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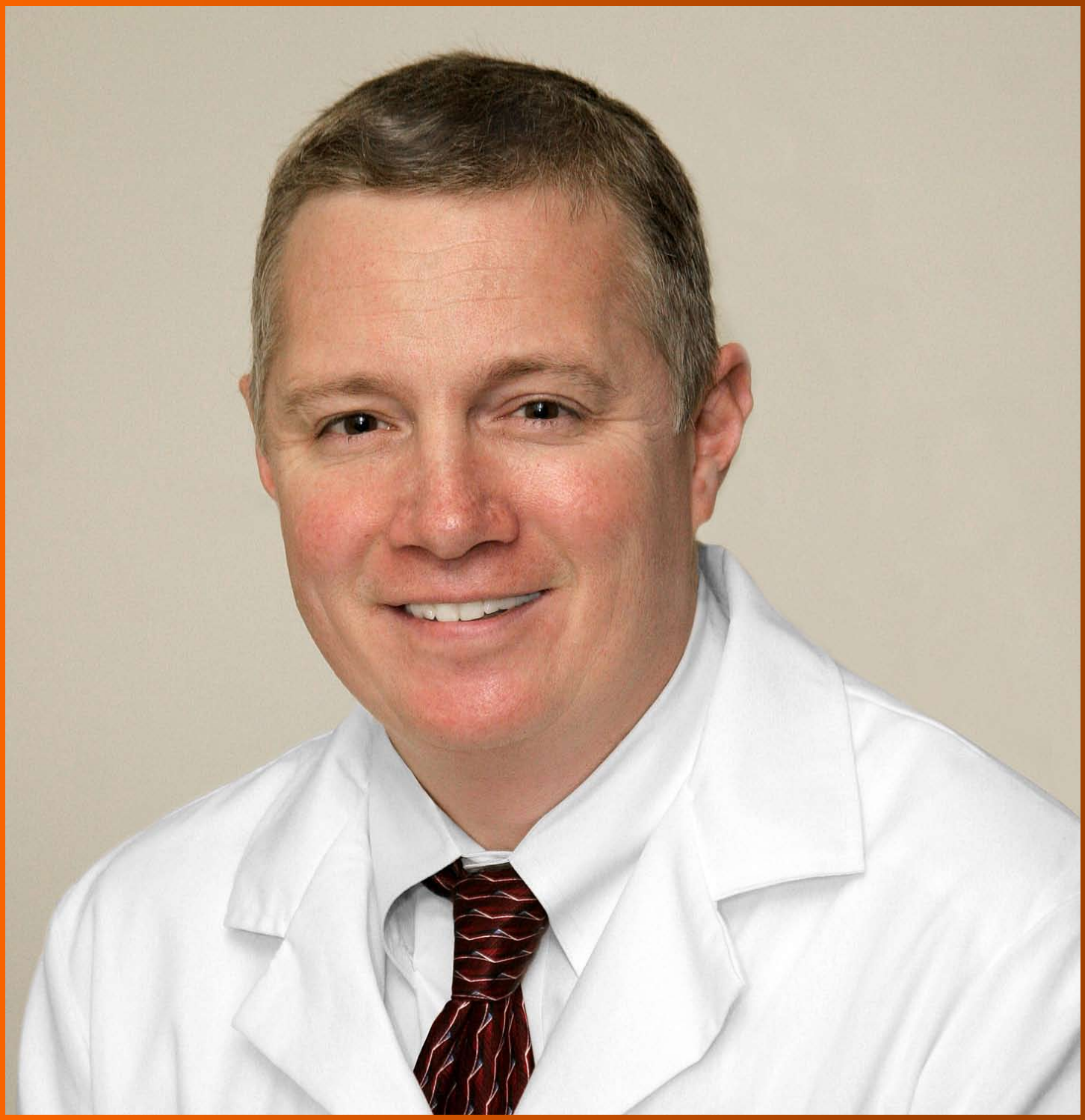

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AIM AND SCOPE

World Journal of Gastrointestinal Oncology (*World J Gastrointest Oncol*, *WJGO*, online ISSN 1948-5204, DOI: 10.4251) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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MINIREVIEWS

Clinical significance of tumor-infiltrating lymphocytes for gastric cancer in the era of immunology

