Clinical research

Prognostic significance of the tumor-stroma ratio in colon carcinoma: a retrospective study

Özgen Arslan Solmaz

Department of Pathology, Elaziğ Training and Research Hospital, Elaziğ, Turkey

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Corresponding author:
Özgen Arslan Solmaz
Department of Pathology
Elaziğ Training
and Research Hospital
Elaziğ, Turkey
Phobe.: +90 5308804123
Fax: +90 424 2121461
E-mail: ozgensolmaz_73@
hotmail.com

Abstract

Introduction: Despite developments enabling early diagnosis and treatment of various types of cancer, cancer-related morbidity and mortality remain a major public health problem. Studies have identified numerous factors associated with survival in colorectal carcinoma patients. Tumor-stroma ratio (TSR) in colon cancer: the TSR refers to the proportion of carcinoma relative to the proportion of tumor stroma in a histopathological tumor specimen. Previous studies showed that the TSR was an important prognostic indicator in many solid tumors and that a high TSR was a determinant of a poor outcome in colon cancer. We aimed to evaluate the prognostic importance of the TSR in colon cancer and its relationship with other prognostic factors to determine its utility in planning treatment of colon cancer.
Material and methods: Ninety-six patients diagnosed with adenocarcinomas were included in the study. The amount of tumor and stroma in tumor areas was determined and the TSR was calculated.
Results: There was a significant correlation between the TSR and sex, tumor diameter, tumor extended, lymphovascular invasion, perineural invasion, and lymph node involvement.
Conclusions: Tumor-stroma ratio is a poor prognostic parameter which is associated with prognostic factors and should be recorded in the surgical pathology report. Especially in stage II patients, it should be considered as one of the risk factors for making chemotherapy decisions.

Key words: stroma, tumor, prognosis.

Introduction

Despite developments enabling early diagnosis and treatment of various types of cancer, cancer-related morbidity and mortality remain a major public health problem. A study by the Internal Agency for Research on Cancer on the incidence, mortality, and prevalence of cancer worldwide reported that 14 million new cancer cases and 8.2 million cancer-related deaths occurred in 2012. The same study reported that lung cancer (1.824 million), breast cancer (1.671 million), and colorectal cancer (CRC) (1.360 million) were the most common cancers [1]. According to Globocan data, by 2015, the incidence of CRC worldwide is expected to be as high as 2 million [2]. Colorectal cancer is the third most commonly diagnosed cancer in the U.S. [3]. The incidence of CRC and CRC-related mortality rates has been declining because of reductions in lifestyle-related risk factors (e.g., smoking), the introduction and dissemination of screening tests, and improvements in treatment [4].

Studies have identified numerous factors associated with survival in CRC patients [5]. Among these factors, intestinal wall penetration, regional lymph node metastasis, and distant organ metastasis are considered the most important prognostic indicators, and these provide the basis for most staging systems [6]. Although various studies have confirmed that the CRC stage at the time of diagnosis was closely related to the patient's prognosis, they also noted the need for additional prognostic indicators [6, 7].

Various studies have examined the tumor–host interaction in metastatic invasion in CRC, focusing on the roles of different host cell types (e.g., fibroblasts, myofibroblasts, endothelial cells, and immune cells) and the extracellular matrix as targets for stromal cell recruitment by tumors. Regarding tumor–host factors, a number of studies have examined the role of the tumor-stroma ratio (TSR) in colon cancer. The TSR refers to the proportion of carcinoma relative to the proportion of tumor stroma in a histopathological tumor specimen [8]. Previous studies showed that the TSR was an important prognostic indicator in many solid tumors and that a high TSR was a determinant of a poor outcome in colon cancer [8–10].

The aim of the present study was to evaluate the prognostic importance of the TSR in colon cancer and its relationship with other prognostic factors to determine its utility in planning treatment of colon cancer.

Material and methods

The study consisted of the same patient's colectomy specimens and preoperative colonoscopic biopsy material obtained from 96 patients diagnosed with adenocarcinomas in the pathology laboratory of our hospital between 1995 and 2017. Sections 3 µm thick that had been routinely stained with hematoxylin and eosin in the laboratory and mounted on slides were re-studied by a single pathologist. The pathologist evaluated the following prognostic factors according to the College of American Pathologists 2016 protocol for colectomy specimens [11]: histological grade, microscopic tumor extension, lymphovascular invasion, perineural invasion, surgical margin involvement, presence and grade of tumor infiltrating lymphocytes (TILs), and lymph node involvement. Subsequently, the malignant epithelial area and stromal content were measured in the most invasive area of the tumor. For these measurements, sections on the slide were measured and separated into 5 × 2 equal parts. These areas were then examined at magnification of 10× under light microscopy. The amount of tumor and stroma in these areas was determined and the TSR was calculated [8].

