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# Lymph node status assessed through the *log odds* ratio – a better tool in the prognosis of colorectal cancer relapse

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## Abstract

The current literature related to colorectal cancer shows there is a great inhomogeneity in patient outcome, even between patients in the same stage, which means that the TNM staging does not seem enough anymore to make a therapeutic decision. This is why many of the recent studies focus on the study of prognostic and predictive factors that would make the therapeutic decision-making process more accurate. In the current study, we focused on the study of two lymph node based scores – the lymph node ratio and the *log odds* ratio and the morphological characteristics of the tumor to try to see if any of them can predict a more aggressive tumor behavior in order to approach the patient in an appropriate way. The study included 25 patients presenting over a period of two years (2009–2011) for a local relapse or a metastasis after curative surgery for colorectal cancer. From the morphological characteristics of the tumor, only the protruding character of the tumor positively correlated at a statistically significant level with the recurrence-free time. We also proved that between the two lymph node scores and the pN stage, the *log odds* ratio was the one that best correlated with both the number of invaded lymph nodes and the number of resected nodes. The *log odds* ratio also proved to correlate well with the risk of developing a distant metastasis. Our study also shows for the first time that the *log odds* ratio is able to stratify patients according to their risk of a fast relapse.

***Keywords***: disease-free interval, lymph node ratio, *log odds* ratio.

## Introduction

As is the case of the large majority of solid tumors, the pathology TNM staging is decisive in choosing the therapeutic approach for each colorectal cancer patient. As such, the pN staging system is one of the most important criteria taken into account when a patient is approached for the first time. However, according to the 7th edition of the *International Union Against Cancer* (*UICC*)/*American Joint Committee on Cancer* (*AJCC*), TNM staging system at least 12 lymph nodes have to be sampled in order for under staging to be avoided in colorectal cancers [1].

Lately, there have been many studies attempting to find new prognostic markers in colon and rectal adenocarcinomas. Some of these studies have focused on systemic markers such as tumor markers or the presence of chronic systemic inflammation (assessed through scores such as the Glasgow score) [2], others focused on the information that pathology based scores can bring, as is the case with the Petersen index and the Jass and Klintrup criteria [3]. Other study groups have focused their attention on molecular markers and are trying to perform a complex portrait of the immune cells that make up the tumor microenvironment [4].

An increasing number of studies are trying to take advantage of the information contained in the number of invaded lymph nodes and the total number of excised lymph nodes, by designing new lymph node scores. The reason behind this interest for lymph node based prognostic scores is that they are cheap and easy to use because they do not require any complex and costly molecular studies.

Another reason for the increased interest in better describing the lymph node status is the fact that over time it has been proven that a higher numbers of excised lymph nodes are correlated with a better outcome but it is not always that a high yield of extracted lymph nodes can be obtained [5, 6]. However, it is not well understood if the difference in the prognosis of patients with more than 12 extracted lymph nodes and the prognosis of those with less than 12 extracted lymph nodes comes from a staging error possibly caused by statistically insufficient extracted nodes or comes from a better surgical technique explaining both the higher number of lymph nodes and the better outcome [7].

In terms of lymph node scores by far the most widely accepted at this time is the lymph node ratio (LNR), which is the ratio between the number of invaded lymph nodes and the total number of resected lymph nodes [8]. The LNR has proved its worth being at the moment an improved classification system in terms of lymph node involvement in stage III colorectal cancer, when it comes to predicting overall patient survival. Its only disadvantage is that it does not bring more information compared to the pN classification when the number of invaded lymph nodes is 0 [9, 10].

Another lymph node ratio that is recently being studied is the *log odds* ratio (LODDS). It is being successfully

employed in the study of breast cancer and gastric cancer where it seems to be able to classify patients in homogenous groups regardless of the total number of harvested nodes [10–12]. In this context, the aim of our study was to prove that the *log odds* ratio can be used as a prognostic tool in colorectal cancer relapse, both to make a prognosis on the aggressiveness of the tumor in terms of how fast a local or distant relapse occurs and also to evaluate if a distant recurrence is more likely than a local one. These correlations sustain the originality of our work because to our knowledge, at the time this article was written, this was the only study using LODDS and not LNR to assess the relapse prognosis and not the overall prognosis in colorectal adenocarcinomas.

