

UNIVERSITATEA DE MEDICINA SI FARMACIE

„CAROL DAVILA”, BUCURESTI

DOCTORAL SCHOOL

FACULTY OF GENERAL MEDICINE

LOCAL RECURRENCE OF RECTAL CANCER AFTER SURGERY

DOCTORAL THESIS SUMMARY

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2022

INTRODUCTION AND MOTIVATION OF THE STUDY

Recurrence of the operated rectal cancer is defined as the reappearance of the dormant tumoral cells and it is facilitated by several trigger predictive factors which determine the metastatic process. The risk factors for recurrence are described in this study with the purpose to identify fast the local recurrence after surgery of rectal cancer and to specify with certainty the extent of the disease.

The recurrence can be controlled or progressive. A controlled recurrence means that it is stabile; the progression means that it continues to evolve or it metastasis in other organs.

The local recurrence appears in 30-50% of the patients, considering both the local-regional recurrence and distance metastasis. Total excision of the mesorectum (TEM) along with neoadjuvant radiotherapy can reduce drastically the local recurrence with a 6% rate [2]. Anastomotic recurrence is found in 5-15% of the patients being considered an extraluminal recurrence, especially in the presacral area and frequently around the anastomosis [3,4].

Salvage surgery in patients with pelvic recurrence is done for only 30-40% of the patients, with a morbidity rate of 44% and mortality rate of 6 % [5,6,7,8].

The importance of following up of the patients and of the implemented programs for recurrence screening can minimize the appearance or it or it can evaluate it in order to elaborate an early treatment [9].

Early detection of the recurrence, while the patient is asymptomatic, increase the probability of a successful treatment [9].

This study tries to clearly define the local recurrence terminology by identifying the patients which were operated for rectal tumours in various stages, with associated risk factors, with multiple surgical rectal interventions, admitted as emergency or chronic patients, by showing and searching a specific control plan to diagnose as soon as possible the local recurrence, improving the future practice with standardized new protocols for rectal surgery.

The local recurrence of rectal cancer represents a “challenge” for the surgeon, who discovers it after approximately 6 months, one year or two years, during post-surgery follow-up, the patient being under oncological treatment or not. With an insidious evolution clinically, diagnosed only imagistic and/or by tumoral markers (elevated CEA), the local recurrence of rectal cancer requires an algorithm for diagnose and multimodal treatment, which I managed to provide in this study.

This study is a retrospective study covering a period of approximately 14 years (2000-2014) and it analyses retrospectively all cases which were surgically treated, which developed local recurrence in Surgery Ward II of the University Emergency Hospital Bucharest (SUUB).

I have assessed 303 patients with operated rectal tumours, sixty-four of them having local tumoral recurrence. To fulfil the purpose of this study I have performed complex research of all patients operated for rectal tumours who have developed local tumoral recurrence.

I am thankful to all my colleagues from SUUB, Surgical Ward II, to Ward Chief Prof. Dr. Neagu Stefan who trustfully facilitated the surgical techniques and provided access to the clinics archives, including all materials needed to prepared this unique study and the published articles in specialty magazines.

This study purpose is to highlight the risk factors of local recurrence of rectal tumours surgically treated : patients age, obesity, advanced tumour stage, undefined cells neoplasms, complicated rectal cancer (occlusion, perforation), surgical manoeuvres and techniques for tumour manipulation, mechanical or manual anastomosis dehiscence, differentiation grade of the tumour and tumoral invasion.

The objectives of the retrospective research were thorough, I have tried to search in the 303 patients with operated rectal tumours how many developed local recurrence and what was special about them.

I have found 64 patients with local recurrence, 35 men and 29 women aged above 60 years.

My main objectives were: clinical and paraclinical data analysis of the operated patients with rectal tumours which developed local recurrence, identifying and categorizing the risk factors with an impact on local recurrence, pointing out the importance if imagistic investigations in local recurrence diagnosis, quantification and evaluation of CEA tumoral marker, identifying the resection surgical techniques, risk patient's monitoring by extending the periodic follow-ups from two to three years and every 3 months visits for the first 2 years, pain management and survival rate at 3 and 5 years.

The inclusion criteria were: all operated patients for rectal tumours which developed local recurrence, all operated patients which had Miles rectal amputation, Hartman operation, tumoral rectal resection with mechanical or manual anastomosis, patients with predictive risk factors for local recurrence, patients who benefited from rectal tumours surgery and upon regular follow-up had vicinity symptomatology.

Exclusion criteria were: patients without local recurrence, patients with mechanical and manual anastomosis with inconclusive biopsy results after several colonoscopies, patients which did not attended the periodic follow-ups and presents uncertainties in diagnostic evaluation.

The observed parameters were: age, sex, comorbidities (HBP, diabetes, tumour localization, anatomopathological type, the number of the lymph nodules, the time interval between the primary tumour -recurrence, the surgery method, the oncological treatment, immunotherapy with Cantastim, the hospitalization period, pain, 3 and 5 years survival).

The research method imposed the subject's selection according to the inclusion criteria, the analysis of all surgical interventions, of the oncological treatment done by the patients with rectal tumours pre and post-surgery, patient's periodical follow-up, imagistic, clinical and paraclinical data, urology and gynaecology follow-ups, predictive risk factors for local recurrence, immunotherapy with Cantastim – research on 90 patients with rectal tumours who had a local recurrence between 2006 and 2009, data analysis and results presentation in published articles in specialty magazines.

The diagnostic algorithm for local recurrence was represented by pain, which was quantified for the majority of patients, characterized by nonspecific irradiation to sacral, pelvic and perineal areas, rectorrhagia, rectal tenesmus, transit disorders (diarrhoea, constipation); subocclusive syndromes at the level of anastomosis by circumferential invasion, urinary symptoms – dysuria, haematuria, fecaluria – in anastomotic fistulas, pyuria. Other clinical manifestations are compressions on the neighbouring organs with invasion in the presacral plexus and disorders that give invasion at the level of the genital organs manifested by metrorrhagia.

