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The double role of depression in Gastric cancer. As a causative factor and as consequence.

Relation of depression and gastric cancer

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Abstract

In this editorial we comment on the article "Hotspots and frontiers of the relationship between gastric cancer and depression: A bibliometric study" by Liu *et al* Gastric cancer (GC) is a common malignancy in the digestive system with increased mortality and morbidity rates globally. Standard treatments, such as gastrectomy, negatively impact patients' quality of life and beyond the physical strain, GC patients face psychological challenges, including anxiety and depression. The prevalence of depression can be as high as 57%, among gastrointestinal cancer patients. Due to the advancements in treatment effectiveness and increased 5-year overall survival rates, attention has shifted to managing psychological effects. However, the significance of managing the depression doesn't lie solely in the need for a better psychological status. Depression leads to chronic stress activating the sympathetic nervous system and the hypothalamus-pituitary-adrenal axis, leading release of catecholamines inducing tumor proliferation, migration, and metastasis, contributing to GC progression. The dysregulation of neurotransmitters and the involvement of various signaling pathways underscore the complex interplay between depression and GC. Comprehensive strategies are required to address the psychological aspects of GC, including region-

specific interventions and increased monitoring for depression. Understanding the intricate relationship between depression and GC progression is essential for developing effective therapeutic strategies and improving overall outcomes for patients facing this complex disease. In this Editorial we delve into double role of depression in the pathogenesis of GC and as a complication of it.

Key Words: Gastric cancer; depression; anxiety; chronic stress; pathogenesis of gastric cancer

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Core Tip: Gastric cancer (GC), a prevalent malignancy in the digestive system, poses a dual challenge with both physical and psychological implications. While standard treatments like gastrectomy impact patients' quality of life, the psychological burden, including anxiety and depression, cannot be overlooked. Depression, reaching prevalence rates of 57%, significantly influences cancer outcomes, affecting mental well-being, treatment adherence, and overall quality of life. Chronic stress and neurotransmitter dysregulation play a pivotal role in GC development, activating pathways that induce tumor progression. Understanding the intricate connection between depression and GC not only highlights the need for comprehensive psychological support but also unveils potential therapeutic targets. Addressing both the physical and psychological aspects of GC is essential for enhancing the overall well-being and outcomes of patients grappling with this complex disease.

INTRODUCTION

Gastric cancer (GC) stands as the most prevalent malignant tumor in the digestive system, holding the record for the third-highest mortality and fifth-highest morbidity

rates among all cancers. Global statistics underscore the gravity of the situation, revealing an estimated 1 million new cases and 760,000 deaths in 2020 alone [1–4]. The standard treatment for GC, gastrectomy, while common, has detrimental effects on patients' quality of life and mental well-being. Total gastrectomy, an aspect of this treatment, triggers substantial weight loss, thereby impacting the nutritional status of individuals with the disease. Gastric cancer alone, can cause disturbing and disabling nausea, vomiting, diarrhea having a significant impact on the patients' nutritional status [2,3,5]. Beyond the physical strain, patients diagnosed with GC confront some psychological challenges, including anxiety, depression, pain, and fatigue [1,3,5,6]. The prevalence of anxiety and depression can reach as high as 47.2 and 57% of patients with gastrointestinal cancer [6]. The last years, having an increased effectiveness of the treatment options and an increased 5y-Overal Survival, the attention shifts to managing the psychological effects accompanying the disease and the treatment. These challenges emphasize the urgent need for interventions aimed to enhance the overall quality of life of these patients. Depression emerges as a pervasive issue among cancer patients, particularly affecting their mental well-being. Contributing factors include the dysregulation of miRNA expression, abnormalities in receptors, and structural changes in the brain [1,7]. Such emotional distress not only shapes the attitude of cancer patients but also influences treatment adherence, underscoring its critical role in determining overall quality of life [1,6]. Psychological distress becomes a notable risk factor for treatment non-compliance, increasing the mortality rates. The repercussions of depression extend further, exerting a negative influence on the prognosis of GC and resulting in poor survival outcomes. Depression in the context of cancer, including GC, is linked to chronic psychological stress. Stress-associated neurotransmitters, particularly catecholamines, emerge as potential influencers of cancer progression [5,8]. Chronic stress, often manifesting as anxiety and depression, can trigger tumor development through pathways involving β2-adrenergic receptors and epithelial–mesenchymal transition (EMT). Despite the acknowledgment of chronic stress and β2-adrenergic receptors in tumor progression, the precise mechanisms of how EMT is

