Original Paper

Colorectal Cancer - Prognostic Correlations

VASILE L.[1], PÎRŞCOVEANU M.[1], MUNTEANU M.[1], PLEŞEA E.[2]

[1]Department of General Surgery, County Emergency University Hospital, Craiova; University of Medicine and Pharmacy of Craiova; [2]Department of Pathology, University of Medicine and Pharmacy of Craiova;

ABSTRACT Significant advances about carcinogenesis and natural history of colorectal cancer (CRC), particularly the establishment of filiations polyp-cancer, are important objectives for a new approach to diagnosis of this disease. Decade 1990-2000 was the decade of CRC detection and prevention, but the decade 2000-2010 is the period of application of new diagnostic and therapeutic concepts. The aim of this study was to highlight the epidemiological, clinical, therapeutic, evolution and prognosis aspects of this cancer. The research was based on examination of the computerized system of C.E.U.H. of Craiova, observation sheets, operation protocols and anatomic-pathological results, from which we identified from January 2003 until December 2005 a number of 134 patients with CRC investigated, treated and followed completely. This was possible thanks to collaboration between surgical, gastroenterology, oncology clinics and anatomopathology laboratory of C.E.U.H. of Craiova, they accumulated a rich experience in diagnosis and treatment of digestive cancers, particularly colorectal one.

KEY WORDS *colorectal cancer, colectomy, rectal amputation*

Introduction

Colo-rectal cancer has had the third frequency both men (663,904 cases, representing 10.0% of all malignancies) and women (571,204 cases - 9.4% of all malignancies) in the hole world. [1] News research about colorectal cancer (CRC) has been imposed by the continuous increase of the disease incidence both in developed countries, which has already registered high levels of prevalence, and in countries where once CRC rates did not concern .

The need of study, detection and prevention CRC remains a major public doubt of health problem. Diagnosis and early detection of CRC is one of the major goals of medical activity and should become a priority for the health system.

Colorectal cancer recognize a natural evolution compatible with a long considerable asymptomatic period, generally estimated to last over five years. This period generally corresponds to early stage of cancer transformation of adenomatous polyps and cancer histological lesion exceeded below mucous membrane. In this context it is considered that the diagnosis of CRC is made most often in advanced stages, when the extent of lesion and its location is identified as key to symptomatic expression of disease and histological invasive lesions overcome beyond mucous membrane.

Currently, all agree that the diagnostic method of choice is rectocolonoscopy, which is applied to all subjects who belong to a category corresponding to this increased risk of cancer sites. However, in practice the most widely used screening test is that of occult bleeding, followed by flexible sigmoidoscopy and colonoscopy. More recently, it is studing DNA research on the faeces for hereditary forms (genetically).

Surgery has been and continues to be the basic therapeutic strategy. If the principles of surgical treatment elements and techniques have not been changed significantly in the last years, what has been changed tactics in complicated cases refers to different meaning approach, which is based primarily on the progress made in intensive care, so necessary for these patients.

The prognosis of CRC patients involves many factors such as histological type of cancer, size, location, degree of tumor invasion, loco-regional metastasis (number of interested nodes) and in other organs. To improve CRC prognosis, fundamental research in genetics and molecular biology, and colorectal screening with the widespread practice of noninvasive techniques (virtual colonoscopy) are some new or relatively new directions to be developed. [2,3,4]

Material and method

We prospectively and retrospectively studied patients with colorectal cancer operated upon in County Universitary Emergency Hospital of Craiova (C.E.U.H.), which has three general surgery clinics, from January 2003 – until December 2005. In collaboration with the gastronterologyclinic, oncology clinics and Morphopathological Laboratory of the C.E.U.H. of Craiova, we performed betwen January 2003 - December 2005 a prospective study in order to identify cases of colorectal cancer, the development of their attitude in relation to therapeutic and surgical oncology, which were

applied, precise and morphological aspects highlighted.

Processed data are from case report forms, patient exit ticket ballot and histopathological examination. Data on survival on 01.07.2010 - when it ends the tracking of patients - were from the Registry of Civil Status of the city of Craiova.