## Materials and Methods

The present study was designed as a retrospective study. We selected a total number of 25 patients that presented over a period of two years, from September 2009 to September 2011, to the First Surgical Clinic of the "St. Spiridon" University Clinical Hospital, Iassy, Romania. The patients included were presenting for local or distant relapse after having undergone a curative procedure for colonic or rectal adenocarcinomas. Recurrence was assessed either by radiological imaging techniques or by histological confirmation on a biopsy sample or an excised tumor specimen.

The Ethical Committee of the "Grigore T. Popa" University for Medicine and Pharmacy, Iassy, approved the study and a signed informed consent form was obtained from each patient.

During this period a total of 91 patients with metastases or local recurrences after having been operated on for colorectal cancer presented to our clinic, but 66 patients (72.52%) were excluded because of one of the following selection criteria:

- Presence of a macroscopically visible metastasis at the time of the first surgery;
- Neoadjuvant radio- and chemotherapy – because of the possible down staging effect of the neoadjuvant therapy on lymph node status;
- Previous neoplastic disease – other than the colorectal cancer that is suspected to be responsible for the recurrence;
- Patients who underwent the first procedure in another clinic – because of the fact that complete medical records were inaccessible;
- Patients with incomplete pathology records – where either or both the number of invaded lymph nodes and the number of harvested lymph nodes was not clearly stated – 14 patients (15.38%).

We inspected medical records searching for sex, age of the patient at the time of the first surgical procedure for colorectal cancer, family history (focusing mainly on neoplastic disease), topography of the tumor, type of recurrence – local *versus* distant. The disease free interval was then calculated and used as an indicator of the aggressiveness of the tumor.

Pathology records consisted of TNM staging, dimensions of the tumor, distance between the tumor and the margin of resection, the presence of tumor perforation and/or a peritumoral abscess, as well as the degree in which the lumen was obstructed. We also analyzed the microscopic description of the tumor – degree of infiltration of the serosa, presence of perineural invasion and tumor emboli, abundance of necrosis (Figure 1), presence of a mucinous component, degree of tumor differentiation (well, moderately and poorly differentiated), the number of harvested lymph nodes and the number of invaded lymph nodes. Images were acquired using a TissueGnostics system connected to a Zeiss Observer Z1 microscope (TissueGnostics GmbH, Vienna, Austria).

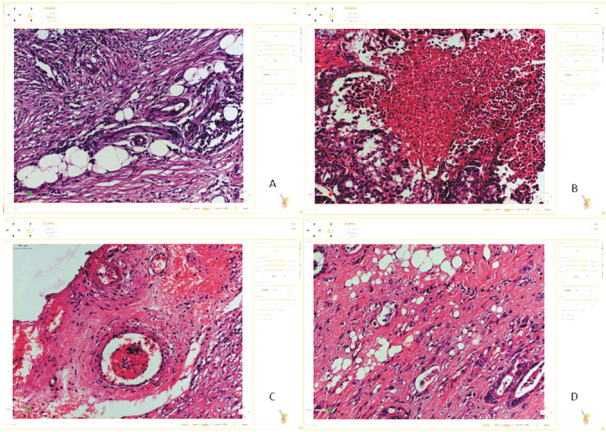


**Figure 1** – ***Histology findings in relapsed colorectal carcinoma patients (HE staining, ×200): (A) Perineural invasion; (B) Intratumoral necrosis; (C) Tumor emboli in blood vessels; (D) Tumor emboli in lymph vessels.***

The number of harvested lymph nodes and the number of invaded lymph nodes were used either as continuous variables and to calculate the lymph node ratio (LNR), and the *log odds* ratio (LODDS). The lymph node ratio was calculated according to the following equation: LNR = invaded nodes/harvested nodes [13, 14], while for calculating the *log odds* ratio the following formula was employed: LODDS = log [(invaded nodes + 0.5)/(harvested nodes-invaded nodes + 0.5)] [14]. Both lymph node ratio and *log odds* ratio were used as continuous variables and as categorical variables depending on the type of statistical analysis performed. In order to be used also as categorical variables we defined LNR and LODDS groups based on quartiles.

Statistical analysis was carried out using SPSS for Windows, version 17. Spearman's rank correlation test was used to evaluate both correlations between different variables and the disease free interval (considered as a continuous variable) and correlations between the same variables and the type of relapse. Kaplan–Meier survival analysis for disease-free survival was also performed. Survival curves were computed for the LODDS categories, LNR categories and pN categories, and the *log-rank* test was used to search for statistically significant differences between the survival curves.

