ANALYSIS OF PROGNOSTIC FACTORS IN COLORECTAL CARCINOMA

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ANALYSIS OF PROGNOSTIC FACTORS IN COLORECTAL CARCINOMA (Abstract): Colorectal cancer is one of the most common malignancies in development countries. The purpose of this study was to analyze the epidemiologic profiles of the disease, to examine the results of survival at five years after diagnosis and how it was influenced by pathological aspects. **Material and methods:** In collaboration with Oncologic Clinic all colorectal cancer diagnosed from January 2002 to December 2006 were included in the study. Medical records of patients were retrieved and we note: age, residence, diagnosis date, grade, and stage and histology variables. Then were analyzed prognosis and survival at 5 years of patients related to these parameters. **Results:** A total of 238 patients with colorectal cancer were identified. The average age at diagnosis was 63.3 years and more than half of cases were men (59%). By the end of the follow-up period 103 patients had died, 66.1% of them representing colon cancer. When analyzing the survival length according to tumor location at the end of the study, we found that are no significant differences between survivals in colic tumors compared to the rectum – 53.9 months for right colon, 51.4 months for left colon and 49.5 months for rectum. The majority of tumors were grade II moderately-differentiated tumors (48.7% (116 of cases), and patients with grade I had the best survival, on average of 84.52 months. Tubular forms of colorectal cancer had the best percentage of five years survival (55.81%) being also the highest rate of survival (45.24% months). **Conclusion:** Factors that contribute to a favorable prognosis in colorectal cancer are tubular microscopic form, disease diagnosed in TNM stage I and II, GI and GII grading. **Keywords:** COLORECTAL CANCER, ADEN CARCINOMA, PROGNOSTIC FACTORS.

Colorectal cancer is one of the most commonly diagnosed cancers worldwide with over 1.2 million new cancer cases and 608700 deaths estimated to occur annually. According to the last global onco-epidemiological analysis it is the second most common cancer among women, and the third most common cancer among men (1, 2).

In Romania, colorectal cancer is the most common gastrointestinal malignancy, representing the third leading cause of cancer death after lung and breast cancer. The highest incidence of colorectal cancer is in patients pertaining to the 60-69 years age group. Since in Romania, based on demographic studies, the population above 65 years old will double in the next 50 years, we have considered a more detailed analysis of the factors then can influence the development of complications and occurrence of postoperative deaths in patients
older than 80 years old that are operated on for colorectal cancer to be useful (3).

New research about colorectal cancer is determined by the continuous increase of disease incidence both undeveloped countries that already register high levels of prevalence, and in countries where colorectal cancer incidence was not regarded as a matter of concern. The increase in incidence of colorectal cancer in Romania and also in Eastern Europe countries could be attributed to lifestyle changes, presumably introduced by westernization, resulting in obesity and physical inactivity (4).

As in any neoplastic disease, the tumor stage remains to be the most important factor of prognosis in colorectal cancer and it is the basis for the authoritative patient management guidelines that influence most patient management decision. The International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC) TNM classification system is the principal staging systems utilized and therapeutic decisions are most often based on this classification system (5). Great changes in the TNM staging system for colorectal cancer have occurred from the 5th edition to the 7th edition, particularly regarding the pN classification.

The diagnosis and early detection of colorectal carcinoma is one of the major goals and should become a priority for the health system. Colorectal cancer recognizes a natural evolution compatible with a long asymptomatic period, generally estimated to last over five years. This period corresponds to early stage of cancer transformation of adenomatous polyps to cancer and invasion beyond the basement membrane. A significant number of patients with colorectal carcinoma who undergo apparently curative surgery develop local recurrence or distant metastases, leading to shorter survival rate of survival.