The inclusion criteria were:

- diagnosis of colon or rectal cancer before surgery,

- surgical resection type,

- histopathological confirmation.

There were excluded from the study endoscopic treatment cases, also cases in which colorectal tumor could not be extirpated from the intervention and colo-rectal resection was performed for diseases such as familial adenomatous polyposis. Also, reintegration after previous interventions (Hartmann) and those without resection followed by anastomosis (lateral colostomy type colorectal cancers presented in bowel obstruction) were not included in the study.

The database of C.E.U.H. surgery performed, in the studied period, extract six types of interventions, namely:

1.right hemicolecomy with ileo-transverse anastomosis;

2. colectomy for transverse colon with colo-colic anastomosis;

3. left hemicolectomy with colo-recto / colo anastomosis;

4. subtotal colectomy with ileo/colo- / rectal anastomosis ileo/colo- / rectal;

5. rectosigmoidian resection (Dixon opperation) with colo-recto anastomosis;

6. amputation of the rectum.

After primary selection, patients were studied in groups according to the wanted parameter: demographic data, clinical data - staging, morphopathological aspects, therapeutic data.

There were analised prognosis and survival of patients examined in the batch related to these parameters. The following types of statistical tests were used for statistical processing of data: tests to measure the dependence between the parameters (chi squared x^2) and significance tests (Anova and Student).

The main statistical analysis software packages were Microsoft Excel 2003 and Epi Info 2000. Also there were drawn by Kaplan-Meier curves for each parameter followed, and compared these curves, achieving survival prognostic correlations.

Preoperatively, patients from the study were investigated by colono / rectoscopy, supplemented by a tumor biopsy harvested endoscopically in some cases, barium enema or barium enema with double contrast. Abdominal ultrasound, chest X-ray and abdominal computed tomography examination balance round lesion detected preoperatively and metastases of any primary tumor. In emergency cases admitted and operated with stenosing complications, perforation or bleeding, investigations were limited to assessing the balance preoperative imaging investigations - with the exception of abdominal radiography and ultrasound - no emergency service available. From clinico-statistical research examined data from the computerized C.E.U.H. Craiova, observation sheets, protocols and anatomo-pathological operators, I identified from January 2003 – until December 2005 a total of 302 colorectal cancer cases. 73 patients of these were sent to other onco-surgery services from the country, 67 patients could not perform surgical resection of the tumor, and 28 patients had clinical and imaging end-stage disease and surgery were palliative.

The remaining 134 patients represented the group that was studied prospectively and retrospectively, these cases benefit from tumor resection (which could be interpreted pathologically) and adapted oncology treatment.

The main objectives proposed for this study were:

- analysis of the main epidemiological, clinical and therapeutic as determining factors in the development of colorectal cancer;

- analysis of surgical therapeutic strategies, adjuvant therapies and prognostic factors;

- analisys of data on survival of study group in epidemiological, therapeutic and pathological terms.

Results

Analysis of 134 CRC cases and operated boarding C.E.U.H.of Craiova, from January 2003 until December 2005 revealed some important demographic data on survival at 5 years after surgery.
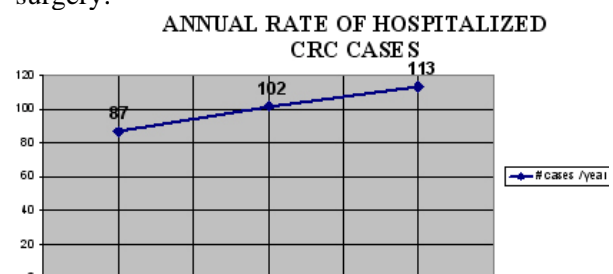
Chart nr.1: Annual rate of hospitalized CRC cases in C.E.U.H. of Craiova.