The histological grade was classified as low or high. Microscopic tumor extension was identified as lamina propria, muscularis mucosa, submucosa, and muscularis propria invasion. Lymphovascular invasion, perineural invasion, surgical marginal invasion and lymph node involvement were considered positive or negative. The TSR was divided into two groups: TSR-high (percentage of stroma < 50%) and TSR-low (percentage of stroma ≥ 50%) [12] (Figure 1). TILs were classified as weak (0–10%), moderate (20–40%), or strong (50–90%).

Statistical analysis

The statistical analysis was performed using SPSS statistical software (version 20; SPSS Inc., Chicago, Illinois, USA). The mode, median, and mean values calculated for all the parameters were close to each other. Thus, the data were considered to be normally distributed. As there were several subgroups of variables, a χ^2 cross-tab analysis was performed to identify possible correlations and statistically significant differences.

Results

Of the 96 patients included in this study, 43.8% (n = 42) were female, and 56.2% (n = 54) were male. The mean age was 62 years; the oldest patient was 92 years, and the youngest patient was 32 years. The mean tumor diameter was 4.66 ±2.1 cm, with the diameter ranging from 1.7 to 11 cm.

There was a significant correlation between the TSR and sex (p = 0.015). The TSR was high in 33 (78.5%) females and low in 9 (21.5%) females, whereas it was high in 30 (53.5%) males and low in 24 (46.5%) males. There was too much epithelial tumor tissue in 78.5% of females and too much stromal tissue in 21.5% of females. There was no significant relationship between age and the TSR in the correlation analysis (p = 0.487). There was a significant correlation between the tumor

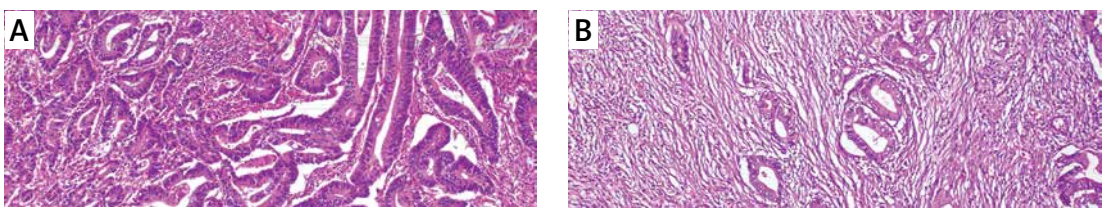

Figure 1. Hematoxylin eosin stained sections of tumor stroma 200×: **A** – high TSR (> 50%), **B** – low TSR (< 50%)

diameter and TSR ($p < 0.001$). In other words, as the stromal component of the tumor increased, the mean tumor diameter increased, whereas the epithelial component decreased. In histologically low-grade CRC cases, 33 (73%) specimens had a high TSR, and 12 (27%) had a low TSR. In histologically high-grade CRC cases, 30 (71.5%) specimens had a high TSR, and 12 (28.5%) had a low TSR. There was no significant correlation between the histological grade and TSR ($p = 0.296$).

In terms of microscopic tumor extension, the tumor extended to the lamina propria, muscularis mucosa, submucosa, and muscularis propria in 14 (22.2%), 32 (50.7%), 10 (15.8%), and 7 (11.3%) of 63 high TSR cases, respectively. In contrast, it extended to the muscularis mucosa, submucosa, and muscularis propria in 1 (3%), 2 (6%), and 30 (91%) of 33 low TSR cases, respectively. There was a significant correlation between microscopic tumor extension and the TSR ($p < 0.001$). In cases where the TSR ratio decreased, tumor extension also increased, with an increase in tumor extension associated with an increase in the tumor stroma.

Of 53 cases without lymphovascular invasion, 45 (84.9%) had a high TSR, and 8 (15.1%) had a low TSR. The TSR was high in 18 (41.8%) lymphovascular invasion-positive cases and low in 25 (58.2%) lymphovascular invasion-positive 43 cases. There was a significant correlation between the TSR and lymphovascular invasion in the statistical analysis ($p < 0.001$). As the percentage of stroma increased, lymphovascular invasion also increased.

Of 71 cases without perineural invasion, the TSR was high in 51 (71.8%) cases and low in 20 (28.2%) cases. Of 25 patients with perineural invasion, it was high in 12 (48%) cases and low in 13 (52%) cases. The statistical analysis revealed a significant correlation between perineural invasion and the TSR ($p = 0.031$). As the percentage of stroma increased, perineural invasion also increased.

In the presence of a high TSR, there was lymph node involvement in 12 (22.6%) cases but no lymph node involvement in 51 (77.4%) cases. In 33 cases with a low TSR, no lymph node involvement was observed in 6 (18.1%) cases, and lymph node involvement was detected in 27 (81.9%) cases. There was a statistically significant negative correlation between lymph node involvement and the TSR ($p < 0.001$). As the TSR decreased, lymph node involvement increased.

