COLORECTAL CANCER: PROGNOSTIC VALUES

Suzana Manxhuka-Kerliu[1*], Skender Telaku[2], Halil Ahmetaj[3], Arijeta Baruti[1], Sadushe Loxha[1], Agron Kerliu[3]

[1] Institute of Pathology, Faculty of Medicine, University of Prishtina, Mother Theresa str., 10 000 Prishtina, Kosovo

[2] Gastroenterology Clinic, Faculty of Medicine, University of Prishtina, Mother Theresa str. 10 000 , Prishtina, Kosovo

[3] Institute of Pathophysiology, Faculty of Medicine, University of Prishtina, Mother Theresa str. 10 000, Prishtina, Kosovo.

* Corresponding author

Abstract

After lung cancer colorectal cancer (Cc) is ranked the second, as a cause of cancer-related death. The purpose of this study was to analyze the Cc cases in our material with respect to all prognostic values including histological type and grade, vascular invasion, perineural invasion, and tumor border features. There were investigated 149 cases of resection specimen with colorectal cancer, which were fixed in buffered neutral formalin and embedded in paraffin. Tissue sections (4(μm thick) were cut and stained with H&E. Adenocarcinoma was the most frequent histological type found in 85,90% of cases, in 60,94% of males and 39,06% of females; squamous cell carcinoma in 7,38%, in 63,63% of males and 36,36% of females; mucinous carcinoma in 4,68%, in 57,15% of males and 42,85% of females; while adenosquamous carcinoma, undifferentiated carcinoma and carcinoma in situ in 0,71% of cases each. Dukes' classification was used in order to define the depth of invasion. Dukes B was found in 68,45% of cases, whereas in 31,54% of cases Dukes C was found. As far as histological grading is concerned, Cc was mostly with moderate differentiation (75,16%) with neither vascular nor perineural invasion. Resection margins were in all cases free of tumor. Our data indicate that the pathologic features of the resection specimen constitute the most powerful predictors of postoperative outcome in Cc. Dukes' stage and degree of differentiation provide independent prognostic information in Cc. However, differentiation should be assessed by the worst pattern.

KEY WORDS: circumferential margin, colon cancer, grade, pathology, prognostic factors, Dukes' system