The treatment algorithm is represented by biochemical laboratory analysis: full blood count, full biochemistry, coagulation, tumour markers: CEA, CA 19.9, CA125. Imaging investigations included simple abdominal radiography, chest X-ray abdomin-pelvic X-ray, colonoscopy, urinoscopy, cystoscopy, iv urography, C-T computer tomograph thorax, abdomen, and pelvis with contrast substance [9], pelvic MRI and gold standard PET-CT. We have established interdisciplinary urological, gynaecological, oncological, and plastic surgery consultations to perform a strict treatment plan.

The surgical treatment of recurrence is decided by the general condition of the patient, by his option to undergo another surgical intervention with a major impact on the patient's quality of life. The need for the surgical intervention depends on the extent of the recurrence and its compression on the neighbouring organs – pelvis, uterus, ovaries, ureters, and sacrum.

Rectum cancer surgery requires the use of therapeutic protocols, preoperative radiotherapy and postoperative chemotherapy and radiotherapy to minimize local recurrence with the improvement of resection techniques, especially the total excision of the mesorectum. In 1982, Heald RJ described that total excision of the mesorectum can reduce local recurrence below 5% [10.11]. The presence of perineal recurrence after rectum amputation is a factor caused by the faulty technique at the first intervention with insufficient removal of the mesorectum or brutal manipulation of the tumour during resection.

Preoperative and postoperative radiation therapy decreases the risk of local recurrence [11].

The results of the retrospective study on the sixty-four patients with local recurrence after the surgically treated rectum cancer indicate that a decrease in the number of local recurrences is expected in the patients treated surgically and having further periodical check-ups every 3

months over a period of 2-5 years. Depending on the primary staging of the surgically treated rectum tumour, the surgical and oncological therapeutic attitude is taken into account in order to minimize the local recurrence rate and its aggressiveness. It will improve pain control in patients diagnosed and who delayed attending periodical check-up, with pain control and palliative treatment and radiotherapy. Predictive factors in the occurrence of local recurrence have been studied and are to be implemented in the diagnostic and treatment protocols.

To conclude, the risk factors in the occurrence of tumour recurrence cannot be modified but can be kept under control with the help of cooperation and permanent monitoring of patients, for each case.

A predictive factor of the local recurrence after the surgically treated rectum cancer is the depth of the local invasion, so the first staging after rectal resection must be taken into account for the oncological treatment: radiotherapy and chemotherapy, to reduce its occurrence.

Multimodal treatment must be adapted specifically for each patient with the contribution of the oncologist, surgeon, plastic surgeon, urologist, gynaecologist after the difficulty of local recurrence.

Local recurrence remains an aspect of special gravity in the evolution of the surgically treated rectal cancer by the difficulty and complexity of the multimodal therapeutic problems it involves (surgical and adjuvants) with a major impact on the mortality which is already so significant in patients with rectal cancer.

LOCAL RECURRENCE IN SURGICALLY TREATED RECTAL CANCER

The occurrence of local recurrence depends on several factors, which makes its incidence communicated by different authors to be within wide limits, from below 4% to over 50% [99,100]. The most important factor considered in explaining these large differences in statistics is the surgeon's ability to perform the appropriate surgery considered curative [99]. Another "human" factor involved in the high variability of the incidence of local recurrences is the pathologist who analyzes the resection piece.

Local recurrence is largely defined as any recurrence developed in the pelvis after surgery for cancer of the rectum. It can be classified into: anastomotic, peri-anastomotic, at the level of the pelvic or perineal wall. Staging of rectum cancer has been shown to be an important risk factor for local recurrence. The multifactorial analyzes performed by Feil W. and col. and by Mc. Coll and col. have established that the important independent factors for the occurrence of local recurrence and for the survival are the stage of the disease, the local extension, lymphatic involvement and the histological degree [102,103]. Fielding and Col. showed in 1978 that the surgeon, per se " is a potential risk factor in the occurrence of local recurrence , [100,107] finding important variations between different surgeons regarding the incidence of local recurrence.

PREDICTIVE FACTORS FOR THE RECURRENCE OF RECTAL CANCER

Several predictive factors can compete with the occurrence of local recurrence after rectum cancer (RC), they can be grouped into several categories: factors related to the stage of the tumor, clinical factors, histopathological factors, and biological factors (onco-genetic and molecular).

- **CLINICAL FACTORS:**

1. Age is an independent risk factor for RC, with the elderly having low survival rates after curative surgery [118].
2. Sex . Women have a more favorable prognosis than men [119].
3. The presence of complications. Complications such as obstruction and perforation significantly worsen survival in rectal neoplasms, with some studies appreciating them as prognostic factors independent of staging [120].
4. Localization of the primary tumor. Localization of rectal cancer at various levels can be a risk factor for survival and local recurrence [119].
5. Symptomatology. Correlating survival over 5 years with the predominant clinical signs, recent studies find the following data: 37% – anemia, 35% – palpable tumor, 24% – signs of obstruction [119]. It is concluded that anemia, the presence of palpable tumor and the occlusive complication at the time of diagnosis have an increased risk in terms of survival at 5 years and the occurrence of local recurrence [119,121,122].
6. Perioperative blood administration is associated with increased recurrence rate, reducing the disease-free range, and even with decreased survival [122].

- **PRIMARY TUMOUR RELATED FACTORS**

1. Tumor stage. The most crucial factors for the prognosis of survival are represented by the degree of tumor invasion in the wall and the presence of metastases in the regional lymph nodes [123].
2. The size of the tumor. A possible explanation would be the fact that the volume of the clinically evaluated tumor is often amplified by peritumoral inflammatory phenomena of the body's defense, in reality the tumor volume itself being lower [119,121,122].
3. Invasion of the peritoneal serous. Three histological patterns of local peritoneal tumor invasion have been defined: 1) an inflammatory and/or hyperplastic reaction of the mesothelium, the tumor being underlying, but without expression on the serous; 2) tumor present on the surface of the peritoneal serous with inflammatory reaction, mesothelial hyperplasia and / or erosion / ulceration; 3) free tumor cells present on the surface of the serous with adjacent ulcerations of the visceral peritoneum. All three aspects are

associated with low survival, but in local recurrence the last two aspects appear in particular [122,124].

