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ABOUT COVER

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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.

WJGO covers topics concerning carcinogenesis, tumorigenesis, metastasis, diagnosis, prevention, prognosis, clinical manifestations, nutritional support, molecular mechanisms, and therapy of benign and malignant tumors of the digestive tract. The current columns of *WJGO* include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography. Priority publication will be given to articles concerning diagnosis and treatment of gastrointestinal oncology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Tumor-stroma ratio as prognostic factor for survival in rectal adenocarcinoma: A retrospective cohort study

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Author contributions: Scheer R and Klaase JM designed the research; Scheer R and Zoidze S performed the research; Baidoshvili A supervised the histological scoring and took final decisions in case of discrepancy in scores between Scheer R and Zoidze S; Elferink MAG collected data from the population-based The Netherlands Cancer Registy and analyzed the data; Berkel AEM, Klaase JM and van Diest PJ supervised and interpreted the results; Scheer R and Zoidze S wrote the paper; all authors critically reviewed and accepted the final version of the manuscript.

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Abstract

AIM

To evaluate the prognostic value of the tumor-stroma ratio (TSR) in rectal cancer.

METHODS

TSR was determined on hematoxylin and eosin stained histological sections of 154 patients treated for rectal adenocarcinoma without prior neoadjuvant treatment in the period 1996-2006 by two observers to assess

reproducibility. Patients were categorized into three categories: TSR-high [carcinoma percentage (CP) ⩾ 70%], TSR-intermediate (CP 40%, 50% and 60%) and TSR-low (CP ⩽ 30%). The relation between categorized TSR and survival was analyzed using Cox proportional hazards model.

RESULTS

Thirty-six (23.4%) patients were scored as TSR-low, 70 (45.4%) as TSR-intermediate and 48 (31.2%) as TSR-high. TSR had a good interobserver agreement (κ = 0.724, concordance 82.5%). Overall survival (OS) and disease free survival (DFS) were significantly better for patients with a high TSR (P = 0.01 and P = 0.02, respectively). A similar association existed for disease specific survival (P = 0.06). In multivariate analysis, patients without lymph node metastasis and an intermediate TSR had a higher risk of dying from rectal cancer (HR = 5.27, 95%CI: 1.54-18.10), compared to lymph node metastasis negative patients with a high TSR. This group also had a worse DFS (HR = 6.41, 95%CI: 1.84-22.28). An identical association was seen for OS. These relations were not seen in lymph node metastasis positive patients.

CONCLUSION

The TSR has potential as a prognostic factor for survival in surgically treated rectal cancer patients, especially in lymph node negative cases.

Key words: Rectal cancer; Adenocarcinoma; Prognosis; Recurrence; Pathology; Tumor-stroma ratio

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Core tip: The tumor-stroma ratio (TSR) can be determined accurately on routine histopathological sections by different observers. The TSR has potential as a prognostic factor for survival in surgically treated rectal cancer patients, especially in lymph node negative cases. It could therefore be useful in decision making regarding adjuvant treatment in individual patients.

Scheer R, Baidoshvili A, Zoidze S, Elferink MAG, Berkel AEM, Klaase JM, van Diest PJ. Tumor-stroma ratio as prognostic factor for survival in rectal adenocarcinoma: A retrospective cohort study. *World J Gastrointest Oncol* 2017; 9(12): 466-474 Available from: URL: http://www.wjgnet.com/1948-5204/full/v9/i12/466.htm DOI: http://dx.doi.org/10.4251/wjgo.v9.i12.466

INTRODUCTION

Colorectal cancer (CRC) is a common form of cancer in both men and women. More than 15000 new patients with a colorectal carcinoma were diagnosed in The Netherlands in 2016[1]. The common form to stage this type of cancer is the TNM staging system of the Union Internationale Contre le Cancer/American Joint Cancer Committee (UICC/AJCC)[2]. This system is also used in decision making about the appliance of (neo)adjuvant (chemo)radiotherapy. Although the TNM staging system is still regarded as the most important prognostic factor[3], it seems insufficiently able to predict the prognosis of the individual patient. This applies in particular to patients with stage II rectal cancer[4]. A part of the patients is overtreated and consequently exposed to a higher risk on therapy related complications, indicating a need for additional prognostic factors.

