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DEMOGRAPHIC, CLINICAL, BIOCHEMICAL, PERIOPERATIVE ASPECTS IN COLORECTAL CANCER PATIENTS, 2002-2014

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ABSTRACT:
BACKGOUND AND AIMS: COLORECTAL CANCER (CRC) IS A NEOPLASM WITH INCREASING INCIDENCE IN THE LAST 20 YEARS, WITH IMPROVED OPERABILITY RATES, PERIOPERATIVE MORTALITY AND HIGHER SURVIVAL RATES, BUT WITH THE PERCENTAGE OF RECURRENCE OF THE DISEASE NOT IMPROVED DURING THE LAST 2 DECADES. THE PURPOSE OF THIS STUDY WAS TO EVALUATE PATIENTS WITH COLORECTAL TUMORS HOSPITALIZED, INVESTIGATED AND OPERATED DURING 13 YEARS, IN A SINGLE CENTER AND TO OBSERVE THEIR EVOLUTION. PATIENTS WITH THE DIAGNOSIS OF CRC HOSPITALIZED IN DR. I. CANTACUZINO HOSPITAL BETWEEN 2002-2014 WERE EVALUATED ON THE BASIS CLINICAL, BIOLOGICAL, ANATOMOPATHOLOGICAL DATA OBTAINED FROM PATIENTS SHEET AND ELECTRONIC DATABASE.

KEY WORDS: COLORECTAL CANCER, NODE STATUS, POSTOPERATIVE COMPLICATIONS, RECURRENCE

Abbreviations:
CRC - colorectal cancer
CC - colon cancer
RC - rectal cancer
EEA - end to end anastomosis
ESA - end to side anastomosis
PC - peritoneal carcinomatosis

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INTRODUCTION

Neoplastic disease is a major worldwide public health problem, prospective studies suggesting that cancer mortality will increase in the coming years, due primarily to the increase in life expectancy of the population, but also through the effect of population demographic development on frequency of cancers (population migration, effect of diet and environmental factors). Colorectal cancer (CRC) is a neoplasm located in the first places as an incidence both internationally and nationally. Among the technical advances that patients currently benefit from it, we can mention: population screening on risk, endoscopic interventions, minimally invasive interventions, mechanical suture devices, new classes of antibiotics, new classes of chemotherapy, immunohistochemistry techniques, multi-organ interventions in experienced clinics, leading to lower perioperative morbidity rates and associated general mortality, but with unchanged values of postoperative relapses over the last 20 years. In 2016, the mortality rate of this neoplasm was reduced below half compared to 1970, and the overall survival rates are 65%, depending on various factors, in particular the tumor stage[5].

Early recurrence is defined as tumor recurrence occurring less than 2 years after the initial tumor resection[6], although there are authors who consider that a 3-year interval would be more appropriate, considering that in the first 2 years postoperatively, local or distant recurrence would in fact constitute insufficient initial evaluation and staging of the neoplasm. CRC relapse is defined as local recurrence or near the initial tumor or at the level of the same organ, as well as metastasis to the adjacent or distant tumor tissue.

PATIENTS AND METHODS

This is a retrospective study in a single center taken between January 2002 and December 2014. The research project aimed to evaluate different patient related factors-demographic, clinical, biochemical, histopathological and perioperative complications and outcomes.

Ethics

The retrospective analysis of the data has been approved by Ethics Committee of the institution within which the work was undertaken and it conforms to the international provisions.

RESULTS

Between the years 2002-2014, during 13 years, the average number of interventions performed on colon and rectum were about 110 interventions/ year, representing 3.74% of the total number of interventions performed in the Dr. I. Juvara Surgery Department of Dr. I. Cantacuzino Hospital, but in increasing percentage until the study end (from 2.85% to 5.28%). It should be mentioned that the pathology operated in the Surgery Department is varied, comprising interventions of the hepato-biliary and pancreatic, abdominal wall surgery, digestive oncological surgery, genital, interventions performed open and laparoscopic, by case, also diabetic foot interventions or on mammary gland. The 1533 patients with surgical interventions on the colon and rectum required 1-6 operations (with an

[5] Cancer Facts & Figures, 2019, American Cancer Society, https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf, last modified June 2019

[6] McArdle CS, Hole DJ. Outcome following surgery for colorectal cancer: analysis by hospital after adjustment for case-mix and deprivation. Br J Cancer.2002;86:331-5

