Retraction Notice

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□ Institution:
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History
Expression of Concern:
☐ yes, date: yyyy-mm-dd
X no

Correction:
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Comment:

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Editor guiding this retraction: IJCM Editorial Board

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The Sarandria Score—Discussion of a New Scoring System in Clinical Medical Oncology

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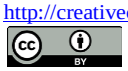


Abstract

This paper focuses on discussing a novel scoring for stage III rectal cancer patients and all the challenges in creating and developing a clinical score. **Background:** It is fundamental in my opinion to give space to new generations of scientists, medical doctors and researchers to study and, backed with evidence-based information, improve the current knowledge of clinical medical science. It is fundamental for result obtained by medical researchers to bring their findings to the scientific community. Every scientific finding is of vital importance. In this essay a new Clinical Scoring system, the Sarandria Score, developed by myself is discussed, together with the methods and path in order for a young medical researcher with an idea to bring it to the scientific community. **Main topics:** Colorectal Cancer (CRC) is a major public health problem, representing the third most commonly diagnosed cancer in males and the second in females. Various studies have reported relevant differences related to CRC primary location site (right-sided colon, left-sided colon, rectum) including response to adjuvant chemotherapy and prognosis. In stage III CRC patients, previous findings showed that higher density of tu- mor-associated neutrophils (TANs) was associated with better response to 5-FU-based chemotherapy. Novel findings were discovered by Dr Nicola Sarandria on the role of neutrophils in rectal cancer, which include different factors which point to an anti-tumoral role of neutrophils in rectal cancer when in presence of chemotherapeutic agents (5-fluorouracil). The clinical significance of TANs was assessed and whether it can be different depended on the location of the primary CRC (right-sided colon, left-sided colon, rectum). **Conclusions:** This essay officially discusses a new clinical prognostic and predictive scoring (Sarandria Score) involving intratumoral neutrophilic infiltration in rectal cancer and the possibility of a new inclusion criteria based on this infiltrate for Stage III rectal cancer patients treated with 5-FU therapy. This paper includes data published on my medical degree thesis and in a previous review (on Journal of Cancer Therapy) showing that higher le-

vels of TANs densities were associated with better disease-free survival (DFS) in 5-FU treated patients affected by rectal cancer (while it was inversely related in patients without 5-FU therapy). This was also as further evidence in support possible conceptual division of what is now known as Colorectal cancer into Colon and Rectal cancer.

Keywords

New Clinical Score, Sarandria Score, Methodology, Rectal Cancer, Neutrophils, 5-Fluorouracil, Neutrophils and Cancer, Colorectal Cancer

1. Background

In the following section I will describe the way I came up with this scoring system (as discussed in my previous publication) [1]. The following data and tables of this "Background section" were first described in my medical graduation thesis and then in my review published last year [1]. In my years at Humanitas University as a medical student, I created one hypothesis and a research objective: to see whether TANs intratumoral (IT) density in Colorectal Cancer has different prognostic and/or predictive value according to tumor primary site location—left colon, right colon and rectum—and whether it differs according to presence or not of adjuvant chemotherapy—5-FU. My hypothesis was that neutrophils (of the N1 polarization) could indeed help the prognosis of the patient under 5-FU (also in accordance with the different publications showing neutrophilic role in the 5-FU action and therapeutic cycle). In the following text I will describe my research and findings (as published in my thesis).

The study type was a retrospective one—a study that compares two groups of people: those with the disease or condition under study (cases) and a very similar group of people who do not have the disease or condition (controls)—(cancer.gov definition of retrospective study) with the focus of finding a correlation between IT PMN in CRC and predictive or prognostic values. The study attempted to correlate polymorphonuclear neutrophil (PMN) tumoral infiltration (TANs) with CRC site—in the presence or absence of adjuvant therapy. It was inquired whether CRC site—whether it was right-sided, left-sided or rectal—had any effect on TANs density (intratumoral density) and whether these densities had any kind of prognostic value—be it in presence of adjuvant therapy or without any adjuvant therapy. According to previous publications, it was revealed that TANs were correlated with positive prognosis when the patients (pts), with Stage III CRC, underwent 5-fluorouracil as adjuvant therapy [2]. Also, it has been revealed that low TANs density in Stage II CRC, could be an index for adjuvant chemotherapy usage. This study focuses on finding whether this correlation holds for the aforementioned CRC sites and whether the pattern is the same for all of them—including focusing on the group of pts who did not undergo adjuvant therapy.