More recently, some studies have focused on the tumor-host interaction in relation to metastatic invasion. This interaction is enacted in an environment including cancer cells, the stromal tissue, consisting of different cell types like fibroblasts, myofibroblasts, endothelial cells and immune cells, and the extracellular matrix[5]. Mesker *et al*[6] showed that a high tumor-stroma ratio (TSR), the proportion of carcinoma relative to the proportion of tumor stroma in the histopathological section through the tumor, is an indicator of a better outcome of disease in colon cancer. This is more outspoken for right sided tumors[6]. Similar results were seen in breast cancer, oral squamous cell carcinoma and prostate cancer[7-9]. A high TSR is possibly related to both a longer disease free and overall survival (OS) according to a study on a small number of rectal cancer patients[10]. In this respect, it is meaningful to explore the relevance of the TSR in a larger cohort of patients with rectal adenocarcinoma.

MATERIALS AND METHODS

Patients

Patients with rectal adenocarcinomas under the peritoneal reflection were identified out of all patients, who underwent surgery for left sided colorectal malignancies at our hospital between 1996 and 2006, by analyzing the histopathological reports. Only patients treated with curative intent were included, *i.e.*, patients without known distant metastases at surgery and radically resected tumors (M0, R0 resections). Patients who received neoadjuvant therapy, with malignancies in the past, other than radically excised basal cell carcinoma of the skin, and cases where no tumor was found in the resected specimen, despite preoperative adenocarcinoma in the biopsy of a suspected abnormality, were excluded. Other exclusion criteria were the presence of synchronous colorectal tumors, Lynch syndrome, familial adenomatous polyposis, and inflammatory bowel diseases. Patients who died within thirty days after surgery, with incomplete follow-up or unavailable histopathological material were also excluded (Figure 1).

Data concerning local recurrences, distant metastases, death, and cause of death were collected from the patient records and by consultation of general practitioners. Furthermore, dates of death were retrieved from the population-based Netherlands Cancer Registry. All data were handled in a coded anonymous

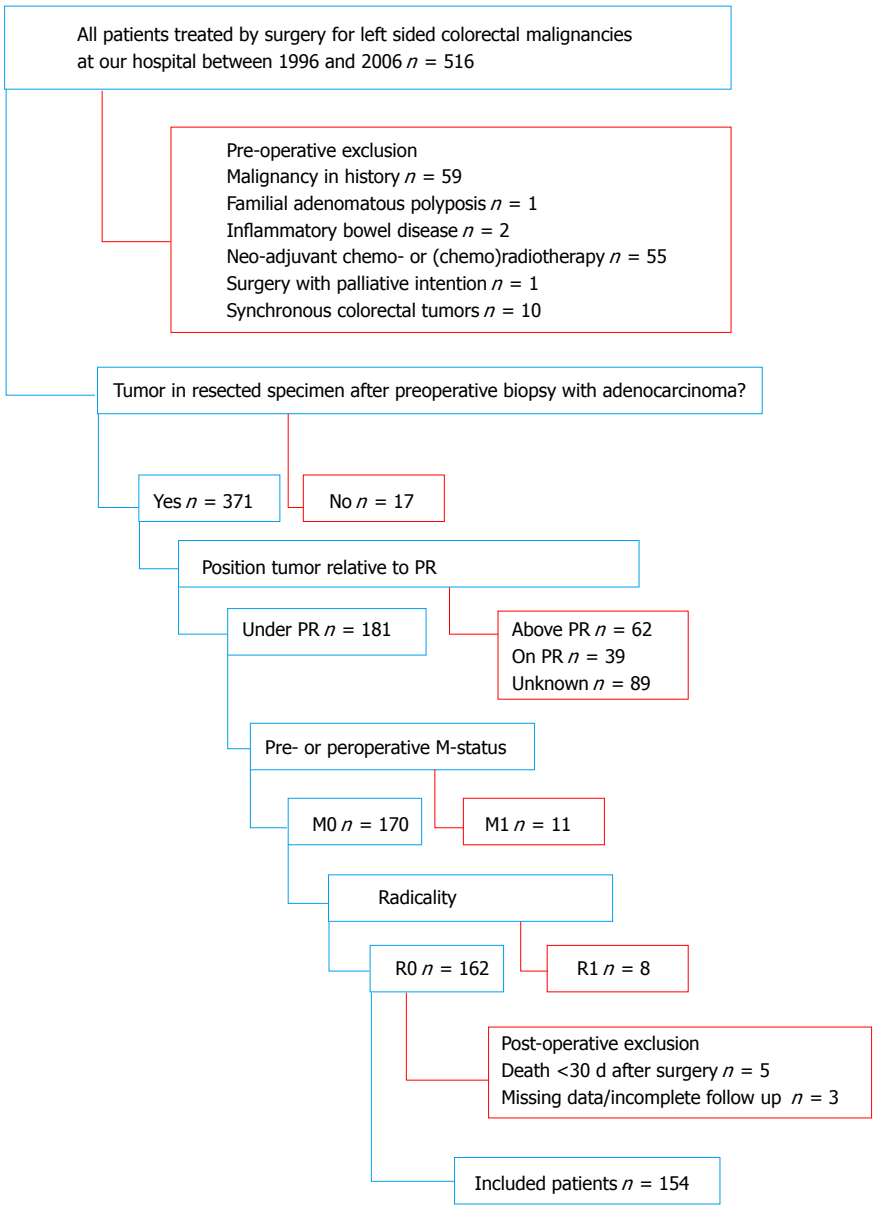

Figure 1 Flowchart of exclusion criteria applied to the dataset of all patients. PR: Peritoneal reflection.