The prognosis of colorectal carcinoma patients involves many factors such as histological type of cancer, size, location, degree of tumor invasion, loco regional metastases, and in other organs (6). Although treatments for colorectal carcinoma have developed rapidly in recent years, colorectal cancer still remains the second common cause of cancer – related death. To improve colorectal cancer prognosis, fundamental research in genetics and molecular biology and colorectal screening with the widespread practice of non invasive techniques (virtual colonoscopy) are some new relatively new directions to be developed (7).

**MATERIAL AND METHODS**

The study registered 238 patients who were diagnosed with colorectal cancer hospitalized in the Filantropia Hospital of Craiova from January 2002 until December 2006. We performed this study in collaboration with the Oncology Clinic in order to identify cases of colorectal cancer, to describe the epidemiologic profiles of the disease, to examine the results of survival at five years after diagnosis and how it was influenced by pathological aspects. Processed data are from case report forms. Data on survival June 1st, 2012 – when the patients follow-up – were from the Registry of Civil Status of Craiova.

**Data collection**

Medical records of the 238 patients were retrieved and the following information abstracted: age, residence, diagnose date, grade, stage, topology, histology variables and treatments. There were analyzed prognosis and survival of patients examined in the batch related to these parameters. Preoperatively patients from the study
were investigated by colonoscopy. Histopathological reports were reviewed to delineate the main citopathologic features, sub-site affection, the presence of any predisposing pathology and disease stage.

In the medical records of patients were found six types of surgery: colectomy for transverse colon with colo-colic anastomosis, subtotal colectomy with ileo/colo/rectal anastomosis, amputation of the rectum, and right hemicolectomy with ileo-transverse anastomosis ileo/colo/rectal, rectosigmoidectomy resection with colo-recto anastomosis and left hemicolectomy with colorectal/colo anastomosis.

**Data processing and analysis**

The main statistical analysis software packages were Microsoft Excel 2003 and Epi Info 2000. The 5-years overall and specific survival rates were estimated using the Kaplan-Meier method and the differences between the categories of each variable were assessed using log-rank test.

**Ethical considerations**

Permissions were obtained from Filantropia Hospital of Craiova as well as from the authorities of the included hospitals after approval of the study protocol and data compilation form. Data confidentiality was maintained all through the study.

The main goals for this study were:
- to identify cases of colorectal cancer;
- to describe the epidemiologic profiles of the disease;
- to examine the results of survival at five years after diagnosis and how it was influence by location and pathological aspect.

**RESULTS**

A total of 238 cases of colorectal cancer were included in registry from January 2002 to December 2006 and 103 patients of these are diseased. The distribution by sex, through the studied period, shows the predominance of male (59%), giving a male: female of 1.4:1.

Patients designated as residing in an urban area constituted 63% of all patients and distribution by area of origin is urban/rural = 1.70. In any given year, between 37 and 60 new cases of colorectal carcinoma were included in registry. Age and tumor site distribution of cases showed that 7.4% of all cases were under the age of 40. The age distribution showed limits ranging between 29 and 82 years with an average of 63.3 years. The maximum age incidence is between 58-74 years. Report colic cancer/rectal cancer was 161/77 = 2.19.

For an effective and comparative analysis of clinical features, treatment and prognosis in colorectal cancer, the large bowel was divided based on embryological, anatomical, clinical, pathogenesis and therapy in three segments: right colon (I) until the splenic angle, left colon (II) until the rectosigmoid junction and rectum (III) (8). According to this, the location of colorectal cancer was: right colon 34 cases (14.3%), left colon 127 cases (53.4%) and rectum 77 cases (32.3%).

The vast majority of patients did not present polyps 234 (98.3%), though of the 4 patients who had polyps, 75% were over the age 40. Adenocarcinoma was the most common histopathology type of tumors 198 (91.2%)

The majority of tumors were grade II moderately-differentiated tumors 48.7% (116 of cases), followed by 23.9% (57 cases) grade III, 15.5% (37 cases) grade I and 11.8% (28 cases) grade IV. The degree of differentiation of colorectal adenocarcinoma showed a large number of patients
Analysis of prognostic factors in colorectal carcinoma

alive with G1 (86.48%), followed by those with G2 (61.20%), G3 (35.08%) and G4 (7.14%). Patients with G1 had the best survival, on average of 84.52 months, followed by those with G2 with an average of 59.21 months, G3 (31.34 months) and G4 (3.86 months).

