ORIGINAL PAPER

Histopathological factors as predictors for survival in colon and rectal cancers

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Abstract

Colorectal cancer is one of the most frequent malignant diseases with a raising incidence in Romania. Survival at 5-years even was improved in the last decade, remains low especially because of delayed diagnosis. Many clinical-biological and pathological factors have demonstrate a good prognostic value over the time but there are not a wide consensus in this field. The aim of our study is to evaluate the accepted pathological prognostic factors of survival for colorectal cancer in relation to management adopted in a general surgical clinic. We included in our study 273 patients with colon and rectal cancers admitted in Surgical Clinic of Military Hospital of Craiova in which we evaluate the clinical-pathological features, location of the distant metastasis, postoperative staging, curability and survival. We established correlations, inside of a same stage of the disease, for pathological features (characters of the tumors, differentiation grade and location) and survival rate. Our results showed that curative resection is one of the most important factors that could improve survival. Tumor differentiation is correlated with survival only for the patients with stage II and III of the disease, perineural invasion and pathologic N stage representing important predicting factors for a shorter survival. Peritoneal washing for cytology prior to surgery is correlated with the stage of the disease and not with tumor differentiation.

***Keywords*:** colon and rectal cancer, histopathological predictors.

Introduction

Colorectal cancer is one of the most frequent malignant diseases with a raising incidence in Romania. In Western Europe and in North America is the second commonest cause of death. For example, in United Kingdom there are about 35 000 new cases annually [1]. In our country survival at 5-years, even was improved in the last decade, remains low especially because of delayed diagnosis, the great majority of cases being discovered in stage III and IV. Surgical resection in oncological limits with adjuvant chemotherapy and/or radiation therapy is the standard approach for treating this disease. Management of stage IV colorectal cancer with incurable metastatic disease is not uniform, considerable effort being orientated in evaluating the prognostic value of a lot of factors [2]. On the other hand, for an adequate tumor staging, a complete resection of lymph nodes is necessary. The presence of malignant lymph nodes is considered an independent predictor for survival [3], but some studies considered that number of examined lymph nodes, itself, is a prognostic value on outcome [4]. Many clinical-biological and pathological factors have demonstrate a good prognostic value over the time but there are not a wide consensus in this field. The aim of our study is to evaluate the accepted pathological prognostic factors of survival for colorectal cancer in relation to management adopted in a general surgical clinic.

Patients and methods

We included in our study 273 patients with colon and rectal cancers admitted in Surgical Clinic of Clinical Military Hospital of Craiova. Routine laboratory measurements were: hemogram, serum levels of urea and glucose, hepatic cytolysis enzymes, albumin, C-reactive protein concentration and CEA. Depends on special conditions of the patients, other biological exams were made. In all patients we achieved colonoscopy and/or double contrast barium enema and,

for selected situations, endorectal ultrasound, CT-scan or MRI.

The clinical-pathological features (location and characters of the tumor, stage of the disease), location of the distant metastasis, postoperative staging, curability and survival data were retrospectively studied using medical records. We established correlations, inside of a same stage of the disease, for pathological features (characters of the tumors, differentiation grade and location) and survival rate.

Colic or rectal resection was achieved in oncological limits beginning with vascular legation and continuing with colorectal excision and lymph node dissection (Figure 1). In the last two years of this study, prior to colectomy we collected peritoneal liquid for cytological examination. This step was achieved immediately after opening peritoneum with special attention to parietal hemostasis in order to eliminate blood contamination of the peritoneal liquid.

All pathological examinations were performed by one pathologist. Formalin-embedded tissues were stained with Hematoxylin–Eosin for histopathological examinations. Tissue samples were collected from the colon or rectal tumor and from resection limits. Lymph nodes were also completely examined. The tumor-related data were depth of tumor invasion, grading (well, moderate or poorly differentiated) and presence of residual tumor at the sample tissue limit. Nodal status, lymph node number, presence of nodal inflammation, lymphatic invasion and, also, neural invasion were documented, too. For the tumors located in right colon, we examined the vermiform appendix and we evaluated the potential influence of the length of resected ileum segment.