Introduction

It is the most common malignancy of the gastrointestinal tract. The life time risk of developing this cancer is 2,5 to 5% in the general population but two to three times higher in individuals who have a first degree relative with colon cancer or an adenomatous polyp. Cc is a disease for which screening and preventive measures have proven effective (1). Significant differences exist within continents, with higher incidences in Eastern and Northern Europe, North and South America, Australia, New Zealand, while in developing countries such as in Africa, Asia and Polynesia still have lower rates of incidence (2). During the last decade of the 20th century, incidence and mortality have decreased (3), whereas in Japan, Korea and Singapore, it is increasing rapidly, probably because of the western life style (4). Chronic inflammatory bowel diseases are important etiological factors in the development of colorectal adenocarcinoma (5). It appears that increasing the fiber content in the Western diet would be useful in the primary prevention of colorectal cancer. Most Cc are located in the sigmoid colon and rectum, but recently cases involving proximal part of the bowel are in increase. The pathology report of a Cc resection specimen typically documents the anatomic site of the malignancy, histological type, the parameters that determine the local tumor stage and the histopathological confirmation of distant metastasis, if present. Other reported features include those having additional prognostic or predictive value as well as those that may be important for clinicopathological correlation or quality control (6). Histology is an important factor in the etiology, treatment, and prognosis of cancer. The defining feature of colorectal adenocarcinoma is invasion through the muscularis mucosae into the submucosa (7). Tissue Carcinoembryonic antigen (CEA) staining is useful in indicating possible vascular invasion even at early stage, whereas vascular invasion by a larger tumor bulk or even tumor metastases may be necessary to produce an increased plasma CEA level that is detectable (8). Postoperative monitoring with carcinoembryonic antigen (CEA) provided a valuable guide as to prognosis in patients operated for potential cure. Similarly, CEA was useful in detection of recurrence and gave a lead time over clinical symptoms in 70% of the patients. (9) Histopathological evaluation can be used to prioritize sporadic colon cancers for microsatellite instability (MSI) studies, but morphological prediction of MSI-H has low sensitivity, requiring molecular analysis for therapeutic decisions (10). The knowledge regarding the molecular biology of Cc has facilitated the study of molecular markers in patients with Cc. Several tumor associated proteins including p53, p21, p27, cyclin D1, PCNA, CD44, Ki67 may be relevant prognostic markers in rectal cancer (11). Dukes classification takes into account two histopathological features: depth of penetration into the wall and the presence or absence of metastasis in regional lymph nodes. The tumor-node-metastasis (TNM) classification is replacing the Dukes classification (12). Staging provides a means to evaluate nonanatomic prognostic factors at specific anatomic stages. The most important challenge facing the TNM classification is how to interface with the great number of nonanatomic prognostic factors that are currently in use or under study. TNM was constructed to assess only the 3 basic facets of anatomic spread. However, at certain sites, histological grading became incorporated into the stage groups (13). CD44 variant 6 (CD44 v6) is well known as a useful marker of tumor progression; however, its relationship to prognosis has not yet been elucidated. The 5-year survival rate was significantly higher in patients with CD44 v6 negative cancer (84%) than in those with CD44 v6 positive cancer (31%). Thus, CD44 v6 could be a reliable prognostic indicator, as well as a predictor of metastatic potential after curative surgery for Cc (14). A grading system using the 3 parameters provides a wider spectrum of 5-year survival rates (18–98%) compared with conventional systems such as Dukes (28–96%), Astler-Coller (45–95%), and the UICC classification (30–96%) from the combined data sets (15). There have been noted that 15% overall survival advantage at 5 years with mesocolic plane surgery compared with surgery in the muscularis propria plane in univariate analysis (16).

The aim of this study was to analyze the Cc cases with respect to all prognostic values such as histological type, grade and stage, vascular invasion, serosal invasion, tumor size, location as well as tumor border features.

Material and Methods

There were reviewed biopsies of 149 patients who underwent resection of Cc during the period 2001-2007. All of the tissues were fixed in 10% neutral buffered formalin (Bio-Optica) and embedded in paraffin (SIGMA). Tissue sections (4μm thick) were cut and

stained with H&E stain. Cc were classified according to the WHO histological as well as TNM classification (2000). Clinical data were collected from the University Clinical Center of Kosovo (UCCK) register as well as follow-up clinic visits of patients referred to the UCC of Kosovo. Measures of tumor burden or tumor behavior have been studied as means to predict outcome, but as of now, none is as important as the pathologic stage. Many individual features of the patient and of the tumor may come into play, however. We have examined the prognostic values of Cc such as gender, age, histology, grade and stage that are shown in tables 1-6. Statistically significant differences were analyzed using the χ^2 test. Histopathological features independently associated with lymph node metastasis were tested using stepwise logistic regression analysis.

Results

During our study out of 149 cases of colorectal cancer, there have been different histological variants found with the adenocarcinoma being the most frequent variant (Table 1).

HISTOLOGICAL VARIANTS	Nº	%
Adenocarcinoma	128	85,9
Sqaumous cell carcinoma	11	7,38
Mucinous adenocarcinoma	7	4,68
Adenosquamous carcinoma	1	0,71
Undifferentiated carcinoma	1	0,71
Carcinoma in situ (High grade intraepithelial neoplasia)	1	0,71
TOTAL	149	100

TABLE 1. Histopathological variants of colorectal cancer

Colorectal cancer in general was more frequent in men than in women (Table 2., Figure 1.), 60,4% vs. 39,59%. However, histological variants of colorectal cancers were analyzed regarding the gender predominance and it was found that they were all more frequent in men than in women except in undifferentiated carcinoma and carcinoma in situ were seen only in females (one case each).