The initial hypothesis was that different site of CRC—right-sided, left-sided or rectal—may hold different values of TANs densities with different prognostic features. This assumption was based on the various differences that these anatomical locations have amongst them such as: different microbiome, different mechanical strains due to different intraluminal fecal consistencies from the cecal area to rectal area, area where maximum water reabsorption occurred in normal physiological process [3] [4] [5]. The tumor and tumoral microenvironment have key differences depending on tumor type and immunological infiltrate affecting it [6] [7] [8]. There is chronic inflammation in the tumor [9] [10] [11] [12] [13] and an abundance of neutrophils. Also, differences in embryological origin and mutational background, e.g. Higher MSI mutational burden in right-sided CRC [9].

Therefore, the principal aim of the study, the research objective, was to find whether these TANs densities (intratumoral) in different CRC sites have any prognostic relevance, in either the pts treated with adjuvant therapies and non-treated ones.

The reason for the study is a need for new prognostic markers for one of the commonest solid tumors in the world, namely the CRC. Also, the importance of understanding differences between CRC having as primary location different sites—focusing on right-sided colon, left-sided colon and rectum—could aid in the future adjuvant therapy selection for different classes of pts. In addition, whether TANs intratumoral density could be not only a prognostic marker but also a predictive marker was also inquired, by checking high TANs in adjuvant therapy pts and the efficacy of the therapy measured by survival parameters. As adjuvant therapy, 5-Fluorouracil was the therapy which was considered in the Galdiero *et al.* study, where a statistically significant correlation was found between patients treated with 5-FU with high intratumoral TANs vs those with low intratumoral TANs densities—namely pts with high TANs had a more favorable prognosis. In the study 178 pts were taken into considerations, 52 did not receive any adjuvant therapy while 126 received 5-FU as adjuvant therapy. All the patients (pts) were Stage III and Microsatellite Stable (MSS). Using the raw data, a multivariate analysis was performed to reach the objective of the study.

In the tumor microenvironment, Neutrophil granulocytes can be classified into N1/N2 type neutral granules, tumor-associated neutrophil TAN and Polymorphonuclear myeloid derived suppressor cells Cell PMN-MDSC [14] [15].

Neutrophils perform different functions when they adapt to different background environments. Neutrophils resist infection with pathogens, but constant infiltration of neutrophils can lead to chronic inflammation and tissue damage [16] [17].

To inquire whether TANs Intratumoral (IT) densities had predictive and/or prognostic value in regards to CRC site—left sided, right sided or rectal—in pts who underwent or not adjuvant chemotherapy with 5-FU, the raw dataset of patients (Stage III colorectal cancer patients) used in the Galdiero *et al.* [18] study from our lab was used.

Furthermore, as reported in a previous study, a new set of pts were taken to assess whether these TANs densities correlations with different CRC anatomical sites and prognosis in pts with 5-FU as adjuvant therapy existed with different types of adjuvant therapies, such as FOLFOX—made up of Folinic Acid (leucovorin—a molecule aiding in normal DNA replication—folate based DNA replication when high dose Metrotrexates, but increase cytotoxicity of 5-FU), 5-FU (a thymidylate synthase (TS) inhibitor and player in possible immune cell activation in the tumor microenvironment), Oxaliplatin (a cytotoxic compound)—or FOLFIRI—5-FU, Folinic Acid, Irinotecan (a topoisomerase inhibitor preventing DNA replication by blocking its unravelling) [19] [20]. Therefore, the research objective of the study was to see whether TANs intratumoral (IT) density in Colorectal Cancer has different prognostic and/or predictive values according to tumor primary site location—left colon, right colon and rectum—and whether it differs according to presence or not of adjuvant chemotherapy—5-FU.