The TSR was high in 61 specimens and low in 31 specimens with tumor-negative surgical margins. In four specimens with tumor-positive surgical margins, the TSR was low in two cases and high in two cases. There was no statistically significant relationship between tumor-positive surgical margins and the TSR ($p = 0.502$).

In 39 cases with low TILs, the TSR was high in 27 cases and low in 12 cases. In 27 cases with moderate TILs, the TSR was high in 18 cases and low in 9 cases. In 30 cases with significant TILs, the TSR was high in 18 cases and low in 12 cases. There was no statistically significant correlation between TILs and the TSR ($p = 0.435$) (Table I).

Discussion

In 2007, the TSR was reported to be a simple, cheap, convenient, and useful method in clinical studies to predict the prognosis of CRC [13]. Later research demonstrated the value of the TSR as a prognostic predictor in various cancers [14, 15].

Normal tissue stroma is essential for repair and unity of epithelial tissues and contains a multitude of cells that collaborate to sustain normal tissue homeostasis. There is a continuous and bilateral molecular relationship between normal epithelial cells and cells of the stromal compartment. So, minor changes in one compartment may cause dramatic alterations in the whole system. A genetic alteration during cancer development will change the stromal host compartment to establish a permissive and supportive environment for the cancer cell [16].

In normal tissue, the stroma provides protection against tumor stromatogenesis. In contrast, in tumor tissue, the stroma is a major part of the tumor microenvironment and can contribute to tumor progression [17]. During early stages of tumor development and invasion, the basement membrane is degraded, and the activated stroma, containing fibroblasts, inflammatory infiltrates, and newly formed capillaries, comes into direct contact with the tumor cells. The basement membrane matrix also modifies cytokine interactions between cancer cells and fibroblasts. These cancer-induced alterations in the stroma will contribute to cancer invasion. During the early stage of tumor invasion, tumor cells penetrate the basement membrane and activate stromal cells to form a tumor microenvironment [16]. Tumor-activated stroma results in the fragmentation of epithelial tissue, immune evasion of malignant cells, and tumor invasion, all of which lead to tumor stromatogenesis [18].

In the present study of colectomy specimens from 96 CRC patients, the results of the statistical analysis revealed a higher percentage of stroma in males than females. Furthermore, as the amount of stroma increased, tumor size, tumor invasion grade, lymphovascular invasion, perineural invasion, and lymph node involvement increased. There was no significant relationship between the TSR and age, histological grade, surgical margin involvement, or TIL grade. Thus, we concluded that a low TSR was a poor prognostic indicator.

Table I. The relationship between tumor stroma ratio and clinicopathological characteristics

Clinical characteristics	High TSR patients	Low TSR patient	*P*-value
Age [years]:			0.487
< 65	42	15	
65–74	12	9	
> 75	9	9	
Sex:			0.015
Male	30	24	
Female	33	9	
Tumor size [cm]:			< 0.001
< 3	21	3	
3–6	33	15	
≥ 6	9	15	
Histological grade:			0.296
Low grade	33	21	
High grade	30	12	
Tumor extended:			< 0.001
To lamina propria	14	0	
To muscularis mucosa	32	1	
To submucosa	10	2	
To muscularis propria	7	30	
Lymph node involvement:			< 0.001
No	51	6	
Yes	12	27	
Lymphovascular involvement:			< 0.001
No	45	8	
Yes	18	25	
Perineural involvement:			0.031
No	51	20	
Yes	12	13	
Margin involvement:			0.502
No	61	31	
Yes	2	2	
TIL:			0.435
Weak	27	12	
Mild	18	9	
Marked	18	12	

TIL – tumor infiltrating lymphocytes.

In common with the findings of the present study, previous studies showed that a high intratumor stroma percentage predicted a poorer prognosis in patients with colon cancer [13, 19]. Park *et al.* [20] studied the relationship between the TSR and prognostic factors in 331 colectomy

specimens. They found a low TSR in cases with a high tumor stage, lymph node tumor invasion, and tumor-positive surgical margins. In the same study, the TSR was not significantly related to age, sex, or vascular invasion. In contrast, Zhang *et al*. [1] observed an increase in tumor size and high tumor grade in low TSR cases. They found no relationship between the TSR and sex, tumor invasion, lymph node metastasis, or venous invasion. Other research found that a low TSR was a good prognostic indicator in esophageal, breast, prostate, and oral cavity tumors but not in colon carcinomas [14].

In conclusion, the present study is limited by the small number of patients. Despite this limitation, the present study provides comprehensive assessment of the associations between TSR and the tumor microenvironment, prognostic factors. TSR is a poor prognostic parameter which is associated with prognostic factors (tumor size, tumor invasion grade, lymphovascular invasion, perineural invasion, and lymph node involvement) and should be recorded in the surgical pathology report. Especially in stage II patients, it should be considered as one of the risk factors for making chemotherapy decisions.

Conflict of interest

The author declares no conflict of interest.

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