ORIGINAL PAPER

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

# The role of clinical and pathological assessment in choosing the best therapeutic management to improve survival in rectal cancer

PAUL CRISTIAN RUSSU[1)], CĂLIN MOLNAR[1)], SIMONA GURZU[2)], IOAN JUNG[2)], TOADER SEPTIMIU VOIDĂZAN[3)], CONSTANTIN COPOTOIU[1)]

[1)] *1st Department of Surgery, Emergency County Hospital, Tîrgu Mureş, Romania; University of Medicine and Pharmacy of Tîrgu Mureş, Romania*

[2)] *Department of Pathology, University of Medicine and Pharmacy of Tîrgu Mureş, Romania*

[3)] *Department of Epidemiology, University of Medicine and Pharmacy of Tîrgu Mureş, Romania*

## Abstract

The main target in rectal cancer management is an individualized therapeutic strategy, based on tumor and patient characteristics. The assessment of clinical and pathological factors is important because they represent powerful predictors of the postoperative outcome and have to be considered in the decision making regarding the appropriate surgical technique. The aim of the study was to analyze how the tumor clinical and pathological features correlate with the chosen type of surgical intervention in influencing survival of rectal cancer patients. We ran a retrospective study on 289 patients (*N*=289) surgically treated for rectal cancer. We analyzed the individual influence of the studied parameter on survival rate in multivariate analysis and we also grouped them in associations of parameter variations and performed a survival analysis for prognostic univariate analysis. For patients with vascular and lymphatic invasion and without perineural invasion, choosing a sphincter function preserving technique brought a better long-term outcome. The TNM stages showed the strongest statistically significant effect upon survival. Patients in $T_3$ or $T_4$ stage benefited best from a performed sphincter saving technique and the positive effect was even higher for those in $N_1$ stage. Assessment of pathological parameters, in association with the type of the surgical procedure, has a strong predictive value upon survival. Sphincter function preserving techniques are followed by good long-term outcome. Accurate preoperative staging can help in choosing the best individualized therapeutic management improving the life expectancy of patients with rectal cancer.

***Keywords***: rectal cancer, sphincter function preserving technique, survival, pathological parameters.

## Introduction

In terms of incidence, in 2013, the colorectal cancer was ranked third of all cancers worldwide. It is also considered to be the fourth leading cause of cancer mortality in the world [1].

From all colorectal cancers, about one-third is localized at the rectal level. The rectal cancers share a worse prognosis cause of the high rate of local recurrence and the higher presence of the metastatic disease at the time of diagnosis [2].

The modern management of rectal cancer is represented by a multidisciplinary and multimodal combined treatment [2–4]. Among this, surgery stands as the most important step that offers the chance of a curative treatment for patients with rectal tumors [2, 4, 5].

If being oncological radical represents the main principle in oncological rectal surgery, the second objective is anal sphincter functional preservation as a factor that increases the patient life quality [5].

Technological progress along with the development of oncological adjuvant and neoadjuvant therapies determined, in the last decades, important changes in the surgical management of rectal cancer. Therefore, we can observe a major decrease in abdominoperineal rectal resection rate with the consecutive increasing in number of sphincter preserving procedures [6, 7].

Nowadays, the main target in rectal cancer management is to achieve an individualized therapeutic strategy based on tumor and patient characteristics [2].

A great deal of importance is now given to the assessment of prognostic factors, patient related, but also involving features of the resection specimen as: histological grade, intra- and extra-mural tumor invasion (T stage), lymph node involvement (N stage), presence of distant metastases (M stage), vascular and perineural invasion, tumor borders. These pathological aspects of the tumor represent powerful predictors of the postoperative outcome and they have to be taken into consideration in the best decision making regarding the opportunity of pre- or post-operative adjuvant therapy but also for choosing the appropriate surgical technique [2, 8].

### Aim

The aim of the study was to analyze how the tumor clinical and pathological features correlate with the chosen type of surgical intervention in influencing the long time survival of patients treated for rectal cancer. We also tried to identify which may represent the most viable parameters that can predict, in combination with a certain surgical technique, the better long-term outcome.

## Patients and Methods

We ran an observational, retrospective study on a group of 289 patients ($N$=289) hospitalized and surgically treated for rectal cancer in the 1st Department of Surgery of the Emergency County Hospital of Tîrgu Mureş, Romania, from January 2005 to May 2015. These patients were selected from a pool of 479 consecutive cases of rectal cancer operated in this service.

