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Assessment of Tumor Parameters as Factors of Aggressiveness in Colon Cancer

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Abstract

Background: Colorectal cancer is a major public health problem worldwide. Tumor volume associated with the number of positive lymph nodes may be a new predictor of 5-year survival in colon cancer.

Material and Methods: We conducted a retrospective study of a prospective database that included all patients diagnosed with colon cancer (CC) between May 2012 and September 2013 in the Surgical Oncology Clinic of the Iasi Regional Cancer Institute. The patients underwent surgical resection and two tumor sizes were recorded. Tumor characteristics and their potential role in tumor aggressiveness were analyzed.

Results: The study group included 138 patients, of which 38 (27.54%) with metastases and 100 (72.46%) without metastases. Maximum tumor diameter showed significant differences depending on the degree of differentiation and histological type, and was significantly correlated with the total number of evaluated and positive lymph nodes (p=0.009 and p=0.00, respectively). Tumor volume was influenced by male gender (p=0.0404), tumor stage (p=0.0192), and type of tumor invasion (p=0.0159) in 23.02 % of cases (p=0.02809). Maximum tumor diameter and tumor volume had poor discriminatory power in predicting survival.

Conclusions: A statistically significant association was found between the metastatic group and advanced disease stages. Maximum tumor diameter and tumor volume could not predict overall survival of patients.

Keywords: Colon cancer; Tumor volume; Maximum tumor diameter; Predictive factors

Introduction

Colorectal cancer (CRC) is a major public health problem worldwide, representing a leading cause of mortality and morbidity. It is the third most common cancer and the fourth leading cause of death worldwide [1]. Surgery is the only treatment with radical intent. Tumor staging (UICC-TNM) is a preocondition for multimodal treatment [2]. Adjuvant chemotherapy is necessary for metastatic cancers (lymph nodes, parenchymal organs, stages III, IV), however approximately 30% of localized cancers (stage II) will recur [2,3]. Currently, TNM staging [4] is the best prognostic factor for CRC, with a mean 5-year survival of 93%, 78%, 60% and 8% for stages I, II, III and IV, respectively. For adequately staging a colon cancer AJCC (American Joint Committee on Cancer) recommended a minimum of 12 lymph nodes to be harvested [5]. Tumor volume associated with the number of positive nodes may be a new predictor of 5-year survival in colon cancer [6].

Material and Methods

The aim of this study was to analyze the tumor characteristics and their potential role in assessing tumor aggressiveness. Another aim was to determine whether increased tumor parameters may influence tumor stage and therefore the presence of lymph node and distant metastases.

Patient Selection

We conducted a retrospective study of prospective database that included all patients diagnosed with colon cancer (CC) between May 2012 and September 2013 in the Surgical Oncology Clinic of the Iasi Regional Cancer Institute. The patients underwent surgical resection and at least two tumor sizes were reported.

The histological type, total lymph nodes evaluated, number of positive lymph nodes, tumor stage according to the TNM staging, T and N stage, and presence of vascular, lymphatic and perineural invasion were analyzed. Maximum tumor diameter was considered as the largest tumor diameter reported by the pathologist. Tumor volume was calculated by multiplying the two largest dimensions reported for each tumor. Tumor volume was related to the percentage of positive nodes (tumor node ratio). The percentage of positive nodes was calculated by dividing the number of positive nodes identified to the total number of nodes in the surgical specimen, multiplied by 100. Depending on the presence or absence of distant metastases, we identified two groups of patients who were subjected to comparative statistical analysis. Patients with metastases were operated on either to improve the quality of life (clinically manifest tumor) or to approach the metastases at a later time. Data were obtained from analysis of clinical observation sheets, medical records and pathology reports. Date of death was obtained from the database of the National Health Insurance Company.

Preoperative Evaluation

All patients received preoperative staging that included medical history, physical examination, chest radiography, abdominal-pelvic ultrasound, computed tomography (CT), colonoscopy with biopsy,

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carcinoembryonic antigen (CEA) and in some patients CA19.9. Complete blood count and EKG were done in all patients. All patients were operated by surgeons experienced in colorectal surgery. The diagnosis was confirmed by histological assessment of both the diagnostic biopsies and surgical resection specimens. Tumor staging was done according to the latest AJCC/UICC TNM classification [4]. No patients received neo-adjuvant therapy. The objective of radical surgery was tumor resection without macro or microscopic residue. Postoperatively, the management included surveillance in the intensive care unit, treatment of pain, and monitoring of abdominal drainage and passage of stool and gas.