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Abstract

Immunotherapy has begun to revolutionize cancer treatment, by introducing therapies that target the host immune system instead of the tumor, therapies that possess unique adverse event profiles, and therapies that may cure certain types of cancer. The immune microenvironment of tumors is emerging as the most important means of understanding the relationship between a patient' immune system and their cancer, informing prognosis, and guiding immunotherapy, such as an antibody blockade of immune checkpoints. For some solid tumors, simple quantitation of lymphocyte infiltration would seem to have prognostic significance, suggesting that lymphocyte infiltration is not passive but may actively promote or inhibit tumor growth. For gastric cancers, several studies have provided strong evidence that immune cells contribute to determining prognosis. However, the exact role of immune cells in gastric cancer remains unclear. Therefore, this review focuses on the clinical significance of immune cells, especially tumor-infiltrating lymphocytes, in gastric cancer.

Key words: Gastric cancer; Tumor-infiltrating lymphocytes; Immunotherapy

Core tip: Tumor-infiltrating lymphocytes (TILs) are considered a manifestation of the host immune response against tumor cells, and several studies have already reported the potential of TILs as a prognostic parameter for various human malignancies. However, only a few studies have investigated the prognostic impact of TILs in gastric cancer. Based on a comprehensive molecular characterization of gastric cancer, TILs could be a potential biomarker. Accordingly, this review focuses on the clinical significance of immune cells, especially TILs, in gastric cancer.

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INTRODUCTION

Gastric cancer is a major public health issue and the leading cause of cancer-related deaths. Despite numerous advances in treatment options, the prognosis for gastric cancer remains dismal, as most patients are in an advanced stage at the time of diagnosis[1]. To improve the survival outcome, a better understanding of the mechanisms of disease progression is crucial, along with elucidating effective predictive or prognostic factors as therapeutic targets. Yet, while many predictive factors have already been evaluated, including clinicopathologic factors, biomarkers, genes, and microsatellite instability, their prognostic accuracies remain controversial[2].

Meantime, immunotherapy has begun to revolutionize cancer treatment by introducing therapies that target the host immune system rather than the tumor, therapies that possess unique adverse event profiles, and therapies that may even cure certain types of cancer. Thus, the immune microenvironment of tumors is emerging as the most important means of understanding the relationship between a patient' immune system and their cancer, informing prognosis, and guiding immunotherapy, such as an antibody blockade of immune checkpoints[3]. For some solid tumors, simple quantitation of lymphocyte infiltration would seem to have prognostic significance, suggesting that lymphocyte infiltration is nor passive but may actively promote or inhibit tumor growth[3]. For example, a meta-analysis showed a significant correlation between tumor-infiltrating lymphocytes (TILs) and clinical traits in breast cancer patients. Thus, higher value of total TILs not only predicts a neoadjuvant chemotherapy response, but also implies a better prognosis[4]. For gastric cancers, several studies have provided strong evidence that immune cells contribute to determining the prognosis. It has been reported that regulatory T cells can play a role of immunosuppression and tumor progression in patients with gastric cancer, leading to a worse prognosis[5]. Plus, an intratumoral high regulatory T cell/$CD8^+$ T cell ratio has been shown as an independent predictor of a poor prognosis for gastric cancer[6]. However, the exact role of immune cells in gastric cancer remains unclear. Accordingly, this review focuses on the clinical significance of immune cells, especially TILs, in gastric cancer.

TILS IN GASTRIC CANCER

Cancer immunity and the role of TILs

The evolution of cancers reflects intricate cellular and molecular interactions between tumor cells and constituents of the tumor microenvironment[7]. In the first step, neoantigens created by oncogenesis are released and captured by dendritic cells for processing. Next, dendritic cells present the captured antigens on major histocompatibility class (MHC) molecules to T cells, resulting in the priming and activation of effector T cell responses against the cancer-specific antigens. Finally, the activated T cells toward to and infiltrate the tumor bed, and destroy their target cancer cells[8]. These may be occurred in the tumor core, invasive margin, or adjacent tumor stroma. The functional activity of lymphoid infiltrates, such as T cells, B cells, and natural killer (NK) cells, depends upon MHC complexes or surface antigen that can be recognized specific manner. These cells can be induced to secrete different types of cytokines based on effector functions[9]. Many cytokines also have the potential to enhance nonspecific inflammatory responses which by themselves may have anti-tumor activity. Plus, the potential of various cytokines to enhance both specific and innate immune responses against tumors has been demonstrated in experimental models and has been realized in clinical practice[10]. Surprisingly, this process is highly regulated through various genes, such as STAT3, High-mobility group protein B1, calreticulin, and endothelial cell adhesion protein[11]. Thus, TILs are incorporated into these multi-factorial interactions and their presence has proved to be a major determinant of tumor characteristics and patient outcome.

