However, it would be beneficial to expand the study and to include in an extensive cohort other reliable factors in predicting relapses such as nutritional balance and immune status. In this regard, we consider that the examination of gut microbiota composition and nutritional and immune status is also compelling. The rationale for focusing on these studies lies in the fact that an imbalance in the microbiota is closely associated with not healthy diets and lifestyles, but disruptions in the integrity of the gut barrier and alterations in the immune response, including the infiltration and activation of immune cells in intestinal tissue[16]. Consequently, a proinflammatory intestinal environment and dysbiosis, probably associated with poor diet, may contribute to tumor growth, progression, and resistance to therapy in colon cancer patients[3]. Although various nomograms with genetic and immune risk factors are being proposed today[39,40], their implementation is still challenging. The great number of analyzed genes, their interpretation in the tumor context, and the heterogeneity of the disease hinder the establishment of a single genetic signature or study panel. However, this analysis provides fundamental data in pursuit of personalized medicine and the early detection of those patients who may relapse or benefit from certain drugs and therapies. Hence, it is crucial to validate the clinical impact and relevance of all these new risk factors and nomograms proposed by studying several populations, subjecting the results to rigorous statistical methods, and comparing them with those obtained by standard management. In addition, to prevent the overfitting of these models to a data set, a large-scale study must be accomplished. Since this exploration requires considerable effort, artificial intelligence, and current data analysis, web tools could greatly contribute to this work[44,45]. It is also relevant to highlight that the detection of gene signatures or microbiome analysis by metagenomic sequencing or metabolome exploration has economic limitations in clinical practice, particularly in resource-limited environments. Genetic markers associated with the immune system[40], or the microbiota[46] can be studied in these cases using cheaper techniques than microarray or next-generation sequencing such as PCR, immunohistochemistry, or immunofluorescence. An exhaustive anamnesis with analysis of the patient's diet and lifestyle can provide significant information regarding the abundance of beneficial gut microorganisms. Finally, a risk factor and microbial biomarker such as F. nucleatum, is enriched on both stools and tumor tissue and can then be detected for the early prognostic prediction of colon cancer[47].

CONCLUSION

The current methods for prognostic evaluation of stage II colon cancer patients, particularly in terms of chemotherapy recommendations based on their clinicopathological characteristics, are inadequate. The reliance on nomogram models that are constructed using only standard treatment

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protocols leads to imprecision in clinical decision-making. This could result in patients being subjected to unnecessary treatments, or worse, in some cases, failing to receive the correct therapy, which could lead to disease recurrence. The limitations of these models lie in their inability to account for the complexity and heterogeneity of colon cancer, as they do not fully capture the diverse biological and clinical features that influence patient outcomes.To address these shortcomings, it is critical to integrate additional factors into the prognostic assessment of stage II colon cancer patients. A more comprehensive approach should involve molecular analyses of biomarkers both before and after surgery, allowing for a more precise prediction of the disease course. For example, evaluating biomarkers that indicate tumor aggressiveness, such as circulating tumor DNA (ctDNA), mesenchymal-epithelial transition markers, or other genetic and epigenetic factors, would provide valuable information that is often missing in traditional nomograms. In addition to molecular markers, the prognostic nutritional index (PNI) and immunoscore are key components that can offer insights into the patient's overall immune response and nutritional status, both of which significantly influence the recovery process and the likelihood of relapse.Another critical aspect of improving prognostic accuracy is the consideration of the tumor microenvironment (TME).

The composition of immune cells, stromal cells, and the extracellular matrix within the TME can offer significant clues about how the cancer may evolve and how it might respond to treatment. A deeper understanding of TME cell composition and its interaction with the tumor cells could allow clinicians to better assess the risk of recurrence and identify which patients are most likely to benefit from adjuvant chemotherapy. Furthermore, these factors should be evaluated not only from the perspective of the primary tumor but also through a comprehensive review of the patient's clinical conditions, including factors such as comorbidities, overall health status, and any other underlying factors that could affect treatment outcomes.By adopting a more holistic approach, clinicians will be able to better classify patients into low, average, or high-risk categories, enabling them to provide personalized treatment recommendations. This individualized assessment can potentially reduce unnecessary chemotherapy use and, at the same time, ensure that high-risk patients receive the appropriate therapies in a timely manner. Ultimately, refining prognostic models to include a broader range of molecular, immunological, and clinical parameters is essential for improving patient outcomes and minimizing the risk of both over- and under-treatment.

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