

University of Medicine and Pharmacy CRAIOVA

DOCTORAL THESIS

ABSTRACT

Therapeutic updates in rectal cancer treatment

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I. STATE OF KNOWLEDGE

INTRODUCTION

Rectal cancer is a major health problem with deep medical, social and economic implications, regardless of the various diagnostic and treatment techniques available at the moment. [Loffeld R. J. L. F., et al. 2013]

Although it is a very common condition, the cause of rectal cancer is still not fully known, only possible predisposing factors are listed in the literature. [O'Meara S. et al. 2004]

This pathology is characterized by a slow growth process and late stages metastasis, rendering great importance to the early stage diagnosis and treatment for better immediate and long term survival. [Fette A. et al. 2012]

The preferred therapeutic strategy for local rectal cancer management involves a multidisciplinary treatment consisting of radiotherapy, chemotherapy and surgery.

The doctoral thesis entitled " Therapeutic updates in rectal cancer treatment" proposes a more complete approach to this problem, developing an epidemiological and therapeutical study. The aim of the research was to highlight epidemiological, theraputic,evolutive and prognostic features of this cancer.

CHAPTER I.

THE ANATOMY OF THE RECTUM

The rectum is a tubular organ, which extends from the third level of the sacral vertebrae to the anus, representing the terminal segment of the digestive tract., [Angelescu N. 2007, Ranga V. 1994]

Rectum originates in the terminal loop of the metenteron (abdomino-pelvic rectum) and in the posterior segment of the cloaca and primitive mesodermal spur (the distal rectum and pelvic perineal rectum). [Ghelase F. et al. 1999]

The rectum is covered by the peritoneum on the anterior and lateral sides. Depending on the position of the peritoneum, rectum has two portions, a peritoneal and an extraperitoneal or subperitoneal one

Arterial blood supply of the rectum is provided by the superior rectal artery (haemorrhoidal), the middle rectal artery, a branch of the internal iliac artery and the inferior rectal artery which is a branch artery of the internal pudendal artery. [Ranga V. 1994]

CHAPTER II

INCIDENCE. EPIDEMIOLOGY. ETIOPATHOGENY OF RECTAL CANCER

Rectal cancer one of the most common neoplastic diseases accounts for about 15% of all neoplasms. [Lee WS, et al. 2013]

In Romania is the second cause of death from cancer after gastric cancer among men and the third leading cause of death after breast cancer and cervix in women. [C. S. Mirea, et al. 2013]

At European level, rectal cancer accounts for approximately 35% of colorectal cancers with a mortality of about 4-10/100.000 inhabitants / year. [Augestad KM et al. 2010]

The frequency of this cancer is high in Western countries with a high standard of living (ranked 2nd in cancer mortality in the U.S.), and lowest in Asia and Africa. [Park JW, et al. 2009]

In our country every year an average of 2,000 new cases are occurring, with a rapidly growing frequency the number rectal cancer cases practically doubled in the last 20 years. [C. Savlovsch, et al. 2013]

Annual deaths in this pathology has been increasing each year, despite numerous therapeutic techniques developed in the medical world, the mortality rate increased from 4150 deaths in 2002 to 4860 deaths in 2006. [Rodríguez-Moranta F et al. 2006]

The cause this condition is not fully known, despite numerous health programs conducted to date. However, numerous studies have demonstrated the existence of

predisposing factors such as environmental factors and genetic factors. [Desch CE, et al. 2005]

Numerous studies have demonstrated that rectal cancer may have, as with colon cancer, a definite precursor, namely rectal adenoma. More than 80% of the rectal cancer patients presented with a previous history of adenoma, or polyp of the rectum. [Roman Corral, et al. 2013]

CHAPTER III

DIAGNOSTIC ISSUES OF RECTAL CANCER

In most cases, rectal cancer is clinically silent, its discovery being in many cases accidental, during a routine checkup. [Bleday R, et al. 1993]

When symptoms are present, the signs are not pathognomonic for either the presence of a primary rectal tumor or for the presence of metastasis. [Yeong Cheol Im, et al. 2013]

When symptoms occurs in this condition, often is an advanced evolutionary stage and needs emergency treatment to adress the symptoms, such as bowel obstruction. [Loffeld R. J. L. F., et al. 2013]