TNM staging of the study group revealed 41 patients in stage I (17.2%), 86 patients in stage II (36.1%), 83 patients in stage III (34.9%) and 28 cases in stage IV (11.8%). Positive nodes were identified in 89 patients with stage III and IV, as follows: stage III - N1-47 cases and N2-36 cases; stage IV – N1-17 cases and N2- 34 cases. Metastatic colorectal cancer was diagnosed in 11.8% of cases, mostly involved peritoneum and liver.

Surgeries were performed on 217 patients. They practiced all six types of surgery listed above: colectomy for transverse colon with colo-colic anastomosis 29 cases, subtotal colectomy with ileo/colo/rectal anastomosis 19 cases, amputation of the rectum 79 cases, right hemicolectomy with ileo-transverse anastomosis ileo/colo/rectal 34 cases, recto-sigmoidectomy resection with colo-recto anastomosis 47 cases and left hemicolecotomy with colo-recto/colo anastomosis 42 cases.

DISCUSSION

Colorectal cancer 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 statistics (9). Following trends in incidence, mortality because of colorectal cancer is much higher in urban areas, without a tendency to change from one year to another.

Numbers 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 represent these patients decreases. 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 colorectal carcinoma associated with increase 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 differentiations, in an early stage), the rest is just temporary and/or limited interventions (several months to several years) due to extension of neoplastic disease.

Results of a European study show that survival at five years in patients with colorectal cancer as a whole is especially influenced by stage and the factors that are directly or indirectly related to the primary tumor. Thus, these prognostic factors that should be considered in assessing the survival and follow-up are: stage, grading and adenopathy (10).

We note an increase in the number of cases from year to year. Thus, in 2002 there were 37 cases diagnosed, in 2003 their number increased to 41 cases, in 2004 we identify 47 cases, 53 cases in 2005 and 60 cases in 2006. The distribution by sex, giving a male: female of 1.4:1. 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.

In agreement with other studies (11, 12), survival rates were significantly higher in women. This association has been attributed to many underlying factors, such
as access to care, sex-specific co morbidities treatment disparities and hormonal status. The CONCORD study observed that in most countries, survival was better in patients with colon cancers than in those with rectal cancers (12). The association found between an excess risk of death and some clinical factors is consisted with the results of previous studies. Advanced stage at diagnosis (13), undifferentiated/poorly differentiated tumors (14) are factors that well known and described in the literature.

According to the present study the average at diagnosis of was 63.3 years. When compared with the reports from developed countries (15, 16), the mean age at diagnosis of colorectal cancer is lower in the Kingdom. In England, some researchers reported that between 1996 and 2004 the mean age at diagnosis of colorectal carcinoma was 68.4 years in men and 69.0 years in women (17). In Australia, the median age at diagnosis of colorectal cancer in 2008 was reported to be 70.0 years (18), similar to that is reported in the United States (19) and Sweden (20).

Since Dukes classification, all classification system of colorectal cancer were the most important predictor of survival, determining prognosis is the reason why they were created. The most used and reliable classification system is the system adopted by the AJCC TNM (American Joint Committee on Cancer) and UICC (International Union Against Cancer) (21). Undoubtedly, the most important prognostic factors for survival are the extent of tumor invasion into the wall and the presence of metastases in regional lymph nodes-the stage in which colorectal cancer was diagnosed (22). Obviously, the more advanced the stage of the cancer of the colon or rectum is, the more the life expectancy is less (23).