### Criteria for inclusion

In order to be included in the study, the patients had to undergo a rectal resection followed by a primary anastomosis or a permanent colostomy, for pathologically confirmed rectal cancer, and could be followed in respect of clinical, pathological and survival data.

Were excluded from the study patients who did not undergo a rectal resection, but other palliative or diagnostic interventions, to whom the rectal resection was made for a benign disease, patients with no available pathological data, with no available or uncertain data on survival. Were also excluded the cases of postoperative deaths, which included patients who died during the first 30 days after surgery.

### Clinical and pathological assessment

Patients were divided in two groups, according to the type of operation they underwent:

▪ Group I – 147 patients ($n_1$=147) with a sphincter function preserving technique (SFPT). In this category were included the anterior rectosigmoidian resections with a hand sewn or a stapled colorectal anastomosis (manual or mechanical Dixon procedure), low rectal resection with sphincter preservation and coloanal anastomosis made peranal or transanal and intersphincteric resections with coloanal anastomosis (Schiessel procedure).

▪ Group II – 142 patients ($n_2$=142) with a non-conservative technique (NCT), which included abdominoperineal rectal resection (Miles operation) and Hartmann I procedure with a permanent colostomy.

The main objective of the study was to analyze how the most important tumor clinical and pathological features (histological grade, TNM staging, vascular, lymphatic and perineural invasion and surgical resection margins) correlate with the chosen type of surgical intervention in influencing the long time survival of patients who underwent surgical treatment for rectal cancer.

As an additional objective, we tried to identify which are the parameters, normally evaluated in any pathological examination that can predict the best, in combination with a certain surgical technique, a better long-term outcome.

We analyzed cases based on clinical and imaging examinations, operative protocols and pathological results collected from the written and electronic database of the 1st Department of Surgery and the Department of Pathology of the Emergency County Hospital of Tîrgu Mureş.

The survival data were gathered from the follow-up database of the 1st Department of Surgery, of the Department of Oncology and also with the help from the Registry of Civil Status of Mureş County.

The study was conducted in accordance with the Declaration of Helsinki (1964) and had been approved by the Emergency County Hospital of Tîrgu Mureş Ethics Committee. All the patients were included in this study under a written informed consent. They met all conditions of EU professional ethics, patients' identity being secret.

### Statistical assessment

Data were processed in Microsoft Excel, and statistical analysis was performed using SPSS software (20th version), designed for biomedical research statistics. We used statistical methods such as descriptive and analytic methods. We used a Student's $t$-test to evaluate the differences between the means of continuous variables in two groups [expressed by mean ± standard deviation (SD)] and a $\chi^2$-test for categorical variables [expressed by No. (%)].

For each group of associated clinical and pathological parameters, we analyzed the individual influence of the studied parameter on survival rate in multivariate analysis and we also grouped them in associations of parameter variations and performed a survival analysis for prognostic univariate analysis.

The analysis for survival was done using the Kaplan–Meier method and the *log*-rank test was used for prognostic univariate analysis. To identify the individual predictive role in the survival multivariate analysis we performed also Cox type regressions.

All the tests we have performed to materiality $p$=0.05 and statistical significance was considered for $p$ values less than the threshold value of significance.

## Results

The patients in Group I and II had a homogenous distribution in terms of gender and age. The gender ratio was of 1.45:1 in favor of male gender in the entire group of patients, with no statistically significant difference between the two groups (Table 1).

**Table 1 –** ***Distribution of clinical and pathological features and of survival rate in the two groups***

| Variables | | Group I (SFPT) *n*=147 | Group II (NCT) *n*=142 | *P*-value |
|---|---|---|---|---|
| *Gender* | Males | 82 | 89 | 0.28* |
| | Females | 65 | 53 | |
| *Age (years ± SD)* | Mean | 62.67±11.23 | 62.65±10.54 | 0.98** |
| *Radiochemotherapy* | Yes/No | 31/116 | 77/65 | 0.0001*** |
| *Histological grading* | Well differentiated | 18 | 18 | |
| | Moderately differentiated | 103 | 101 | 0.94*** |
| | Poorly differentiated | 26 | 23 | |