Due to absence or poor implementation of screening programs, most cases are diagnosed in an advanced stage when treatment can only be palliative. [Lee WS, et al. 2013]

Among the symptoms that a patient with rectal cancer may present are included:

- Rectoragy: minimum at the beginning, but as the disease progresses they become significant and independent of defecation.
- Changes in bowel habits - diarrhea, constipation, alternating diarrhea / constipation, change in consistency and color of the stool.
- Colicky abdominal pain and flatulence. [Di Valentin T, et al. 2013]
- Weight loss, fatigue.
- Clinical signs of intestinal obstruction. [Solanki AA, et al. 2013]

Diagnosis of this disease is based on clinical and paraclinical examination, diagnostic certainty being obligatorily connected with histopathological confirmation. [Rodríguez-Moranta F et al. 2006]

CHAPTER IV

HISTOPATHOLOGICAL ASPECTS OF OF RECTAL CANCER

Rectal cancer can occur on any area of the rectum, from the recto-sigmoid junction up to the anal canal. [Kodeda K, et al. 2010]

Rectal cancer diagnosis is based on clinical examination and laboratory explorations with histo-pathological confirmation being mandatory. For a histopathological results as accurately as possible one must consider in addition to the removed piece also the proximal, distal and circumferential excision margins and the regional lymph nodes. It is mandatory to determine the degree of differentiation and the extent of local and vascular invasion..

Adenocarcinoma is the most common diagnosis, representing 98% of the pathological forms. [Sobhani I, et al. 2011]

CHAPTER V

RECTAL CANCER TREATMENT

Rectal cancer treatment is complex, multidisciplinary and includes in addition to surgical techniques of radical resection (standard gold), local excision techniques, derivative procedures and specific oncological therapy. [Lujan J, et al. 2013]

Multimodal therapy for rectal cancer is represented by:

- Surgical treatment, curative or palliative, depending on the type of approach, it can be distinguished as:

- *classic*: abdomino-perineal resection with the sacrifice of sphincter apparatus, amputation of the rectum, abdominal transanal resection and anterior resections being operations that preserve sphincter apparatus; [Lincender-Cvijeta et al. 2012]

- *laparoscopic*: Conventional laparoscopic or robotic-assisted laparoscopy in single trocar, using the same technical options listed above;
- *endoscopic*: transanal endoscopic microsurgery (TEM) techniques of interventional endoscopy.
- Radiotherapy: rectal adenocarcinomas are sensitive to radiation therapy, which may be applied preoperatively, intraoperatively and postoperatively, with or without associated chemotherapy;
- Chemotherapy: 5-fluorouracil, Oxaliplatin, Irinotecan, Capecitabine - last used especially in metastatic rectal cancer [Rodríguez-Moranta et al. 2006]
- Targeted Molecular Therapy: is a promising treatment, but a good portion of the drugs introduced (Bevacizumab, Cetuximab, Panitumumab, etc.) have not yet found place in current protocols.

CHAPTER VI

SCREENING. PROGNOSIS.

CONSEQUENCES OF COLORECTAL SURGERY. SHORT AND LONG TERM PROGNOSIS

Current studies suggest that progression from normal rectal mucosa to invasive carcinoma occurs over a period of 4-10 years. Therefore, this period is crucial and is an ideal opportunity to exploit the current screening methods based on risk identification in an attempt to improve overall survival by a definitive therapeutic intervention as early as possible. [Avital I, et al. 2013 JS Pelletier, et al. 2013]

Upon presentation to the hospital, about one in four patients have early stage disease with negative lymph node invasion, but over 50% of patients have lymph node metastases, distant metastases or recurrent disease. [Pelletier J. S. et al., 2013]

Current studies have shown that in terms of rectal cancer, 5-year survival is 72% for stage I, 54% for stage II, 39% for stage III, 7% for stage IV. [Audisio R A. et al. 2000]

Surgical resection is the main treatment modality for patients with rectal cancer, but unfortunately, one third of these patients will develop recurrence. If detected early, recurrent disease could be solved by surgery and this provides motivation for a close follow-up for patients with resected rectal cancer. [Rodríguez-Moranta F et al. 2006]

II. PERSONAL CONTRIBUTIONS

CHAPTER VII

MOTIVATION AND SPECIFIC OBJECTIVES

The need for further research in the area of rectal cancer is justified due to the annual increase in the incidence of disease in developed countries and in developing countries, countries where until a few years ago, the incidence of this type of cancer was fairly small.