## Results

From a total of 25 patients included in our study 44% ($n$=11) presented for metastasis and 56% ($n$=14) were admitted after having developed a loco-regional relapse. The mean disease free interval was 19.73±14.81 months. Table 1 shows the descriptive statistics of the

study group and also the correlations between the type of relapse, age, gender and time to relapse. As it can be seen there were no statistically significant correlations between these variables and the rapidity of the recurrence.

**Table 1 – *Descriptive statistics of the study group and the correlations of clinical variables to the time to relapse***

| | | No. of cases | Percent out of total no. of cases | Average | Time to relapse | |
|---|---|---|---|---|---|---|
| | | | | | *Rho* | *P-value* |
| *Type of relapse* | Metastases | 11 | 44% | – | 0.168 | 0.423 |
| | Local relapse | 14 | 56% | | | |
| *Gender* | Male | 11 | 44% | – | 0.145 | 0.198 |
| | Female | 14 | 56% | | | |
| *Onset age* | <66 years | 12 | 48% | 62.28± 14.45 | -0.266 | 0.488 |
| | ≥66 years | 13 | 52% | | | |

From a point of view of the macroscopic morphology of the tumor, there were seven patients with a tumor less than 50 mm in diameter and 18 patients with tumors larger than 50 mm in diameter. In 14 (56%) of the cases, the tumor was protruding in the colonic lumen. For 16% (*n*=4) of the patients, we found that the tumor was perforated and in 60% (*n*=15) of the cases, we found the tumor to be circumferential. Macroscopic infiltration of the serosa was found in 80% (*n*=20) of the cases.

Microscopically, inflammation was present in 48% (*n*=12) of the cases. In most of these cases (*n*=10), an acute inflammatory infiltrate was detected. From a tumor differentiation point of view, 20% (*n*=5) of the cases were well-differentiated tumors, 68% (*n*=17) were moderately differentiated and 12% (*n*=3) were poorly differentiated.

Because of the possible negative effect on patient outcome, we also investigated the presence of a mucinous component, the perineural invasion, the presence of vascular tumor emboli and the abundance of necrotic tissue. We found that in 32% (*n*=8) of the cases there was a mucinous component present. Perineural invasion was only present in 20% (*n*=5) of the cases, while intravascular tumor emboli could be found in 36% (*n*=9) of the cases. Abundant necrosis was found in 60% (*n*=15) of the 25 cases that composed the study group.

We also assessed the correlations between these morphological characteristics of the tumor and the time to relapse and found that only the protrusive character of the tumor positively correlated at a statistically significant level with the recurrence-free time. Table 2 shows the results of the Spearman's rank correlation test between morphological characteristics and time to recurrence.

**Table 2 – *Table showing the results of the Spearman's rank correlation test between morphological characteristics of the primary tumor and the time to recurrence***

| | Relapse free interval | |
|---|---|---|
| | *Rho* | *P-value* |
| *Size of the tumor* | -0.197 | 0.346 |
| *Tumor protruding in the lumen* | 0.514 | 0.009 |
| *Perforated tumor* | 0.136 | 0.516 |
| *Stenotic tumor* | 0.055 | 0.792 |
| *Resection margin (continuous variable)* | -0.111 | 0.599 |
| *Infiltrated serosa* | 0.069 | 0.742 |
| *Acute inflammation* | 0.123 | 0.558 |
| *Chronic inflammation* | -0.085 | 0.685 |
| *Peritumoral abscess* | -0.104 | 0.621 |
| *Degree of tumor differentiation* | 0.309 | 0.133 |
| *Mucinous component* | 0.166 | 0.426 |
| *Perineural invasion* | 0.305 | 0.138 |
| *Intravascular tumor emboli* | 0.035 | 0.869 |
| *Necrosis* | 0.238 | 0.252 |
| *pTumor* | 0.022 | 0.924 |

On a more in depth analysis of the lymph node status, we found that the number of invaded lymph nodes varied between 0 and 10 with a mean of 2.72, while the number of harvested lymph nodes ranged from 3 to 49 with an average of 15±10.13. Out of the 25 patients selected, only 52% (*n*=13) had more than 12 harvested lymph nodes.

The descriptive statistics for the lymph node ratios showed that the LNR had a minimum of 0 and a maximum of 0.9 with an average of 0.24±0.3, while LODDS ranged between -1.8 and 0.9 with a mean of -0.65±0.74 when assessed for all the patients and between -1.77 and -0.28 with an average value of -1.02±0.46 when it was calculated only for the patients with at least 12 harvested lymph nodes (*n*=13).

Results of Spearman's rank correlation between the number of invaded lymph nodes, the number of harvested lymph nodes, LNR, LODDS and the pN classification can be found in Table 3.