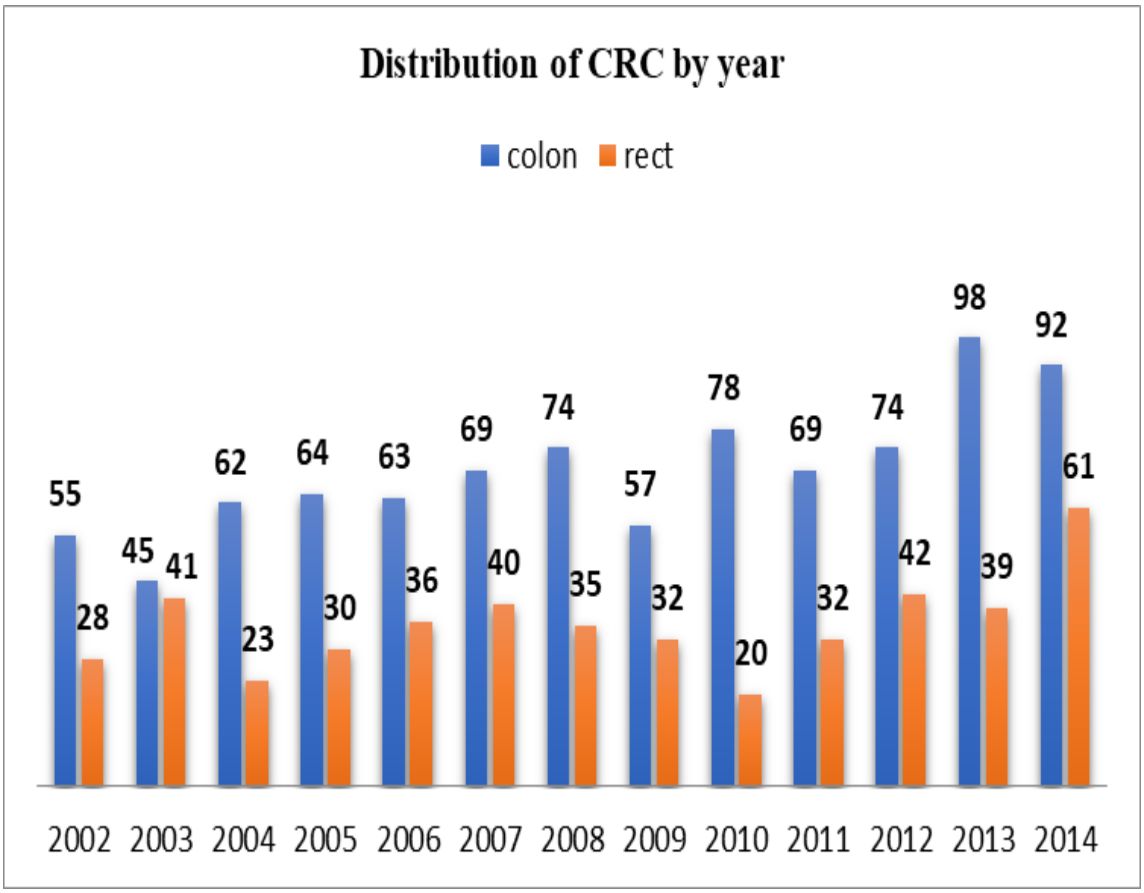
average of 1.17 interventions/ patient), within the same hospitalization or in iterative hospitalizations, the most common for postoperative or recurrent complications, local or at a distance.

We found a series of patients difficult to fit into a category, due to the lack of continuity of investigations or lack the data available for follow-up - of these, only 3% returned to the Surgery Department to the Medical or Gastroenterology Departments. These patients, who accidentally presented to the doctor or clinic, often after a rectal bleeding episode or due to a colonoscopy to investigate intestinal transit disorders, were in a very small number, difficult to include in subsequent analysis. There have been found the cases with surgical interventions performed on colon tumor without postoperative histopathological confirmation (without a malignancy confirmation), trans-anal polypectomies/colotomy-polypectomy and colon suture, and patients with malignant recto colonic polyposis, totaling a total of 98 patients. We also excluded a number of 23 cases, surgery performed without identifying a tumor formation per se ("false image"), in cases which suspicion was supported by imaging investigations (radiological, tomographic) or endoscopic.

We noticed in the selected group the presence of 8 cases of surgery in patients with known inflammatory bowel disease (Crohn's disease) or with complicated diverticular disease, 3 cases with intestinal lymphoma or gastro intestinal stromal tumor with colonic localization, and 17 cases of other neoplasms with invasion of the digestive tract, respectively colon, which required segmental colectomies or hemicolectomies. Multiple primary cancers may occur in an individual due to genetic predisposition, exposure to environmental factors, secondary to chemotherapy or radiation, or due to immunological deficiencies. Of the associated neoplasms in the selected group, we mention: lung (2 cases), cervical (2 cases), gastric (5 cases), laryngeal (1 case), breast (5 cases), malignant melanoma (1 case), ovary (1 case), lymphoma, multiple myeloma (4 cases), prostate (2 cases) histiocytoma and cerebral glyosarcoma (one case each). In an article published in 2002, based on the study of The Thames Cancers Registry (UK) database, which includes 1.5 million patients with CRC followed from the time of diagnosis till death, from 1961 to 1995, it found the onset of a second primary neoplasm in about 5% of them. Neoplasms induced by chemotherapy or radiotherapy occur in predictable time intervals from primary CRC treatment, thus 1-5 years for acute myeloid leukemia and 10-25 years for solid tumors[7].