4. Invasion of adjacent organs. Tumors invading the wall or other organs (such as the bladder, ureter, prostate, uterus, ovaries, pelvic wall) and with peritoneal carcinomatosis require PET-CT to highlight the degree of local or advanced recurrence[119].
5. Macroscopic appearance of the primary tumor.
6. The degree to which the tumor obstructs the lumen of the rectum. The more obstructive the tumor is, the more reserved the prognosis is [122,123]. The stenotic, obstructive, infiltrative aspect proved to be a predictive factor of tumor recurrence.
7. Residual tumor – resection edges. The chance of a residual tumor remaining, and the occurrence of an early local recurrence is, however, significantly increased in the case of a free resection edge below 1 mm. In rectal cancer, it is considered, classically, that for oncological security the edge of distal resection free must be at least 5 cm. Studies have shown that 2 cm of histopathological free distal edge is enough without negatively influencing either survival or the occurrence of local recurrence [122,125]. The importance of lateral (radial) border invasion in rectal cancer has only been recognized recently, being considered an important predictor of local recurrence [122]. Thus, 85% of patients with positive radial edges have local recurrence, compared to only 3% of those with negative radial margins [122,126]. In fact, being an R1 stage, it is not about recurrence, but about the continuation of malignant tumor activity. Lateral tumor invasion of the mesorectum is considered to be a predictive factor for both local recurrence and remote survival after potentially curative resection in rectal cancer surgery [122,127]; It is also associated with an increase in the risk of remote metastasis [122,128]. Negative radial margins smaller than 2 mm are associated with increased risk of local recurrence [122,128], and in these cases, adjuvant radiation therapy cannot compensate for this risk [122,129].

- **BIOCHEMICAL AND GENTIC FACTORS**

1. High preoperative levels of carcinoembryonic antigen (CEA) are associated with a higher risk of RC recurrence. The CEA is included in most national surveillance programs after the curative surgery of RC [118].
2. Tumors from different parts of the colon have different genetic traits. For example, microsatellite instability (MSI), which is a good prognosis marker, is more common in the right colon than in tumors of the left colon and rectum [118].
3. Patients with cancer of the rectum have a 200% higher risk of local recurrence or isolated lung metastases compared to colon cancers. Moreover, rectal cancers spread more frequently in extra-abdominal sites [118]. There are three molecular subtypes recognized in sporadic (unfamiliar) RC : microsatellite instability (MSI), chromosomal instability (CIN– chromosomal instability), and Isle-isle Methylator

Phenotype (CIMP) phenotype. Microsatellites are short and repetitive sequences of nucleotides distributed along the DNA chain, and MMR proteins are DNA repairing enzymes that correct insertions or deletions of DNA fragments [128].

- **HISTOPATOLOGICAL FACTORS**

1. Invasion of regional lymph nodes.
2. The degree of differentiation of the tumor (histopathological grading) has prognostic influence also by correlating with local invasion at the level of the intestinal wall and adjacent organs, with venous invasion and lymphatic invasion [122,126,130].

- **HISTOPATHOLOGICAL ASPECT OF THE TUMOR**

It has a negative prognosis significance proven only in the case of special types of adenocarcinomas: colloid (mucinous) carcinoma, cell carcinoma "seal ring", small cell carcinoma and scirrhous carcinoma [122].

- **PERINEURAL INVASION**

Its presence translates into a significantly increased local recurrence rate and a lower 5-year survival compared to those without perineural invasion (7% and 35% respectively) [121,122,123,126].

- **INVASION OF LYMPHATIC VESSELS**

The incidence of invasion of lymphatic vessels (ILV) varies between 8 and 73%, being proportional to the tumor stage and the degree of differentiation [121,122,126]. The presence of ILV also correlates with the increased frequency of local recurrences [122,126],.

- **INVASION OF BLOOD (VENOUS) VESSELS**

Invasion of venous vessels (IVV) includes both the invasion of blood vessels inside the intestinal wall (intramural vascular invasion) and the invasion of blood vessels outside the intestine, from the peritoneal and perirectal fat (extramural vascular invasion) [122].

- **MECHANISMS OF TUMOR INVASION AND DEFENSE[122] :**

1. The mechanism of lympho-vascular invasion
2. The phenomenon of budding
3. Highlighting circulating tumor cells
4. Peritumor immune reaction

STUDY PURPOSE. RESEACH OBJECTIVES.

The purpose of this paper is to highlight the risk factors in the occurrence of local recurrence in surgically treated rectum cancer, to find solutions in order to limit and reduce them. The local recurrence after the operated rectum cancer represents "a challenge" for the surgeon, sometimes having a slow evolution, or more aggressive being detected at postoperative check-ups more frequently up to 2 years postoperatively or less often after 2 years. Age, obesity, advanced stage of tumor, complicated rectum cancers, anastomosis dehiscence, degree of parietal invasion, number of metastatic lymph nodes, the presence of lymphatic invasion, neurovascular, and immunotherapy with ethanolic extract of *Pseudomonas Serotype XV* (CANTASTIM), survival of patients at 3 and 5 years was analyzed in this study.

RESEARCH OBJECTIVES

1. Analysis of clinical and paraclinical data obtained from the patient's observation charts surgically treated for rectal tumors who have developed local recurrence.
2. Identification and systematization of risk factors with impact in the occurrence of local recurrence.
3. Quantification and evaluation of tumor markers in postoperative development of local recurrence.
4. Localization and staging of rectal tumors, degree of tumor fixity, invasion of lymph nodes, perivascular invasion, neural invasion.
5. The period between surgery and recurrence.
6. Surgical interventions performed, in emergency or elective for tumors of the rectum and the appearance of local recurrence.
7. Treatment performed neoadjuvant or adjuvant, immunotherapy for the period 2006-2009.
8. Patients' survival with local recurrence at 3 years and at 5 years postoperatively.

METHODOLOGY OF SCIENTIFIC RESEARCH

The present study is a retrospective analysis of the cases surgically treated for rectal cancer that have recurred locally in the Surgery Clinic II of the University Emergency Hospital (SUUB) in the last 14 years (2000-2014).