fashion according to the Code for proper secondary use of human tissue from the Dutch Federation of Medical Scientific Societies and with respect to the Helsinki Declaration.

TSR assessment

TSR was determined on hematoxylin and eosin (H and E) stained histological sections. The section with the most invasive part of the tumor was identified to semiquantitatively assess the carcinoma percentage (CP) in 10% steps. The CP is a derivative of the TSR and is complementary to the percentage of stroma and other components, like mucus. For example, a CP of 20% corresponds to a stroma percentage of 80%, which coincides with a low TSR. The section was viewed with a 5 × objective (50 times magnification). The CPs were determined on all image fields of the entire section with tumor cells in all sides of it (North-East-South-West). Areas with the lowest CP were given more weight in rating the mean CP of the total assessed area, as is common practice in routine pathology in determining tumor differentiation. All sections were assessed separately by two observers (René Scheer and Shorena Zoidze) to allow assessment of reproducibility.

The absolute CPs were categorized for a good clinical reproducibility and clarity reasons into three categories, finally. TSR-low including the CP-values $\leqslant$ 30%, TSR-intermediate including the CP-values 40%, 50% and 60%, and TSR-high including the CP-values $\geqslant$ 70% (Figure 2). In the results only the categorized TSR are shown for clarity.

In case of a difference of 10% in determined CPs, which lead to a different TSR category, the lowest CP was used for the determination of the final TSR. The sections were reviewed by a third observer (AB) in case of > 10% difference in determined CPs leading

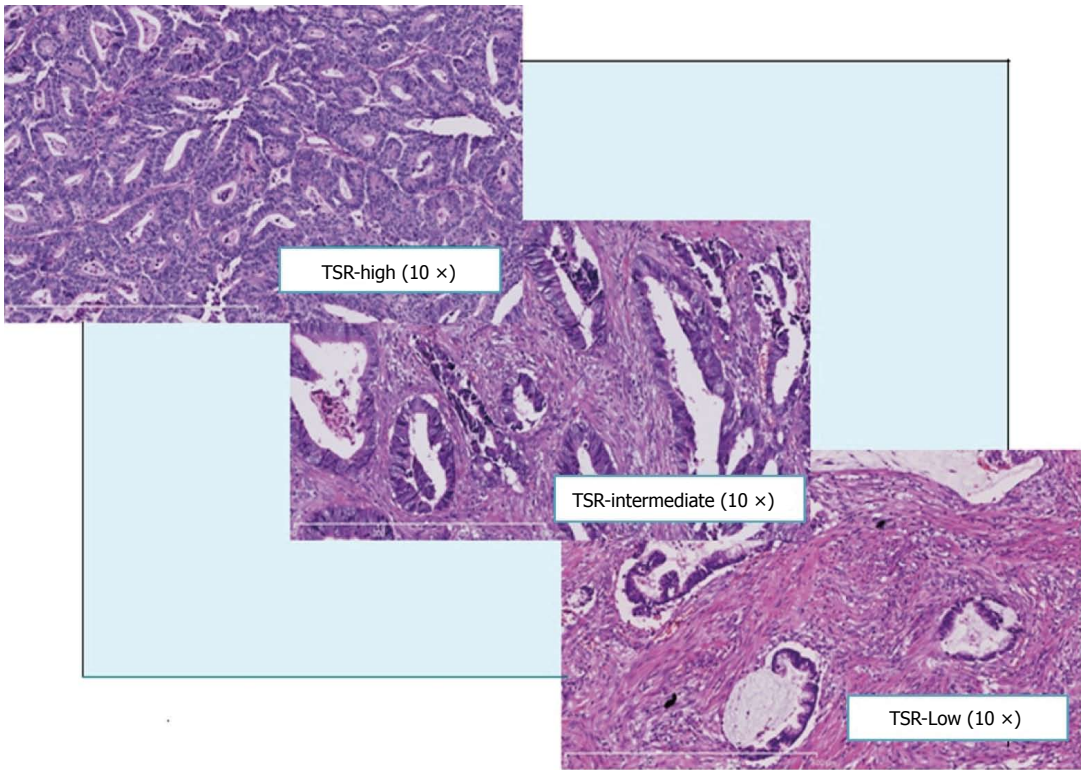

Figure 2 Examples of different categories of the tumor-stroma ratio. H and E stained 2 μm paraffin sections of primary rectal adenocarcinoma. TSR-high (carcinoma percentage ⩾ 70%), TSR-intermediate (carcinoma percentage 40%, 50% and 60%), and TSR-low (carcinoma percentage ⩽ 30%). TSR: Tumor-stroma ratio.