I have chosen this topic as a subject of my thesis because of the major national and international importance due to the high morbidity and mortality of this condition.

The purpose of this study is to analyze the effectiveness of surgical treatment alone and in combination with oncological treatment in the management of rectal cancer.

Study objectives were:

- Establishment of an algorithm for diagnosis and treatment of rectal cancer to improve results
- Comparative study of conventional and laparoscopic surgery in the treatment of rectal cancer
- Monitoring the influence of neoadjuvant oncological treatment on the results of surgical treatment in patients with rectal cancer

CHAPTER VIII

MATERIAL AND METHOD

This study was performed during the doctoral scholarship I received under the contract POSDRU/CPP107/DMI1.5/S/82705, "Developing doctoral schools by providing scholarships for PhD students" - ID 52826.

We performed a retrospective study of 347 patients diagnosed with rectal cancer. The patients were divided into two groups:

- **Lot A** - 237 rectal cancer patients hospitalized in the Department of Surgery and Oncology Clinics in the Emergency County Hospital Craiova 2005-2012
- **Lot B** – 110 patients diagnosed with rectal cancer and treated in the Department of Surgery and Department of Oncology University Hospital Archet 2 in Nice, France in 2008-2010.

All patients were informed of the treatment and have consented to it and the use of data for scientific research.

Anamnesis, clinical data, laboratory results, treatment and evolution for all 237 patients were taken from clinical observation sheets. The surgical protocols and histopathological bulletins were studied.

Surgical procedures used:

- Palliative: supratumoral anus
- Radical: Hartmann operation, resection of the rectum (Dixon), abdominal pelvic resection (Miles).

Statistical analysis used

For data processing were used Microsoft Excel (Microsoft Corp., Redmond, WA, USA) with XLSTAT suite for MS Excel (Addinsoft SARL, Paris, France) and SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Parameters measured for subjects in this study were stored in Excel files.

Processing data, calculating fundamental statistical parameters, mean and standard deviation of their report - the coefficient of variation and their graphic representation was performed in Excel with Pivot Tables commands,-Statistical Functions, Chart and Data Analysis module. To achieve data normality tests (Shapiro-Wilks and Anderson-Darling) and Mann-Whitney-Wilcoxon tests, command from XLSTAT module were used. Advanced statistical tests were done using SPSS for verification of results.

CHAPTER IX

RESULTS

THE STUDY OF DIAGNOSIS AND TREATMENT ALGORITHMS FOR RECTAL CANCER

Lot A included 237 patients diagnosed with rectal cancer in 2005-2012 in the Clinic of Surgery in the Emergency County Hospital Craiova. In this period there were 221 surgeries performed, 16 patients not benefiting from treatment due to comorbidities and complications associated with surgery.

We observed that 146 patients were male (61.6%) and 91 were female (38.4%), as shown in Table 9.1.

Analyzing the environment of origin, we observed that the proportion was similar, 127 patients from rural areas (53.5%) and 110 from urban areas (46.5%), values that have been exhibited in Table 9.2 .

We noticed that every year was characterized by the increasing number of cases. This can be explain based on improved methods of diagnosis and screening programs and their implementation in many medical centers. We have recorded: 22 patients in 2005, 17 in 2006, 28 in 2007, 29 patients in 2008, 40 in 2009, 42 in 2010, 30 in 2011 and 29 patients in 2012.

Analyzing patients from this project, I noticed that most were aged between 61-80 years and very few patients were aged less than 50 years, detail that I thoroughly exemplified in Table 9.4. There was no case under 20 years, 21-30 years group had one case, in group 31-40 years were 4 cases, in group 41-50 years were 13 cases, in group 51 -60 years were 43 cases, in group 61-70 years were 79 patients in 71-80 group 77 patients and over 80 years of age were 18 patients.