Out of a total of 303 patients with surgically treated rectum tumors of which 64 had local tumor recurrence (20%).

In order to achieve the research purpose, we conducted a complex retrospective study of all patients surgically treated for rectal tumors who developed local tumor recurrence.

The data taken came from the patients' observation charts, imagistic data, histopathological examinations of the resection pieces, surgical protocols.

The existing documentation came from the archive of the Surgery II Clinic and corroborated with the data provided by the electronic database of the University Emergency Hospital (SUUB).

INCLUSION CRITERIA:

1. All patients surgically treated for rectal tumors who have developed local recurrence:

- rectum amputation (Miles)

-Hartmann surgery

-rectal tumor resection with mechanical or manual anastomosis.

2. Patients who regularly attended the postoperative check-ups.

EXCLUSION CRITERIA:

1. Patients who did not attend the regular postoperative check-ups.

GENERAL DESCRIPTION OF THE DATA

We had 303 patients of which sixty-four with local recurrence.

The following types of data were used for the study:

1. Nominal scale data
 1. Sex
 2. Year of hospital admission
 3. Year of hospital admission category
 1. <2010
 2. >=2010
 4. Obesity
 5. Smoker
 6. Alcohol
 - T2DM (type 2 diabetes mellitus)
 7. HBP (high blood pressure)
 8. Recurrence localization (3 values of the location code)
 1. Superior rectum
 2. Medium rectum
 3. Inferior rectum
 9. Resections – Performed surgery
 10. Resection of large categories (anterior variable grouped)
 11. Peritonitis
 12. Metastases
 13. Extended resections
 14. Gynecology
 15. Viscerolysis
 16. Appendicectomy
 17. Stoma
 18. Surgical complications
 19. Anastomotic fistula
 20. Diarrhea
 21. Clostridium difficile infection
 22. RECURRENCE

23. Immunotherapy with Cantastim
 24. Distant metastases
 25. Neoadjuvant Therapies
 26. Neoadjuvant therapy large categories
 27. Neoadjuvant therapy if it includes RxT
 28. Pain
 29. Survival at 3 years
 30. Survival at 5 years
 31. Resection edges
2. Ordinal qualitative data
1. ASA score (4 values):
 1. I
 2. II
 3. III
 4. IV
 2. ASA2 score (idem)
 3. Operator volume
 4. TNM Classification
 5. TNM large categories
 6. Grade G (4 values)
 1. 0
 2. 1
 3. 2
 4. 3
 7. Stage (8 values)
 1. 0
 2. I
 3. IIA
 4. IIB
 5. IIIA
 6. IIIB
 7. IIIC
 8. IV
 8. Dukes (4 values)

1. A
 2. B
 3. C
 4. D
9. The degree of recurrence tumor fixity
 10. Pathological anatomy (3 values)
 1. ADK poorly differentiated
 2. ADK moderately differentiated
 3. ADK well differentiated
3. Discrete quantitative data
 1. Total number of ganglia
 2. Duration of hospitalization
 3. ICU Days
 4. Interval of surgery-recurrence
 5. Number of positive lymph nodes
 4. Range data
 1. Age
 2. Charlson score (infectious comorbidity score with 4 groups 0 – without pathology, 1-2 pts low score, 3-4 pts moderate score, 5-high score)
 3. WBC (leukocytes count)
 4. HB
 5. Urea
 6. Creatinine
 7. Glu
 8. AST
 9. Old

We analyzed the three types of localization/regions depending on whether or not the local recurrence occurs. No statistical relationship between localization and recurrence was found (X-squared = 2.5256, p-value = 0.2829). It can be concluded, however, that the lower localization offers an increased risk of recurrence, illustrated by the higher incidence of recurrence for this localization compared to the superior localization (26.3% vs. 17.4%)

Localisation	Superior	Median	Inferior
Recurrence: No	95	74	70
Recurrence: Yes	20	19	25

Table 1 Distribution of patients on Recurrence and Localization

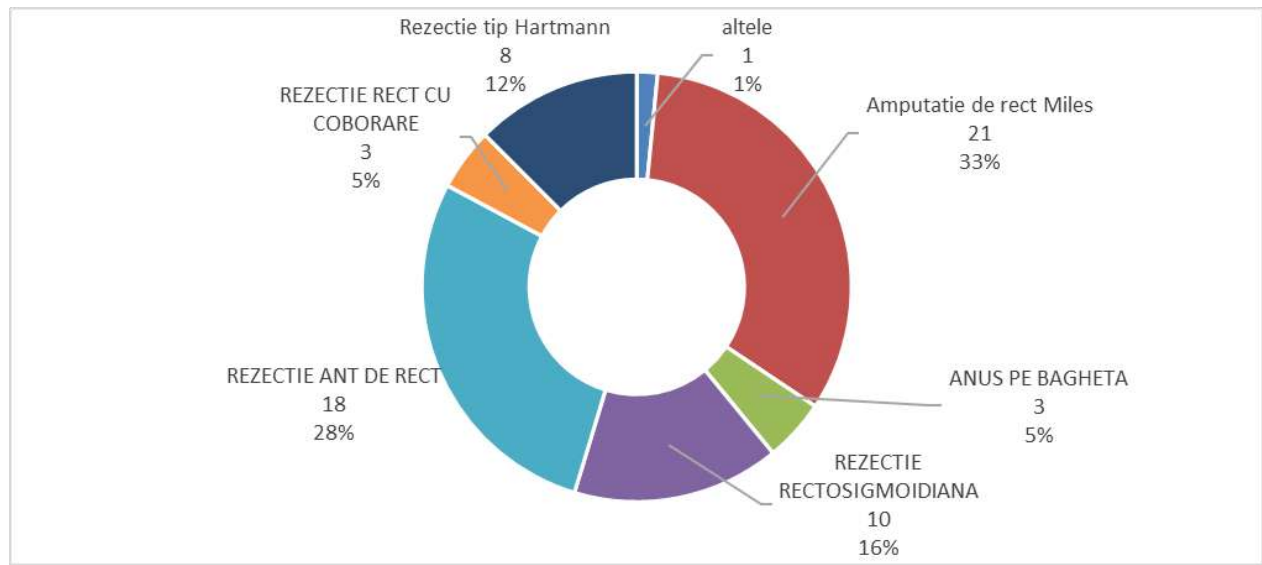


Figure 1. Distribution of those with Recurrence depending on the type of Resection