Following the observations in pervious paragraphs we obtained a number of 1359 of patients, and their yearly distribution is presented in Graphic 1. It can be observed the progressive increase in the number of cases, at the beginning approximately 90-100 / year, exceeding 150 at the end of the study.

[7] H S Evans, H Moller, D Robinson, C M Lewis, C M J Bell, and S V Hodgson,
The risk of subsequent primary cancers after colorectal cancer in southeast England, Gut. 2002 May; 50(5): 647–652



Graphic1. Distribution of CRC cases by year

DISCUSSION

Age and gender

Most patients with CRC are elderly person at the moment of diagnosis, but frequently we are dealing with younger patients under 50 years, time at which the disease evolves for a long time and rectal bleedings were attributed to the hemorrhoidal disease, so that these patients come late to doctor (stage III-IV). In the case of the young patients, tumors are located distal from splenic angle more frequent, and rectal tumors occur in up to 39% of these cases[8].

For RC, in the group herein, we found an increasing frequency by age, with a maximum peak between 66 to 72 year in female gender and similar to male with a maximum peak of frequency between 64 to 71 age (Graphic 2,3). We noticed a similar peak between 51 to 58 for men, but with a smaller representation. We also found that 14, 4% of male patients are younger than 50, while only 8,3 % female patients are under 50 years age.

[8] Elizabeth A Myers, Daniel L Feingold, Kenneth A Forde, Tracey Arnell, Joon Ho Jang, and Richard L, Colorectal cancer in patients under 50 years of age: A retrospective analysis of two institutions' experience, Whelan World J Gastroenterol. 2013 Sep 14; 19(34): 5651–5657