Exclusion Criteria

Were excluded the patients in which radical surgery was not possible, those with tumor recurrence, and the patients diagnosed with rectal cancer due to different patient management.

Statistical Analysis

The database was created using Microsoft Excel 2010version. Data were analyzed in SPSS V.19.0. Data analysis included: descriptive statistics and analytical statistics. Continuous variables were reported as mean/median and standard deviation. Categorical variables were expressed as percentages. The study on the influence of some parameters on the value of maximum tumor diameter was based on the results of multiple correlation for which a generalized regression model was used. The significance level (p-value) (maximum probability of error) was considered 0.05 (5%) with a probability (confidence interval) of 95%. Survival analysis was performed using Kaplan Meier curve. To assess the discriminatory power of the values of a parameter on patient survival we used ROC curve (Receiver Operator Characteristic Curve) to express the relationship between sensitivity and specificity of the prediction method and to characterize the test performance.

Results

Demographic Data and Evaluation of T, N and VELIPI Categories

The study group consisted of 138 patients of which 38 patients (27.54%) had one or more tumor metastases at the time of diagnosis of clinically and clinically manifest tumor. In the remaining 100 patients (72.46%) the preoperative and intraoperative investigations did not detect metastases. The study patients had a mean age of 65.2 years ± 10.64SD, range 35-87 years. The number of male patients was substantially equal to that of females (47.1% and 52.9 %, respectively).

Metastases were more frequently present in advanced stages of disease ($p << 0.01$) 53.62% of the patients with metastases were T3 and 39.8% T4. The presence of metastases was significantly correlated with T stage (p=0.00001) and the progressive involvement of regional lymph nodes in 78.95% of the cases (p=0.00004) with a significant correlation between the presence of distant metastases and lymph node invasion ($p << 0.01$). In the metastatic group, vascular invasion was present in 84.21% compared to 47%, significantly less, in the nonmetastatic group (p=0.00008). Nonparametric analysis demonstrated a significant correlation between vascular invasion and the presence of metastases (p=0.00006), with a risk of vascular invasion presence of 1.8 (RR=1.79) and a 6-fold increased probability. Lymphatic invasion was significantly present in 81.58 % found in a significant proportion of patients (81.58%) (p=0.00037) with a 4.8-fold higher risk of occurrence (OR=4.8) in the group with secondary lesions. Perineural invasion was found in a small number of cases (17.39%) and was associated statistically significant with the presence of metastases 34.21% (p=0.00131). The probability the patients with metastases to present perineural invasion is 4-times higher (OR=4.21) with a prospective risk of occurrence of 3 (HR3.1) (Table I).

Evaluation of the Maximum Tumor Diameter

In the patients with metastases (F=5.95, p=0.0023) the maximum tumor diameter showed significant differences depending on the degree of differentiation and histological type (adenocarcinoma versus mucinous adenocarcinoma). A statistically significant correlation was found between maximum tumor diameter and the total number of evaluated nodes (r=0.422, p=0.009) in both study groups, and the number of positive nodes (p=0.007) in the group with metastases. In the group without metastases, maximum tumor diameter showed a slight tendency to increase in relation with the number of positive lymph nodes, but this was not statistically significant. In the case of bone metastases maximum tumor diameter was significantly larger than in other locations (liver (p=0.0011), peritoneal (p=0.0017), and lung (p=0.00438)). No significant differences in age, sex, serosal invasion, histological type and tumor invasion, or tumor topography in the colon were found (Table II).

Table I: General Characteristics of Cohort Patients.