In Figure 2 we can see the division of patients by **stage** but at the same time as they have or have not had recurrence. However, stage and recurrence are statistically associated: **X-squared = 14.014, p-value = 0.05093.**

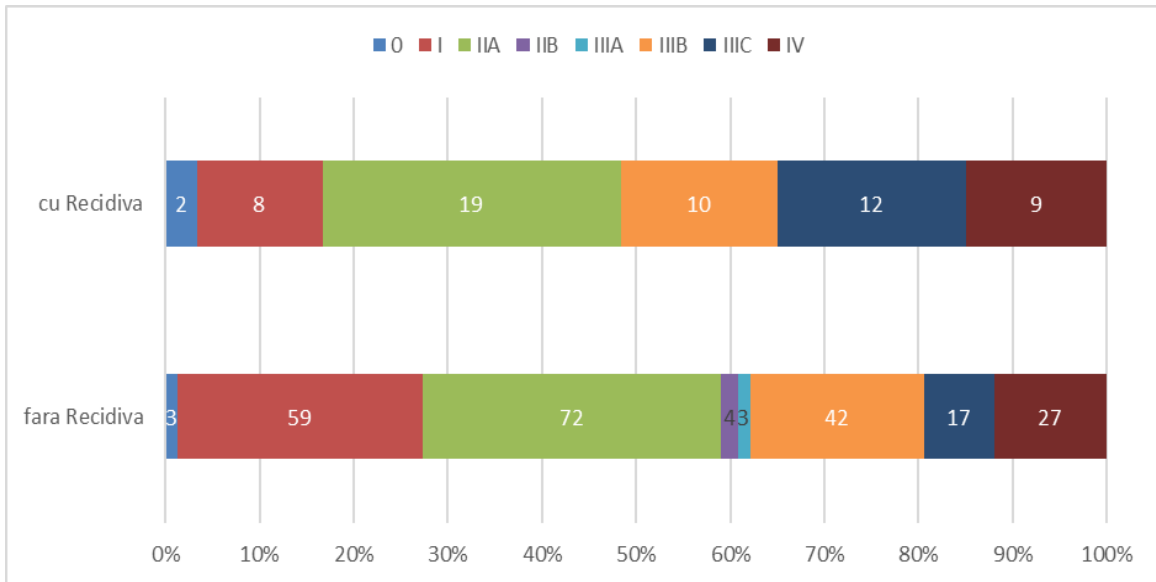


Figure 2. Distribution of patients by stage and the presence of recurrence

Local pain in the case of local recurrence was analyzed, being present in two thirds of cases.

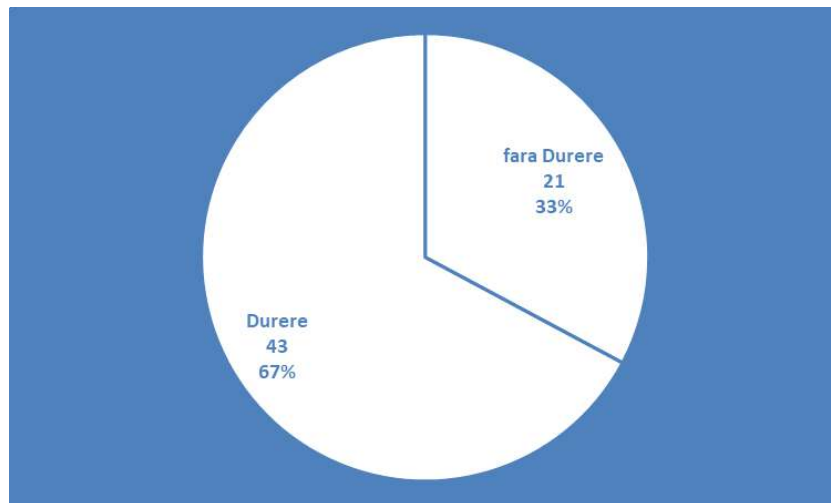


Figure3. Distribution of pain in the recurrence

	No recurrence (N=239)	Recurrence (N=64)	Total (N=303)	p-value
Age_cat>=60				0.794
FALSE < 60	67 (78.0%)	19 (22.0%)	86	
TRUE ≥ 60	172 (79.2%)	45 (20.8%)	217	

As for the age expressed categorically (<60 years, respectively > = 60 years), we see that there is no addition (see p-value in the table). However, one can see how the percentage of those at least 60 years old is the majority among those recurrence, corresponding to the number increasing with age of rectal cancer patients.

Statistical conclusions

Among the categorical or ordinal variables, we have identified as statistically relevant relative to recurrence:

1. rectal cancer stage: X-squared = 14.014, p-value = 0.05093;
2. operator volume: p-value = 0.01679;
3. appendectomy: X-squared = 5.1137, p-value = 0.02374;

As for the numerical ones:

4. HB: W = 6467, p-value = 0.05774;
5. number of days in ICU: W = 8589, p-value = 0.08636 (partial statistical significance);
6. number of positive lymph nodes: W = 6199, p-value = 0.006949.

Regarding the division of data according to the period of hospitalization (until 2010 or since 2010) and relative to the types of resections, it was statistically different from one period to another: X-squared = 55,366, p-value <<< 0.0001. In addition, when we analyzed the preference for smoking, we noticed how for the period starting with 2010, the values are much different from smoker to non-smoker (more specifically, the percentages of recurrences in the total): p-value = 0.0812. In general, even in those cases where no values below the threshold of 0.05 (significance threshold) were observed, in most variables the p-value had more significant (lower) values in the period since 2010. The survival at 3 years in the first period (of those hospitalized until 2010) was

significantly different from that of 5 years: X-squared = 4.5652, p-value = 0.03263. And in the case of the other period, after, the difference from 3 to 5 years was even more significant: X-squared = 6.8571, p-value = 0.008829. The difference from one category to another can also be seen by comparing the variable degree of fixity with the period of hospitalization in an overall/global way: X-squared = 6.4114, p-value = 0.04053. Charlson score evaluation (independent of recurrence or does not show that the median is lower for those hospitalized after 2010. This difference is statistically significant: W = 13237, p-value = 0.006594. As for the pathological anatomy, from one period to another (not taking into account the recurrence) there are statistical differences between the 3 frequencies: X-squared = 10.755, p-value = 0.004618. Again, the period was relevant when comparing the distribution of patients according to the two types of margins of resection: p-value = 0.02115. From one year to another, if we refer to what types of interventions were performed, the results are much different: p-value = 0.0004998.