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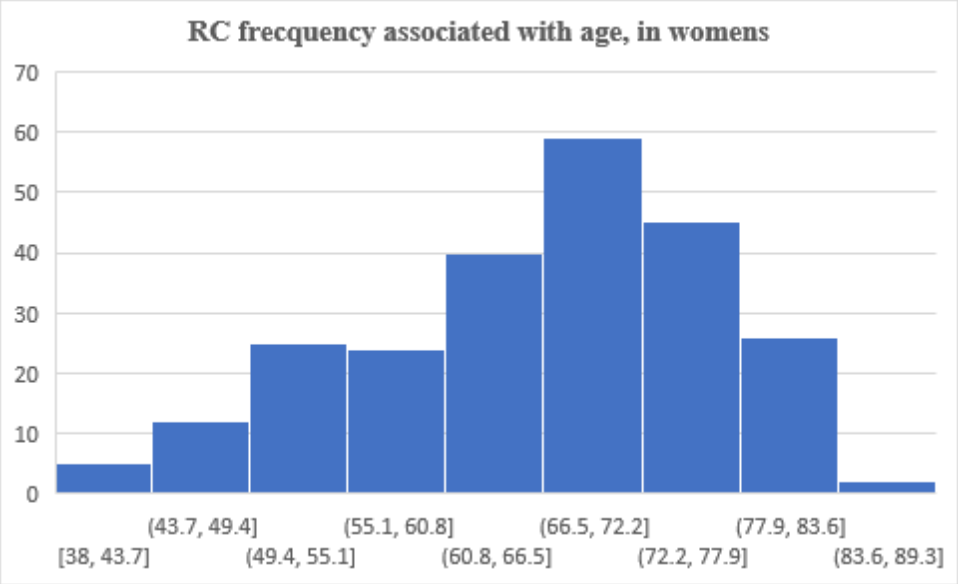
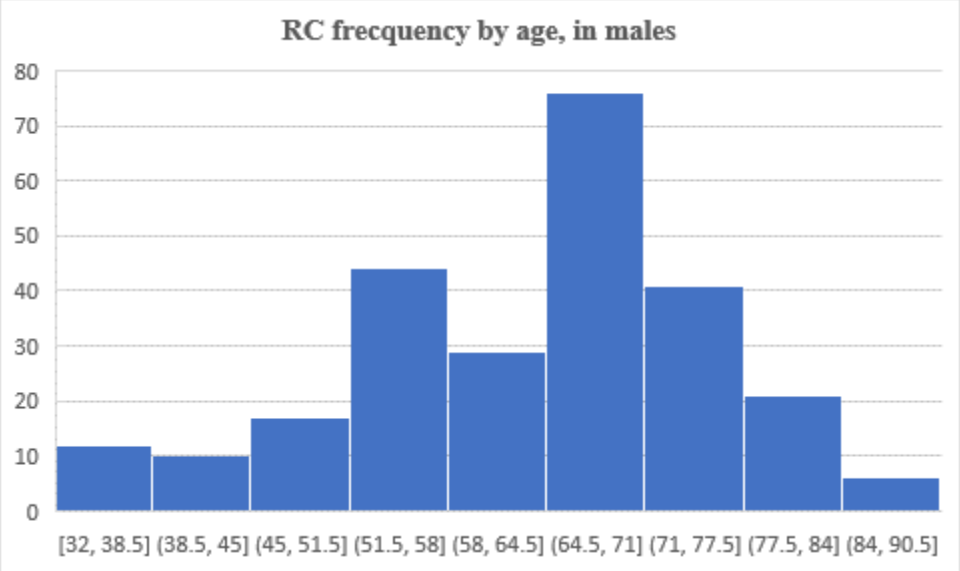
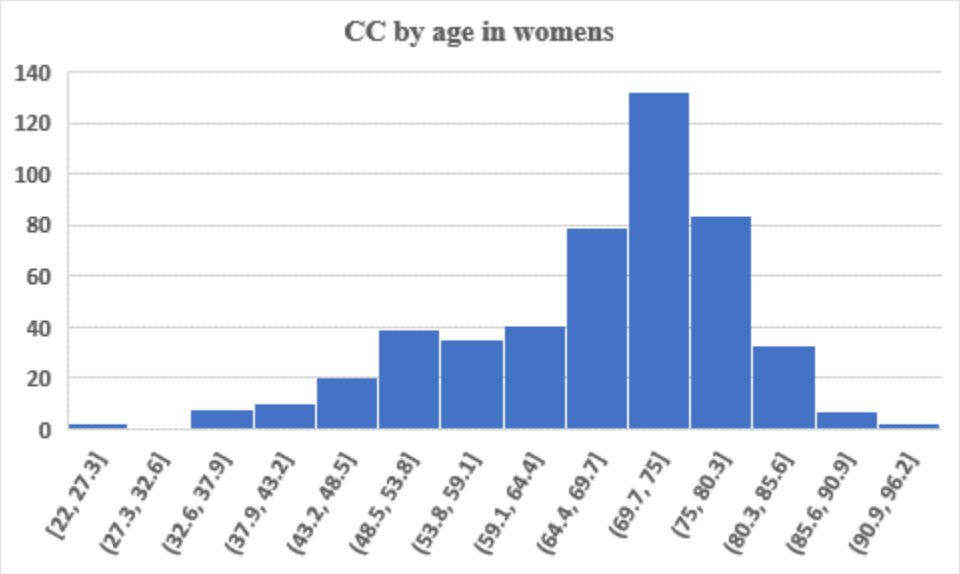


Graphic 2: RC frequency by age, in women

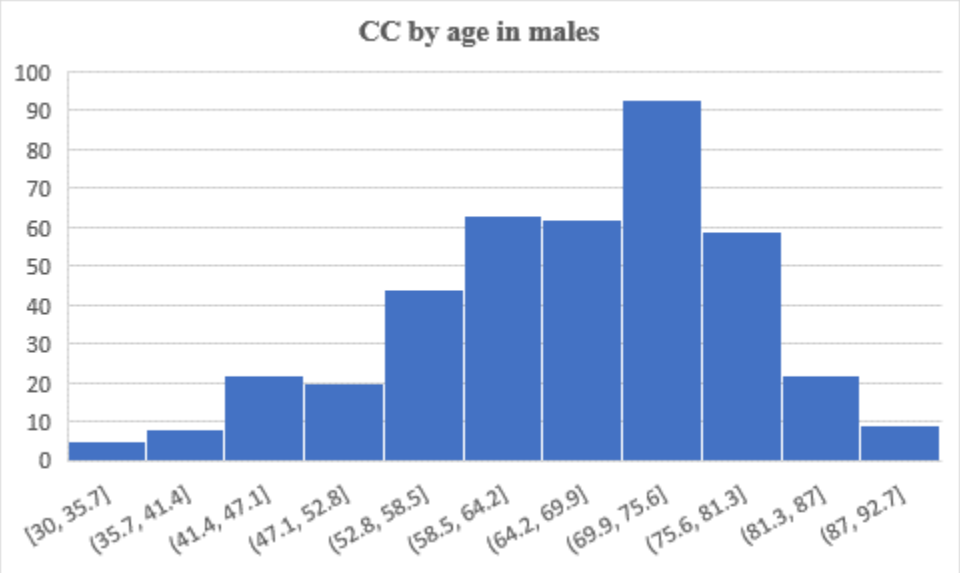


Graphic 3: RC frequency by age, in males

In the group of patients with CC there are no important differences in terms of distribution by gender in the studied group, with a similar mean age (67,44 vs. 67,21), and also for patients under 50 years age (11,67% vs. 11,41%). (Graphic 4, 5)