| Variables | | Group I (SFPT) *n*=147 | Group II (NCT) *n*=142 | *P*-value |
|---|---|---|---|---|
| *Vascular invasion* | Yes/No | 30/117 | 56/86 | 0.005* |
| *Lymphatic invasion* | Yes/No | 65/82 | 66/76 | 0.72* |
| *Perineural invasion* | Yes/No | 47/100 | 61/81 | 0.06* |
| *Surgical resection margins* | Free/Infiltrated | 139/8 | 130/12 | 0.35* |
| *T stage* | $T_1/T_2$ | 39 | 36 | |
| | $T_3$ | 97 | 96 | 0.95*** |
| | $T_4$ | 11 | 10 | |
| *N stage* | $N_0$ | 82 | 77 | |
| | $N_1$ | 42 | 39 | 0.83*** |
| | $N_2$ | 23 | 26 | |
| *M stage* | $M_0$ | 134 | 127 | 0.69* |
| | $M_1$ | 13 | 15 | |
| *Survival (% ± SD)* | 6 months | 95.4±1.8% | 92.9±2.2% | |
| | 1 year | 90.8±2.5% | 80.4±3.4% | 0.001**** |
| | 2 years | 81.1±3.5% | 67.6±4% | |
| | 3 years | 73±4% | 58.3±4.3% | |
| | 5 years | 62.9±4.4% | 44.2±4.3% | |

SFPT: Sphincter function preserving technique; NCT: Non-conservative technique; SD: Standard deviation; *Fisher's exact test; **Student's *t*-test; ****Chi*-square test; *****Log*-rank test.

From all clinical and pathological parameters that have been studied, statistically significant differences of distribution between groups presented only the associated preoperative radiochemotherapy, vascular and perineural invasion. For the others, no significant difference was found (Table 1).

The survival analysis showed a statistically significant difference between the two groups ($p$=0.001). For all the studied intervals, the survival rates were better for the patients who underwent a SFPT then for those with a NCT (Table 1; Figure 1).

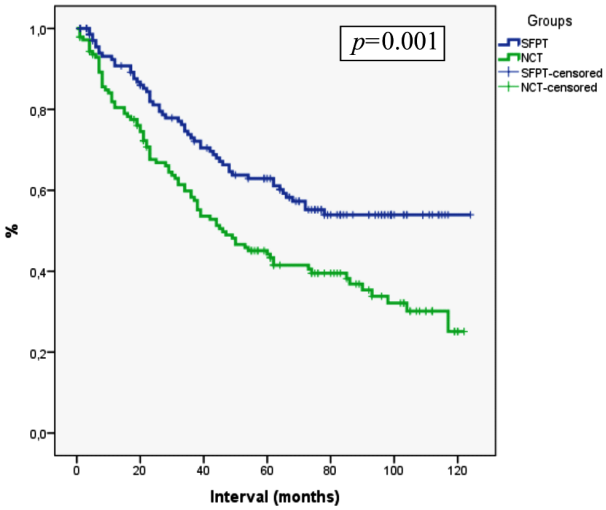


**Figure 1** – ***The Kaplan–Meier surviving curves for Group I (SFPT) and Group II (NCT). SFPT: Sphincter function preserving technique; NCT: Non-conservative technique.***

When we studied, in multivariate analysis, the correlation between groups and histological grade, only the type of surgical intervention had a statistically significant positive influence in increasing the survival rates. The histological grade produced no significant effect upon survival (Table 2). For each histological grade, a better survival rate was present in patients from the group with SFPT than in those with a NCT (Figure 2a).

**Table 2** – ***Predictive role in the survival analysis using Cox type regressions for variables in multivariate analysis***

| Associated parameters | Individual influence of each parameter on survival rate in multivariate analysis | *P*-value (Cox regressions) |
|---|---|---|
| *Groups and histological grade* | Groups | 0.001 |
| | Histological grade | 0.923 |
| *Groups and vascular invasion* | Groups | 0.078 |
| | Vascular invasion | 0.008 |
| *Groups and lymphatic invasion* | Groups | 0.047 |
| | Lymphatic invasion | 0.004 |
| *Groups and perineural invasion* | Groups | 0.090 |
| | Perineural invasion | 0.001 |
| *Groups and surgical resection margins* | Groups | 0.036 |
| | Surgical resection margins | 0.015 |
| *Groups and T staging* | Groups | 0.0001 |
| | T staging | 0.0001 |
| *Groups and N staging* | Groups | 0.0001 |
| | N staging | 0.0001 |
| *Groups and M staging* | Groups | 0.0001 |
| | M staging | 0.0001 |

