Review Article

The Role of Tumor Parenchymal and Stromal Ratios in Colorectal Cancer

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Abstract

Objective: To evaluate the implications and significant role of parenchymal and stromal ratio in colorectal cancer (CRC).

Materials and methods: In our review, we involved English studies from common databases such as Web of Science, Scopus, Google Scholar, PubMed, and the Cochrane Library using the following keywords “colorectal cancer”, “tumor stromal ratio”, “tumor parenchymal ratio”, and “prognostic marker” till December 2023.

Results: The majority of CRC patients are usually diagnosed at late stages, which may lead to missing out on the chance to get radical therapy. Patients with unfavorable prognosis have epithelial malignant tumors with a high amount of stroma, more than 50% stroma, while tumors with a low amount of stroma, less than 50%, and abundant carcinoma tissue have a better prognosis.

Conclusion: Tumor-stromal ratio is a valuable, cheap, and fast modality that provides valuable prognostic data of colorectal carcinoma and other cancers.

Keywords: Colorectal Cancer; Tumor Stromal Ratio; Tumor Parenchymal Ratio

Introduction

Colorectal cancer (CRC) is the third most prevalent diagnosed malignancy in both genders worldwide. It is also considered the second most popular etiology of cancer-related death**.** It is thought that CRC is a multifactorial disease that has both genetic and environmental risk factors (1). Except for younger

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people under the age of 50, the frequency of newly diagnosed cases and mortality has been progressively declining over the previous few years. This might be due to better treatment choices and expanded cancer screening programs. Inherited syndromes, including Lynch syndrome and Familial Adenomatous Polyposis, account for about 5% of all CRC cases. Throughout 10 to 15 years, several germline (inherited) and somatic (acquired) genetic abnormalities must accumulate for the normal epithelium of the colon to change into a precancerous lesion and, finally, an invasive carcinoma (2, 3).

More than 90% of CRCs are adenocarcinomas; the other, less common types are squamous, spindle, adeno-squamous, and undifferentiated carcinomas. In total, CRCs are mostly carcinomas. Patients in the early stages of CRC are often asymptomatic. In contrast, with the disease progression, patients may complain of abdominal pain, bleeding per rectum, anemic manifestations, abdominal pain, abdominal distention, or intestinal obstruction (4). Generally, there is a wide variation of the clinical manifestations of intestinal malignancy according to various physiological and anatomical conditions of the disease. Various anatomical locations have distinct clinical presentations for various types of tumors. Alteration in defecation patterns is more prevalent in rectal cancer, bleeding per rectum and intestinal obstruction are prevalent in left colon malignancy. In contrast, systemic manifestations and abdominal swelling are more common in right colon cancer (5). Many factors determine the optimal treatment choice, including the patient's age and overall health, the type and grade of the tumor, its size, and whether it has any local or distant metastasis (6). The tumor microenvironment is becoming an increasingly important topic of study in the field of biomarker development. Although it is possible to identify molecular biomarkers based on tumor features, it is important to consider the valuable information the tumor microenvironment provides, that is, the tumor's stromal compartment. Tumor-stroma interacts with both malignant and nonmalignant cells during all phases of carcinogenesis, from tumor development to invasion and metastasis, and thus plays a significant role in the origin and progression of cancer (7,8). This review aims to evaluate the implications and significant role of parenchymal and stromal ratio in CRC.

In our review, we focused on studying CRC regarding its nature, etiology, clinical characteristics, and the role of parenchyma-stromal ratio in determining the therapeutic options and the prognosis of the disease.

There is increasing interest in integrating a novel prognostic modality in patients with CRC. Tumor-stroma ratio (TSR) is a reliable prognostic factor. Large studies evaluating TSR have validated its predictive value in various cancers, including CRC, esophageal carcinoma, breast cancer, lung cancer, and cancer cervix.

This review aims to evaluate the implications and significant role of parenchymal and stromal ratio in CRC.

Anatomy of the large intestine

The colon, rectum, and anal canal are all components of the large intestine. The colon is further separated into the right colon (cecum, ascending colon, and right 2/3 transverse colon) and the left colon (left 1/3 transverse colon, descending colon, and sigmoid colon). The mesenteric artery provides the main blood supply for the colon, accompanied by veins running the same course as the artery and having the same names. Regional lymph nodes serve as the lymphatic network's drainage conduit. Pelvic nerves and the vagus nerve are responsible for colon innervation. The left colon's main function is stool storage and expulsion, while the right colon's primary role is the absorption of water and certain nutrients. Furthermore, alkaline mucus molecules and gastrointestinal hormones are secreted by the colon (9–11).