Starting with the initial group of 302 patients identified with CCR, we note an increase in the number of cases from year to year. Thus, in 2003

there were 87 cases diagnosed, in 2004 their number increased to 102 cases and in 2005 we identify 113 cases. (chart nr. 1)

However, in the group studied it is showed a downward trend of the number of cases in which tumor resection is practiced. Thus, the number drops to 61 patients resected in 2003, to 40 in 2004 and 33 in 2005. (chart nr. 2) This could be explained by the broader public access to the methods of early diagnosis of CRC and endoscopic treatment options in early stages. Reasoning should not be disregarded to establish onco-surgical pilot centers specializing in CRC therapy (Bucharest, Cluj-Napoca).

Table. 1: Summary table of the CRC study group

	# patients	Deaths patients(%)	Alive patients(%)	Average survival months	Standard deviation	Lower limit months	Upper limit months
Women	55	31(56,3%)	24(43,6%)	49.800	4.599	40.786	58.814
Men	79	52(65,8%)	27(34,1%)	47.613	3.658	40.444	54.783
Urban	79	46(58,2%)	33(41,7%)	51.136	3.735	43.814	58.457
Rural	55	37(67,2%)	18(33,7%)	44.612	4.393	36.001	53.223
<50 years	11	4(36,3%)	7(63,6%)	67.545	8.018	51.830	83.261
50-70 years	71	42(59,1%)	29(40,8%)	53.195	3.933	45.486	60.904
>70 years	52	37(71,1%)	15(28,8%)	38.230	4.444	29.519	46.941
Elective surgery	65	24(36,9%)	41(63,0%)	70.761	3.087	64.710	76.812
Emergency surgery	69	59(85,5%)	10(14,4%)	28.764	3.364	22.172	35.357
Right colon	32	18(56,2%)	14(43,7%)	53.958	6.054	42.092	65.825
Left colon	56	31(55,3%)	25(44,6%)	51.006	4.538	42.112	59.899
Rectum	46	34(73,9%)	12(26,0%)	41.496	4.503	32.670	50.321
Rectal amputation	13	9(69,3%)	4(30,6%)	46.308	8.269	30.100	62.516
Subtotal colectomy	4	2(50,0%)	2(50,0%)	44.750	11.329	22.546	66.954
Transverse colectomy	4	3(75,0%)	1(25,0%)	31.750	11.766	8.689	54.811
Right hemicolectomy	27	14(51,8%)	13(48,1%)	57.074	6.571	44.194	69.954
Left hemicolectomy	48	29(60,4%)	19(39,5%)	47.604	4.901	37.999	57.209
Rectosigmoidectomy	38	26(68,4%)	12(31,5%)	41.155	4.811	31.725	50.585
Ulcerative	52	37(71,1%)	15(28,8%)	45.374	4.434	36.684	54.064
Infiltrative	52	30(57,6%)	22(42,3%)	47.885	4.790	38.497	57.272
Vegetant	30	16(53,3%)	14(46,6%)	55.602	6.108	43.630	67.574
Stage I	18	7(38,8%)	11 (61,1%)	67.968	5.802	56.596	79.341
Stage II	73	35(48,0)	38(52,0%)	62.516	3.182	56.279	68.752
Stage III	3	1(33,3%)	2(66,6%)	17.000			
Stage IV	40	40(100%)	0(0,0%)	13.375	2.341	8.786	17.964
ADK G1	10	1(10%)	9(90%)	81.333			
ADK G2	105	70(66,6%)	35(33,3%)	46.469	3.092	40.409	52.529
ADK G3	19	12(63,1%)	7(36,8%)	36.105	7.321	21.757	50.453
Ulcerative	6	3(50%)	3(50%)	22.500	2.376	17.843	27.157
Tubular	91	59(64,8%)	32(35,1%)	47.926	3.442	41.180	54.672
Mucipar (coloid)	24	14(58,3%)	10(41,6%)	46.073	7.500	31.372	60.773
Papillary	13	7(53,8%)	6(46,1%)	48.231	6.074	36.326	60.136

.