Both, the presence of vascular invasion and perineural invasion induced a powerful effect upon survival, greater than that of the type of surgery performed, in multivariate

analysis (Table 2). They were associated with a worse long term outcome in both SFPT and NCT patients groups (Figure 2, b and d). The differences were more obvious for vascular invasion in NCT group (Figure 2b).

For the associations between the groups of surgical procedure (SFPT/NCT) and lymphatic invasion respectively, the aspect of the surgical resection margins, both the surgical parameter and the tumor pathological feature presented, in survival multivariate analysis, a statistically significant role. However, for the pathological parameters the statistical influence on survival was more powerful (Table 2). The presence of lymphatic invasion and positive surgical resection margins had a negative effect upon survival for all patients (Figures 2c and 3d). From all the cases with lymphatic invasion, the best survival rate had those to whom a SFPT was done (Figure 2c). The same positive effect of a SFPT, compared to a NCT, was more obvious in patients with free surgical resection margins (Figure 3, c and d).

When correlating the TNM features with the type of surgical procedure, in the multivariate analysis, we found for both type of parameters a strong statistically significant individual influence upon survival ($p$=0.0001) (Table 2).

The Kaplan–Meier survival analysis, made to correlate TNM and surgical features, showed that, in almost all the cases, a higher grade of T, N and M was associated with a worse long time survival for the patients in each type of surgical procedure category. Only for $T_4$ stage in patients with SFPT the survival pattern was not worse than that of the other T stages and for $N_1$ and $N_2$ stage in the NCT group, the long term outcomes were very similar (Figure 3, a–c).

For $T_3$ and $T_4$ stages, patients treated using a SFPT had better survival rates that those with a NCT procedure while the patients in the $T_1/T_2$ group had similar survival patterns, regardless of the surgical type of intervention (Figure 3a).

In $N_0$ and $N_1$ stages, the survival was better for the cases with a SFPT, more obvious in $N_1$ group. For patients with a $N_2$ stage, the long-term outcome was similar for both SFPT and NCT groups (Figure 3b).

Patients with SFPT had a better survival rate in both $M_0$ and $M_1$ stages, with a higher significance in that matter for $M_0$ cases (Figure 3c).