to different TSR categories. This third opinion was considered as decisive.

Statistical analysis

Data were analyzed using SPSS, version 19.0 (SPSS Inc., Chicago, IL, United States) and Stata, version 12.0 (StataCorp LP, College Station, Texas, United States). The statistical methods of this study were reviewed by Elferink MA, from the Netherlands Comprehensive Cancer Organization.

Patient characteristics were compared using Pearson χ^2 tests and one-way ANOVA. Interobserver reproducibility for the absolute and categorized CPs was analyzed by using Cohen's Kappa (κ) coefficient. A κ-value of 0.0 or less was considered to represent poor agreement, 0.01-0.20 slight agreement, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 sufficient to good, and 0.81-1.00 near-perfect agreement[11]. Survival analyses based on categorized CPs included comparison of OS, disease free survival (DFS), and disease specific survival (DSS) by Kaplan-Meier survival analysis and log-rank statistics. Follow-up time in OS analyses was defined as the period between the date of primary surgery and the date of death from any cause, or the date of last follow-up. The DSS was restricted to death from rectal cancer only. Follow-up time in DFS analyses was defined as the time from the date of primary surgery until the date of a local recurrence or distant metastasis (irrespective of site). In DFS analyses, cases were censored in case of a second primary tumor (colorectal or other types) or death. The date of last follow-up was used as endpoint to calculate follow-up time, if none of these events occurred.

The relation between categorized TSR and survival (OS, DFS, and DSS) was analyzed, and adjusted for confounders (age, gender, grading, pathological T- and N-stage, and adjuvant treatment), using Cox proportional hazards model. Probability values < 0.05 (2-sided) were considered statistically significant.

RESULTS

Patient characteristics

A total of 154 patients met the inclusion criteria for this study. Three types of resections were used: Abdominoperineal resection in 67 (43.5%), low anterior resection in 63 (40.9%), and Hartmann resection, a modulated low anterior resection without construction of an anastomosis, in 24 patients (15.6%). The median follow-up of all patients was 5.3 years. Out of the analyzed samples, 36 (23.4%) were scored as TSR-low, 70 (45.4%) as TSR-intermediate, and 48 (31.2%) as TSR-high. There were more lymph node metastasis positive patients with a low TSR in comparison with patients with a higher TSR (P = 0.029), who consequently received adjuvant treatment. Radiotherapy was the most common form of adjuvant therapy. Detailed patient characteristics are shown by categorized TSR in Table 1.

Table 1 Patient characteristics by categorized tumor-stroma ratio

	TSR-low (*n* = 36)		TSR-intermediate (*n* = 70)		TSR-high (*n* = 48)		*P*-value[1]
	n	%	*n*	%	*n*	%	
Gender							NS
Male	24	66.7	44	62.9	32	66.7	
Female	12	33.3	26	37.1	16	33.3	
Age (yr)	M 68.0 (range 49.0-82.0)	SD 8.0	M 67.3 (range 40.0-87.0)	SD 10.3	M 65.7 (range 43.0-91.0)	SD 10.3	NS[2]
Treatment							NS
APR	19	52.6	31	44.3	17	35.4	
LAR	11	30.6	28	40.0	24	50.0	
Hartmann	6	16.7	11	15.7	7	14.6	
T-status							NS
pT1	1	2.8	1	1.4	4	8.3	
pT2	9	25.0	23	32.9	18	37.5	
pT3	24	66.7	43	61.4	25	52.1	
pT4	2	5.6	3	4.3	1	2.1	
N-status							0.029
pN0	16	44.4	44	62.9	34	70.8	
N1	15	41.7	13	18.6	11	22.9	
N2	5	13.9	13	18.6	3	6.3	
Stage							NS
I	7	19.4	21	30.0	17	35.4	
II	9	25.0	23	32.9	17	35.4	
III	20	55.6	26	37.1	14	29.2	
Grading							NS
Well	0	0	1	1.4	3	6.3	
Moderate	31	86.1	58	82.9	40	83.3	
Poor	5	13.9	11	15.7	5	10.4	
Adjuvant treatment	19	52.8	21	30.0	11	22.9	0.012[3]
Radiotherapy	17		18		9		
Chemoradiotherapy	1		3		2		
Chemotherapy	1		-		-		