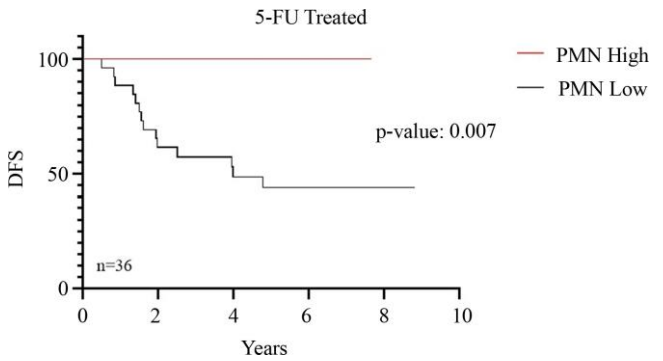
In the dataset, Intratumoral (IT) TANs were measured by Immunohistochemical process, labelling neutrophils via CD 66b + Ab labelling. While the analysis on that study focused on CRC and presence or not of 5-FU, here the focus of the analysis shifted to the three aforementioned CRC sites with the presence or not of Adjuvant therapy. Therefore, a different analysis with different parameters was performed on the set of pts mentioned before.

The primary sites of CRC which were taken into consideration were therefore three: Right-sided colon, Left-sided colon (not including rectum) and Rectum.

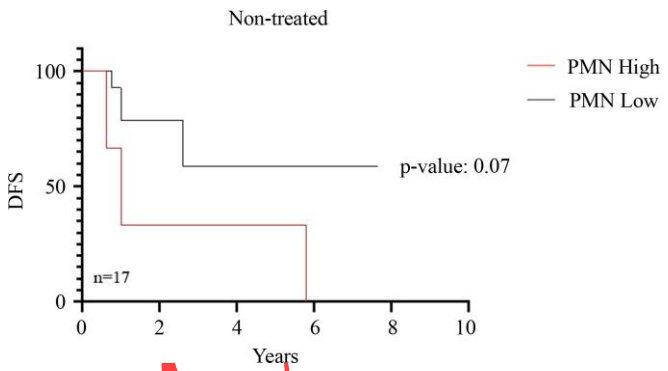
For 5-FU treatment the CRC site which was correlated to Intratumoral neutrophils in regards to Disease Free Survival of patients, was the rectum. The data revealed that High IT PMNs were strongly correlated to better DFS in 5-FU1 patients with rectum located CRC, compared to those with Low IT PMNs. This relationship was inversed in regards to 5-FU0 patients (High IT PMNs = Worst Prognosis).

In the data published in my thesis, a univariate analysis was also performed regarding the significance of IT TANs (PMNs) in rectal-cancer patients as shown in **Table 1**, where it can be seen that in patients with rectal cancer (stage III), there is a strong statistically significant better DFS in 5-FU treated patients having high IT PMNs (polymorphonuclear) density (HR: 0.06, p-value: 0.003) compared to patients with low IT PMNs density.

The data therefore suggest a possible predictive and prognostic value for IT PMNs (TANs) to be used in the clinical practice in patients with Stage III rectal cancer, where high Tumor Associated Neutrophils in the intratumoral histological section could be an inclusion criterium for 5-FU based adjuvant chemotherapy while a low value could be an exclusion criterium for this therapy (see **Figure 1**) and where high IT TANs in 5-FU treated patients could be a positive predictive and prognostic indicator for Disease Free Survival (DFS). In fact, it was also observed how high IT PMNs were associated with a worst DFS in patients with stage III rectal cancer but not treated with 5-FU (this possibly due to criteria of the patients.