Graphic 4. CC frequency by age in women



Graphic 5. CC frequency by age in males

There are studies which suggest that women over 65 years of age have higher mortality rates and a shorter 5-year survival[9]. The causes that would produce this effect are not known, but observational studies indicate socio-cultural factors for certain populations, which are related to diet, hormonal status; also, women develop more frequent tumors in the right (proximal) colon that cause more aggressive forms of the disease, compared to those in the left (distal) colon[10]. In the right colon there are more frequent flat tumors, more difficult

[9] Sung-Eun Kim, Hee Young Paik, Hyuk Yoon, Jung Eun Lee, Nayoung Kim, and Mi-Kyung Sung, Sex- and gender-specific disparities in colorectal cancer risk, World J Gastroenterol. 2015 May 7; 21(17): 5167–5175

[10] Hansen IO, Jess P., Possible better long-term survival in left versus right-sided colon cancer - a systematic review, Dan Med J. 2012; 59: A4444; Rene Warschkow, Michael C Sulz, Lukas Marti, Ignazio Tarantino, Bruno M. Schmied, Thomas Cerny, and Ulrich Guller, Better survival in right-sided versus left-sided stage I - III colon cancer patients, BMC Cancer. 2016; 16: 554

to detect by colonoscopy, as opposed to the polypoid formations, which are more frequent in the left colon[11]. CRC screening is not differentiated by sex, but the sensitivity of the Hemoccult test, frequently used, is different in women and men[12]. However, there are articles in the literature that have found that recurrence occurs earlier and more frequently in young patients, and especially in men[13].

BMI, nutritional status

It is a well-known fact that obesity is a risk factor for CRC, as well as for the death associated with neoplasia. The negative association between BMI and recurrence risk was not observed in female patients, but men with BMI > 35 kg/m show a reduction in disease-free interval, compared to normal-weight patients. Also, the underweight patients have a decreased time interval until the moment of recurrence, and a stronger association with the male gender[14].

|In the group of patients from 2002-2014, based on the data available from the electronic archive and the observation sheets, we found the association with diabetes mellitus at 10.15% for RC and 9.00% for CC. Is a known fact that diabetes mellitus and CRC show similar nutritional risk factors as promoters of the disease. Obesity (BMI > 35) was identified in less than 1.5% of cases, and malnutrition or neoplastic cachexia in less than 2% of cases, when it was associated with all advanced stages, with secondary hepatic determinations, and most commonly in rectal tumors on elderly. We looked for the presence of nutritional factors, because the literature described that the risk of more frequent postoperative complications is associated with obesity and cachexia (anastomosis fistula).

Another factor that can influence the postoperative evolution, as well as the risk of recurrence, is the preoperative anemia, which we objected in 12.2% cases of RC and 15.7% cases of CC. In our group, secondary anemia in varying degrees was observed in all cases with secondary hepatic determinations (stage IV).

In the studied group we also identified associated cardio-vascular pathology (9.65% RC, 14.32% CC), liver cirrhosis / VHC (1.52% CR, 2.07% CC), symptomatic gallbladder lithiasis (1.84% cases). Cholecystectomy, as concomitant intervention, did not changed the rate of postoperative complications or the risk of recurrence.

Location of tumor

Primary tumor localization appears to be a prognostic factor, cancers located at/or below the peritoneal segments (rectum and sigmoid) have 5-year survival rates lower than for proximal tumors. Similar to the rectum, distal tumors have a more reserved prognosis[15].