Histopathological variant	F		M		Total	
	Nº	%	Nº	%	Nº	%
Adenocarcinoma	**50**	39,06	**78**	60,94	**128**	100
Sqaumous cell carcinoma	4	36,36	7	63,63	11	100
Mucinous adenocarcinoma	3	42,85	4	57,15	7	100
Adenosquamous carcinoma	0	0	1	100	1	100
Undifferentiated carcinoma	1	100	0	0	1	100
Carcinoma in situ (High grade intraepithelial neoplasia)	1	100	0	0	1	100
Total	**59**	**39,59**	**90**	**60,4**	**149**	**100**

TABLE 2. Colorectal cancer with regard to gender

Cc mainly occurred in the third to eighth decade of life. Most frequent age group at presentation of Cc in was 71-80, in 37.58% of cases. (Table 3, Figure 2).

Age group (year)	Nº	%	χ^2-test	p-value
71-80	56	37,58	39,12	<0,01
61-70	32	21,47	2,07	NS
51-60	26	17,47	0,05	NS
41-50	18	12,08	1,36	NS
31-40	16	10,73	2,46	NS
21-30	1	0,67	20,99	<0,01
Total	149	100	66,05	<0,01

TABLE 3. Colorectal cancer with regard to age

Out of 149 Cc, 37 (24,83%) had lymph node metastasis, while 112 (75,16%) had no lymph node metastasis (Table 4).When compared with node-negative tumors, node-positive tumors were characterized