The sigmoid colon ends with the rectum, which in turn ends up joining the anal canal at the level of the dentate line. Superior and inferior rectal arteries supply the rectum. The superior rectal veins carry the venous reflux to the liver. Lymph nodes around the rectal arteries and pararectal lymph nodes provide the lymph supply of the rectum. Autonomic nerves innervate the rectum. The primary functions of the rectum include defecation and absorption of water, drugs, glucose, and salt (10). The sigmoid colon, representing 55% of all colon cancers, is the most prevalent location, followed by the ascending colon, representing about 23.3%, transverse colon, representing about 8.5%, descending colon, representing about 8.1%, cecum representing about 8.0%, and crossing site representing about 2.1% (12, 13).

Epidemiology

CRC is the third most common cancer diagnosed globally, with men ranking third and females ranking second, affecting more than 135,439 new patients

annually. It is considered the second most popular cause of mortality in the USA, responsible for an about 50,260 deaths. Since 2004, the CRC incidence has been declining by 3% per year while increasing by 2% per year among screened young people (those under 50) (14, 15). It is believed that the incidence of CRC varies according to different factors, including religious factors, lifestyle, environmental factors, and diet. The population of underdeveloped countries is less likely to be affected than people in developed countries. A low socioeconomic level is strongly associated with a higher risk of CRC, which corresponds to risky behavior and poor access to medical care. Epidemiologic studies showed a steady change in the anatomic distribution of CRC from the left side of the colon distally to the right-sided or proximal end, which was previously associated with more successful left-sided screening methods. Epidemiologic studies showed a steady change in the anatomic distribution of CRC from the left side of the colon distally to the right-sided or proximal end, which was previously associated with more successful left-sided screening techniques (16-18).

Etiology

Although there is no clear etiology for CRC, it is thought that it is a multifactorial disease with genetic and environmental factors. The genetic element is believed to be responsible for approximately 20% of all CRC. Research has shown that the first-generation relatives of CRC patients had a three-fold greater chance of developing cancer. It has been shown that a genetic disease called Familial Adenomatous Polyposis (FAP) predisposes people to colorectal cancer (CRC) and that hereditary CRC is also associated with the Mismatch Repair Gene (MMR) (19). Regarding the dietary factor, it is thought that low cellulose food, high protein, and high animal fat diet are associated with an increased risk of CRC. Consuming excessive amounts of fat will increase intestinal carcinogens, anaerobic bacterial activity in the gut, bile production, and bile acid breakdown (20).

Furthermore, various non-cancerous colon diseases may increase the risk of developing CRC, including inflammatory bowel diseases (Crohn's disease and ulcerative colitis), colorectal adenoma, or colorectal polyps. Previous studies demonstrated that about 3–5% of people with ulcerative colitis will have CRC. In patients with ulcerative colitis that lasts longer than 20 years, the rate of malignant transformation is more than 10% (3). Colonic polyps are the source of 15-40% of colon cancer cases, and they may develop into cancer over a period of 2-5 years. Less than 2% of adenomas with a diameter of less than 1 cm will develop into cancer, but more than 40% of adenomas with a diameter of more than 3 cm have a high risk of developing malignancy (21). Patients receiving treatment with pelvic radiation have a greater incidence of rectal and sigmoid malignancy. Overweight and sedentary lifestyles are risk factors for (CRC) (22).

Pathogenesis

The transformation of normal healthy epithelial cells into malignant cells undergoes a sequential manner from normal colorectal mucosa, which proliferates rapidly and causes hyperplasia, which may be atypical with various degrees, and adenoma, which may finally change to carcinoma in situ and invasive carcinoma. This process that yields malignant transformation usually requires genetic and DNA structural mutation due to combined inherited susceptibility and carcinogenic factors (22). With the advancement of research, three confirmed molecular mechanisms lead to the occurrence and progression of CRC. First, the instability of chromosomes, such as familial polyposis coli. The second is the mutation of genes such as MMR mutation and Lynch syndrome, while the third is the CPG island hypermethylation in particular gene promoter areas (22). These processes are strongly associated with alteration in various genes such as K-ras, DCC, APC, P53, c-MYC, MCC, and MMR-related genes (hMLH1, hMLH3, hMSH2, hMSH3, hMSH6, hPMS1, and hPMS2).