If we focus only on those who have recurrence and their relationship with survival at 3 years, in order to see their most relevant characteristics, we can see that among the first variables that have important relevance is type 2 diabetes mellitus (DZ2), with a p-value of 0.036. Another variable with statistical significance was diarrhea: p-value = 0.082. The pain was also relevant to the extent to which it survived at 3 years old: p-value = 0.062.

The age expressed as a category (under 60 years versus ≥ 60 years) also represented a statistically significant variable: p-value = 0.003.

In the case of recurrences and their relationship with survival at 5 years, sex has a word to say, because it has converted into a statistically significant variable, at least taken individually: p-value = 0.026. And being a smoker is quite relevant even if not below 0.05 as a p-value. Another relevant category was this time the type of intervention / resection: p-value = 0.088. Age as a category also has statistical significance this time: p-value = 0.009. We remind you that it is about category <60 years old or ≥ 60 years. Grade G also has statistical significance: p-value = 0.09259.

In logarithmic regression models that combine various predictive factors, we have identified the location of the lesion as the most important factor. However, factors with quite good p-values were also the number of positive lymph nodes, the pathological anatomy (especially in the contrast formed by the moderately differentiated ADK with poorly differentiated ADK) and less, the age category (70 years was the threshold).

In the regression model that has as a variable dependence survival, there were identified instead (this model was made only with patients with local recurrence) several statistically

significant variables: age (60 years was the threshold this time), the degree of fixity of the recurrence tumor (especially in contrast to grade 3 with 1), pathological anatomy (especially in the well-differentiated ADK-ADK ratio poorly differentiated) and the G degree of staging.

CONCLUSIONS

1. Regarding age as the numerical variable, it was found that both in terms of standard deviations and the Mann-Whitney-Wilcoxon test and the Charlson score lead to the non-incrimination of age as a risk factor for local recurrence. However, we suggest, as an element of prevention, that when several factors are met proven as high-risk elements, to pay increased attention in tracking cases over and under 40 years of age, performing PET-CT as mandatory exploration at 6 months in the first 2 years post-surgery.

2. Analyzing the Hg value (hemoglobin), we found a real involvement of this parameter, its average being significantly higher in the case of patients without recurrence ($p=0.05$), the low value of Hg can be recognized as a risk factor for local recurrence.

3. In terms of the number of positive lymph nodes, it was found that in cases without recurrence, 83% of cases did not have ganglionic invasion (N0) while for cases that developed local recurrence only 17% did not have ganglion invasion, the difference appearing obviously signifying

4. The analysis of the cases divided into two periods of time, before and after 2010, finds that the respective lots are statistically similar totaling 129 cases, with 30 local recurrences (23,26%) before 2010 and 174 cases after 2010 with 34 local recurrences (19,54%). The difference in the incidence of local recurrence in the two periods was not large, statistically insignificant ($p=0.5$), but can notice the tendency to decrease the risk of local recurrence after 2010, explainable, both by factors related to the group component and by factors related to surgery and adjuvant therapy. The analysis according to sex, does not show significant differences between the two periods, sex not being a risk factor for local recurrence neither before, nor after 2010, there is still a predominance of local recurrence for the female sex before 2010 (26% compared to 21.5%) which, however, fades after 2010 (21.6% vs. 18%).

5. Obesity was analyzed in the two periods, finding that it is not a risk factor with statistical significance neither before ($p = 0.69$) nor after 2010 ($p = 0.4$). However, there may be a tendency to increase the number of cases with obesity after 2010.
6. The analysis of cases depending on the consumption of alcoholic beverages, smoking and diabetes did not find statistically significant differences between cases with local recurrence and those without local recurrence during the analyzed periods, so these factors cannot be considered as risk factors. It can be noted, however, that both for the consumption of alcoholic beverages and for smoking their incidence in cases of local recurrence is below the value of the incidence of local recurrence in both periods (22.6% and 11.1% compared to 23.3% for alcohol; 21.4% and 4.5% compared to 23.3% for smoking).
7. The analysis of cases with HBP, the study of the ASA and ASA 2 score shows that these factors are not risk factors for local recurrence.
8. Analyzing the incidence of local recurrence depending on the location of the lesion at the level of the upper, middle, and lower rectum in the two periods, it can be found that there is no statistically significant correlation between the 3 localizations and the local recurrence ($p=0.48$ and 0.33). We can, however, notice a relatively significant decrease in the incidence of local recurrence in the case of localization at the lower rectum level, from 28.8% to 24% this being without statistical significance.
9. The analysis of the local recurrence depending on the surgical intervention practiced correlates with the location of the lesion, the results being similar to this, finding that there are no statistically significant differences from the point of view of the local recurrence between the types of surgical interventions practiced neither before nor after 2010. ($p=0.65$ and $p=0.62$).
10. The presence of postoperative complications has proven to be a risk factor for local recurrence, there are also big differences between the first and second periods, explainable being the deficiencies in completing the observation sheet, especially in the first period.
11. Of the postoperative complications, clostridium difficile infection reported only after 2010, when it was present, the cases that recurrence represented only 7% (1 case to 15), while for cases without infection the recidivism rate was 20% (33 cases out of 159), the difference not being statistically significant ($p = 0.30$).