In terms of distributions of colon tumors, we noticed the preponderance at the level of the sigmoid/rectosigmoid junction (42%), followed by the localization at the caecum or

[11] Kaku E, Oda Y, Murakami Y, Goto H, Tanaka T, Hasuda K, Yasunaga M, Ito K, Sakurai K, Fujimori T, et al, Proportion of flat- and depressed-type and laterally spreading tumor among advanced colorectal neoplasia, Clin Gastroenterol Hepatol. 2011; 9:503–508

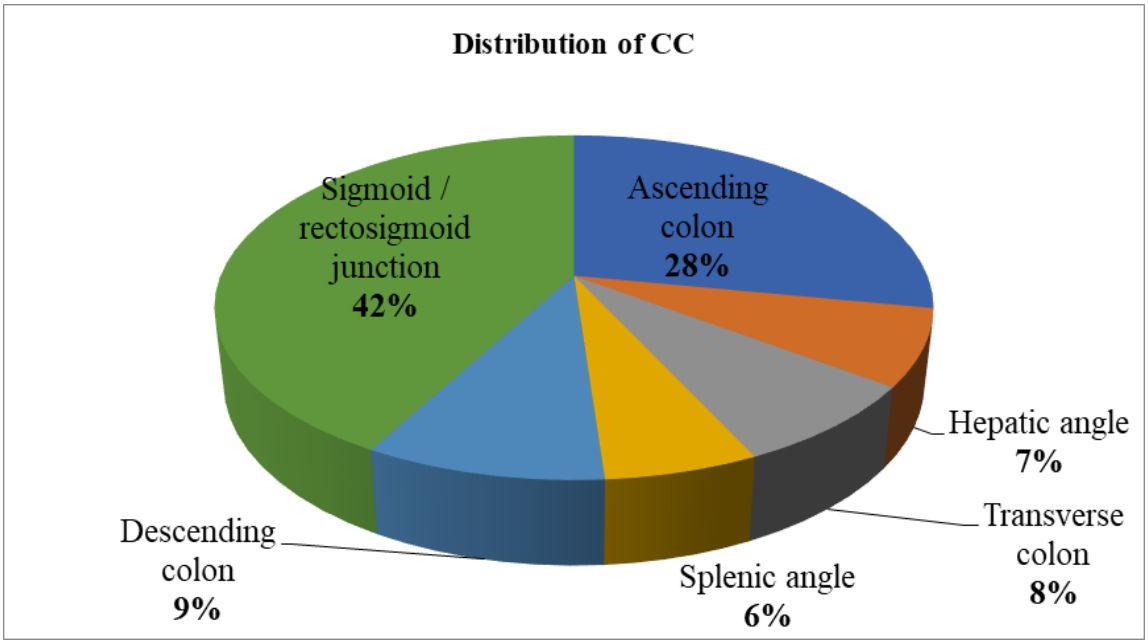
[12] Brenner H, Haug U, Hundt S, Sex differences in performance of fecal occult blood testing, Am J Gastroenterol.2010;105:2457–2464

[13] Aghili M, Izadi S, Madani H, Mortazavi H, Clinical and pathological evaluation of patients with early and late recurrence of colorectal cancer, Asia Pac J Clin Oncol. 2010 Mar;6(1):35-41

[14] Frank A Sinicrope, Nathan R Foster, Greg Yothers, Al Benson, Jean Francois Seitz, Roberto Labianca, Richard M. Goldberg, Aimery DeGramont, Michael J O'Connell, and Daniel J Sargent, Body Mass Index at Diagnosis and Survival Among Colon Cancer Patients Enrolled in Clinical Trials of Adjuvant Chemotherapy, Cancer. 2013 Apr 15; 119(8): 1528–1536.

[15] Halvorsen TB, Johannesen E, DNA ploidy, tumour site, and prognosis in colorectal cancer, Scand J Gastroenterol. 1990;25(2):141–8

ascending colon (28%), descending colon (9%), transverse (8%), hepatic and splenic angle (7%, 6%). Articles from literature highlights a similar distribution[16].



Graphic 6. Distribution of CC

The surgical interventions performed for CC were according to the tumor location, the biological and nutritional status of the patient and the intraoperative aspect (right/enlarged ileo-hemicolectomy with ileo-transverse EEA or ESA, segmental ileo-colectomy with ileo-ascending ESA, segmental colectomy splenic or hepatic angle with EEA, transverse colon segmental colectomy with EEA, left/wide hemicolectomy with transverse-sigmoid EEA, left hemicolectomy with colostomy, Hartmann's recto-sigmoid resection or with colorectal EEA or ESA, subtotal ileo-hemicolectomy with ileo-sigmoid ESA). We found 26 cases of synchronous tumors, either preoperative (colonoscopy) or intraoperative, which determined the extent of exertion. The most frequent associations were of rectal and sigmoid tumors (8 cases), followed by the ascending-hepatic, transverse-descending and other localization, without a significant association (transverse-sigmoid, hepatic-angle, caecum-sigmoid, sigmoid- hepatic/ splenic angle, sigmoid-ascending, sigmoid-descending, sigmoid-transverse-hepatic angle).