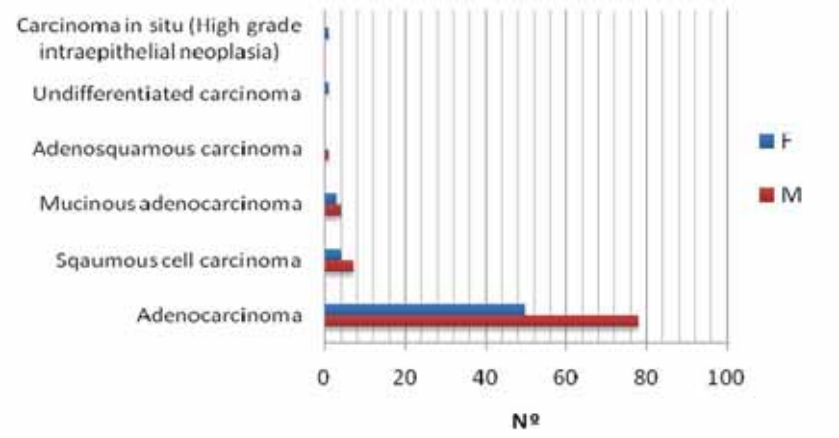

FIGURE 1. Colorectal cancer with regard to gender

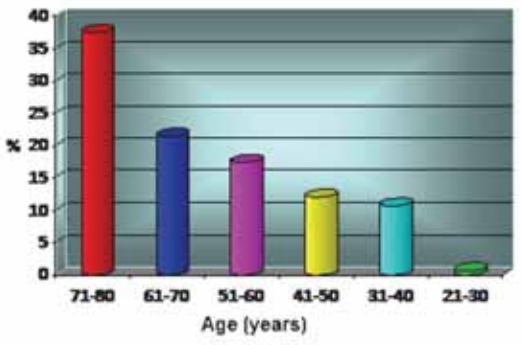

FIGURE 2. Colorectal cancer with regard to age

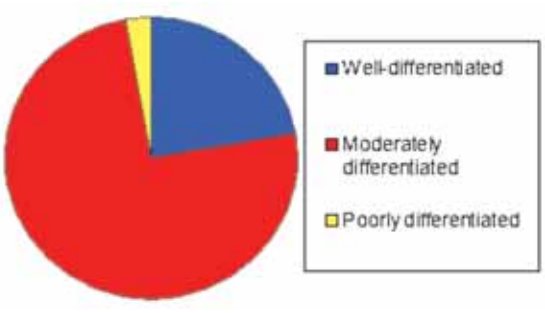

FIGURE 3. Differentiation

by high frequency of tumor size greater than 6 cm (15,17% vs. 21,62,), serosal invasion (15,17% vs. 81,08% P<0,01), lymphatic invasion (0% vs. 100%), vascular invasion (0% both), and histological type adenocarcinoma, poorly differentiated (0,89% vs. 81,1%).

	Node negative n=112	Node positive 75,16%	n=37	24,83%		
	No	%	No	%	χ^2	p value
Site					**37,56**	**<0,01**
Right colon	3	2,67	1	2,7		
Left colon	35	31,25	12	32,43		
Rectum	74	66,07	24	64,86		
Tumor size (cm)					**0,95**	**NS**
<6	95	84,82	29	78,37		
≥ 6	17	15,17	8	21,62		
Serosal invasion					**50,22**	**<0,01**
Absent	95	84,82	7	18,91		
Present	17	15,17	30	81,08		
Lymphatic invasion						**<0,01**
Absent	112	100	0	0		
Present	0	0	37	100		
Vascular invasion						**<0,01**
Absent	112	100	37	100		
Present	0	0	0	0		
Differentiation-grading					**7,44**	**<0,05**
Well-differentiated	25	22,32	8	21,62		
Moderately differentiated	86	76,78	26	70,27		
Poorly differentiated	1	0,89	3	8,1		

TABLE 4. Risk factors for lymph node metastasis in Colorectal cancer

As far as histological grading is concerned, Cc was mostly with moderate differentiation (75.16%) with neither vascular nor perineural invasion (Figure 3, Table 5).

Dukes' classification was used in order to define the depth of invasion. Dukes B was found in 68,45% of cases, in 31,54% of cases Dukes C was found, whereas resection margins were free tumor tissue in all investigated cases.

Differentiation-grading	**N°**	**%**
Well-differentiated	**33**	**22,14**
Moderately differentiated	**112**	**75,16**
Poorly differentiated	**4**	**2,68**
Total	**149**	**100**
Staging	**N°**	**%**
Duke's staging system		
A	**0**	**0**
B	**102**	**68,45**
C	**47**	**31,54**
D	**0**	**0**
Total	**149**	**100**

TABLE 5. Differentiation-grading/staging of colorectal cancer

Sensitivity in the diagnosis of lymph node metastasis was high for tumor size and for serosal invasion 84,8% vs. 84,8%, for differentiation was low 22,3%, whereas specificity was low for serosal invasion and for tumor size 45,9% vs. 58%. Positive predictive value was high for lymphatic invasion (92,5%), whereas negative predictive value was high for serosal invasion, 95,7% (Table 6).

Discussion

According to recently published data Cc mortality rates declined. Most experts attribute this decline to the increased use of screening and earlier diagnosis of cancers of the colon and rectum. Studies on the effectiveness of the four most commonly used screening methods indirectly support these findings. About 96% of Cc were adenocarcinomas, approximately 2% were other specified carcinomas (including carcinoid tumors), about 0,4% were epidermoid carcinomas, and about 0,08% were sarcomas. The proportion of epidermoid carcinomas, mucin-producing

	Sensitivity (%)	Specificity (%)	Positive predicted value (%)	Negative predicted value (%)
Tumor size (cm)				
<6 vs. ≥ 6	84,8	58	32	68
Serosal invasion				
absent vs. present	84,8	45,9	92,5	95,7
Lymphatic invasion				
absent vs. present	0	0	0	0
Vascular invasion				
absent vs. present	0	0	0	0
Differentiation				
Well-differentiated vs. others	22,3	235,1	25	75,8