(a)



(b)

Figure 1. Prognostic significance of CD66b in patients with Stage III CRC located in the rectum. Kaplan–Meier survival curves show DFS ((a), (b)) for patients presenting a high or low density of neutrophils (PMNhigh or PMNlow, respectively) in the IT (intratumoral). (a). shows DFS amongst IT PMN high vs. PMN low ones amongst 5-FU treated patients, n = 36, p-value: 0.007. (b). shows DFS amongst IT PMN high vs. PMN low ones amongst non-treated patients, n = 17, p-value: 0.07. Upper quartile values were employed to divide tumors into high and low CD66b+ immunoreactive area. The p-value was found using the Log-rank test.

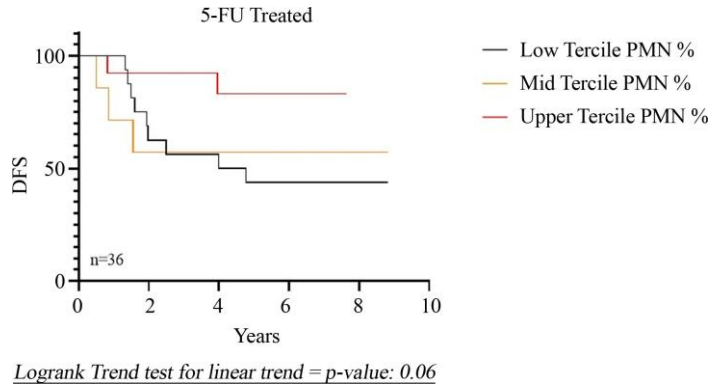
Table 1. Rectal cancer and IT PMNs.

Rectal cancer	Non-Treated Patients 5-FU treated patients	
	Univariate analysis HR (95% CI) p-value	Univariate analysis HR (95% CI) p-value
IT PMNs Density	1.00 Ref.	1.0 Ref.
<1.197	3.5 (0.81 - 15)	0.06 (0.0005 - 0.45)
≥1.197	0.11	0.003*

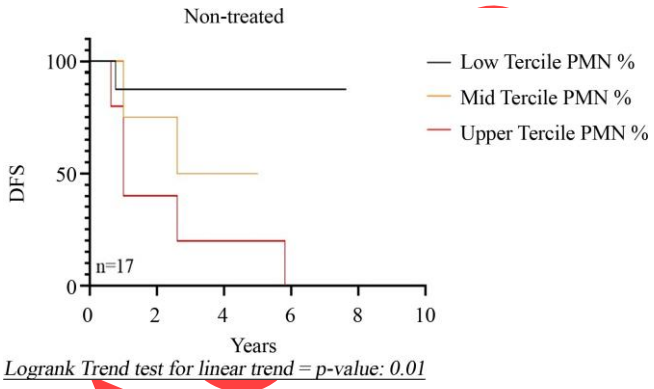
a. statistical test used: Firth's Method. *Statistically significant.

This was confirmed also when dividing in terciles to search for linearity (**Figure 2**). Figures and tables published on my thesis in 2020 [2].

For the patients with rectal cancer, I wanted to check also if the same association between IT PMNs density and DFS was present when looking at survival (DSS—Disease Specific Survival). See **Figure 3**.



(a)



(b)

Figure 2. Prognostic significance of CD66b in patients with Stage III CRC located in the rectum. Kaplan-Meier survival curves show DFS ((a), (b)) for patients presenting levels of PMN according to 3 terciles (low, mid, and upper terciles of IT PMN density) in the IT (intratumoral). (a) shows DFS amongst 5-FU treated patients, n = 36, p-value for linear trend: 0.06. (b) shows DFS amongst non-treated patients, n = 17, p-value for linear trend: 0.01. The Logrank Trend test was used to find the linear trend between the survival curves in each graph.

2. Main Topics

Therefore, in this section the Sarandria Score will be discussed in more detail. The discussed data showed (that I demonstrated in my graduation thesis for my medical degree) where patients with Stage III CRC located in the rectum and having High IT PMNs, benefit from receiving 5-FU adjuvant chemotherapy. While, patients with Low IT PMNs and CRC located in the rectum, do not benefit from 5-FU adjuvant chemotherapy (on the contrary they show a worst DFS compared to the patients who did not receive 5-FU).