In the series herein the distribution of neoplasia in the rectum showed that 52,55% of the tumors develop in lower part, followed by 37,75% in the superior segment and 9,69% in the anorectal region. In the case of patients with RC, the following surgical procedures were performed: with a curative intention (64.7%), continuous colostomy (18.18%), colostomy and tumor biopsy (7.48%), trans anal tumor biopsy (8.02%), exploratory laparotomy (1.6%).

Surgery was performed with a curative intention on 298 patients, depending on the tumor localization; abdominoperineal amputation, anterior Dixon low resection and Hartmann operations were performed.

[16] Kari Hemminki, Irene Santi, Marianne Weires, Hauke Thomsen, Jan Sundquist, Justo Lorenzo Bermejo, Tumor location and patient characteristics of colon and rectal adenocarcinomas in relation to survival and TNM classes, BMC Cancer 2010, 10:68

Stage, TNM

In the case of CC, relatively few tumors were identified in T1, T2 stage, most being T3 or T4. Node status N0 was identified in 38,12% of cases, majority. It should be mentioned that the dissection and identification of the lymph nodes on the postoperative specimen was done by the Histopathology Department. Similarly, in the case of RC most were T3 tumors and N1 status were predominant.

In this retrospective group, we detected 234 patients with stage IV. Of these, 87 patients with rectal cancer had distant metastases (18,85 %) with a mean age of 62.33 (32-75 years), respectively 147 patients with colon cancer with distant metastases (16,33 %) with mean age of 65.77 (36-91 years). There were few cases of young patients (under 55 years old or younger) whose first presentation in the Clinic detected the presence of secondary hepatic metastases concomitantly with the CRC diagnosis. Most commonly we found hepatic localization (100%), preoperatively detected by imaging investigations and / or an intraoperative identification, followed by pulmonary localization (M2, 4 cases), ovary (M2, 2 cases), bone (M2 vertebral, 1 case). Over 50% of cases with secondary hepatic metastases showed peritoneal carcinomatosis +/- ascites.

CRC in emergency

The patient admission for CRC can be precipitated by obstruction, perforation and, less often, by bleeding. For right colon tumors, right hemicolectomy or bypass may be taken into consideration, and for left and right colon tumors, external derivation along with stenting, represents alternatives, depending on the particularities of the case. Stenting is recommended by many authors, as a first step of therapeutic approach, due to the decreased morbidity and mortality associated with an emergency colonic intervention. The technical success of the stenting was reported at 89-96%, and the clinical success at 85-92%. The mortality related to the procedure is about 1.5%, and the complications can be stent migration (4.4-11.8%), perforation (2.5-4.55) and obstruction (7.3-12%)[17].

In the retrospective study less than 5% of patients were admitted in an emergency complication. The causes of the sudden emergency hospitalization in colonic cancers were intestinal occlusion (3.69%), in decreasing order of frequency of localization, in the rectosigmoid, ascending colon, followed by transverse and caecum. For rectal cancer, occlusive phenomena at admission and emergency surgical intervention occurred in 4.06% of cases. There have also been cases of tumor perforation with localized or generalized peritonitis (caecum, splenic angle, descending and ascending colon) as well as a patient with pelvic abscess in the case of a large, superinfected, neglected rectal tumor.

We have observed frequently that occlusive phenomena were manifestations at admission and indication for emergency intervention in patients with local recurrence, especially in RC and those with PC.

We did not identify cases of severe bleeding in the studied group that required emergency surgery, possibly due to the fact that Dr. I. Cantacuzino Hospital did not have an emergency surgical or interventional endoscopy department at that time.

Postoperative complications

We chose to evaluate the postoperative complications, according to the Clavien-Dindo classification, excluding those of the first and second grade, without a major impact on

[17] Katsanos K, Sabharwal T, Adam A, Stenting of the Lower Gastrointestinal Tract: Current Status Cardiovasc Intervent Radiol 2010, Jun;34(3):462-73

the subsequent evolution. For colon cancer degree III b, IV complication (total 7.16%) were, as follow: anastomotic leak with peritonitis (3.69%), postoperative bleeding or hematoma, postoperative paralytic occlusion (1.61%), evisceration, acute mesenteric ischemia (2 cases, one requiring total colectomy). Two cases of grade V complications: a case of transverse segmental colectomy with anastomotic fistula and a subphrenic abscess in a right hemicolectomy case.

Anastomotic leak was the most frequent complication, the other postoperative complication occurred in a smaller percentage, several cases in each group, including the wound infection that required surgery under general anesthesia; the deaths occurred during the same hospitalization, postoperatively, after subsequent surgeries, in patients with multiple comorbidities.