regulated by β2-AR remain elusive [4,8]. Consequently, there is a need for a deeper understanding of these mechanisms to guide more effective therapeutic strategies. Recognizing the gravity of depression's impact on cancer outcomes, proper treatment is deemed essential for cancer patients. This treatment aims not only to mitigate adverse effects but also to improve symptoms, ensuring the long-term efficacy of interventions for individuals grappling with the complexities of gastric cancer.

ROLE OF DEPRESSION IN GASTRIC CANCER DEVELOPMENT

Under the influence of chronic stress, the sympathetic nervous system is activated as well as the hypothalamus-pituitary-adrenal (HPA) axis, thereby triggering the release of neurotransmitters such as norepinephrine and epinephrine ($p<0.005$) [5]. The increased expression of catecholamines within the tumor microenvironment has been revealed to induce the proliferation, migration, and metastasis of many tumors, such as breast, lung, and colon cancer. Catecholamines play a significant role in promoting epithelial-mesenchymal transition (EMT) by utilizing signaling pathways like c-Jun [4,5,8]. Anxiety and depression can accelerate the onset and advancement of gastric cancer through multifaceted mechanisms (e.g., influencing reactive oxygen species-activated ABL1) and modulating the hypothalamic–pituitary–adrenal axis (e.g., FK506 binding protein 5 gene polymorphisms), thereby inducing disease deterioration and increasing the possibility of recurrence in gastric cancer patients [9,10].

Functioning as neurotransmitters, catecholamines can influence tumor characteristics, including phenotypic transformation, apoptosis, and drug resistance. The acquisition of a neuroendocrine phenotype in cancer cells strongly correlates with neoplasm metastasis, drug resistance, advanced cancer stage, and the increased expression of neuroendocrine markers—SYP, CD44, and chromogranin A (CHGA) [5]. The binding of catecholamines to the beta-2 adrenergic receptor (β2-AR) upregulates MACC1 expression, leading to neuroendocrine phenotypic transformation, GC invasion, and metastasis. In this process, α-AR does not exhibit any discernible role. MACC1, an oncogene regulated by c-Jun, controls c-Met transcriptional levels, enhancing EMT. The

activation of the hepatocyte growth factor receptor (c-Met) orchestrates neuroendocrine features in advanced prostate cancer, assuming a parallel role in GC development. Reversal of these effects in mouse models and *in vitro* is achieved through treatment with β2-AR antagonists or MACC1 silencing [5]. MACC1 also forms a complex with synaptophysin (SYP), a marker of neuroendocrine phenotypic characteristics, utilizing the MACC1/SYP signaling pathway in the neuroendocrine phenotypic transformation triggered by catecholamine. Targeting β2-AR mitigates depression-induced neuroendocrine phenotypic transformation and lung metastasis of GC, providing potential therapeutic targets for enhancing outcomes in GC patients with concurrent depression. β2-AR stimulation may additionally induce EMT, migration, and invasion by ERK (Extracellular-signal-regulated kinase) phosphorylation [8]. Lu *et al* observed that salbutamol, a β2-AR agonist, heightened the expression of the mesenchymal marker N-cadherin and reduced the epithelial marker E-cadherin in transplanted tumor tissue, thereby inducing further EMT [8]. They also supported the idea that the β2-AR agonist isoproterenol promotes EMT of gastric cancer cells through the STAT3-CD44 pathway, shedding light on the association of depression with GC [11]. The β2-AR-HIF-1α-Snail signaling pathway influences the EMT of gastric cancer cells, promoting the invasion and migration of gastric cancer [12]. Last but not least, Liu *et al* observed that the activation of β2-AR increases the expression of PlexinA1, activates JAK-STAT3 signaling, and further promotes EMT in human gastric cancer cells. Consequently, chronic stress is intricately linked with the pathogenesis of GC [4].