[1]Pearson χ^2 test; [2]One-Way ANOVA; [3]*P*-value for adjuvant treatment in general. Significant *P*-values are shown bold. *n*: Number of patients; %: Percentage; Age defined as period from birth until date of primary surgery; LAR: Low anterior resection; APR: Abdominoperineal resection; pT: Pathological tumor status; pN: Pathological nodal status; Stage according to UICC/AJCC TNM staging system, 5th edition; TSR: Tumor-stroma ratio; UICC/AJCC: Union Internationale Contre le Cancer/American Joint Cancer Committee.

Interobserver reproducibility

A third opinion about a final TSR in case of interobserver disagreement about CPs with > 10% difference in determined CPs leading to different TSR categories was needed in 12 patients (7.8%). Mainly strong heterogeneity of the tumor complicated the determination of the CP for the total section. CPs were scored in a range between 10 and 90 percent. Lower CPs were found in mucinous adenocarcinomas.

Cohen's Kappa (κ) coefficient for interobserver agreement of the absolute CP showed a moderate agreement (κ = 0.522, concordance 59.1%). By categorizing the CP into three categories TSR (TSR-low, TSR-intermediate, and TSR-high) the κ-value improved and showed a good agreement (κ = 0.724, concordance 82.5%).

Prognostic impact on outcome

The 5-year survival rate for OS was 64.6% in the TSR-high population, *vs* 50.0% and 55.6% in the TSR-intermediate and TSR-low population, respectively. For the DFS, the 5-year survival rates for TSR-high, TSR-intermediate, and TSR-low were 77.2%, 51.8%, and 55.2%, respectively. The OS and DFS were significant different between the three TSR categories (*P* = 0.01 and *P* = 0.02, respectively). The 5-year survival rates for DSS were 81.6% for TSR-high, 60.3% for TSR-intermediate, and 63.9% for TSR-low. Although a higher DSS for the TSR-high population was thereby seen, the differences between the three TSR categories were just not significant (*P* = 0.06). The Kaplan-Meier survival curves are shown in Figure 3.

After adjusting for known prognostic factors (age, grading, and the use of adjuvant therapy), an intermediate TSR in lymph node metastasis negative patients showed a trend to a lower OS rate (HR = 2.04, 95%CI: 0.99-4.21) in comparison with a high TSR. There were no statistical differences between the TSR categories in OS among lymph node metastasis positive patients (Table 2). A statistically significant worse DFS was seen among the lymph node metastasis negative patients with an intermediate TSR (HR = 6.41, 95%CI: 1.84-22.28) compared to patients with a high TSR. Among lymph node metastasis positive patients, no statistically significant differences were seen between TSR categories for DFS (Table 3). Lymph node meta-