ANNUAL RATE OF CRC STUDIED CASES
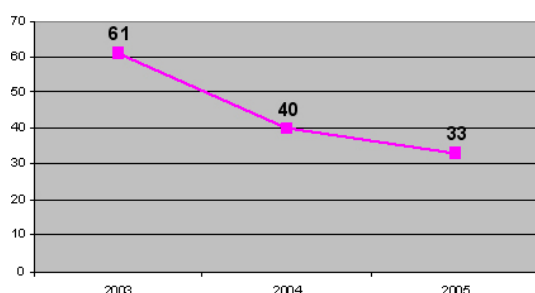
Chart nr.2: Annual rate of CRC studied cases.

The distribution by sex, throughout the studied period, shows the predominance of male cases (79 men and 55 women) with a ratio of M / F = 1,43:1. This report is descending in the years studied evolution (39 men/22 women = 1,72 in 2003; 22 men/18 women = 1,22 in 2004, 18 men/15 women = 1,2 in 2005). This change in the M/F ratio is not statistically significant, although there are european studies that confirm the increased incidence of malignancies in women in particular. (table nr.1)

Distribution by area of origin is Urban / Rural = 79/55 = 1,43.

The age distribution shows limits ranging between 33 and 91 years with an average of 65,34 + / - 1,86 years. The maximum age incidence is between 60-79 years - 82 patients (61,1%). Report colic cancer / rectal cancer was 91/43 = 2,11.

Neoplasia segments location showed high percentage of sigmoid location (30,5%), followed by rectum (18,6%), recto-sigmoid jonction (13,4%) and cecum-ascending (11,9%). I met two locations synchronous (cecum-ascending / transverse and transverse / sigmoid). It is proposed

that modern reporting the location of CRC to be made on three major segments - right colon, left colon and rectum - taking into account the embryological origin and evolutionary trends of this cancer. (table nr.1) [5]

Surgeries were performed on 65 patients elected, as there were also 69 cases in which the emergency occurred, they were showing occlusive, perforation or bleeding complications. They practiced all six types of surgery listed above: right hemicolecomy with ileo-transverse anastomosis (27 cases), transverse colectomy with colo-colic anastomosis (4 cases), left hemicolectomy with colo-recto anastomosis (48 cases), subtotal colectomy with ileo-colo anastomosis or colo-rectal anastomosis (4 cases), rectosigmoidectomy (Dixon) with colo-recto-anastomosis (38 cases), amputation of the rectum (13 cases).

Macroscopic aspects of excision parts showed the following: infiltrative - 34 cases, ulcerative - 18 cases, vegetant - 25 cases, ulcerative and vegetant - 34 cases, infiltrative and ulcerated - 18 cases, infiltrating and vegetant - 1 case, vegetant-infiltrative-ulcerated - 4 cases.

TMN staging of the study group revealed 18 patients in stage I, 73 stage II patients, 3 patients in stage III and 40 cases on stage IV. Microscopic types identified showed a predominance of tubular shapes (67,16%), followed by coloid (15,67%), papillary (9,70%) and others (7,46%). In terms of site gradding, we highlighted 10 cases of G1, G2 105 cases and 19 cases of G3. All patients were taken in the oncology service record and made chemo-radiotherapy treatment indicated by the practitioner.

On 01/JUL/2010, the data provided by the Registry of Civil Status of the city of Craiova, after patients personal numeric codes, we noted that 51 patients (38,05%) were alive. (chart nr. 3)
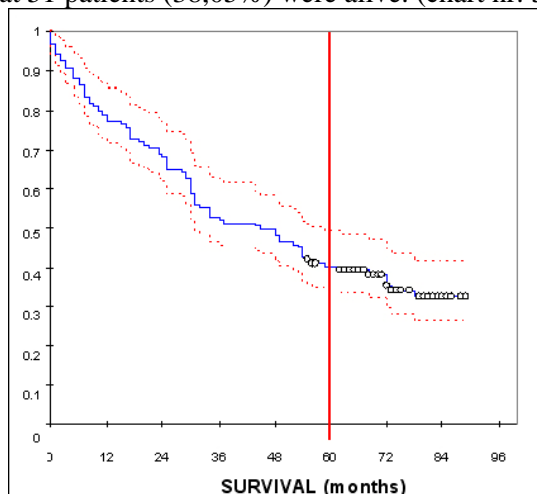
Chart nr.3: Survival in the studied group on 01/JUL/2010.