In the early stages of the disease, CRC affects only the mucosa and submucosa of the intestine. In early CRC, lymphatic metastasis often does not happen. About 10% of individuals get lymphatic metastasis when the tumor invades the submucosa. The gross picture of this tumor may appear as an infiltration, ulceration, or uplift. In contrast, the microscopic picture may include papillary adenocarcinoma, signet-ring cell carcinoma, mucinous adenocarcinoma, undifferentiated carcinoma, tubular adenocarcinoma, carcinoid carcinoma, squamous cell carcinoma, and adenosquamous carcinoma (22). A five-year retrospective analysis of 1092 patients with CRC demonstrated that about 93.4% of participants had adenocarcinoma, about 3.9% of patients had mucinous adenocarcinoma, signet ring carcinoma, and carcinoid carcinoma accounted for 0.6 and 0.2%, respectively (23). The following four mechanisms are

the major ways that CRC metastasizes: Local invasion: The tumor spreads to nearby structures and within proximity of the original lesion. Regarding lymphatic metastasis. Approximately 60% of CRC metastases come from this pathway. The neoplastic cells reach the regional lymph nodes by invading the intramucosal lymphatic system and finally cause distant lymph node metastasis. Concerning hematogenous metastasis: The blood vessels allow the malignant cells to spread. About 30% of CRC cases spread via hematogenous metastasis, with the liver and lung being the most frequently targeted organs. Eventually, the cancer cells are implanted in the pelvic peritoneum and abdomen to generate metastatic foci after they have fallen off (24, 25).

Clinical manifestations and evaluation

Asymptomatic early CRC is common. As the illness worsens, the following signs and symptoms usually appear. Hematochezia: When there is little to no blood in the stool, there may be no obvious changes, but a positive fecal occultation test may occur. When there is a lot of blood in the stool, it may look as jam-like, bloody, or mucus-like; intestinal obstruction is a common feature of advanced CRC; symptoms include nausea, vomiting, abdominal pain, diarrhea, abdominal discomfort, and distention brought on by the expansion of the tumor, abdominal mass: This symptom is a palpable, somewhat enlarged mass that often arises with right colon cancer, and systemic symptoms as CRC usually does not exhibit any noticeable symptoms in its early stages, which means that the illness progresses slowly and causes symptoms such as tumor growth, anemia, cachexia, and emaciation (5).

The clinical presentations of tumors in various anatomical locations vary due to the distinct physiological and anatomical roles played by the colon and the rectum. In general, changes in defecation patterns are more prevalent in rectal cancer. Bleeding per rectum and intestinal obstruction are prevalent in left colon malignancy. In contrast, systemic manifestations and abdominal swelling are more common in right colon cancer (5).

Treatment

The basic principle of CRC treatment is an individualized, all-encompassing approach that includes surgery as the main component, with other treatments such as immunotherapy, chemotherapy, radiation, and molecular targeted therapy (26). Surgical intervention showed promising outcomes in patients, particularly in the early stages of CRC. Therefore, it is the treatment of choice of those patients. However, patients with evidence of metastases and inoperable patients may receive neoadjuvant therapy before the surgical intervention to improve the radicality of treatment and decrease the recurrence rate (27).

Parenchymal-Stromal Ratio in CRC

To the best of our knowledge, many variables determine the best treatment option, including the patient's age and general health, the nature and grade of the tumor, its size, and the possibility of local or distant metastases (6). Current research is increasingly focused on identifying novel prognostic markers, studying their association with known aggressive cancer characteristics, and developing more effective therapy techniques as a result. Recent models developed during the previous decade incorporate the tumor-host interface and the function of stroma tissue (28). The microenvironment of tumors is becoming an increasingly important topic of study in the field of biomarker development. Although tumor characteristics may be used to discover genetic biomarkers, it is essential to consider the useful information provided by the tumor microenvironment. Tumor parenchyma and stroma interact with both malignant and nonmalignant cells during all phases of carcinogenesis, from tumor development to invasion and metastasis, and thus play a significant role in the origin and progression of cancer (7).