12. In terms of adjuvant and neoadjuvant associated therapies, we found that in the cases of preoperative RXT and postoperative RXT association, no local recurrence occurred, which is also confirmed in the cases of preoperative RXT and postoperative RXT + postoperative PCT, the small number of cases not allowing statistical conclusions.
13. In terms of survival at 3 years for cases that developed local recurrence, it is found that for the first period it was 37%(11 cases out of 30), while in the duo period it was 53% (18 cases out of 34), the difference not being statistically significant, but the difference was not statistically significant, but the relevance for an improvement in the results in the second period (X- squared = 1.11, p=0,29).
14. The same aspect is maintained for the survival at 5 years of the cases with local recurrence, this being of 10% (3 cases out of 30) for the first period and of 21% (7 cases out of 34) for the second period, the difference being also statistically insignificant (X- squared = 0.67,p=0.4). However, the difference in survival between 3 and 5 years was statistically significant p being 0.03 for the first period and 0.008 for the second period.
15. Regarding the presence of resection edge infiltration, its analysis in the two periods showed that it does not influence the occurrence of local recurrence as we would logically have expected. Thus, for the first period, the local recidivism rate for cases with positive margins was 21.7% (5 cases out of 23) compared to 23.9% (22 cases out of 92) for cases with negative margins, and for the second period it was 6.7% for cases with positive margins (1 out of 15) and 20.1% (28 cases out of 139) for cases with negative margins, the obvious and significant improvement {p=0,02} of the results in the second period can be explained by the association in the cases with infiltrated margin of the post-surgery radiotherapy after 2010.
16. The number of metastatic ganglia proved to be the most statistically relevant variable: with each additional positive ganglion, the probability of developing local recurrence increases by 1.11 times.
17. For the recurrence cases we found that of the analyzed parameters, statistical significance we had the age over 60 years (p=0,003), the presence of type II diabetes (p=0,036),the presence of diarrhea in symptomatology (p=0,082),the pain sprinkled (p=0,06).

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PUBLISHED WORKS

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Author: D. A. Pesu, S.I. Neagu, R.V. Costea, C.V. Dumitrescu
2. "Aspecte imagistice si terapeutice ale abceselor hepatice" – poster (Imaging and therapeutic aspects of liver abscesses)- poster (co-author), Conferinta Nationala de Chirurgie 2013, Sinaia
Author: C.C. Popa, O. Rusu, D. A. Pesu, M. Panescu, R.V. Costea, S.I Neagu
3. "Abces hepatic lob stang perforat acoperit cu mic epiploon" (Perforated and covered with small omentum left lobe liver abscess)– poster (co-author) Chirurgia Pancreasului, Congresul National de Chirurgie 2012, Timisoara.
Author: S.I Neagu, O. Rusu, C.C. Popa, D. A. Pesu, E. Ursache

4. "Fasceita necrozanta, aspecte anatomo clinice si terapeutice" - poster (Necrotising fasciitis anatomo-clinical and therapeutic aspects)- co-author poster, Conferinta Nationala de Chirurgie,Sinaia 2013
Author: O. Rusu, M. Hassouna, D. A. Pesu, R.V. Costea, S.I. Neagu, A. M. Oproiu.
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Author: D. A. Pesu, V.Tutu Pata
6. "Medicina bazata pe dovezi in osteoporoza postmenopauza" (Evidence based medicine in postmenopausal osteoporosis)- author, 2007 licence dissertation
Author: D. A. Pesu, M. Berteanu.
7. "Abcesul hepatic.Particularitati clinice si terapeutice" Congresul National de Chirurgie 2014,Sinaia (Liver absces.Clinical and therapeutic features) co-author poster
Author: C.C.Popa, M.Panescu, D. A. Pesu, R.V. Costea, S.I. Neagu
8. "Metastaza epiploica intr-un sac de hernie ombilicala incarcerala la un caz de neoplasm colonic stang" autor poster, CNC 2014,Sinaia (Epiploic metastasis in an incarcerated umbilical hernia at a case of left colonic cancer)
Author: D.A. Pesu, H. Mohsen, N. Sanda, S.I. Neagu
9. "Sarcom de parti moi al bratului stang recidivat" autor poster - Congresul National de Chirurgie 2014,Sinaia (Soft tissue recurrent sarcoma of the left arm")
Author: D.A. Pesu,S.I. Neagu, R.V. Costea, H. Mohsen
10. "Caz rar de sarcom de tesuturi moi la adult "co-author poster (Rare case of adult soft tissue sarcoma") Congresul National de Chirurgie 2014,Sinaia
Author: N. Sanda, D.A. Pesu, N.O. Zarnescu, S.I. Neagu
11. "Rabdomiosarcom gigant al peretelui abdominal" -autor poster (Giant abdominal wall rhabdomyosarcoma) 2015,CNC Bucuresti
Author: D. A. Pesu, N.O.Zarnescu, A.Iliesiu, R.V.Costea, S.I. Neagu
12. "Recidiva perineala dupa amputatie de rect " autor poster (Local perineal recurrence after anterior rectal resection) 2015,CNC Bucuresti
Author: D. A. Pesu, M. Panescu, C. Soare, A. Iliesiu, M. Sajin, R.V. Costea, S.I. Neagu
13. "Gangrena perineo-scrotala cu extensie la peretele abdominal anterior "(Perineum and scrotal gangrene extending to the anterior abdominal wall) Congres National de Chirurgie 2016, Sinaia
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16. Recidiva anastomotica dupa rezectia anterioara de rect" (Local recurrence after rectal cancer resection) , 2016 Congresul National de Chirurgie, poster author
Author: D. A. Pesu, C. Dumitrescu, R.V. Costea, A. Iliesiu, S.I Neagu
17. „Asocierea tumora gastrica mezenchimala si tumora giganta sarcomatoasa intraperitoneala " case presentation (Association of gastric mesenchymal tumour and giant sarcomatous intraperitoneal tumour) - poster Congres Chirurgie 2017
Author: D. A. Pesu; Co- author: R.V. Costea, H Mohsen, A. Chirca, A. Iliesiu, S. Neagu
18. „Tripla asociere patologica:litiaza biliara,carcinom gastric si miastenia gravis" (Triple association: biliary lithiasis, gastric carcinoma and myasthenia gravis) - poster Congres Chirurgie 2017
Author: D.A. Pesu, Co-author: A. Chica, A. Iliesiu, O. Penes, I. Mocioi, R. V. Costea, S.I. Neagu
19. „Sindrom subocluziv prin sarcom stromal endometroid gigant" (Sub-occlusive syndrome due to giant stromal endometrial sarcoma) - poster Congres Chirurgie 2018 SINAIA
Author: D. A. Pesu; Co-authors: I. Mocioi, A. Chirca, A. Iliesiu, R.V. Costea, S. I. Neagu
20. „Recidiva locala dupa chirurgia cancer rectal" (Local recurrence in rectal cancer surgery)-clinical presentation, poster Congres Chirurgie 2018 SINAIA
Author: D. A. Pesu, Co-author: N.C. Sanda, A. Iliesiu, C.V. Dumitrescu, R.V. Costea, S.I Neagu
21. „ Ocluzie intestinala in carcinom de unghi splecic al colonului la o luna si 3 luni dupa colecistectomie laparoscopica" (Bowel obstruction due to carcinoma of the splenic angle of the colon at one and three months after laparoscopic cholecystectomy) – case presentation, poster Congres UMF CAROL DAVILA 2018
Author: D.A Pesu, Co-author: R.V. Costea, C.V. Dumitrescu, A Chirca, .A. Iliesiu, S.I Neagu