According to stage, patients that are still alive had a median survival of 73.61 months for stage I, 54.13 months for stage II, 43.6 months for stage III and 9.21 months for stage IV. Wilcoxon test showed the same high statistical significance differences between stage, with a p-value of less than 0.0001 (Fig. 1).

According to the TNM classification (24) pT4 is the most advanced stage of local tumor development in colorectal cancer, including both direct tumor invasion of adjacent structures (pT4) and invasion of visceral peritoneum with invasion of adjacent structures (pT4) including here free perforation into the peritoneal cavity. The most important and damaging to prognosis characteristics of colorectal tumor failing in T4 is the serous as a separate anatomo-pathological variable demonstrated in the multivariate analysis that this is an independent negative prognostic factor (25). In our study we find 28 patients in stage IV, 11 patients with peritoneal metastases and 19 with hepatic metastases.

When analyzing the survival length according to tumor location at the end of the study, we found that are no significant differences between survivals in colic tumors compared to the rectum – 53.9 months for right colon, 51.4 months for left colon and 49.5 months for rectum. Kaplan-Meier curves showed no significantly higher survival rated for colon compared to the rectum (fig. 2).

Gross pathological form is a parameter in formulating prognosis, tumor appearance reflecting its biological nature. Exofitic or polipoid tumor patients seem to have a better prognosis than those with ulcerated or infiltrative tumor. In our study macroscopic aspects of excision parts showed the following: infiltrative-48 cases (22.1%), ulcerative–35 cases (16.1%), vegetant–32 cases (14.7%), ulcerative and vegetant–56
cases (25.8%), infiltrative and ulcerated–21 cases (9.7 cases), infiltrating and vegetant–13 cases (6.0%), vegetant – infiltrative - ulcerated–21 cases (5.5%).

Concerning the microscopic examination, the highest percentage of patients alive was recorded in tubular forms (55.81%), followed by papillary forms (46.55%), rare/particular (45.83%) and mucinous (31.42%). In terms of number of cases tubular colorectal cancer had the best percentage of five years survival (55.81%) and longest higher survival (45.24%). Kaplan-Meier curves showed significantly higher survival rates for mucinous compared to tubular forms (Fig. 3).

Colon cancer, as well as rectal cancer treatment, changed over time, in our study adjuvant chemotherapy was administered.
to 138 (85.71%) of patients with colon cancer and 56 (72.72%) with rectal cancer. By the end of follow-up, 103 patients had died: 68 deaths (66.1%) were due specifically to colon neoplasm and 35 (33.9%) were to rectal cancer (Fig. 4).

Fig. 3. Kaplan-Meier survival curves and CRC microscopic aspects

Fig. 4. Kaplan-Meier survival curves and CRC adjuvant therapy

Evaluating lymph node metastasis has become a prognostic factor for CRC, and LNR is an important component of staging. LNR has also been identified as being of significant prognostic value in breast and gastric cancer. Berger et al were the first to suggest LNR as an important prognostic factor after curative resection for CRC. It was then established as a powerful independent index of CRC that reflected the probability of positive lymph nodes based on the number of retrieved lymph nodes.
The total number of lymph-nodes resected was not found to be a significant predictor of survival under univariate analysis (P=0.44), survival for patients grades N1 and N2 was 32.3% and 43.5% at 5- years respectively (Fig. 5).

**Fig. 5.** Kaplan-Meier survival curve for node-positive patients stratified by N stage

**CONCLUSIONS**

Colorectal cancer recognizes a natural evolution compatible with a long asymptomatic with a long asymptomatic period, generally estimated to last over five years. The introduction of new techniques for screening the population, the increasing educational level of the population, the use of recent advances in laparoscopic surgery and oncology management, properly improved the result. Factors that contribute to a favorable prognosis in colorectal cancer are tubular microscopic form, disease diagnosed in TNM stage I and II, GI and GII grading.

Using routinely collected data, at no inconvenience to patients, we have identified some important areas relating to early deaths from colorectal cancer, which merit further research.

**REFERENCES**


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