- In the study group we encountered the following risk factors:
- Age over 50 years - 217 patients representing 91.5% of the study group
- Male gender was encountered in 146 patients, representing 61.6%
- Positive family history of colorectal cancer - 2 patients, which represented 0.84%
- Diabetes - 18 patients (7.59%)

- Obesity - 87 patients, accounting for 36.7% of the cases
- Colorectal medical history: 7 patients were registered with colonic polyps, representing 2.9% of cases and 21 patients with colorectal cancer surgery, representing 8.86% of cases
- Regular consumption of alcohol was noted in 60 patients represented 25.31% of the studied cases
- Smoking - 76 patients, representing 32%
- Occupational toxicants sometimes incriminated in the etiopathogenesis of rectal cancer were noted in 5 patients, representing 2.1% of the study group
- Diet rich in fat - 154 patients (64.97%)
- Diet low in dietary fiber - 143 patients (60.3%)

Most patients presented to the doctor after a period of 1-6 months, approximately 54% of all patients, 20% presented to the doctor at the appearance of first symptoms, 16.4% addressed a physician less than one year after the onset of symptoms, and about 8% of patients had symptoms which they ignored more than a year.

Analysis of rectal tumor topography in the study group revealed the following:

- Rectosigmoidian junction tumors - 96 cases, representing 40.5% of patients
- Upper rectal tumors - 39 cases, representing 16.4% of the study group
- Middle rectal tumors - 54 cases, accounting for 22.7% of cases
- Lower rectal tumors - 48 cases, representing 20.2% of the cases studied

For characterization of rectal tumors we used AJCC TNM staging and UICC, which is in effect at the moment.

So were recorded:

- 18 patients in stage I, representing 7.6%
- 38 patients in stage II, 16% of patients
- 122 patients in stage III representing 51.4%
- 59 patients in stage IV (24.9%). (Table 9.8, chart 9.8)

In terms of tumor size, we noticed that the vast majority were sized 3-6 cm.

In terms of histopathology, I noticed that the most common type of cancer was adenocarcinoma in about 136 cases.

Of the 237 cases of rectal cancer, 221 cases were operated, representing 93.2%. 16 patients (6.8%) did not receive surgery because of advanced disease or they refused surgery

Neoadjuvant therapy was applied as follows:

- 100 cases of radiotherapy (42,2%)
- 87 cases of chemotherapy (36,7%)

Neoadjuvant therapy resulted in a reduction of the tumor or, in some cases, the disappearance of the tumor. In generally neoadjuvant chemoradiotherapy was used for locally advanced rectal cancer (T3/T4 or N1/N2). This aspect was not followed and analyzed in group A, being treated in the second part of the thesis.

Of the 221 surgeries, 159 were scheduled interventions, representing 71.9%. The remaining interventions (62) were performed as emergency, representing 28.1%. Planned interventions were performed:

- Dixon – 106 interventions, representing 47,9%
- Miles – 47 interventions, representing 21,2%
- Left proctocolectomy – 6 cases, representing 2,7%

Emergency procedures :

- Hartmann – 37 cases, representing 16,7%, of which, 26 cases presented for restoration.
- Ileo-anal pouch – 25 cases, representing 11%. 13 cases presented for step 2 of the intervention (resection)

COMPARATIVE STUDY OF LAPAROSCOPIC SURGICAL TREATMENT VS. CLASSIC SURGERY IN RECTAL CANCER

Lot B included 110 patients diagnosed with rectal cancer and treated in the Department of Surgery and Department of Oncology University Hospital Archet 2 in Nice, France in 2008-2010.

Lot B was later divided into two subgroups: (table 9.13. Graphically 9.13.)

- The laparoscopic lot – 50 patients, representing 45,4%
- Classic surgery lot– 60 patients, representing 54,6%

In terms of age, we observed that the average age in the laparoscopic group was 65 years compared to the classic surgery group where the average age was 61.8 years. Male / female ratio was 1.2 / 1 in the laparoscopic group, and 1.3 / 1 in classic surgery group. Body mass index (BMI) averaged 27.2 for the laparoscopic group and 30.9 for the classic surgery group.

In terms of the TNM staging in the laparoscopic group we have met 22 cases in stage I, 25 cases in stage II and 3 cases in stage III, while in classic surgery group we had 26 patients in stage I, 30 patients in stage II and 4 patients stage III. The average distance from the tumor to the external anal orifice was 6.3 cm in the laparoscopic group and 6.1 cm in the classic surgery group.