The presence of distant metastasis was documented according to the preoperative imaging studies and it was confirmed during the surgery with histopathological confirmation. Extra abdominal metastases were documented imagistically and, in all cases where was possible, we obtained a histological confirmation.

Morbidity was assessed using medical records realized during the hospitalization. Operative mortality includes death occurring during hospitalization or during the first 30 days after the surgery. Postoperative evaluation was achieved daily during hospital stay and, after discharge, at one, 3 and 6 months and, after that, biannually.

Survival was analyzed by the Kaplan-Meier method, and the variables were compared using the log-rank test. Multivariate analysis was performed with the Cox proportional hazard model. The relationships for each patient's characteristic was assessed by means of the chi-square test or Fischer's exact test, p-values of less than 0.05 being considered statistically significant.

Results

Hundred and sixty-one from all 273 patients were males and 112 females, with a sex ratio of 1.44 : 1. The mean age was 59.5 years (range 26–86 years). Female average was 61.1 years and male 58.9 years. Seventy-nine patients (25.3%) were admitted in emergency conditions. The median follow-up was 12.3 months (range from one to 73 months). Survival was determined, too, by studying Oncological Registry from Dolj County (Romania), which is residence place for a great majority of our patients.

Localization of the tumors was the following: right ascending colon and cecum – 72 cases (26.37%); transverse colon – 22 cases (8.06%); left descending colon – 38 cases (13.92%); sigmoid colon – 45 cases (16.48%); rectum – 96 cases (35.17%).

According to disease stage, distribution of patients is presented in Table 1.

Table 1 – ***Stage of the disease***

Stage of the disease	Differentiation grade		
	Well	***Moderate***	***Poorly***
Stage I	4	10	6
Stage II	14	24	18
Stage III	29	61	37
Stage IV	9	37	24

As we can see on the table, colorectal cancers were discovered in stage I and II in a lower percentage: stage I (20 patients, 7.33%), stage II (56 patients, 20.51%), stage III (46.52%) and stage IV (70 patients, 25.64%). Survival in stage I was not statistically influenced by the differentiation grade in our study ($p = 0.1$), the same result obtaining for stage IV.

In stage II and III colorectal cancer, we discovered a good correlation between survival and tumor cell differentiation ($p<0.005$ for stage II and $p<0.01$ for stage III).

Histopathological examination revealed adeno-carcinoma. From differentiation point of view tumors were well differentiated (Figure 1) in 56 cases (20.51%), moderate differentiated (Figure 2) in 132 cases (48.35%) and poorly differentiated (Figures 3 and 4) in 85 cases (31.14%).

Perineural invasion of the tumor (Figure 5) was discovered, in our study, in 22 patients and the survival rate was shorter comparing with same stage and differentiation grade tumors for stage II, III and IV.

Lymph node status is considered, in literature, as one of the most important predicting factors [5]. In our study, nodal involvement (Figures 6 and 7) is correlated with shortly survival and a greater risk for local – regional relapsing of the tumor in stage II and III ($p<0.01$ for stage II and $p<0.005$ for stage III). Stage IV colorectal cancers are statistically independent from nodal involvement.

For stage IV colorectal cancers the main site for metastasis was liver (51 patients, 72.86%), followed by the lung (12 patients, 17.14%) and peritoneum (eight patients, 11.43%).

Eleven from all 70 patients had more than one localization for metastasis.

Peritoneal liquid was obtained from 62 patients and we discovered malignant cells in nine patients (14.51%). Reporting at the stage of the disease peritoneal liquid was positive as it follows:

- in 0 from four patients with stage I;
- in 0 from 18 patients with stage II;

▪ in six from 27 patients with stage III (22.22%);
▪ in three from 13 patients in stage IV (23.08%).

Results suggest that positive cytology is corresponding with advanced disease with no differences between stage III and IV. The reduced number of patients included in this study, unfortunately, could not sustain a conclusion in this direction.