The morphological examination of the tumor microenvironment in traditional, ordinary hematoxylin and eosin (H&E) stained tissue sections gives helpful data with a strong predictive value. Previous research showed that patients with unfavorable prognosis have epithelial malignant tumors with a high amount of stroma, more than 50% stroma. In contrast, tumors with a low amount of stroma, less than 50%, and abundant carcinoma tissue have a better prognosis. This raised the concept of involving the tumor-stroma ratio (TSR) as a reliable prognostic factor. Large studies evaluating TSR have validated its prognostic value in various cancers, including CRC, esophageal carcinoma, breast cancer, lung cancer, and cancer cervix (29, 30).

The TSR was estimated using the slide used in normal diagnostic pathology to assess the T-status. Traditional microscopy was used to examine 4 m thick H&E-stained tissue slices from the tumor. As shown by previous studies, TSR is a quick and inexpensive procedure (30). Studying many slides

from many regions of the tumor showed that scoring of the TSR in CRC is best obtained from the most invasive area of the lesion. Although TSR may be precisely measured in patients undergoing surgery for a primary epithelial malignant tumor, Neoadjuvant chemotherapy- and/or radiation therapies may alter the cellular architecture and the tumor microenvironment composition, resulting in stromal development around the tumor. As a result, individuals who have had chemotherapy or radiation should be excluded from TSR analysis. Pre-treatment tumor biopsy might be a viable option for these individuals (7).

Materials and methods

General background: CRC is the second most popular etiology of cancer-related death. More than 90% of CRCs are adenocarcinomas; the other, less common types are squamous, spindle, adeno-squamous, and undifferentiated carcinomas. In total, CRCs are mostly carcinomas. CRC is a silent disorder in the early stages of the disease. Patients usually have vague and non-obvious clinical manifestations, yielding a significant defect in the rate of early diagnosis. It is essential to consider the useful information provided by the tumor microenvironment. Tumor parenchyma and stroma interact with both malignant and nonmalignant cells during all phases of carcinogenesis, from tumor development to invasion and metastasis. Parenchyma and stromal ratio in CRC have a valuable role in determining the prognosis of the disease.

Inclusion criteria

1. All study designs of the articles were included, such as case series, randomized clinical trials, case-control, or systematic review.

2. We included studies evaluating the implications and the prognostic role of TSR in CRC.

3. Most included studies should be recent, from 2018 to 2023.

Exclusion criteria

1. Studies and articles that were not peer-reviewed, procedures, opinions, letters, and proposals.

2. Old studies that were conducted before 2010.

3. Studies unrelated to our topic or their aim were not related to ours.

Information sources: We utilized the following online databases: Web of Science, Scopus, Google Scholar, PubMed, and the Cochrane Library using the following keywords “colorectal cancer”, “tumor stromal ratio”, “tumor parenchymal ratio”, and “prognostic marker” till December 2023. We retrieved studies by combining each set of keywords.

Data collection: The included studies were reviewed following three stages. The first involved using EndNote Software to import the findings from electronic databases into a Microsoft Excel sheet. The articles entered into the Excel sheet were screened for titles and abstracts in the second stage. The third stage involved screening the included citations from Stage 2's full text. In addition, we manually checked the included publications' references for any potentially overlooked studies.

Statistical analysis: We conducted a qualitative study of the previously published studies. We could not do a quantitative analysis because our study is a narrative review. The outcomes that will be measured in the quantitative analysis must be specified, and more than two studies reporting data on these outcomes must be located and compared to draw a conclusion. We attempted a quantitative analysis in our research but could not identify specific results relevant to our subject or papers that presented similar data. To get strong evidence and current results and conclusions, we conducted a qualitative analysis of papers relevant to our topic, presented their findings, and compared them.

Results

CRC is a silent disorder in the early stages of the disease. Patients usually have vague and non-obvious clinical manifestations, yielding a significant defect in the rate of early diagnosis. Therefore, the majority of CRC patients are usually diagnosed at late stages, which may lead to missing out on the chance to get radical therapy.

Therefore, any patient reporting vague, non-explained abdominal symptoms, progressive weight loss, or unexplained anemia should undergo meticulous physical examination and proper investigation. A barium enema or CT colonography may be used in the primary assessment modalities, but a colonoscopy is eventually necessary for tissue biopsy (31–34).

Discussion

There are published studies that have tried to determine the prognostic factors of colorectal cancer; however, there is a lack of studies that have attempted to identify a comprehensive analysis of the

parenchyma-stromal ratio in patients with colorectal cancer. In our article, we tried to evaluate the role and implication of tumor stromal ratio in this disease and how we can benefit from its great value.