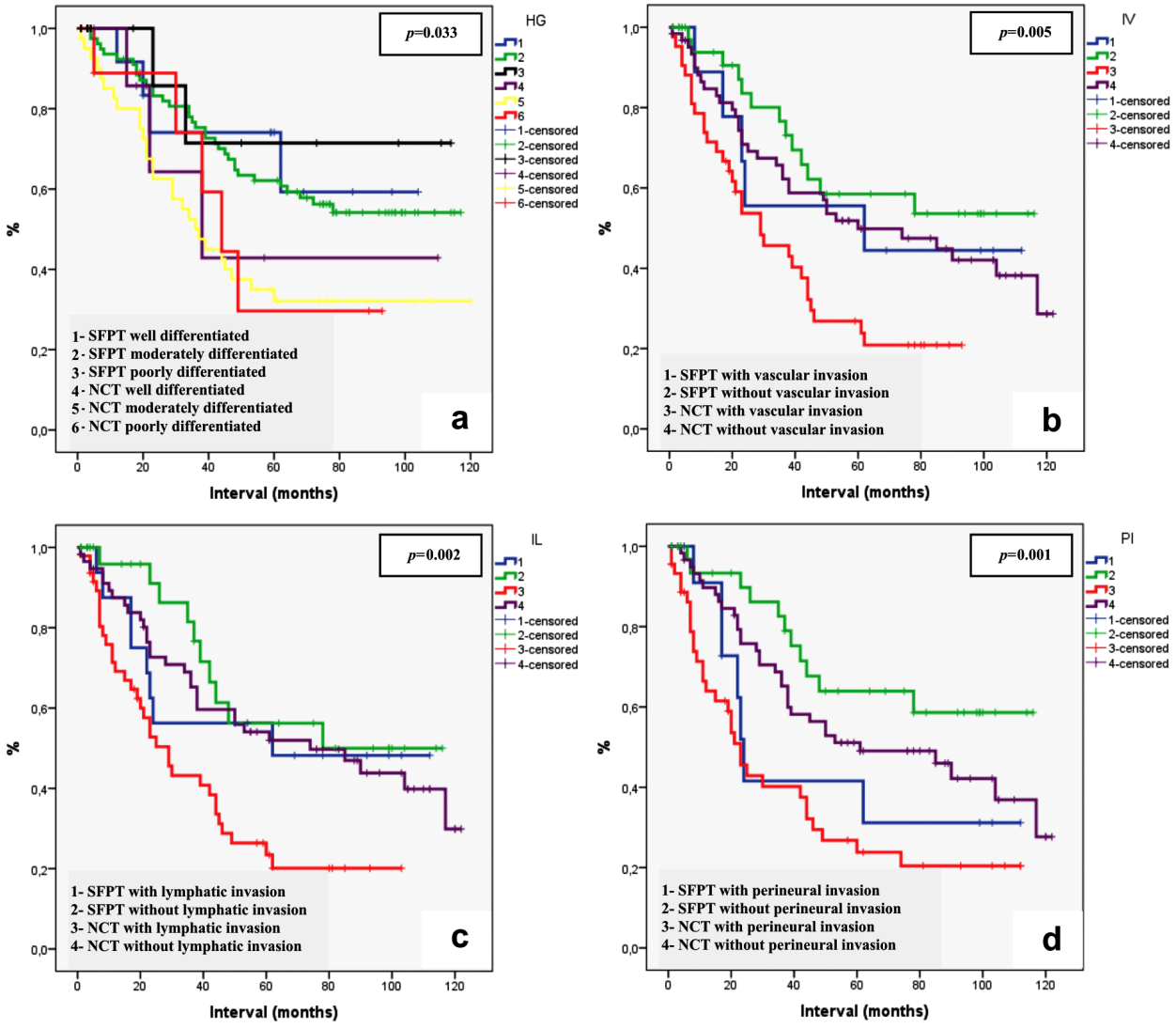


**Figure 2** – ***The Kaplan–Meier surviving curves for: (a) Groups and histological gradient; (b) Groups and vascular invasion; (c) Groups and lymphatic invasion; (d) Groups and perineural invasion. SFPT: Sphincter function preserving technique; NCT: Non-conservative technique.***