	Metastasis Group	No Metastasis Group	Spearman-rank	Chi -square
Patient number	38 (27.54%)	100 (72.46%)		
Tumor stage				
1	0%	5 (5%)		
2	0%	50 (50%)		
3	1 (2.63%)	45 (45%)		
4	37 (97.37%)	0 (0%)	p<<0.01	p<<0.01
T stage			r=0.726; p<<0.01	
T1	0 (0.00%)	2 (2%)		
T2	1 (2.63%)	6 (6%)		
T3	9 (23.68%)	65 (65%)		
T4	28 (73.68%)	27 (27%)	p<<0.01	p=0.00001
N stage			p<<0.01; r=0.641	p=0.00004; $\chi 2$=22.79
N0	7 (18.42%)	55 (55.00%)		
N1	13 (34.21%)	32 (32.00%)		
N2	17 (44.74%)	12 (12.00%)		
Nx	1 (18.42%)	1 (1.00%)		
Vascular invasion			r=0.714, p=0.00006, 95%CI	p=0.00008; χ^2=15.57
Present	32 (84.21%)	47 (47.00%)		
Absent	6 (15.79%)	53 (53.00%)		
Lymphatic invasion			r=0.65, p=0.0003, 95%CI	p=0.00037, χ^2=12.68
Present	31 (81.58%)	48 (48.00%)		
Absent	7 (18.42%)	52 (52.00%)		
Perineural invasion				p=0.00131, χ^2=10.32
Present	13 (34.21%)	11 (11.00%)		
Absent	25 (65.79%)	89 (89.00%)		
Degree of differentiation			r=-0.1025, p=0.231, 95%CI	
Gx	9 (23.68%)	15 (15.00%		
G1	8 (21.05%)	24 (24.00%)		
G2	19 (50.00%)	48 (48.00%)		
G3	2 (5.26%)	11 (48.00%)		
G4	0 (0.00%)	2 (2.00%)		

Analysis of the Influence of Predictive Parameters on Maximum Tumor Diameter, Tumor Volume, and Tumor Volume Rate

The maximum tumor diameter was influenced by the histologic type (p=0.043), type of tumor invasion (p=0.0253), and the number of positive lymph nodes (p=0.0339) in 40.13% of the patients (p=0.038). Tumor volume was influenced by male sex (p=0.0404), tumor stage (p=0.0192), and invasion type (p=0.0159) in 23.02% of cases (p=0.02809). The presence of metastases had no influence on tumor volume. Tumor volume rate was influenced by male gender (p=0.0026), tumor stage (p=0.0005), presence of metastases (p=0.0404), and total lymph nodes (p=0.0017) (Table III).

Evaluation of the Predictive Value of Maximum tumor Diameter for Survival

To determine the discriminatory power of maximum tumor diameter values in predicting survival of study patients a ROC curve was obtained. The results showed an AUC value of 0.575 (p=0.394, 95% CI: AUC→0436-0713), demonstrating a poor discriminatory power of maximum tumor diameter for survival. Maximum tumor diameter did not significant influence the survival of study patients (Figure 1 and Table IV).

Cutt-off values were used to assess the predictive power of maximum tumor diameter for survival. The study results indicated a cut-off value of 4.40 in predicting survival time with a sensitivity of 40% and a specificity of 83% (Figure 2).

Evaluation of Tumor Volume in Predicting Patient Survival

To assess the discriminatory power of tumor volume in the survival of the study patients a ROC curve was obtained. The results showed AUC value of 0.594 (p=0.484, 95% CI: AUC→0406-0782), which showed poor discriminatory power values of tumor volume on survival (Figure 3 and Table V).

Cut-off value of tumor volume in predicting patient survival time was 15.40, with a sensitivity of 52% and a specificity of 80%, which showed that survival time of study patients was not influenced by tumor volume (Figure 4).

Discussion

The course of cancer is usually predicted by assessing the tissue samples taken during the surgical resection of primary tumor, mainly focused on histological features. So far, tumor staging (AJCC/UICC-TNM classification) includes data on tumor stage and size (T), presence of tumor cells along drainage ducts and in the regional lymph nodes (N), and evidence of metastases (M). Statistical data available for patients with similar progression features and current progression parameters, such as disease-free survival (DFS) and overall survival are used to make estimates. These estimates were used to predict cancer progression [7-9]. However, it is known that cancer progression may vary significantly among patients with the same tumor stage. The progression of locally advanced cancer may remain stable for years

Table II: Statistical Indicators of Maximum Tumor Diameter.