The assessment of suspected patients may include various assessment techniques. Suspected patients for CRC must undergo a digital rectal examination. Other diagnostic methods include (i) occult blood test in stool, which has a crucial value as it detects about 5 ml of blood in the gastrointestinal tract. (ii) Tumor markers: Although CRC has no specific tumor markers, CA19–9 (carbohydrate antigen 19-9) and CEA (carcinoembryonic antigen) are currently utilized widely. The sensitivity of combining the two markers' detection is greater than each one alone, which has essential clinical implications for assessing the effectiveness of treatment and tracking the recurrence of the disease. (iii) Colonoscopy can directly visualize the shape, size, and position of the tumor in addition to the ability to obtain a biopsy from the suspected lesion. Colonoscopy has a very high sensitivity, up to 94.7%, but it may miss lesions mainly in the right side of the colon (35). (iv) Following a barium enema, an X-ray examination may detect evidence of mucosal damage and filling defects at the tumor site. When detecting colon cancer with a tiny lesion, gas-barium double contrast is useful, but it is not recommended for individuals who have intestinal blockage. (v) If present, ultrasonography can detect abdominal lymph nodes and intestinal mass. (vi) Computed tomography (CT) is a very helpful diagnostic modality that may help with clinical staging by demonstrating the size of lesions and their connection to surrounding abdominal lymph nodes, tissues, and organs (27, 36). (vii) Nuclear magnetic resonance (NMR) is a modality comparable to CT but with superior tissue resolution, particularly for pelvic lesions such as rectal cancer, making preoperative assessment of amazing therapeutic importance. (viii) Positron emission computed tomography (PET/CT) is a diagnostic tool that is very useful for diagnosis, staging, and recurrence assessment of CRC as it offers insights into the tumor's anatomical location and metabolic features (37).

Previous studies assessed the 5-year survival rate of patients who received surgical management in the early stage of CRC. They reported a survival rate higher than 90% (38). Surgical options may be radical or palliative according to the stage of the tumor. Previous studies showed that neoadjuvant chemotherapy combined with radiotherapy has an excellent impact in downgrading the tumor stage, improving the patient’s quality of life, and decreasing post-treatment recurrence rate. Following major surgery, adjuvant chemotherapy may eradicate any residual tumor cells and enhance the effects of the procedure (39).

Furthermore, the use of molecularly targeted medications has shown major benefits with mild adverse effects. There are two types of molecularly targeted drugs in treating CRC. The main molecularly targeted medications include bevacizumab and cetuximab, which are categorized as anti-angiogenesis and anti-epidermal growth factor drugs, respectively. These drugs are non-cytotoxic medications that may be used combined with chemotherapy without increasing the side effects of chemotherapeutic agents (26). A previous review showed that radiation may increase the rate of local control, enhance quality of life, and increase survival (40). A previous study showed that immunotherapy may extend a patient's survival rate (41, 42). TSR scoring is a reliable system that requires minimal additional time and money and has the potential to be adopted in everyday practice. The procedure is extremely repeatable, with slight variance across observers. However, TSR scoring may be challenging. A previous study reported difficulty differentiating smooth muscle fibers from stromal tissue, especially in stage 2 CRC (7). A prior meta-analysis including 51 studies evaluated the implications of TSR in different cancers in addition to disease-free survival (DFS) and the overall survival (OS) in patients based on TSR score. They found that malignant tumors differed in their high TSR rates. Better survival rates were substantially associated with higher TSR, while some malignant tumors showed no association at all or the inverse correlation (43).

The primary issue with this article is that it is a narrative review. The included research results are presented in written paragraphs in a narrative review. They don't undertake any pooled analysis using the data from the summarized studies. Real objectivity and pooled analysis are therefore precluded. A narrative review serves as a collated source of the most widely accepted views at the time of publishing. This may be useful to understand a body of evidence fully. As it does not thoroughly consider the alternative hypothesis, it does not guarantee that the prevailing ideas are true.

Conclusion

TSR is a valuable, cheap, and fast modality that provides valuable prognostic data of CRC and other cancers. Patients with unfavorable prognosis have epithelial malignant tumors with a high amount of stroma, more than 50% stroma. In contrast, tumors with a low amount of stroma, less than 50%, and abundant carcinoma tissue have a better prognosis. TSR has no role in patients who received chemotherapy and/or radiation therapies as they alter the cellular architecture and the tumor microenvironment composition, resulting in stromal development around the tumor.

Conflict of Interests

Authors declare no conflict of interests.

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