Stromal TILs and intratumoral TILs

Several recent studies have evaluated the prognostic and predictive importance of TILs in gastric cancer[12]. TILs are the major type of infiltrating immune cells, and are represented by T cells, B cells, and NK cells. These cells can infiltrate stroma and tumor cells, and are considered a manifestation of the host immune response against tumor cells[13]. Previous studies of TILs in gastric cancer have evaluated stromal and intratumoral lymphocytes separately, where a visual assessment of standard hematoxylin and eosin (H and E)-stained sections is the most commonly used approach to measure TILs[3,14]. Based on a histopathologic analysis of TILs using H and E-stained slides, Kang *et al*[15] suggested that stromal TILs can be defined as a tumor stroma area containing infiltrating mononuclear inflammatory cells, while intratumoral TILs can be defined as intraepithelial lymphocytes or mononuclear cells within tumor cells. As a result, they documented that stromal TILs can be used to predict recurrence-free survival (RFS) and disease-free survival (DFS). In contrast, another study found that increasing intratumoral TILs was significantly associated with improved cancer-specific survival (CSS)[16] (Table 1). In fact, stromal TILs are well known as a superior and more reproducible parameter in breast cancer[14]. Notwithstanding, there is no current consensus on the

Table 1 Tumor-infiltrating lymphocytes associated with the prognosis of gastric cancer

Ref.	Sample size	Patient group	Location	Criteria (cut-off)	Prognostic role
Kang *et al*[15]	120	EBVaGC	Stromal	High infiltration	Decreased DFS and RFS
Grogg *et al*[16]	110	G	Intratumoral	High infiltration	Increased CSS
Lee *et al*[17]	220	G	Intratumoral	High density	Increased OS

EBVaGC: Epstein-Barr virus-associated gastric cancer; DFS: Disease-free survival; RFS: Recurrence-free survival; G: Gastric cancer; CSS: Cancer-specific survival; OS: Overall-survival.

Table 2 Lymphocyte subtypes associated with the prognosis of gastric cancer

Ref.	Lymphocyte subtypes	Sample size	Patient group	Criteria (cut-off)	Prognostic role
Lee *et al*[17]	$CD3^+$, $CD8^+$, $CD45RO^+$	220	G	High density	Increased OS
Thompson *et al*[18]	$CD8^+$	43	G/GEJ	High density	Decreased PFS and OS
Kawazoe *et al*[33]	$CD8^+$	487	G	High density	Increased OS
Wakatsuki *et al*[30]	$CD45RO^+$	101	G	High numbers	Increased PFS and OS
Chiaravalli *et al*[34]	$CD3^+$, $CD8^+$	96	MSI-H G	High numbers	Increased OS
Kim *et al*[22]	$CD8^+$, $FOXP3^+$	99	MSI-H G	High density	Increased OS
Liu *et al*[23]	$CD8^+/FOXP3^+$ ratio	166	G	High ratio	Increased OS
Shen *et al*[26]	$FOXP3^+/CD8^+$ ratio	133	G	High ratio	Decreased OS
Wang *et al*[5]	$FOXP3^+$	107	G	High expression	Increased OS
Haas *et al*[20]	$FOXP3^+$	52	G	High numbers	Increased OS
Mizukami *et al*[24]	$FOXP3^+$	120	G	Diffuse pattern	Decreased OS
Perrone *et al*[25]	$FOXP3^+$	110	G	High numbers	Decreased RFS and OS
Zhou *et al*[27]	$FOXP3^+$	133	G	High numbers	Decreased OS
Choi *et al*[19]	$FOXP3^+/CD4^+$ ratio	28	G	High ratio	Increased OS
Kim *et al*[21]	$FOXP3^+/CD4^+$ ratio	180	G	High ratio	Decreased OS
Dong *et al*[35]	$CD20^+$	100	G	High density	Increased OS
Ishigami *et al*[31]	NK cells	146	G	High numbers	Increased OS
Rosso *et al*[36]	NK cells	72	G	High concentration	Increased DFS and OS
Ishigami *et al*[37]	NK cells	169	G	High numbers	Increased OS
Ubukata *et al*[28]	Th1/Th2 ratio	157	G	High ratio[1]	Increased OS
Liu *et al*[29]	Th22, Th17	32	G	High numbers[1]	Decreased OS