**Table 3 – *Table showing the results of the Spearman's rank correlation test between the number of invaded lymph nodes, the number of harvested lymph nodes, LNR, LODDS and the pN classification***

| | | No. of invaded lymph nodes | No. of harvested lymph nodes | LNR | LODDS | LODDS12 | LNR quartiles | LODDS quartiles |
|---|---|---|---|---|---|---|---|---|
| *LNR* | Rho | 0.945 | -0.247 | – | 0.938 | 0.990 | 0.949 | 0.899 |
| | *P*-value | <0.001 | 0.235 | – | <0.001 | <0.001 | <0.001 | <0.001 |
| *LODDS* | Rho | 0.872 | -0.498 | 0.938 | – | – | 0.898 | 0.961 |
| | *P*-value | <0.001 | 0.011 | <0.001 | – | – | <0.001 | <0.001 |
| *LODDS for patients with ≥12 harvested lymph nodes (LODDS12)* | Rho | 0.951 | -0.517 | 0.990 | – | – | 0.847 | 0.917 |
| | *P*-value | <0.001 | 0.07 | <0.001 | – | – | <0.001 | <0.001 |
| *LNR categories defined by quartiles (LNR quartiles)* | Rho | 0.848 | -0.315 | 0.949 | 0.898 | 0.847 | – | 0.892 |
| | *P*-value | <0.001 | 0.126 | <0.001 | <0.001 | <0.001 | – | <0.001 |
| *Log odds ratio categories defined by quartiles (LODDS quartiles)* | Rho | 0.785 | -0.579 | 0.899 | 0.961 | 0.917 | 0.892 | – |
| | *P*-value | <0.001 | 0.002 | <0.001 | <0.001 | <0.001 | <0.001 | – |

Furthermore, we performed Kaplan–Meier survival analysis for a 3 year disease-free survival (Figure 2) and the *log-rank* test showed that there were statistically significant differences in survival between different patient groups, only when the groups were defined according to the pN classification ($p$=0.021) or the LODDS ($p$=0.014) and not when the groups were defined according to the LNR.

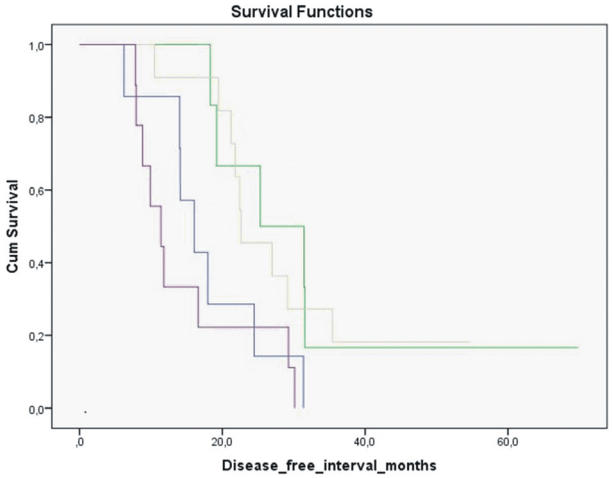


**Figure 2 –** ***Kaplan–Meier survival curves for groups of patients defined according to the LODDS ratio.***

We also analyzed correlations between these lymph node based scores and the type of cancer relapse. The results of this analysis are shown below in Table 4.

**Table 4 –** ***Table showing correlations between the type of relapse and various lymph node based scores***

| | Type of relapse | |
|---|---|---|
| | ***Rho*** | ***P-value*** |
| *No. of invaded lymph nodes* | -0.490 | 0.013 |
| *No. of harvested lymph nodes* | 0.157 | 0.454 |
| *Lymph node ratio* | -0.526 | 0.007 |
| *Lymph node ratio categories* | -0.561 | 0.004 |
| *Log odds ratio* | -0.464 | 0.019 |
| *Log odds ratio categories* | -0.503 | 0.010 |
| *pN categories* | -0.05 | 0.83 |

## Discussion

The TNM staging system which is currently used for defining the prognosis of colorectal cancer patients is being updated and completed by various other scores or supplementary parameters because of the emergence of different novel therapies such as monoclonal antibodies which are only suitable for a subset of patients [15, 16], or because of the new studies that show an inhomogeneous outcome for patients within the same TNM staging group [8, 17–19]. Many authors have decided to explore clinicopathological factors of prognostic such as necrosis and local and systemic inflammation [2]. Some authors have included the POSSUM score along with tumor based scores and inflammation based scores [3, 20].