Distal resection margin averaged 3.8 cm for the laparoscopic lot, respectively 3.5 cm for the classic surgery lot. The average operative time was 225.7 minutes for laparoscopic lot and 164 minutes for the classic lot.

Preservation of the sphincter was performed at 38 cases in the laparoscopic lot (76%) and 48 cases in classical surgery lot (80%).

Blood loss averaged 115 mL for laparoscopic lot respectively 287.5 ml for classic surgery lot. Time needed to resume transit for gases averaged 38.3 hours for the laparoscopic lot, namely 52.6 hours for the classic surgery lot. Average postoperative hospitalization was 7.8 days for the laparoscopic lot, 12.2 days for classic surgery lot. The average number of lymph nodes resected was 18.7 for laparoscopic lot respectively 20.5 for classic surgery lot. (Graphic 9,12,14)

STUDY ON THE IMPACT OF NEOADJUVANT TREATMENT IN RECTAL CANCER

Only 90 patients in group B received neoadjuvant radiotherapy and chemotherapy performed in the Department of Oncology. The other patients were hospitalized in the Department of Surgery after neoadjuvant treatment in another Oncology Center. I watched in terms of neoadjuvant therapy only these 90 patients.

The gender distribution of patients was as follows: 55 men (61.1%) and 35 women (38.9%). In terms of age, patients had a mean age of 58.8 years with a range between 45-68 years. Pathological diagnosis of the patients included in this study was rectal adenocarcinoma. Duration of time after the end of therapy until surgery ranged

from 28 days to 65 days. The length from the neoadjuvant treatment until the end of surgery divided the 90 patients in 3 groups.

Regarding the characteristics of the tumor, it should be noted that the distance from the anal canal to the tumor was 5.9 cm on average, ranging from 1 cm to 15 cm.

There is significant variation in the response to neoadjuvant treatment in the 3 groups.

Thus, in group 1 the tumor shrinkage was seen in 80.8% of patients, in group 2 the tumor shrinkage was seen in 60% of patients and in group 3 only 44.4% of tumors decreased in size. Thus we see a decrease in the percentage of favorable response with the remoteness time of surgery to the time of conclusion of the neoadjuvant treatment.

Complete tumor regression was observed in 14.8% of cases in group 1, 8% of cases in group 2 and 5.5% of cases in group 3. The same decrease in the percentage of cases with complete oncologic response is found with increasing interval between neoadjuvant therapy and surgery.

Absence of response to treatment was recorded in 4.2% of cases of group 1, 32% of cases group 2 and 50% of group 3. There is an increase in the percentage of cases without response along with the delay of oncologic surgery.

Percentage of the sphincter preservation surgery was 89% in group 1, 60% in group 2 and 33% in group 3. There is decrease in the chance of performing an intervention with sphincterian preservation as we move from the moment of the neoadjuvant therapy.

CHAPTER X

DISCUSSIONS

In most countries and in Romania in many areas, population is not informed about the possibility of cure for various forms of cancer, the existence of national health programs that involve the detection of early-stage cancers in a population at risk.

Colorectal cancer is one of the most common causes of cancer-related morbidity and mortality worldwide, being the third most common cancer in men (10% of all cancers) and the second in women (9.4% of all cancers) . [Ferlay J et al., 2008]

Risk factors related to the patient's lifestyle include obesity, sedentary lifestyle, smoking, diet low in fruits, vegetables and fiber and rich in meat, especially processed meat.

In this thesis I tried to find risk factors involved in both rectal cancer occurrence and the prognosis of this disease.

Thus we observed that male gender, age group 60-80, the length of time since the occurrence of the first symptoms until presentation to the doctor, the way of presenting to the doctor, disease stage, tumor size, type of surgery and intra and postoperative complications .

In terms of gender distribution of patients included in this study, we observed that the ratio obtained in my analysis the respected and was similar to that described in other studies, namely 1/3 women-men. [Loffeld R. J. L. F., et al. 2013]. The reason this ratio remains constant is not yet fully known.