[1]Peripheral blood. G: Gastric cancer; OS: Overall-survival; G/GEJ: Gastric/gastro-esophageal junction cancer; PFS: Progression-free survival; MSI-H: Microsatellite instability-high; RFS: Relapse-free survival; DFS: Disease-free survival.

best TILs distribution for predicting survival in gastric cancer. Therefore, the methodology of interpreting TILs and cut-off values for gastric cancer needs to be standardized.

Composition of TILs and their clinical significance

TILs are represented by T cells, B cells, and NK cells. The subset of T cells include $CD8^+$ cytotoxic T cells, $CD4^+$ T helper cells, $CD45RO^+$ memory T cells, $FOXP3^+$ regulatory T cells, and NK cells[12]. In gastric cancer, the prognostic role of each lymphocyte is summarized in the Table 2[5,17-38]. A high-density of $CD3^+$, $CD8^+$, and $CD45RO^+$ cells has been strongly associated with patient survival and regional lymph node metastasis[17]. Recently, Thompson *et al*[18] reported that the increasing $CD8^+$ infiltration was correlated with impaired survival and higher programmed death-ligand 1 (PD-L1) expression, indicating an adaptive immune resistance mechanism. Meanwhile, the presence of $FOXP3^+$ regulatory T cells has been associated with both good and bad prognosis[5,19-27]. Among the other $CD4^+$ T cell subpopulations, a high T helper 1/T helper 2 ratio has been implicated as a favorable prognostic factor in gastric cancer[28]. T helper 17 and T helper 22 cells, producers of proinflammatory interleukin, also appear to have an effect on tumor progression in gastric cancer, while high $CD45RO^+$ memory T cells are associated with better survival of gastric cancer patients[29,30]. Furthermore, the precise role of B cells and NK cells is currently not well defined and remains controversial[31,32].

Impact of TILs on subtypes of gastric cancer

The Cancer Genome Atlas Research Network recently provided a comprehensive molecular characterization of 295 gastric cancers using various platforms, and proposed four distinct subtypes, as follows: Epstein-Barr virus (EBV)-positive tumors, microsatellite unstable tumors, genomically stable tumors, and tumors with chromosomal instability[38]. Among these, EBV-positive tumors and microsatellite unstable tumors often show immune cell signaling activation. Therefore, these findings point to the possibility of TILs as prognostic and predictive markers in gastric cancer patients with EBV or mismatch repair-deficient tumors, suggesting the pivotal role of the immune mechanism in these subsets of gastric cancer. Significant correlations have also been found between microsatellite instability (MSI)

and TIL positivity[39]. Plus, higher densities of both $CD8^+$ and $FOXP3^+$ TILs have been associated with good prognosis in MSI-high gastric cancer[22]. Interestingly, Chiaravalli *et al*[34] reported that a high number of $CD3^+$ and $CD8^+$ TILs is a characteristic of gastric cancer with MSI and EBV, correlating with a favorable prognosis. In a separate study, MSI and EBV tumors showed significantly increased TILs compared with non-MSI and non-EBV tumors, and the number of TILs was significantly associated with CSS in EBV tumors[16]. Meanwhile, recent data showed an independent association between high TILs and favorable RFS or DFS in 120 patients with EBV-associated gastric cancer (EBVaGC), suggesting that TILs exhibit a host cellular immune response against tumors and immunotherapy may have a potential role in patients with EBVaGC[15]. Plus, although their mechanisms and effects on cancer are still unknown, previous reports have indicated that local triggering of cellular immune responses, like activated cytotoxic T cells in EBVaGC, prevents lymph node metastasis, and various molecules, such as chemokines, interleukins, intergrins, and adhesion molecules, may contribute to immune surveillance and immunogenic apoptosis[11,40].