A great number of studies have focused their attention towards molecular predictors such as KRAS or BRAF mutations [21, 22], while some have assessed the information that other markers such as Ki-67, p53 and other such molecular markers bring in addition to the classical TNM and differentiation staging [23, 24] and have even designed a comparative study of the expression of these markers in colonic and rectal adenocarcinomas [25].

The role that the tumor microenvironment plays in determining the outcome of the tumor is also being intensively discussed in the literature, many authors trying to study in greater detail the role that each type of inflammatory infiltrate plays in determining the outcome of the patient [26, 27].

In our study, we set upon trying to correlate different lymph node based scoring systems with either disease-free survival or the type of relapse in an effort to see if the pN classification can be completed or replaced. The reason for this is the fact that at this moment the pN score can only be assessed if the number of harvested lymph nodes is at least 12 [1] and in a lot of cases the total number of lymph nodes resected is under this limit, therefore not being assessed and therefore all information contained in the number of invaded lymph nodes being lost.

By comparing different lymph node ratios, we found out that only the LODDS significantly correlates to both the number of invaded lymph node and the total number of harvested lymph nodes, regardless of the number of harvested lymph nodes, while the LNR only correlated with the number of invaded lymph nodes at a statistically significant level.

In a similar study, in which data from 179 patients who had fewer than 12 resected lymph nodes was collected, the authors found that the lymph node ratio along with preoperative carcinoembryonic antigen levels could be better predictors of disease-free survival and was considered to be an important prognostic factor for such patients [13]. Unfortunately, the study quoted above did not investigate the LODDS along with the LNR. In our study, LNR only correlated to the number of invaded lymph nodes.

Thus, when compared to the LODDS it could be said that the LNR only contains information about the number of invaded lymph nodes and not the total number of harvested lymph nodes, which in our study correlated well with both the total number of resected lymph nodes and the number of invaded lymph nodes as well as the LNR and the pN categories. This would lead to the conclusion that LODDS retains at least as much information about lymph node involvement as the pN staging but can be calculated even in the cases where the total number of resected lymph nodes is less than 12. This is in agreement with Persiani *et al.* who proved on a group of 258 patients that the predictive power of LODDS is much less likely to be influenced by total number of resected lymph nodes, when assessing the overall outcome of the patient [14].

Another novelty of our study is that we also tried to see if one of these lymph node ratios can be used to predict the type of relapse that the patient was likely to have. We found that both a high number of invaded lymph nodes, a high LNR ratio and a high LODDS ratio correlated with the appearance of a metastasis at statistically significant levels ($p$=0.013 for the number of invaded lymph nodes, $p$=0.007 for LNR and $p$=0.004 for LODDS). No correlation was found in our study

between the pN and the type of relapse. From a patho-physiological point of view, this is an expected outcome because lymph node involvement means a higher chance of dissemination through the lymphatic system, which in turn means a higher likelihood of developing a metastasis.

Finally, we performed a Kaplan–Meier survival analysis trying to see if the risk of developing a relapse could be stratified according to LODDS or LNR categories. We found out that both pN and LODDS can be used to stratify patients depending on disease-free survival but not LNR. The *log-rank* test was used to attest the statistical significance of the differences between the survival curves and for both pN and LODDS the *p*-value obtained with the *log-rank* test was under 0.05. Our results would seem to be in contrast to a study conducted by Kim *et al.* that found LNR to be a possible prognostic factor for disease recurrence in rectal cancer patients treated with post-operatory chemotherapy [28]. This possible difference could possibly be the result of the small number of patients in our study, a variable that we are trying to exclude by increasing the total number of patients in a future study.

## Conclusions

Our study found that the LODDS ratio contains more information about lymph node involvement than other lymph node ratios even if the total number of resected lymph nodes is fewer than 12. Furthermore, we concluded that the LODDS ratio can be used to stratify colorectal cancer patients in terms of relapse-free survival and to our knowledge, it is the first time that the LODDS and not the LNR is used to assess relapse prognosis. The LODDS ratio can also be used to select patients at higher risk of developing a metastasis *versus* a local relapse. It is our belief that LODDS could turn to be a powerful predictor tool and this is in our opinion due the fact that it brings the most information about the number of invaded lymph nodes and resected lymph nodes and is not influenced by the fact that a total of less than 12 lymph nodes are resected but larger studies are necessary to prove our hypothesis and to make LODDS part of the daily clinical decision-making process.

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