These results were corroborated with the epidemiological, demographic, surgical and oncological treatment, but also it encountered morphologically allowing assertion of conclusions.

Discussion

In our country, in 2005, the incidence of colon cancer was on the fifth rank of all malignant tumors, and together with the jonction rectosigmoidian was on the third place. Colon cancer mortality was on the fourth place of the deaths rank cancer in 2005 and 2006, and mortality rises with jonction rectosigmoidian on the third. [6]

In Romania, the incidence of CRC increased from 7,62 / 100 000 inhabitants in 2003 to 8,23 / 100,000 inhabitants in 2005. Although the reports are uniform worldwide, colorectal cancer is unknown and separate figures for neoplasia locations intestine segments. Thus, colon cancer is two times more frequently than cancer of the rectum [7].

Number of new cases of colorectal cancer detected are variable from one year to another, but with a growing medium and long term, despite the fact that the people of Romania that generates these patients decreases in absolute numbers. In other words, the incidence of this cancer is increasing in our country, this fact is evidenced by a study carried out, estimating that this trend of increasing incidence will occur at least until they reach the values reported by industrialized countries. Increasing incidence of CRC associated with increases in both prevalence and mortality of this disease, suggests that current methods of treatment, only few cases are actually curable, with a tendency to heal (cytological forms a good degree of differentiation, in an early stage), the rest is just temporary and/or limited interventions (several months to several years) due to extension of neoplasic disease.

In all three years of study, the incidence of cancer by sex is higher for males. Although there are constant from one year to another, these differences are not large enough to be considered statistically significant.

The people living in highly industrialized areas suffering of colorectal cancer is higher. This is maintained in our country, the incidence of CRC is higher on people from urban areas.The incidence of CRC represents 8% of all malignancies. Reffering to age groups, the incidence is higher than the average at age over 50 years and then it increases almost exponentially. Latest trends show an increase in cecum cancer

incidence from 5% to 36%, transverse cancer incidence increased from 15,8% to 17,2% and sigmoid cancer incidence decreased from 36% to 33,4% . The rest of 15% representing rectal cancer. [8]

CRC mortality in Romania has followed a steady increase from 14 ‰ to 18,3 ‰ for men and women in the years 1960-1990 to about 22,2 ‰ in 1995-2003 and decreased slightly to 19,2 ‰ in 2008, after the last statistical EU [8]. Following trends in incidence, mortality because of CRC is much higher in urban areas, without a tendency to change from one year to another. Following the death rates at national level we see that there are areas where values are closer to those from central and NW Europe (Arad, Bucharest, Timis) and areas (Vaslui, Ialomita, etc..) which has very low mortality similar to Mediterranean countries (Greece, Albania).

Mortality in this form of cancer depends on many factors including disease incidence values, clinical stage at admission (locoregional extension or at distance), primitive tumor and possible metastases, surgical treatment method applied, histopathological type, susceptibility methods of adjuvant chemotherapy and radiotherapy, immunological and general status of the subject, age, nature and number of associated comorbidities and coexisting diseases. Analysing survival in the study group noted a report M / F = 7/24 = 1,12 and urban / rural = 33/18 = 1,83. About the age groups, survival of the entire group at 01/JUN/2010 revealed that 44 (86,27%) patients were alive from group under 50 years, although the median survival in months is higher in patients under 50 years . This is explained by the fact that aggressive forms (G3) are the preserve of young age, and among them, those who survive have a greater life expectancy. (table nr.1 and chart nr. 4)
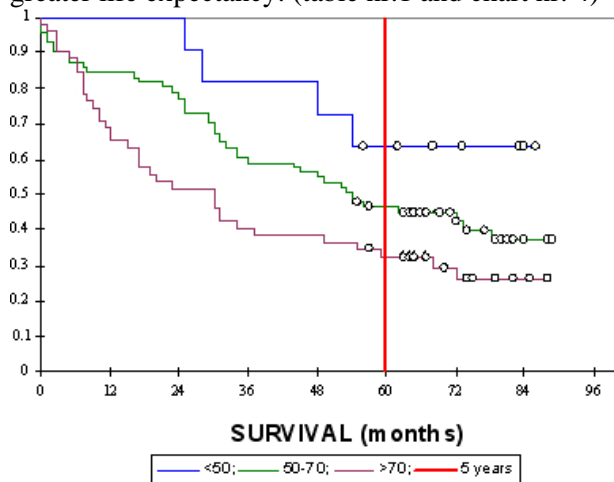

