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# Tumor-Stroma Ratio is an independent predictor for overall survival and disease free survival in gastric cancer patients

*Paolo Aurello* [a], *Giammauro Berardi* [a,*], *Diego Giulitti* [a], *Antonio Palumbo* [b], *Simone Maria Tierno* [a], *Giuseppe Nigri* [a], *Francesco D'Angelo* [a], *Emanuela Pilozzi* [b], *Giovanni Ramacciato* [a]

[a] *Department of General Surgery, University of Rome, "La Sapienza", Sant'Andrea Hospital, Via di Grottarossa, 1035-1039, 00189, Rome, Italy*

[b] *Department of Pathology, University of Rome, "La Sapienza", Sant'Andrea Hospital, Via di Grottarossa, 1035-1039, 00189, Rome, Italy*

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ABSTRACT

*Background:* Despite different prognostic factors have been already studied, patients undergoing potentially curative resection for gastric cancer, still have a poor outcome. There is therefore the need to identify novel prognostic factors. Recently, Tumor-Stroma Ratio (TSR) was proven to be associated with prognosis in different types of cancers. Aim of this study was to evaluate the prognostic value of TSR in gastric cancer patients.

*Methods:* 106 patients underwent gastrectomy between January 2004 and December 2015. Demographics and histopathological characteristics were collected. We considered a 50% TSR cutoff value to divide patients in Stroma-Rich (≥50%) and Stroma-Poor (<50%) groups.

*Results:* Forty-one (38.7%) patients were classified as Stroma-Poor while 65 (61.3%) as Stroma-Rich (61.3%). The Stroma-Rich patients had a higher number of positive lymph-nodes, lymph node ratio (LNR), a higher percentage of T3/T4 local invasion and N2/N3, and a more advanced TNM. Moreover, these patients showed a higher percentage of lymphovascular and perineural invasion. With a median FU of 38 months Stroma-Rich patients had a significantly worse 5-years actuarial overall survival (OS) and disease free survival (DFS) compared to Stroma-Poor patients. Moreover, the multivariate analysis showed that Stroma-Rich was the only independent factor associated with OS and DFS together with TNM-Stage.

*Conclusions:* TSR is an independent marker of poor prognosis in patients with gastric cancer that should be readily incorporated into routine clinical pathology reporting. Identification of sensitive markers for patients who had undergone curative gastrectomy and who are at high risk of recurrence could provide useful information for planning follow-up after surgery or intensive and or/targeting adjuvant chemotherapy.



* *Corresponding author.*
E-mail address: gberardi1@gmail.com (G. Berardi).

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## Introduction

Gastric cancer is the fourth most common malignancy and the second most common cause of cancer-related death worldwide.[1] Tumor stage, size, grade of differentiation and lymph-node metastasis are well-established prognostic factors as well as lymphovascular and perineural invasion.[2,3]

Despite these prognostic factors, even in patients undergoing potentially curative resection, survival remains poor with a 5-years rate around 30%.[2] Clearly, it remains a need to identify novel prognostic markers alongside current pathological staging in order to optimize patient's management and improve oncological outcomes.

In recent years, there has been a growing interest towards tumor's microenvironment and its role on tumorigenesis.[4,5]

To date, it is increasingly acknowledged that Tumor Stroma is indispensable for cancer initiation, progression and metastatic potential and that cells components of the stroma hold the potential of influencing prognosis.

Recently, Tumor-Stroma Ratio (TSR) was proven to be a new prognostic factor in different types of cancers such as colon, prostate, early breast, ovarian and cervical cancer, nasopharyngeal cancer, hepatocellular carcinoma, esophageal and lung cancer [3,6–16]: an increase in the proportion of Tumor's Stroma has been associated with poorer prognosis in these solid tumors.

Despite this, different results have been reported speculating that a positive prognostic effect associated with high Tumor Stroma percentage could exist, concluding that TSR should not be considered as a universal prognostic marker for all types of tumor but rather as differently related to prognosis depending on type of cancer.[17]

To the best of our knowledge, the role of TSR and its eventual prognostic value remains unexplored in gastric cancer.

The aim of this study was to evaluate the prognostic value of TSR in gastric cancer patients who underwent potentially curative gastrectomy and to explore its relationship with other prognostic factors.

## Materials and methods

One hundred forty-two consecutive patients underwent resection for gastric cancer between January 2004 and December 2015, at S. Andrea Hospital, "Sapienza", University of Rome. All patients had undergone gastrectomy and modified D2 lymphadenectomy with curative intent according to tumor location and extent of disease.

Combined resection of adjacent organs was performed in case of direct invasion. Patients with residual disease either microscopically or macroscopically were excluded from the study. None of the patients included in the study had liver or distant metastases at the time of surgery.

No patients underwent neoadjuvant chemotherapy and all were treated with adjuvant chemotherapy (oxaliplatin and capecitabine) after surgery as proposed in the "Associazione Italiana di Oncologia Medica" (AIOM) guidelines (www.aiom.it).

T-stage and nodal status were determined using the American Joint Commission on Cancer Staging (AJCCS) Manual, 7th edition.[18] The Lymph-Node Ratio (LNR) was calculated based on the relationship between positive nodes and total nodes.[19]

For histological parameters, multiple samples of 2.5 × 3.3 cm tissue extent were obtained from every surgical specimen; 4 μm-thick sections of each formalin-fixed paraffin-embedded tissue block were cut and H&E stained. Each slide was carefully and separately reviewed by two of the authors (AP and DG) in blind.

Lymphovascular invasion was considered positive when either single tumor cells or cell clusters were clearly visible within an endothelium-lined vessel-like structures.

Perineural invasion was defined as the presence of cancer cells along nerves and/or within the epineurial, perineurial and endoneurial spaces of the neuronal sheath including cases in which the cell circumscribed at least 33% of the nerves.[20]

Tumor-Stroma Ratio was calculated by dividing the total tumor count over the total stroma count for each case; in case of tumor heterogeneity stroma rich areas were considered decisive for Tumor-Stroma Ratio evaluation because already considered to be of worse prognosis.[21] Using a 4× microscope objective (40× total magnification), the most invasive areas of the tumor were selected for further evaluation. Subsequently, microscopical fields where both stroma and tumoral tissue were present were scored with a 10× objective (100× total magnification). The estimate was then recorded as the Tumor-Stroma Ratio and scored per tenfold percentage.

Furthermore, we considered a 50% TSR cutoff value to divide patients in Stroma-Rich (proportion of stroma ≥50%) and Stroma-Poor (proportion of stroma <50%) groups.[6,9,10,12,16,17,20]

Patients who died within 30 days of surgery were excluded as well as patients lost to follow-up. The study was approved by the Institutional Review Board.

### *Statistical analysis*

Comparison of categorical variables was performed using the $\chi^2$ test with yates correction or fisher's exact test as appropriate. Comparison of continuous variables was performed using the unpaired t-student test or the Wilcoxon–Mann–Whitney test as appropriate.

Overall survival (OS) was defined as the interval between the date of operation and the date of death for any cause or last patient visit. Disease free survival (DFS) was defined as the time from operation until tumor relapse either local or distant. Kaplan–Meier curves were generated and differences in survival rates between groups were compared by the long-rank test. A backward stepwise cox regression model was used to identify variables influencing OS and DFS. Significance was defined as a *P* value of less than 0.05. All statistical analysis was performed using the SPSS for Mac version 17.0 (SPSS, Inc., Chicago, IL).

## Results

One hundred six patients (49 females and 57 males) with a mean age of 70.1 ± 11 years with Stage Ib/II/III gastric cancer

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