Metastases	Degree of Differentiation	Mean max. diameter	Mean			Median	p
			-95%	95%	SD		
Absent	Gx	6.9	5.56	8.24	2.41	6	**0.026047**
	G1	4.78	4.05	5.51	1.73	4.05	
	G2	5.09	4.34	5.84	2.58	4.65	
	G3	6.13	4.54	7.72	2.22	6	
	G4	6.85	4.12	7.82	2.33	6.85	
Present	Gx	6.39	4.4	8.37	2.58	6	**0.002323**
	G1	3.75	2.51	4.99	1.49	3.75	
	G2	4.55	4.01	5.08	1.11	4.5	
	G3	0.7			0	0.7	
Absent	ADK.	5.23	4.71	5.76	2.43	5	**0.036433**
	Mucinous ADK	6.73	5.59	7.87	1.89	6	
Present	ADK	4.31	3.54	5.08	1.98	4	**0.02308**
	Mucinous ADK	6	4.95	7.05	1.37	6	
Present	Hepatic	4.38	3.53	5.24	1.72	4.25	**0.010395**
	Peritoneal	4.62	3.74	5.51	1.53	4.75	
	Pulmonary	4.75	2.86	6.64	1.19	4.25	
	Bone	12			0	12	

Table III: Multivariate Analysis and Partial Correlation between Variables and Maximum Tumor Volume, Maximum Tumor Diameter and Tumor Volume Rate.

Partial Correlation *vs.*	P (volume T) 95% confidence interval	P(ø max T) 95% confidence interval	P (volume rate T) 95% confidence interval
Intercept	0.030779	0.087216	0.004428
Sex (male)	**0.040422**	0.097637	**0.002674**
Age	0.831834	0.207553	0.2047
Tumor location	0.424817	0.615374	0.247058
Metastases type	0.470563	0.258878	0.425377
Serous invasion	0.351947	0.592135	0.071775
Histological type	0.946217	**0.043613**	0.844324
Degree of differentiation	0.396712	0.694775	0.266766
Invasion	**0.015949**	**0.025329**	0.635929
Metastases	0.961018		**0.040478**
Tumor stage	**0.019287**		**0.000563**
No. total lymph nodes evaluated	0.360405	0.492002	**0.001787**
No. positive lymph nodes	0.79246	**0.033966**	0.053011

Table IV: Parameters Estimated in ROC Curve Analysis.

Area Under the Curve					
Test Result Variable(s)	Area Under the Curve (AUC)	Std. Error	Asymptotic Sig.[b] (p)	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Maximum tumor diameter	**0.575**	0.071	0.394	0.436	0.713

[b]Null hypothesis: true area = 0.5

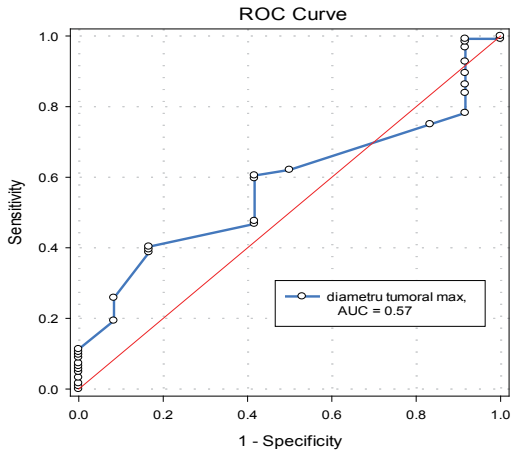

Figure 1: ROC Curve (Receiver Operating Characteristic) for Maximum Tumor Diameter for Survival.