Chart nr.4: Survival on 01/JUL/2010, reported to age intervals, on the study group.

After the time of surgery - elective or practiced in emergency, the occurrence of occlusive, perforation or bleeding complications - note that survival is greater, statistically significant, on the planned interventions (41/10 = 4,1). (chart nr. 5)
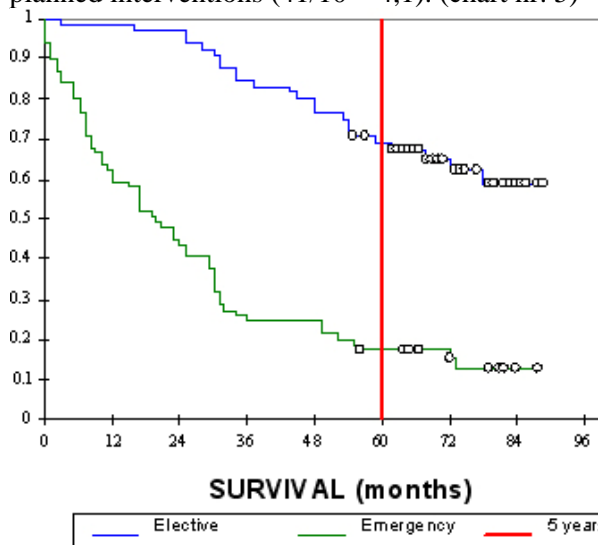
Chart nr.5: Survival on 01/JUL/2010, after the time of surgical procedure.

Analysis of cases by disease stage, as we expect to be, showed high survival in the early stages compared with advanced ones. (chart nr. 6)
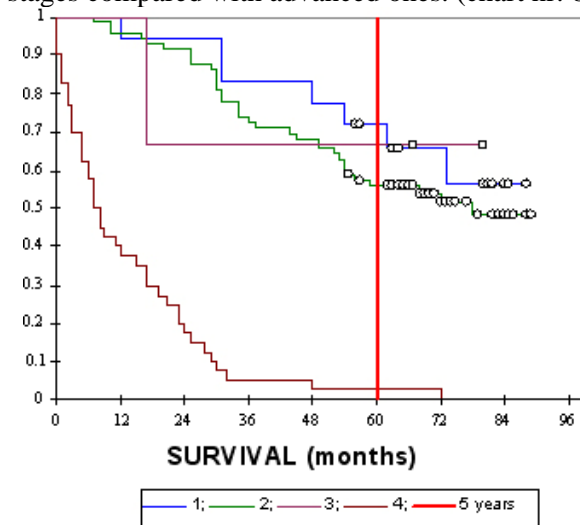
Chart nr. 6: Survival on 01/JUL/2010 after TNM stage.

Comparing survival of study group (38,05%) with literature data, we note that the average survival at 5 years after diagnosis of CRC is 62% in South Korea, 61% in the United States of America and 76% in Victoria, Australia. In stage I the survival is 92% (61,1% in our study), in stage II is 83% (52,0% in our study group), in stage III is 54% (66,6% in our study group) and 5% in stage IV (0% in our study). [9,10]

Conclusions

1. Colorectal cancer have a tendency to increase the incidence and prevalence lately. CRC is on the first rank among digestive malignancies and third rank, after lung and breast cancer. We find values above the national average in terms of incidence, prevalence and mortality in Dolj county.

2. The establishment of pilot centers in onco-surgical treatment, determine the number of CRC cases reported by local hospitals to be in slight decline.