22. „Carcinom microinvaziv vulvar pe fond de infectie HPV” -case presentation, poster CONGRES 2019 CRAIOVA
 Author: D.A. Pesu, Co-author: N. Sanda, A. Iliesiu, I. Mocioi, M. S. Neagu, R.V. Costea ,S.I. Neagu
23. „Carcinom rectal –Incidentalom intr-un caz de pioovar bilateral’ (Rectal carcinoma – incidentaloma in a case of bilateral pio-ovary) – case presentation, poster CONGRES 2019 CRAIOVA
 Author: D.A. Pesu, Co-author: G. Stroie, A. Neagu, A. Iliesiu, N. Sanda, M. S. Neagu, R.V. Costea ,S.I. Neagu
24. „ Ischemie mezenterica” (Mesenteric ischaemia)- poster Congres Craiova 8 MAI 2019
 Author: N. Sanda Co-author: N.O. Zarnescu, D. A. Pesu, R.V. Costea, S.I. Neagu
25. “Abdomen acut prin infarct jejunal segmentar” (Acute abdomen due to segmental jejunal infarction) - poster CONGRES 2019 CRAIOVA
 Author: N. Sanda, N.O. Zarnescu, D. A. Pesu, R. V, Costea, S.I Neagu
26. . “Abces retroperitoneal voluminos (Voluminous retroperitoneal abscess)” - case presentation
 Author: Nicoleta Sanda, Daniela Aurora Pesu, Ioana Mocioi, R. Costea, S.I. Neagu
 POSTER CONGRES 2019 CRAIOVA
27. “Carcinom de glanda sudoripara axilara sau metastaza de carcinom mamar?” (Sweat axillary gland carcinoma or mamaryc arcinoma metastasis?) - Poster Congres 2019 CRAIOVA
 Author: N. Sanda, D. A. Pesu, M. Sajin, R.V. Costea, S.I. Neagu
28. „Studiu clinico-statistic al tumorilor multiple sincrone și metacrone” (Clinical-statistical study of multiple synchronous and metacrone tumors) -published article
 Author: CS Dr. Nicoleta Aurelia SANDA¹, Conf. Dr. R.V. COSTEA^{1,2}, Asist Univ. Dr. C.C. POPA^{1,2},CS Dr. Daniela Aurora PEȘU¹, Dr. M.R. RISTEA³, Prof. Dr. S.I. NEAGU^{1,2,4,1} 1.Secția de Chirurgie Generală II, Spitalul Universitar de Urgență, București, 2.UMF „Carol Davila“, București, 3.Secția Chirurgie Plastică, Spitalul Județean, Constanța, 4.Academia Oamenilor de Știință din România ARTICOL Practica Medicală – Vol. 14, Nr. 2(66), An 2019
29. „ Recidiva anastomotică după neoplasm rectal 1/3 medie operat cu conservarea sfinterului anal ” (Anastomotic recurrence after 1/3-year rectal neoplasm operated with preservation of the anal sphincter) – published article
 Author: CS Dr. D.A. Peșu¹, Conf. Dr. R.V. Costea^{1,2}, Asist Univ. Dr. C.C. Popa^{1,2}, CS Dr. N. Sanda¹, Asist. Univ. Dr. A. Ilieșiu^{2,3}, Prof. Dr. Ș.I Neagu^{1,2,4}; 1Secția de Chirurgie Generală II, Spitalul Universitar de Urgență, București, România; 2UMF „Carol Davila“, București, România; 3Secția de Anatomie Patologică, Spitalul Universitar de Urgență, București, România; 4Academia Oamenilor de Știință din România ARTICOL B PRACTICA MEDICALĂ – VOL. 14, NR. 2(66), AN 2019

30. "Factori predictivi ai recidivei tumorale după chirurgia cancerului de rect" (Predictive factors of tumour recurrence in rectal cancer surgery) – Article published in PRACTICA MEDICALĂ – VOL. Ref: Ro Med J. 2020;67(2) DOI: 10.37897/RMJ.2020.2.5

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31.,, Cancerul mamar în România, o patologie ce necesită campanii de informare și educare – factori de risc și profilaxie “ (Breast cancer in Romania, a pathology that requires information and education campaigns “– risk factors and prophylaxis) – article [full text] — Ref: Ro Med J. 2021;68(1). DOI: 10.37897/RMJ.2021.1.6

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31. "Impactul imunoterapiei cu extract etanolic de Pseudomonas seitiip vx (Cantastim) asupra recidivei local in carcerul de rect operat “ (Impact of immunotherapy with Pseudomonas serotype xv ethanolic extract (Cantastim) on local recurrence and survival at 3 and 5 years in operated rectal cancer)-article [full text]— Ref: Ro Med J. 2022;69(2). DOI: 10.37897/RMJ.2022.2.4

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