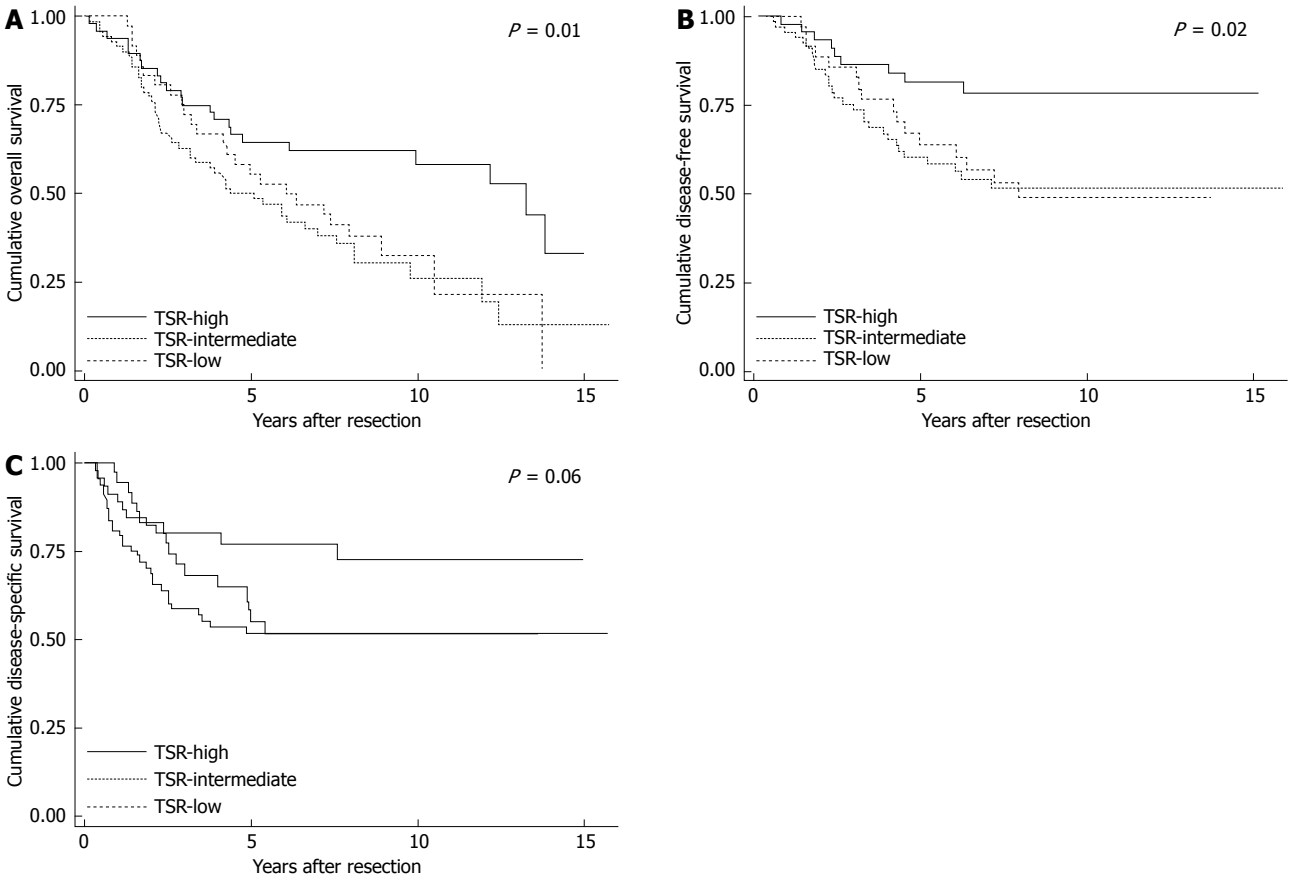

Figure 3 Kaplan-Meier survival curves of overall survival, disease free survival and disease specific survival by categorized tumor-stroma ratio. A: Overall survival; B: Disease free survival; C: Disease specific survival. *P*-values of Log-rank statistics. TSR-high (carcinoma percentage ⩾ 70%), TSR-intermediate (carcinoma percentage 40%, 50% and 60%), and TSR-low (carcinoma percentage ⩽ 30%). TSR: Tumor-stroma ratio.

stasis negative patients with an intermediate TSR had a higher risk of dying from rectal cancer (HR 5.27, 95%CI: 1.54-18.10) in comparison with patients with a high TSR. These differences were not seen in lymph node metastasis positive patients (Table 4).

DISCUSSION

This study, analyzing data of 154 patients with rectal adenocarcinoma diagnosed in the period 1996-2006, showed that the TSR is a prognostic factor for patients without lymph node metastasis. In such cases, a high TSR had a longer local recurrence and distant metastasis free period, and a lower risk of death from rectal adenocarcinoma. Besides, a high TSR was associated with a lower risk of death from any cause. The determination of the TSR may therefore contribute to stratify patients for prognosis. Determination of the TSR turned out to be feasible and reproducible among observers on routinely made sections of rectal cancers. The TSR therefore has the potential to contribute to decision making regarding the individual treatment policy in rectal cancer.

The relation between the prognosis and the TSR may be explained pathophysiologically. A dual effect of the tumor stroma in the tumor-host interaction has been described. The tumor stroma is able to exert inhibitory effects on the malignant cells at first. With ongoing tumor growth, the tumor can exploit its stroma, for example by changing its composition (*e.g.*, vasculature), to promote tumor growth and metastasis. A process called stromagenesis, which occurs parallel with tumor progression. Stromagenesis is characterized by bidirectional communication between the tumor and its stroma. The interactional pathways are multiple and complex[12-14]. Despite this complexity it is justifiable to conclude that the stromal tissue is not a passive component surrounding the tumor. A sufficient amount of stroma contributes to a more aggressive phenotype of tumor, as is shown in this study as well.