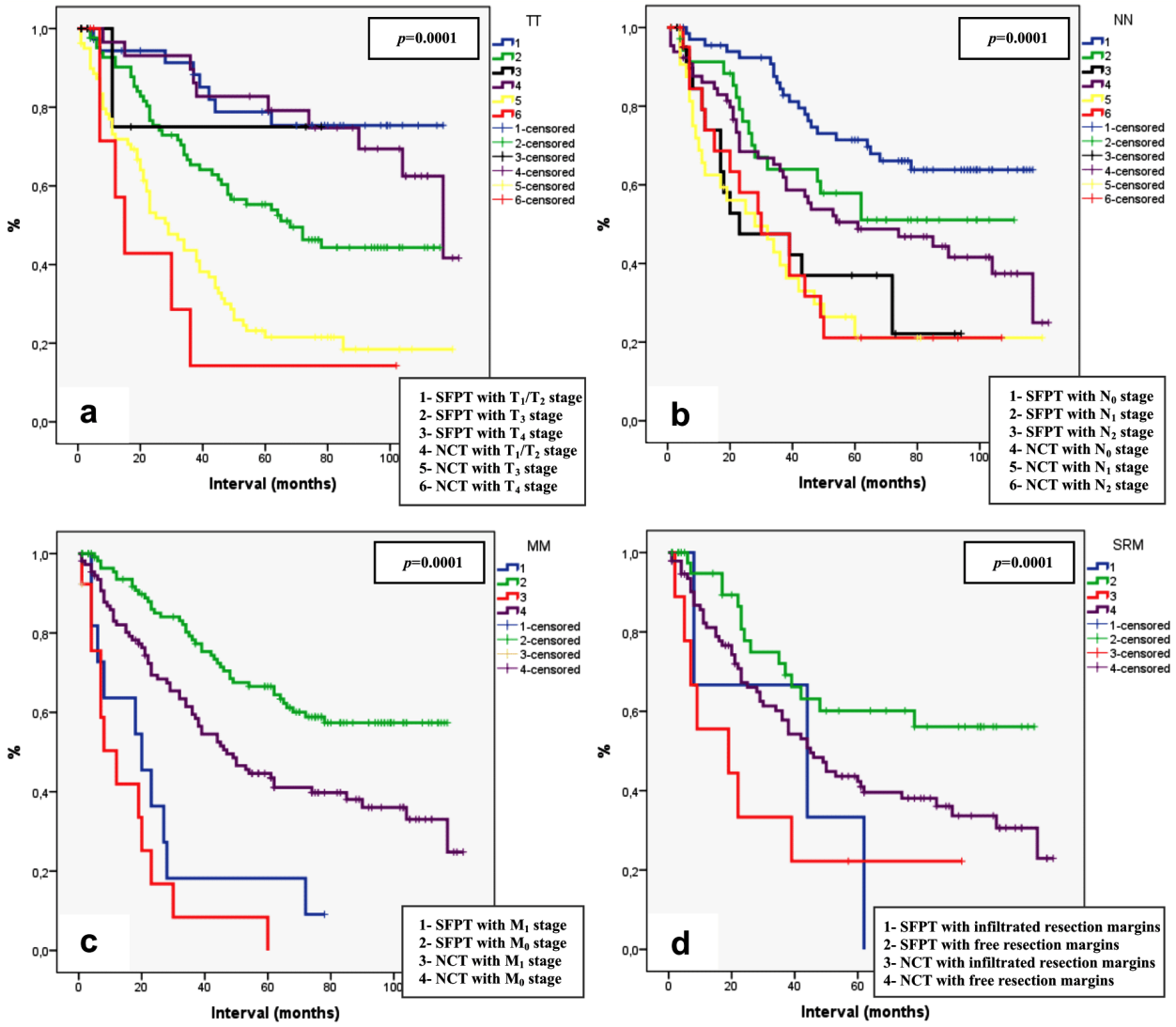


**Figure 3** – ***The Kaplan–Meier surviving curves for: (a) Groups and T staging; (b) Groups and N staging; (c) Groups and M staging; (d) Groups and free surgical resection margins. SFPT: Sphincter function preserving technique; NCT: Non-conservative technique.***

## Discussion

The therapeutic management of rectal cancers has to meet two principles: one related to oncological radicalism, targeting the local control of the disease and long-term survival and one in respect to the functional result, about preserving the anal sphincter function and conserving the sexual and urinary function, aiming to maintain a good quality of life [9].

From the oncological point of view, the abdominoperineal rectal resection still represents an important landmark of radical surgery in rectal cancer. It is considered to be one of the procedures followed by the best outcome and a surgical technique with which any sphincter saving procedure must be compared [10]. Despite the increasing tendency for preserving the sphincter function, the abdominoperineal rectal resection still stands for 30–60% of rectal cancer resections [11].

As a result of the progresses made in the therapeutic approach and the understanding of rectal cancer, the oncological viability of sphincter preservation techniques has been proved and accepted [6, 7].

It is considered now that, in order to achieve the best local control and to decrease the recurrence rate, a total mesorectal excision (TME) has to be performed and a distal resection safety margin of 2 cm is necessary [12–14].

All rectal resections in our study were radical resections. For all of them, a TME was done as a standard technique and a 2 cm distal safety margin was attempted. Therefore, the oncological safety was the main criteria in choosing the surgical technique.

The associated preoperative radiochemotherapy is considered to improve local control but there is no significant evidence for improving the survival rate [15]. Because, in regard of neoadjuvant radiochemotherapy, the patients in our study did not followed a standard protocol, the statistically significant differences between the two groups (SFPT and NCT) had no actual clinical significance. This is why we did not include this clinical-therapeutic feature in our analysis upon survival.

Our study found, with a statistically significant difference ($p$=0.001), for all the studied intervals (six months, one year, two years, three years and five years), that the survival rates were better for the patients who underwent a SFPT then for those with a NCT.

We found, in the literature, only few studies that actually compare the long-term survival after SFPT with those after NCT, in rectal cancer. Some of them support our findings, proving a better long-term outcome for patients who underwent a SFPT when compared to those where a NCT was done [16, 17]. Other, found no significant differences between the two techniques [18].