TABLE 6. Sensitivity, specificity, positive and negative predicted value

carcinomas, and carcinoid tumors was greater among females (17). Similar data were found in our material too: we have found adenocarcinomas in 85,90%, and other histological variants in 14,19%. Epidermoid carcinomas were found to be increased in our material 7,38% in correlations to other published data. Furthermore, males were attacked more than females from colorectal cancer in most histological variants, except in undifferentiated and Carcinoma in situ cases (0,71% each). With respect to age, higher percentages of sarcomas, mucin-producing adenocarcinomas, signet ring cell tumors, and carcinoid tumors were found in individuals under age 40. Overall, adenocarcinomas were more likely to be diagnosed at regional stages with moderate differentiation. Compared with other adenocarcinomas, signet ring cell tumors were more often poorly differentiated and were at distant stage at diagnosis (18). According to our data all diagnosed variants of colorectal carcinomas were found to be greater in cases over age 70. In Cc, factors independently associated with lymph node metastasis are serosal invasion, lymphatic invasion, and histological type (19, 20, 21). Similar data were found during our research, too. Early diagnosis is essential to improved survival and advanced stage at presentation has been a limiting factor in improving survival rates. The majority of tumors were Grade 2 at presentation; however, 77% presented at T3 or higher and almost one third of patients had metastatic disease at diagnosis. Mean age at diagnosis was 66 years. Younger patients showed poorer prognosis and greater likeliness for recurrence. However, males presented poorer outcome than females. Those presenting younger had a poorer prognosis and were more likely to recur. However males had a poorer outcome than females. In this series, it appears that Cc presents late and at an advanced stage in this demographic area and younger patients tends to have more advanced disease at diagnosis and poorer outcomes overall (21). We have found the mean age at diagnosis higher in correlation with published data, over the age of 70 were 37,58%. As far as grading is concerned, the same data were found in our material too, grade 2, in 75,16%. Patients over 70 years of age are more likely to present in the early stages of Cc (Dukes stage A or B) than are younger patients, who have more aggressive disease for a given stage of presentation (22, 23, 24) . This was the case in our study too, most patients were over the age of 70 (37,58%) and with the Duke's stage B (68,45%) while with the Duke's stage C were found less (31,54%). Factors independently associated with lymph node metastasis of colorectal cancer were serosal invasion, lymphatic invasion, and histological type of tumors. Therefore, these three parameters are useful and important for assessing the curability of the disease and whether additional lymph node dissection is necessary after local treatment of Cc (25.). Our study has shown the same data.

Conclusion

Tumor characteristics such as histology, differentiation, size, macroscopic appearance and inflammation give, irrespective of Dukes' stage, valuable information on prognosis and are mandatory in planning the treatment of Cc. In Cc, factors independently associated with lymph node metastasis are serosal invasion, lymphatic invasion, and histological type. When these three parameters are favorable, local treatment of Cc does not require additional lymph node dissection.
Our data indicate that the pathologic features of the resection specimen constitute the most powerful predictors of postoperative outcome in Cc. Dukes' stage and degree of differentiation provide independent prognostic information in colorectal cancer. However, differentiation should be assessed by the worst pattern. Distinct demographic and clinical patterns associated with different histological pictures may be helpful for future epidemiologic, laboratory, and clinical studies.

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References

(1) Rudy D.R. and Zdon M. Update on colorectal cancer. Am. Fam. Physician. 2000; 61:1759-70:1773-1774

(2) Cooper G.S., Yuan Z., Stange K.C., Rimmm A.A. Use of Medicare claims data to measure county-level variations in the incidence of colorectal carcinoma. Cancer. 1998; 83:673-678.

(3) Garfinkel L., Mushinski M. US. Cancer incidence, mortality and survival:1973-1996. Stat. Bull. Metrop. Insur. 1999; 80:23-32.