Furthermore, there is a linear correlation between IT PMNs and DFS in both 5FU0 and 5FU1 patients having CRC located in the rectum (correlation not seen neither in the left-sided CRC nor in the right-sided CRC). This correlation was inversed in regards to 5-FU0 patients (High IT PMNs = Worst Prognosis). The data therefore suggest a possible predictive and prognostic value for IT PMNs (TANs) to be used in the clinical practice in patients with Stage III rectal cancer,

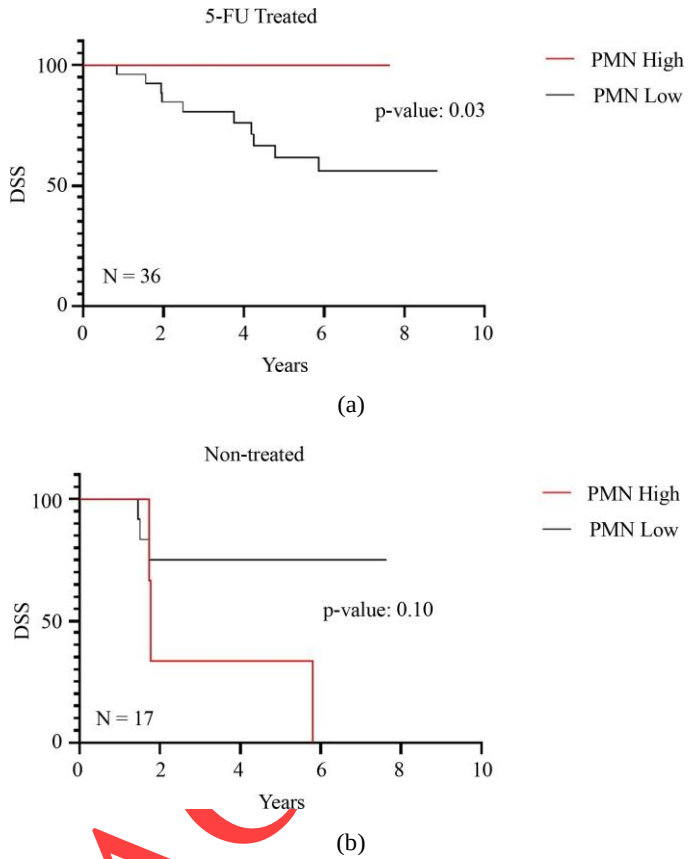


Figure 3. Prognostic significance of CD66b in patients with Stage III CRC located in the rectum. Kaplan-Meier survival curves show DSS ((a), (b)) for patients presenting a high or low density of neutrophils (PMNhigh or PMNlow, respectively) in the IT (intratumoral). (a) shows DFS amongst IT PMN high vs. PMN low ones amongst 5-FU treated patients, n = 36, p-value: 0.03. (b) shows DFS amongst IT PMN high vs. PMN low ones amongst non-treated patients, n = 17, p-value: 0.10. Upper quartile values were employed to divide tumors into high and low CD66b+ immunoreactive area. The p-value was found using the Log-rank test.

where high Tumor Associated Neutrophils in the intratumoral histological section could be an inclusion criterium for 5-FU based adjuvant chemotherapy while a low value could be an exclusion criterium for this therapy (see **Figure 1**) and where high IT TANs in 5-FU treated patients could be a positive predictive and prognostic indicator for Disease Free Survival (DFS) and Disease Specific Survival (DSS). This scoring system (named the "Sarandria Score" or in Italian nomenclature the "Scala di Valutazione Sarandria") could truly help in choosing candidates for 5-FU therapy (or possible other chemotherapeutical agents) among Stage III rectal cancer patients and could give prognostic and predictive insights to these patients. Furthermore, the fact that a worst DFS was found in patients not treated with 5-FU and having Stage III Rectal cancer, could be an important prognostic indicator for these subsets of patients also.