Another risk factor involved in the development of rectal cancer is age. I noticed that a considerable number of patients included in my study were aged 60-80 years, which may decrease the chances of complete healing due to poor condition and age-related comorbidities.

Most patients (about 80%) presented for medical check-up in more than a month after the onset of symptoms, allowing the growth and multiplication of cancer cells and thus the occurrence of metastasis. The longer the time was until presentation to a physician the more advanced the stage was and the treatment less effective. The same conclusion also reached Ostenfeld Eva Bjerre et al. [Eva Bjerre Ostenfeld et al. 2013]

Mode of onset or diagnosis of rectal cancer is another negative prognostic factor. Thus, patients who were admitted through the emergency room with intestinal obstruction or peritonitis had a poor prognosis compared with patients who were hospitalized for rectal or pelvic-abdominal pain. Fortunately, for many patients rectoragy are a quite alarming sign and they see a doctor immediately if these symptoms occur. Both Masljankov in 2013 and Boostrom SY and colleagues had similar findings. [Masljankov SI. 2013 Boostrom SY et al. 2013]

Evolutionary stage of the tumor and its size were other items that we have analyzed in my PhD thesis. So I noticed, as explained by Austin H et. al that an

advanced stage is associated with a higher rate of immediate and distant mortality. In our study, over 75% of patients were diagnosed in stages III and IV of the disease. [Austin H et al, 2013]

Also tumor size had a negative impact on the evolution of patients due to decreased or the lack of treatment response and due to complications caused by a large tumor mass. Most patients had a tumor sized at least 5-6 cm, which generated major digestive disorders and decreased surgical excision capacity.

The current therapeutic approach to cancer of the rectum is complex, involving multidisciplinary teams of surgeons, anesthetists, medical oncologist. Treatment includes surgical techniques for radical resection (gold standard), limited excision techniques and specific oncological treatment.

Surgery was and still is the basic treatment of rectal cancer. We can not talk about cure without regard to a surgical sequence. In our study, 93.2% of patients were operated. 16 patients (6.8%) did not receive surgery because of advanced disease or refused surgery.

The vast majority of surgical interventions (72%) were scheduled. There were practiced 106 Dixon proctosigmoidectomies, 46 Miles abdominoperineal amputation of the rectum and 6 left proctocolectomies. The remaining 28% of interventions were under emergency conditions. There have been 37 Hartmann operations and 25 ileo-anal pouches. During the surgical interventions node dissection and total excision of the mesorectum were performed as principle. Lymphadenectomy: a minimum of 12 lymph nodes were excised for stage confirmation (AJCC, College of American Pathologists), although there is no consensus.

In case of colorectal anastomosis, protection colostomy or ileostomy was not used. Transanastomotic intubation with Faucher probe was used and maintained until the resumption of bowel movements. Regarding protective stoma in rectal surgery, we had witnessed a seemingly endless debate on the role and opportunity of colonic or ileal derivation.

Postoperative complications were general and local. Of general complications we met: cardiovascular - 3 cases, respiratory - 8 cases, renal failure - 1 case, sepsis - 6 cases and MSOF - 5 cases.

Laparoscopic techniques for the treatment of rectal cancer have been widely accepted because of their benefits. Although global laparoscopic surgery in rectal cancer was successfully introduced a long time in our country the proportion of laparoscopic rectal resection is less than 10%.

We performed a prospective study comparing two groups of patients, one consisting of patients operated laparoscopically and one of patients with classic surgery. The purpose of the analysis was comparative to find a convenient and reliable method for the treatment of patients diagnosed with rectal cancer.

Comparing the two groups, laparoscopic and classic, showed no statistically significant differences regarding the average age of patients, male / female ratio, tumor staging and the average distance to the OAE. There were statistically significant differences in terms of body mass index but we believe that this did not affect the study results.

Comparing variables tracked in the two groups revealed significant differences between laparoscopic group and classic surgery group.

There were no statistically significant differences in terms of distal resection margin which averaged 3.8 cm in the laparoscopic group versus 3.5 cm in the classic surgery group.