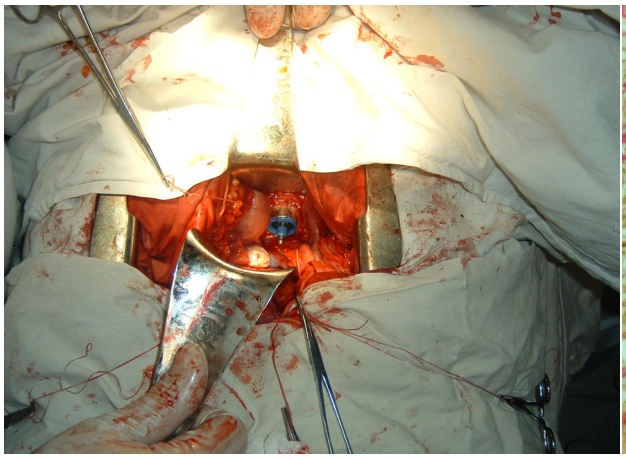

Figure 1 – ***Preparing a stapled colorectal anastomosis after a left hemicolectomy (Dr. G. Ianoşi collection)***

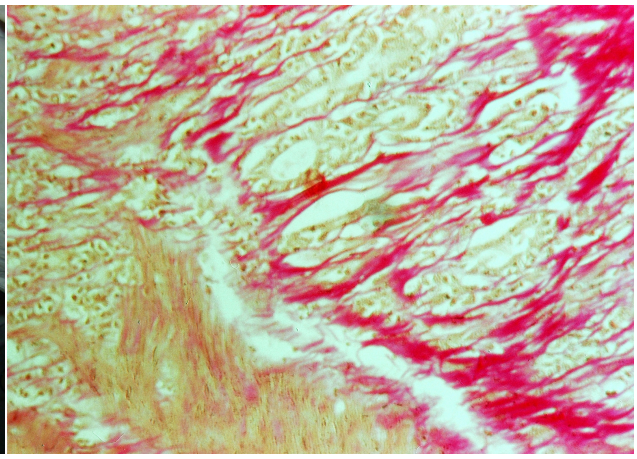

Figure 2 – ***Moderate differentiated adenocarcinoma stage II with muscular invasion (Van Gieson staining, ob. ×20)***

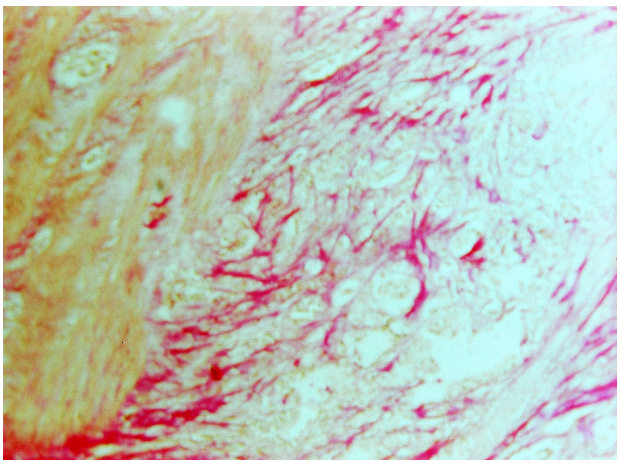

Figure 3 – ***Moderate differentiated adenocarcinoma stage III with tumor necrosis and muscular invasion (Van Gieson staining, ob. ×20)***