Indeed, the poor prognosis for lymph node negative patients with an intermediate TSR is remarkable. The survival rates for death from all causes, death from rectal cancer, and the occurrence of local recurrences and distant metastasis are the lowest for this group of patients. This may be explained by a favorable balance between the tumor and its stroma. In this way, the tumor may be able to exploit the surrounding tumor stroma very efficiently. The concept of a balance between pro- and antitumor factors had been hypothesized earlier. For example, there is a relation between the degree of the peritumoral inflammatory

Table 2 Cox multivariate analysis for overall survival

	N0		N+	
	HR	95%CI	HR	95%CI
Age				
< 70 yr	1	Ref.	1	Ref.
> 70 yr	3.32[a]	1.75-6.28	2.26[a]	1.10-4.65
Grading				
Poor	1	Ref.	1	Ref.
Moderate	1.03	0.43-2.49	0.52	0.25-1.10
Well	0.36	0.04-2.99	0.56	0.06-5.31
Adjuvant treatment				
No	1	Ref.	1	Ref.
Yes	0.47	0.06-3.50	0.66	0.27-1.60
TSR				
TSR-high	1	Ref.	1	Ref.
TSR-intermediate	2.04	0.99-4.21	1.19	0.50-2.84
TSR-low	1.43	0.57-3.60	1.04	0.40-2.69

[a]$P < 0.05$. Age defined as period from birth until date of primary surgery. N0: Lymph node metastasis negative patients; N+: Lymph node metastasis positive patients; TSR: Tumor-stroma ratio.

Table 3 Cox multivariate analysis for disease free survival

	N0		N+	
	HR	95%CI	HR	95%CI
Age				
< 70 yr	1.00	Ref.	1.00	Ref.
> 70 yr	0.36	0.13-1.01	0.89	0.36-2.22
pT-status				
T1	1.00	Ref.	1.00	Ref.
T2	0.11	0.01-1.21	0.66	0.10-4.44
T3	0.85	0.09-7.58	1.51	0.31-7.30
T4	1.61	0.07-39.27	[1]	
Grading				
Poor	1.00	Ref.	1.00	Ref.
Moderate	1.43	0.29-6.99	0.58	0.25-1.35
Well	[1]		[1]	
Adjuvant treatment				
No	1.00	Ref.	1.00	Ref.
Yes	0.2	0.01-2.57	1.04	0.32-3.41
TSR				
TSR-high	1.00	Ref.	1.00	Ref.
TSR-intermediate	6.41[a]	1.84-22.28	1.31	0.49-3.51
TSR-low	3.7	0.84-16.42	0.93	0.31-2.74

[a]$P < 0.05$; [1]Too small numbers to analyze. Age defined as period from birth until date of primary surgery. N0: Lymph node metastasis negative patients; N+: Lymph node metastasis positive patients; pT: Pathological tumor status; TSR: Tumor-stroma ratio.

reaction and its ability to destroy invading colorectal malignant cells[15]. Lymph node metastasis can be seen as an expression of a developed tumor that has exploited its environment successfully. When lymph node metastasis has occurred, the effect of the tumor micro-environment may be negligible. This statement may explain why we did not find differences in survival in lymph node metastasis positive patients survival based on the TSR.

The effect of a high TSR on survival demonstrated in this study is in line with other studies on the prognostic impact of the TSR in colorectal carcinomas (CRCs) and

Table 4 Cox multivariate analysis for disease specific survival

	N0		N+	
	HR	95%CI	HR	95%CI
Age				
< 70 yr	1.00	Ref.	1.00	Ref.
> 70 yr	0.47	0.16-1.40	1.19	0.53-2.67
pT-status				
T1	1.00	Ref.	1.00	Ref.
T2	0.12	0.01-1.29	0.48	0.06-3.50
T3	0.69	0.08-6.25	1.29	0.27-6.07
T4	0.46	0.02-8.70	[1]	
Grading				
Poor	1.00	Ref.	1.00	Ref.
Moderate	1.03	0.20-5.30	0.46	0.21-1.04
Well	[1]		[1]	
Adjuvant treatment				
No	1.00	Ref.	1.00	Ref.
Yes	0.2	0.01-2.57	1.04	0.32-3.41
TSR				
TSR-high	1.00	Ref.	1.00	Ref.
TSR-intermediate	5.27[a]	1.54-18.1	1.60	0.54-4.70
TSR-low	3.48	0.78-15.55	1.22	0.41-3.66

[a]$P < 0.05$; [1]Too small numbers to analyze. Age defined as period from birth until date of primary surgery. N0: Lymph node metastasis negative patients; N+: Lymph node metastasis positive patients; pT: Pathological tumor status; TSR: Tumor-stroma ratio.

other malignancies[6-10,16]. The present study is however the first that has identified a subgroup of patients with rectal cancer, namely lymph node metastasis negative patients with an intermediate TSR, whereby the TSR is a strong prognostic factor.