(4) Honda T., Kai I., Ohi G. Fat and dietary fiber intake and colon cancer mortality: a chronological comparison between Japan and the United States. Nutr Cancer. 1999: 33:95-99.

(5) Riddel R.H., Goldman H., Ranshoff D.F. et al: Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications. Hum. Pathol. 1983; 14:931-968.

(6) Compton C.C. Colorectal carcinoma: Diagnostic, Prognostic and molecular features. Mod Pathol. 2003;16 (4):376-388.

(7) Stanley R., Aaltonen L.A.: Pathology & Genetics. Tumors of the Digestive System. WHO. IARC Press, 2000.

(8) Ng I.O.L., Ho J., Pritchett C.J. CEA tissue staining in colorectal cancer patients - correlation with plasma CEA, Histol. Staging Pathol. 1993; 25: (3): 219 - 222.

(9) Bjerkeset T. Symptoms in colorectal cancer and their relation to tumour characteristics and survival. Dig. Surg. 1988; 5:61-65.

(10) Alexander J., Watanabe T., Wu T.T. et al. Histopathological identification of colon cancer with microsatellite instability. Am. J. Pathol. 2001;158:527-535.

(11) Peng J.J., Cai S.J., Lu H.F., et al: Predicting prognosis of rectal cancer patients with total mesorectal excision using molecular markers. World. J. Gastroenterol. 2007; 13(21): 3009-3015.

(12) UICC: TNM classification of malignant tumors. Wiley Press: New York .1998.

(13) Greene F. L., Sobin L.H. The Staging of Cancer: A Retrospective and Prospective Appraisal. CA Cancer. J. Clin. 2008; 58:180-190

(14) Nihei Z., Ichikawa Z., Kojima K. The positive relationship between the expression of CD44 variant 6 and prognosis in colorectal cancer. Surgery Today 1996; 26: (9) 760-761.

(15) Ueno H., Price A.B., Wilkinson K.H.: A New prognostic staging system for rectal cancer. Ann. Surg. 2004; 240(5): 832–839.

(16) West N.P., Morris E.J.A., Rotimi O. Pathology grading of colon cancer surgical resection and its association with survival: a retrospective observational study. Lancet. Oncol. 2008; 9: 857-865.

(17) Stewart, Sh., Wike J., Kato I.. A population-based study of colorectal cancer histology in the United States, 1998-2001. Cancer 2006; 107: 1128-1141.

(18) Deans G.T., Parks T.G., Rowlands B.J., Spence R.A.J. Prognostic factors in colorectal cancer. Br. J. Surg. 1992;79:608–613.

(19) Watson G.J., Roche M., Beral V., Patnick J. Stage, grade and morphology of tumours of the colon and rectum recorded in the Oxford Cancer Registry, 1995–2003.*Br J Cancer*. 2007; 96: 140–142.

(20) McKeown M.G., Lynch W., Keane M. Stage and grade of colorectal cancer at presentation in the West of Ireland. J. Clin. Oncol. 2008; 26: (15): 150-195.

(21) Dukes C.E. The classification of cancer of the rectum. J. Pathol. Bacteriol. 1932;35:323-332.

(22) Dukes C.E., Bussey H.J.R. The spread of rectal cancer and its effect on prognosis. Br. J. Cancer 1958;12:309–320.

(23) Chapuis P.H., Dent O.F., Fisher R. et al. A multivariate analysis of clinical and pathological variables in prognosis after resection of large bowel cancer. Br. J. Surg. 1985;72:698–702.

(24) Adachi Y., Yasuda K., Kakisako K. Histopathologic criteria for local excision of colorectal cancer: Multivariate Analysis. Ann. Surg. Oncol.1999; 6(4):385–388.

(25) Adachi Y., Sato K., Shiraishi N., Kakisako K., Tanimura H., Kitano S. Tumor size of colorectal cancer: indication for laparoscopic surgery. Surg. Laparosc. Endosc. 1998;8:269–272.