3. CRC is not statistically significant in a relationship with sex patients (M / F = 1,43), although we notice a slight increase of the number of women suffering of CRC. 5-year survival was higher at women (43,6%) than men (34,1%). In the study conducted, most patients come from urban areas (U / R = 1,43), confirming the name of "disease of industrialized countries". In five years, most survivors were from urban areas (41,7%) compared with those in rural areas (33,7%), age groups most commonly affected are the 60-70 decades (61,1%) with a tendency to decrease in average age and best survival occurring it is younger than 50 years old (63,6%), even if this was the lowest numerically cases.

4. Doctors are asked by the patients in advanced stages, when present clinical signs of disease or occlusive, perforation or bleeding complications. This fact is emphasized by the report of the elective surgery / emergency = 0,94. Scheduled surgery patients had a 63,0% survival, compared with 14,4% in emergency surgery.

5. The most common sites of CRC were left in the colon, rectum and then the right colon, and 5 year survival was best to the left location recorded (44.6%) than to the right (43.7%), but not semnificative.

6. Ulcerated and infiltrative macroscopic forms of CRC have been most often and equally encountered (77,6%), and the best survival forms was vegetant (46,6%).

7. From the microscopic point of view, tubular adenocarcinoma was most common (67,9%) and the best survival was in the ulcerative (50,0%) and papillary (46,1%) form. Most common gradding was G2 (78,3%), and the longest survival recorded was in G1 (90,0%), although these forms were seen at 10 patients only.

8. The largest number of cases were diagnosed in stage II (54,4%) followed by stage IV (29,8%) and 5 year survival was for 51 patients (38,0%), only at patients with stage I, II and III .

9. Surgery treatment followed tumor resection, being dictated by the tumor location, disease stage, histological type and presence or absence of complications. Surgical intervention was associated with chemo-radio therapy.

10. Postoperative morbidity after colo-rectal surgery was the postoperative occlusion, bleeding exteriorized on the tube drain, fistulas with postoperative peritonitis, pulmonary embolisms, strokes, pneumonia, acute myocardial infarction etc.. The immediate postoperative mortality was 12 patients (8,9%).

11. Overall survival in our study group was 51 patients (38,05%), indicating that the results were good, even if we had a high percentage of emergency interventions practiced in advanced stages of disease. The introduction of new techniques for screening population, increasing educational level of population about adressing to the doctor, application of new advances in laparoscopic surgery and oncology management properly, all these assumptions can be verified now clear that results can be improved.

References

1. GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide in 2008, International Agency for Research on Cancer
2. Ciurea T, Pascu O, Stanciu C. Gastroenterologie şi hepatologie - Actualităţi 2003, Editura Medicală, 2003
3. Hamilton SR, Rubio CA, Vogelstein B - Tumors of the colon and rectum, în World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Digestive System. Hamilton SR, Aaltonen LA (eds), IARC Press, Lyon, 2000,103-145;
4. Jass J.R.. Serrated route to colorectal cancer: back street or super highway? The Journal of Pathology, 2001, 193(3):283-285
5. Feng-ying Li and Mao-de Lai, Colorectal cancer, one entity or Three, J Zhejiang Univ Sci B. 2009 March; 10 (3): 219-229
6. Centrul de Statistică al Ministerului Sănătăţii
7. Guidelines for the Management of Colorectal Cancer 3rd edition, Issued by The Association of Coloproctology of Great Britain and Ireland at The Royal College of Surgeons of England, 2007
8. Cancer European Observatory, 2008
9. N. Angelescu - Tratat de patologie chirurgicală - Ed. Medicală, Bucureşti, 2003
10. Popescu I. – Tratat de chirurgie,Ed. Academiei Române,2009; 9(2), 226-28

Correspondence Adress: Vasile Liviu, MD, PhD, Department of General Surgery, County Emergency University Hospital, Craiova, University of Medicine and Pharmacy Craiova, Str Petru Rares nr. 4, 200456, Craiova, Dolj, Romania