Following this analysis, we found that laparoscopic surgery was longer on average 225.7 min compared to conventional surgery where the average was 164 min. Gong J, et al. reached the same result, with 216.4 minutes for laparoscopic surgery and 162.7 min for conventional surgery. [Gong J et al, 2012]

Radiotherapy regimen and the time from completion of neoadjuvant therapy until the operative moment remains a big controversy. Some specialty reports considers that a higher period of time is benefic and reduces the recurrence rate. Thus, although in U.S. middle and lower rectal adenocarcinoma is treated with long course neoadjuvant radiotherapy for 6-8 weeks at a dose of 50 Gy in combination with radiosensitizing chemotherapy with 5-FU followed by surgery at 8-12 weeks, European pre-operative therapeutic approach relates to protocols that are standard short course of 25 Gy administered over 5 days followed by surgery one week after the completion of

radiotherapy. Article from experts in the field state that a longer period of time is beneficial and reduces the recurrence rate. [Kang SB 2010]

We studied three subgroups of patients:

- Lot 1 - 47 patients (52%) received surgery after about 4 weeks
- Lot 2 - 25 patients (27%) after 6 weeks
- Lot 3 - 18 patients (21%) after a period longer than 7 weeks.

For lot 1, of patients with surgery at 4 weeks the results were: at 80.8% (38 patients) a tumor decrease was noted, tumor disappearance in 14% (7 patients), 4.2% (2 patients) had a negative response. In 89.3% (42 patients) sphincter preserving surgery was performed.

For group 2, of patients with surgery at 6 weeks, the results were: in 60% (15 patients) a tumor decrease was found, in 8% (2 patients) the tumor disappeared and in 32% (8 patients) the response was unfavorable. In 60% (15 patients) sphincter preserving surgery was performed.

For group 3 of patients with surgery at more than seven weeks, the results were: 44.4% (8 patients) had a decrease in tumor size, 5.5% (1 patient) registered a tumor disappearance and in 50% (9 patients) the response was negative. 33.3% (6 patients) had sphincter preserving surgery.

It appears that favorable results predominate in group 1 with 95% favorable outcomes following oncologic treatment and 89% benefiting of sphincter preservation interventions. In group 2 favorable results were only 68% and sphincter preservation interventions were performed only in 60%. The weakest results were in group 3 with patients operated over seven weeks, with 50% favourable results and only 33.3% sphincter preservation interventions.

We emphasize the need for randomized trials and meta-analyzes to support our results and require the establishment of guidelines for the treatment of rectal cancer worldwide.

CHAPTER XI

CONCLUSIONS

1. Rectal cancer incidence is increasing worldwide. Our study has shown a steady increase in the annual number of cases from 2005 to 2010. However, the last 2 years of the study showed a slight decrease in the annual number of cases.
2. Gender distribution showed a predominance of males with 61.6% of cases compared to females which recorded 38.4% of cases.
3. Diagnosis of cancer of the rectum is determined still quite late in our study over 75% of cases were diagnosed in stages III and IV according to TNM staging.
4. The main steps of the therapeutic algorithm recommended for rectal cancer are:
 - Preoperative Diagnosis, based on clinical, biological and imaging findings
 - Tumor biopsy - histopathological examination
 - Neoadjuvant treatment - radiotherapy with / without chemotherapy
 - Surgery - performed at least 10 weeks after radiotherapy
 - Postoperative diagnosis for the extension degree of the disease
 - Oncological monitoring intended to determine the opportunity adjuvant treatment (radiotherapy and chemotherapy)
5. Rectal cancer treatment is multimodal, involving surgery, radiotherapy and chemotherapy. Neoadjuvant therapy resulted in a reduction tumor or, in some cases, the disappearance of the tumor.
6. Surgical treatment is the most important therapeutic sequence. Lymphadenectomy and total excision of the mesorectum are used routinely in interventions with curative intention.
7. Laparoscopic surgery for rectal cancer is both safe and feasible, with clinical and oncologic outcomes comparable to open surgery.
8. No significant differences were found between laparoscopic and classical surgery in terms of the proportion of sphincter preservation interventions, oncological resection margins, the size of the piece of resection, number of resected lymph nodes or postoperative complications.

9. Neoadjuvant cancer treatment has an absolute indication for rectal cancer. Surgery performed 4-6 weeks after chemo-radiotherapy has the best results in terms of oncologic response and proportion of sphincter preservation interventions.

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