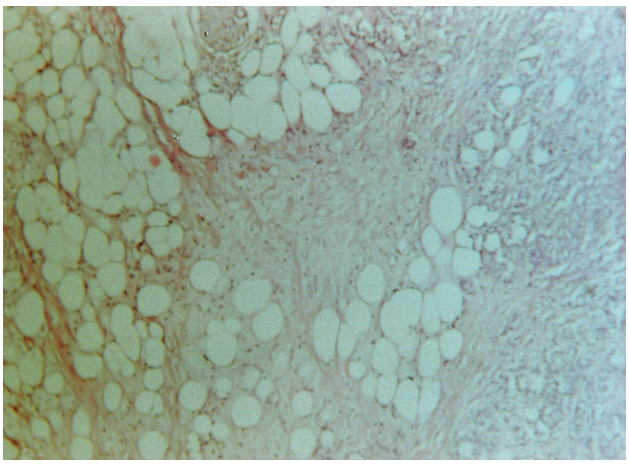

Figure 4 – ***Poorly differentiated adenocarcinoma stage III with serous invasion (HE staining, ob. ×10)***

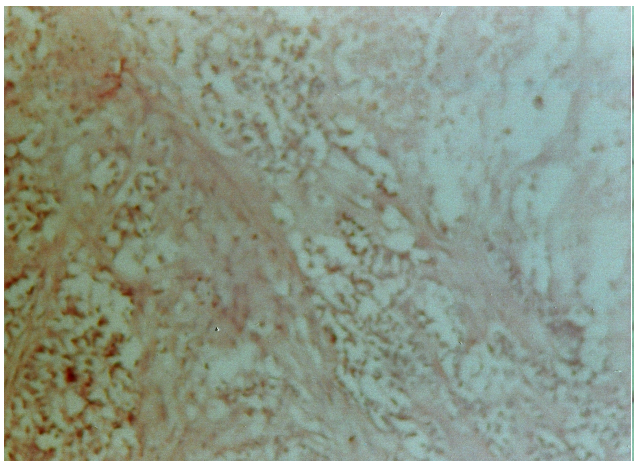

Figure 5 – ***Poorly differentiated adenocarcinoma stage III with tumor necrosis (HE staining, ob. ×10)***

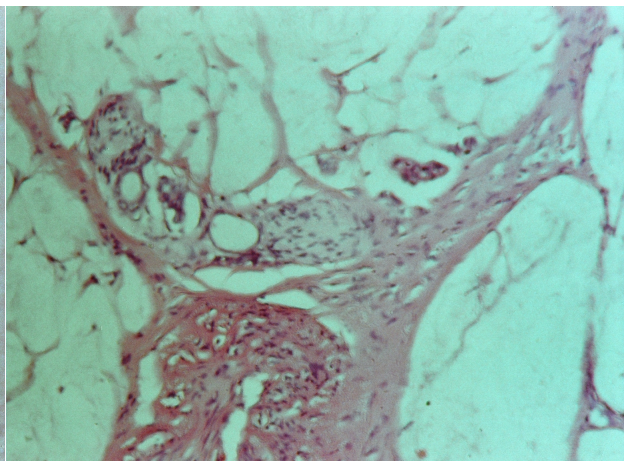

Figure 6 – ***Moderate differentiated mucinous adenocarcinoma with perineural invasion (HE staining, ob. ×20)***

Figure 7 – ***Lymph node with metastasis of mucinous adenocarcinoma and capsule invasion (HE staining, ob. ×20)***

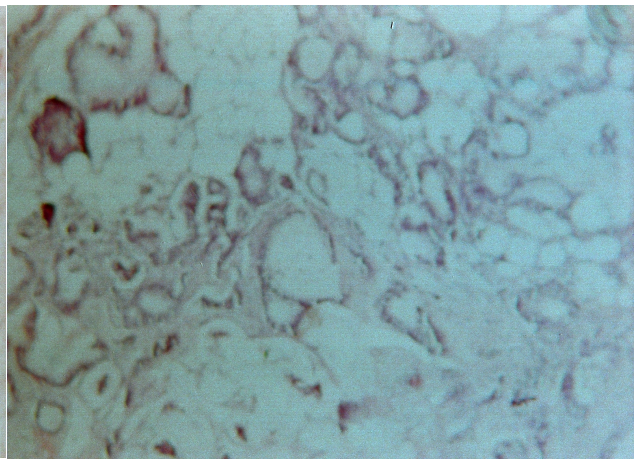

Figure 8 – ***Lymph node with massive metastasis of mucinous adenocarcinoma (HE staining, ob. ×20)***

Discussion

Data on the prognostic factors of survival and recurrence in patients with colorectal cancers, in generally, are limited. Improving survival in colon and rectal cancers is one of the most important objectives for all clinicians all over the world.