The interobserver agreement for absolute scores was moderate. The correlation coefficient improved to good, when grouping as TSR-low, TSR-intermediate, and TSR-high. The categorization into these categories was performed with the aim of generating enhanced prognostic information based on the TSR, which had been executed earlier in a previous study on the TSR in oesophageal adenocarcinomas[17]. Other studies concerning the TSR used an arbitrary cut-off value of 50%. No differences in the given survival rates were found at this and other cut-off values in our population (Appendix 1). The rate of agreement of the present study is slightly lower compared to these studies[7,8], which may be attributed to the determination of absolute CPs before the categorization and the addition of an extra CP-category.

This study has some shortcomings to be noted. Neo-adjuvant radiotherapy for rectal malignancies was applied more frequently at our hospital relatively late in the study period and consequentially patients received adjuvant therapy frequently. Neoadjuvant treated patients were excluded, while in most cases a neoadjuvant (chemo)radiotherapy regimen is given nowadays. Though, it remains valuable to investigate tissue based prognostic factors in non-pretreated patients. There is a tendency to treat elderly, for whom there is an increasing incidence of rectal cancer, without neoadjuvant radiotherapy due to postoperative

wound complications in The Netherlands. According to the Dutch Surgical Colorectal Audit, no neoadjuvant therapy was used in 26% of cT2 patients aged > 75 years with rectal carcinoma in comparison with 14% in younger patients[18]. Furthermore, there is still a debate about adjuvant chemotherapy for rectal cancer. Future research about the balance between the oncological benefit, *i.e.*, relative risk reduction of 50% in local recurrences and the side effects, *i.e.*, relative risk increase of 50% in acute treatment-relate toxicity, and long-term anorectal and sexual dysfunction[19-21] of neoadjuvant radiotherapy will help to determine the position of pretreatment dependent tissue-based markers like the TSR in predicting an individual prognosis.

It would be of interest to analyze the TSR and its prognostic value in biopsy specimens of well described areas of a rectal tumor. Prognostic information could then be provided before the use of neoadjuvant therapy. The visual estimation of the TSR could be made more accurate by the use of tumor or stroma specific stainings. Besides, it would be desirable to develop a more objective instrument to determine the TSR than the visual estimation in this study. This could be provided by the use of tumor specific staining and the development of computer software in the growing field of digital pathology.

Determination of the TSR has the potential to identify patients without lymph node metastasis with a good and a poor clinical outcome and can thereby help in decision making on (neo)adjuvant treatment policy in individual cases. Determination of the TSR in routine sections is feasible and can be done with a good concordance by different observers.

COMMENTS

Background

Colorectal cancer is one of the most common form of cancer in both men and women. The TNM staging system, the most common system to stage colorectal tumors, is used to discriminate between patients with a better and a poor prognosis, but it seems insufficiently able to predict the prognosis of the individual patient. Additional prognostic factors are desirable, because a part of the patients is overtreated and consequently exposed to a higher risk on therapy related complications. The tumor-stroma ratio (TSR), the proportion of carcinoma relative to the proportion of tumor stroma in the histopathological section through the tumor, has proven to be of prognostic value in several malignancies.

Research frontiers

A previous study, on a small number of rectal cancer patients, showed that a high TSR is possibly related to both a longer disease free and overall survival. In this respect, it is meaningful to explore the relevance of the TSR in a larger cohort of patients with rectal adenocarcinoma, as the authors did.

Innovations and breakthroughs

This paper showed that the TSR has potential as a prognostic factor for survival in surgically treated rectal cancer patients, especially in lymph node negative cases. The effect of a high TSR on survival demonstrated in this study is in line with other studies on the prognostic impact of the TSR in colorectal carcinomas and other malignancies. The present study is however the first that has identified a subgroup of patients with rectal cancer, namely lymph node metastasis negative patients with an intermediate TSR, whereby the TSR is a strong prognostic factor.

Applications

The determination of the TSR may contribute to stratify patients for prognosis and has the potential to contribute to decision making regarding the individual treatment policy in rectal cancer.

Terminology

The TSR is the proportion of carcinoma relative to the proportion of tumor stroma in the histopathological section through the tumor. The carcinoma percentage (CP) is a derivative of the TSR and is complementary to the percentage of stroma and other components, like mucus. TSR-low including the CP-values $\leqslant$ 30%, TSR-intermediate including the CP-values 40%, 50% and 60%, and TSR-high including the CP-values $\geqslant$ 70%.

Peer-review

The study is well designed and clearly presented and the topic of high interest for oncologists that should decide after surgery what patients will benefit more from an adjuvant treatment.

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