It is of relevance to do further studies in finding the correlation between neutrophils and rectal cancer, most importantly checking for: 1) Neutrophil polari-

zation (my supposition if that neutrophils in the tumor microenvironment of rectal cancer is of N1 phenotype). This can be checked with Arginase assay. 2) Correlation between neutrophils, rectal cancer and predictive/prognostic value also in patients undergoing different therapies—such as FF etc. It is my opinion, that neutrophilic infiltrate could become a staging system for rectal cancer patients for prognostic and predictive significance, much like immunoscore is now days used alongside TNM staging for colon cancer. As a matter of fact, it would be interesting to see whether the immunoscore (based on Jerome Galon's finding from 2006 which revealed a positive association of cytotoxic and memory T cells with survival of colorectal cancer patients) would change in terms of the location of the CRC (namely left, right or rectal cancer). Therefore, this review highlights also a new scoring system based on neutrophilic infiltration of intratumoral section of stage III rectal cancer patients developed by myself, Dr Nicola Sarandria MD [1] [2] (proposed name of the score: Sarandria Score, see **Table 2**). Furthermore, it is of my opinion that this could serve as further evidence in support of the future division of what is now known as Colorectal cancer into Colon and Rectal cancer, two different entities with different clinical and etiopathological courses. Therefore, as an addition to review the current state of knowledge on neutrophils and rectal cancer and with the aforementioned considerations in mind, the following scoring system, the Sarandria Score [1], can be seen in **Table 2**.

On a side note, regarding the process of advancing a medical researcher own ideas, backed by scientific evidence-based facts, it is of relevance to state that independently of everything that goes among peers and academic members, it is always the intellectually right and morally, duty-bound and scientifically correct path to advance with the focus to bring your findings to the public, and never surrender to forms of pressures from members of the academic boards (which independently of everything I have always respected, admired and extremely

Table 2. Sarandria score.

Sarandria Score: With Positive Predictive and Prognostic score: association with better prognosis and therapy outcome					
CD 66b stained Intratumoral cells density (Intratumoral neutrophils) (PMN Sum % Area)		**Resulting Predictive Score****	**Resulting Prognostic Score****	**5-Fluorouracil Therapy Inclusion***	**Resulting Prognostic Score (no 5-FU)*****
<1.197	**Low Intratumoral Neutrophils**	Negative	Negative	Low efficacy	Positive
≥1.197	**High Intratumoral Neutrophils**	Positive	Positive	Yes	Negative prognostic score

*Inclusion to a 5-Fluorouracil (5-FU) therapy to be considered in addition and conjunction to all other clinical aspects/criteria for the suitability and applicability of such therapy; **In patients being treated 5-FU chemotherapy; ***In patients not treated with 5-FU chemotherapy.

grateful for all the knowledge they passed on to me) to hide findings or stay silent. Furthermore, regarding my findings, it must be added that the same correlation in regards to IT PMNs and DFS in CRC patients undergoing 5-FU therapy, is not seen in the other CRC sites (left-sided and right-sided). Therefore, this score would be based on whether or not the intratumoral section at immunohistochemistry (CD 66 b ab stain) has a high value of neutrophilic infiltrate (set at ≥1.197 of neutrophilic density, calculated as "Sum % Area").

Regarding possible pathophysiological mechanisms of effect on why the high level of neutrophils was associated with a positive prognosis and had a predictive effect on therapy could be the association between the 5-FU therapy and the TANs, namely that studies have shown that 5-FU activates immune effectors and eliminates immunosuppressive cells [19].

3. Conclusion

In order to conclude, it is of vital importance for clinical medical findings to reach the scientific community. In this paper I have outlined my medical clinical score, the Sarandria Score. It is also relevant to do further research on the topic to see further findings regarding the association of tumor associated neutrophils and rectal cancer patients' prognostic and predictive score. It is fundamental for scientific results to be shown to the scientific community and to be discussed and its finding to be studied and advanced. In the end, the main aim of all medical clinical research is in my opinion to finally help save human lives and improve the quality and length of life for the patients worldwide. If there is even one possibility that a medical researcher finding could achieve this, that is to save human lives, then it is the moral, scientific and human duty of that person to bring to the scientific community the data.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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