A study realized in Sweden and published in 2005 [6] showed that 5-year relative survival rate for cancer of the colon improved significantly from 39.6% in 1960–1964 to 57.2% in 1995–1999 and for rectal cancer from 36.1 to 57.6%, respectively.

Corresponding observed survival improved from 31.2 to 44.3% for colon cancer and from 28.4 to 45.4% for rectal cancer. The largest improvement of survival were seen during the later part of the period observed.

Factors influencing survival were evaluated in specific situations. A recent study from Hong Kong published in *World Journal of Surgery* [7] evaluated survival and recurrence in patients who had T1 and T2 colorectal cancers. Their observations showed that the presence of lymphovascular permeation was the only independent factor associated with a higher incidence of lymph node metastasis on multivariate analysis. There were no significant differences in disease-free 5-year survival and 5-year cancer-specific survival in patients with T1 and T2 tumors.

Patients with lymph node metastasis had a significantly shorter disease-free 5-year survival and 5-year cancer-specific survival when compared with those having a negative lymph node status. Lymph-model node-status was the only significant independent factor predicting cancer-specific survival and disease-free survival.

They concluded that presence of lymphovascular permeation would have a significant higher chance of lymph node metastasis, positive lymph node status was predictive of poorer survival in patients with T1 or T2 colorectal cancers and for those cancers with positive lymphovascular permeation, radical surgery is recommended.

For stage Dukes B, colon cancer some differences in prognosis exists with respect to positive lymph nodes at immunohistochemistry [8]. Some studies have documented that positive immunohisto-chemical status is correlated with prognosis and local recurrence [9], but others found no difference in survival rates between positive and negative immuno-histochemical status when sufficient numbers of dissected lymph nodes were examined [10].

The prognosis of stage IV colorectal cancer is poor and the management of it is not classified. As we discover in our study, the most common site of distant metastasis is liver followed by the lung and peritoneum [11]. According with the literature, prognosis of these patients is affected by numerous parameters like male gender, older age, differentiation of the tumor, CEA level, resection of primary tumor, number of metastatic lesions and adjuvant therapy [2, 12–14]. Even curative resection is the procedure of choice for resectable stage IV cancer; it is possible only in 20–30% of these patients [2].

Patients with untreated metastatic disease have a median survival period of less than 10 months and a 5-year survival of less than 5% [12]. Operative treatment is necessary for the patients with complications such as obstruction, bleeding or abdominal pain, but surgical treatment for symptoms-free patients is debatable [2]. Is generally accepted that the major goal for these patients is to maintain quality of life and to prolong the survival time. In the field of cytological study of peritoneal washing, this technique is considered a good way to discover malignant cells.

In a study, Benezra *et al.* [15] achieved 928 samples with no false-negative results. Peritoneal inflammation could overload the differentiation between benign reactive and malignant cells. Malignant cells are present in peritoneal washing liquid between 3–35% in colon cancer [12]. In our study, this percent was 14.5%. Some studies sustain that peritoneal washing achieved after or during the tumor resection showed an increase percent of positively that could explain recurrences at the anastomosis level [16].

Conclusions

Curative resection of colorectal cancers is one of the most important factors that could improve survival. Resection of primary tumor is statistically correlated with a better survival in stage IV colorectal cancers.

Tumor differentiation is correlated, in our study, with survival only for the patients with stage II and III of the disease but bigger cohorts are necessary for a better result.

Perineural invasion and pathologic N stage represent important predicting factors for a shorter survival.

Peritoneal washing for cytology prior to surgery is correlated, in our study, with the stage of the disease and not with tumor differentiation but limited number of patients and limited follow-up brake a conclusive approach of it as survival predictor.

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