For the rectal cancer according to the same classification we found in 9.13% of the patients operated, complications III b and IV degree: postoperative paralytic occlusion (the most common reason for early postoperative reintervention), few cases of postoperative bleeding at the rectal operative site, segmental intestinal necrosis, anastomosis necrosis, evisceration, perineal cellulitis, localized or generalized peritonitis, enteral fistulas.

Recurrence

Depending on the locations and the dedicated surgery, the recurrence in the CC were located as follows: sigmoid/rectosigmoid (13.42%), hepatic angle (7.69%), descending colon (7.14%), caecum-ascending colon (5.56%). The overall recurrence in the group with patients (CC) operated between 2002-2014 was 8.45% in a time interval of 1 to 7 years after the intervention with the curative intention.

The recurrence observed during the studied time of RC was 10.74% (1 to 7 years). Several authors have observed that the risk of recurrence increases as the tumor is located more distally, especially, below the level of peritoneal segment[18].

Different patient related factors - demographic, clinical, histopathological and outcomes are summarize in the tables 1, 2.

[18] Berrino F, De Angelis R, Sant M, Rosso S, Bielska-LasotamM, Coebergh JW, Santaquilani M, Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995-99: results of the EUROCARE-4 study, Lancet Oncol. 2007; 8:773–783; Alan White, Lucy Ironmonger, Robert JC Steele, Nick Ormiston-Smith, Carina Crowford, Amanda Seims, A review of sex-related differences in colorectal cancer incidence, screening uptake, routes to diagnosis, cancer stage and survival in the UK, December 2018, BMC Cancer 18: 906; Lan YT, Chang SC, Yang SH, Lin CC, Wang HS, Jiang JK, Chen WS, Lin TC, Chiou SH, Lin JK, Comparison of clinicopathological characteristics and prognosis between early and late recurrence after curative surgery for colorectal cancer, Am J Surg. 2014 Jun;207(6):922-30

Age and gender	**Male** Average 61.23 (min=32; max=89) 14.4 % < 50 years	
	Female Average 59.7 (min=43; max=89) 8.3 % < 50 years	
Distribution of tumors	Upper rectum	37.75 % (173)
	Lower rectum	52.55 % (241)
	Anorectal	9.69 % (44)
Tumor (T) status	T1	1.64 % (8)
	T2	25.41% (115)
	T3	46.72 % (213)
	T4	27.05 % (123)
Node (N) status	N0	29.93 % (138)
	N1	40.27 % (185)
	N2	29.71 % (136)
Stage	I	13.11 % (60)
	II	22.95 % (105)
	III	45.08 % (207)
	IV	18.85 % (87)
Recurrence	1 – 7 years	10.74 % (50)

Table 1. Patient related factors in RC

Age and gender	**Male** Average 67. 44 (min=30; max=92) 11.67 % < 50 years	
	Female Average 67.21 (min=22; max=91) 11.41 % < 50 years	
Distribution of tumors	Sigmoid/rectosigmoid	42 % (378)
	Caecum, ascending colon	28 % (252)
	Descending colon	9 % (81)
	Transverse colon	8 % (72)
	Hepatic angle	7 % (63)
	Splenic angle	6 % (54)
Tumor (T) status	T1	2.03 % (19)
	T2	13.00% (117)
	T3	48.37 % (438)
	T4	35.78 % (326)
Node (N) status	N0	38.12 % (343)
	N1	33,12 % (298)
	N2	28.78 % (259)
Stage	I	11 % (99)
	II	27 % (243)
	III	45.67 % (411)
	IV	16.33 % (147)
Recurrence	Sigmoid/rectosigmoid	13.42 %
	Hepatic angle	7.69 %
	Descending colon	7.14 %
	Caecum, ascending colon	5.56 %

Table 2. Patient related factors in CC

CONCLUSION

The average number of interventions performed on colon and rectum for neoplastic disease were in increasing number until the study end (from 2.85% to 5.28%), according to increasing prevalence. In terms of distributions of colon tumors, we noticed the preponderance at the level of the sigmoid/rectosigmoid junction, followed by the localization at the caecum or ascending colon. The distribution of neoplasia in the rectum showed that majority of the tumors develop in lower part, followed by those in the superior segment. There are still many young patients, especially men, with stage III, IV CRC tumors, despite numerous screening programs and awareness campaigns. The causes of the sudden emergency hospitalization in colonic cancers were intestinal occlusion. Anastomotic leak was the most frequent complication, the other postoperative complication occurred in a smaller percentage. The recurrence rate observed during the studied time for both, CC and RC, are still high.

CONFLICTS OF INTEREST

Authors declare no conflict of interest in relation to our study and the publication of this article. No financial support has been received for this work.

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