Roles of programmed cell death protein in immune cells of gastric cancer

Immune evasion is now recognized to play a key role in carcinogenesis. The strong growth potential and invasive nature of malignant tumors are at least partially attributed to the ability of the tumor cells to escape the host immune surveillance[41]. In particular, the effector T-lymphocyte recognizes the tumor cell through interaction between the T-cell receptor and MHC on the tumor cell. After the immune response has been mounted, the tumor is able to express PD-L1 on its surface. The subsequent binding between PD-L1 and programmed cell death-1 (PD-1) will shut down the immune response and allow the tumor cells to escape death[8]. PD-1, which belongs to the CD28 family of proteins, is a receptor expressed on a number of immune cells, including T cells, B cells, monocytes, NK cells, and dendritic cells. It has two ligands, PD-L1 and PD-L2. PD-L1 is broadly expressed[42]. Several studies have already demonstrated that PD-L1 or PD-1 is highly expressed on tumor cells in gastric cancer patients[43-46]. A recent study reported that 53.8% of patients were positive for PD-1 expression which was mainly restricted to TILs and 30.1% were positive for PD-L1 expression in the tumor cells, respectively[47]. Although expression of PD-L1 and PD-1 in gastric cancer is closely linked to the prognosis, the results remain inconsistent[41]. A recent meta-analysis by Zhang *et al*[48] evaluated the prognostic value of PD-L1 in gastric cancer. Based on 1,901 patients in 10 studies, the final hazard ratio for overall-survival (OS) of 1.64 showed a significant difference in terms of PD-L1 expression (95%CI: 1.11-2.43, P = 0.01). Interestingly, this meta-analysis indicated that PD-L1 had no correlation with gender, age, cancer location, differentiation, depth of invasion, and tumor stage. Therefore, this study provided evidence to support benefit from targeted therapy against PD-L1 in the case of gastric cancer. Indeed, we already evaluated the tissue samples that were obtained from patients included in a previous study of EBVaGC[15]. We found that intratumoral PD-L1 was significantly associated with DFS in these patients group. These observations have given rise to the hypothesis that specific inhibitors for PD-L1 or PD-1 would be potential therapeutic candidates that can affect a variety of gastric cancer.

Several therapeutic antibodies against this pathway have been developed and clinical trials are ongoing. KEYNOTE-012 was a phase 1b that evaluated pembrolizumab, a humanized IgG4 monoclonal antibody against PD-1, in patients with PD-L1-positive recurrent or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction. In this trial, pembrolizumab had a 22% response rate and manageable toxicity[49]. Recenly, nivolumab, a human IgG4 anti-PD-1 monoclonal antibody, has been clinically explored following the failure of standard of care. This trial (ONO-4538-12), which compared nivolumab to placebo in patients with unresectable advanced or recurrent gastric cancer, including gastroesophageal junction cancer, refractory to, or intolerant of, standard therapy, also showed a significantly prolonged OS for the nivolumab arm[50]. Therefore, the success of these agents has prompted its clinical investigation in a first-line setting and clinical trials for first-line treatment are now ongoing.

CONCLUSION

This article summarized the association of TILs with the prognosis of gastric cancer. While TILs can be easily detected by analyzing slides of tumor sections stained with H&E, methodologic improvements are needed for more accurate determining the density and distribution of immune effectors within and around gastric cancer cells. With the development of more precise methods for analyzing immune infiltrates, it is becoming clearer that distinct infiltrating cell types have different prognostic and predictive significance. In particular, the presence of TILs may be an important biomarker for the treatment of TIL-rich tumors, such as EBV-positive or MSI-high gastric cancer, while immunotherapy including an immune checkpoint blockade can become an important part of the cancer armamentarium. Plus, specific inhibitors for PD-L1 or PD-1 would be potential therapeutic candidates that can affect a variety of gastric cancer. Therefore, understanding the effect of TILs on the natural outcome of gastric cancer will herald new opportunities for personalized therapy.

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