T helper (Th) cells modulate the stress response, oxidative stress, and neuroinflammation, potentially participating in the pathogenesis of anxiety, depression, and cognitive impairment. Th1 (P = 0.017) and Th17 (P = 0.049) levels were found to be elevated in patients with depression compared to those without depression [13].

When depression is quantified by the PHQ-9 score, a positive correlation is observed with serum levels of epinephrine, noradrenaline, MACC1, as well as TNM stage, supporting the association of depression with GC pathogenesis [5].

DEPRESSION AS A RESULT OF GASTRIC CANCER

Gastric cancer patients face many psychological challenges, including anxiety, depression, pain, and fatigue, underscoring the need to prioritize their quality of life (QoL). The prevalence of depression among these patients is often underestimated, despite its effects on prognosis and QoL [2]. Notably, depression has been linked to increased suicidal thoughts, anxiety, distress, and fatigue in cancer patients, with studies emphasizing in the need of increased monitoring for this condition [14]. The impact of depression is particularly significant among gastric cancer patients, while they are already at risk for malnutrition, lower body mass index, reduced physical activity, and social isolation, exacerbating their susceptibility to depression [2].

The comorbidities accompanying gastric cancer and its treatment introduces additional challenges, as gastrectomy, a commonly employed strategy for curative resection, profoundly affects patients' QoL and mental well-being. Total gastrectomy, in particular, results in substantial postoperative malnutrition, with patients experiencing significant weight loss within the first year of surgery [2].

Several studies highlight the prevalence of depression among gastric cancer patients, ranging from 4.0% to 68% with a mean of 37% (95%CI). The variability in prevalence underscores the need for comprehensive and region-specific approaches to address this psychological aspect of the disease. A study by Kouhestani in 2020, drawing data from the National Health Service Sample Cohort, revealed a higher risk of new-onset depression in gastric cancer patients, particularly in females aged 60-69 Living in metropolitan regions with high income [2].

Kwon investigates the correlation between depression and stomach cancer further, emphasizing the stressful aspect of cancer diagnosis and therapy, which causes anxiety and depression in a considerable proportion of patients [6].

Patients with recurrent stomach cancer had greater levels of anxiety and sadness than newly diagnosed patients and healthy controls. Age above 60 years, diabetes, TNM stage at diagnosis, shorter duration to recurrence, and distant metastases at recurrence

were all risk factors for anxiety. Age above 60 years, diabetes, tumor site upon diagnosis, and shorter time to recurrence were all risk factors for depression [6].

Liu investigates factors associated with anxiety and depression in gastric cancer patients, revealing that coping style, type D personality, and neutrophil-to-lymphocyte ratio (NLR) contribute to preoperative anxiety and depression. Additionally, genetic factors, including polymorphisms in genes related to apoptosis, may play a role in susceptibility to gastric cancer and associated psychological distress [3,15].

However, Lou 2021 *et al* observed that polymorphisms of BNIP3 and DAPK1 were associated with a protective effect against GC. These two genes are shown to also have a protective effect against depression [15].

CONCLUSION

Considering the global significance of gastric cancer as the fifth most frequently diagnosed cancer, efforts to understand and address the psychological impact of the disease, particularly depression and anxiety, are essential. Efforts should involve a multidisciplinary approach, considering both the physical and mental well-being of patients to improve overall outcomes and quality of life.

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