This proved influence of the chosen surgical technique upon survival, makes from this clinical-therapeutic parameter an important prognostic factor in the management of the rectal cancer disease.

In finding the best individualized therapeutic approach for each patient with rectal cancer, it is considered of paramount importance the assessment of the prognostic factors [2]. In this regard, a primary role has the evaluation of the pathological characteristics of the resected specimen. The pathological stages (TNM stages) and other independent pathological prognostic factors (histological grade, vascular and lymphatic invasion, perineural invasion and tumor resection margin features) are considered very important predictors of the postoperative outcome [2, 8, 19–22]. Some of those tumor depending prognostic factors can be evaluated also in the pre-therapeutic stage using imaging exams. For that, high-resolution pelvic magnetic resonance imaging (MRI) is recognized for its accuracy in preoperative staging and assessment of extramural tumor invasion and allows a decision-making in therapeutic management for patients with rectal cancer [23–25].

In assessing the TNM features, we have evaluated them according to the 7$^{th}$ revision of TNM staging published by the *International Union for Cancer Control* (UICC) and the *American Joint Committee for Cancer* (AJCC) [26]. Subsequently, in order to facilitate the statistical analysis, we associated $T_1$ and $T_2$ stages in a single $T_1/T_2$ category, $N_{1a}$, $N_{1b}$ and $N_{1c}$ in a single $N_1$ group, $N_{2a}$ and $N_{2b}$ in a unique $N_2$ category and $M_{1a}$ and $M_{1b}$ in a single $M_1$ group of distant metastases.

The results of our study confirmed the individual predicting value for all of those pathological parameters, except for histological grading, who showed no significant influence on survival rates. The T, N and M stages showed the strongest statistically significant effect upon the long-term outcome.

Starting from those results, we went further, to see if, by combining a strong clinic and therapeutic prognostic factor, the type of surgical procedure, with each pathological prognostic features, we can identify an even more specific association of parameters, with a stronger predictive power on the postoperative outcome.

What we found was that the patients with vascular and lymphatic invasion, both negative prognostic factors [2] would benefit more from the positive influence upon survival of a SFPT then those without these features. On the other hand, the benefic role on survival of a SFPT will have a higher significance for patients with free surgical margins and for those without perineural invasion.

Regarding the T stage, we proved that for patients in $T_3$ or $T_4$ stage is best to choose a SFPT. They had a significantly better long-term outcome than those with a NCT. In $T_1/T_2$ stage, both SFPT and NCT had similar survival rates. The patients have benefited from SFPT in $N_0$, but the benefic effect was higher for $N_1$ stage. For $N_2$ stage, the type of surgical procedure had little influence upon survival. In both $M_0$ and $M_1$ stages, SFPT represented a better choice.

Finding that the degree of effect, of choosing SFPT over NCT, upon survival was significantly influenced by the TNM stages, we have to recognize the importance of a preoperative adequate staging in choosing the best therapeutic approach for the patients with rectal cancer.

### Drawbacks of our study

Cause of the gaps in the registration of data procedures, there were some discontinuity in the series of data, so, the patients with incomplete or uncertain data were excluded from the analysis. Therefore, the number of patients included in the study was smaller than the initial consecutive case series.

## Conclusions

If the oncological principles are respected, sphincter function preserving techniques, used for rectal cancer, are followed not only by a better functional outcome but also by a good prognosis, in terms of survival. Assessment of pathological parameters with prognostic role may guide the therapeutic approach. TNM staging in association with the type of the surgical procedure has a strong predictive value upon long-term survival. The use of MRI for accurate preoperative staging has to become a standard protocol for patients with rectal cancer. This can help in choosing the best individualized therapeutic management improving the life expectancy of patients with this disease.

### Conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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***Corresponding author***
Călin Molnar, Associate Professor, MD, PhD, 1st Department of Surgery, Emergency County Hospital, Tîrgu Mureş, University of Medicine and Pharmacy of Tîrgu Mureş, 38 Gheorghe Marinescu Street, 540139 Tîrgu Mureş, Romania; Phone +40265–215 551, Fax +40265–210 407, e-mail: molnar.calin@yahoo.com

*Received: June 5, 2016*

*Accepted: December 30, 2016*