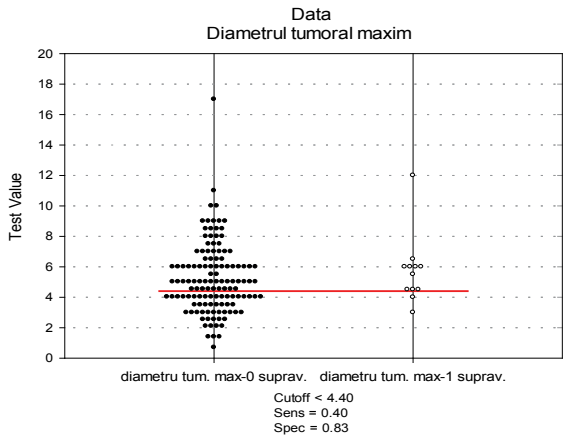

Figure 2: Point-Pair Histogram for the Cut-off Values of Maximum Tumor Diameter vs. Survival.

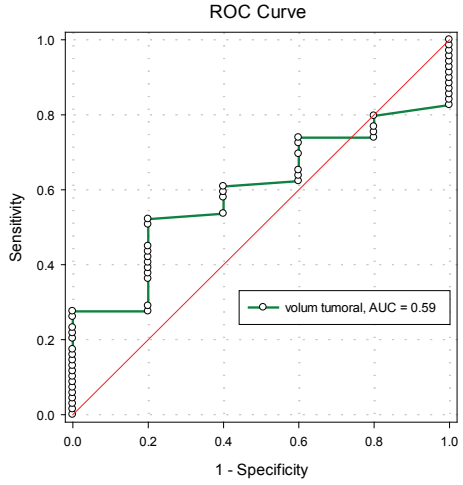

Figure 3: ROC Curve (Receiver Operating Characteristic) Tumor Volume in Predicting Patient Survival.

and partial or complete regression of large metastatic lesions may also occur spontaneously [10-12].

According to international guidelines, the key determinant in the management of colon cancer is histopathologic stage, so specific strategies are recommended for each stage separately [13-15]. As to surgical treatment, one of its goals is the resection of the involved colon segment together with the draining lymph nodes [14].

According to the 7th AJCC/UICC edition, for a good staging of both colon and rectum cancer it is recommended that a minimum of 12 lymph nodes to be evaluated pathologically [16]. As to the favorable prognosis and survival of patients with colon cancer, a very important role it played by the number of harvest nodes [5,17]. Thus, it is considered that the surgical gesture can have an impact on the harvest nodes. The total number of nodes found in the surgical excision specimen can vary according to age, sex, degree of tumor differentiation, or tumor site. The number of positive lymph nodes plays an important role in TNM system, but N stage is slightly influenced by the extent of lymph node removal, technique used by the surgeon, and thoroughness of the pathologist [18-21]. Stage migration can occur due to these factors. In some cases, such as stage T4, as many as possible lymph nodes should be examined for a better assessment of the disease stage. Patients without lymph node involvement (N0) but in which less than 12 nodes were identified and analyzed are under staging and can be considered high risk patients [13]. Until now, no other TNM independent prognostic factors able to predict the progression of colon cancer have been identified. Nowadays trend is to find as many as possible predictive markers for this disease. For a predictive marker to be incorporated into a staging system it has to have a strong and reproducible impact on the clinical outcome of patients, independent of tumor invasion [22]. The markers can be obtained by analyzing the surgical specimens or diagnostic biopsy samples [23,24].

TNM staging is based on tumor invasion into colonic wall, lymph node status, presence of lymphatic, vascular, and perineural invasion, and of distant metastases. Tumor size and tumor volume were not found useful in this staging system and in predicting the clinical outcome of patients. Although TNM staging is the only strong prognostic marker for identifying patients at high risk of recurrence, however, it can not discriminate patients in the same stage of disease [2,3]. Category N in the TNM classification appears to have the greatest prognostic power, well-known being the fact that the presence of vascular-lymph node invasion is a negative prognostic factor [5].

This study represents an attempt of identifying tumor parameters as potential predictive factors in colorectal cancer. Statistical analysis was based on comparing two groups of patients: group 1 included patients with metastases at the time of admission, and group 2 patients without metastases at diagnosis. In our study, the analysis of maximum tumor diameter showed a statistically significant association with the degree of differentiation, number of invaded lymph nodes, and the number of positive nodes in both study groups. The comparative analysis of the two study groups showed differences in depth of colon tumor invasion, vascular and lymph node invasion. In the group of patients with metastases the results showed a statistically significant higher frequency of T4 tumors with a significant presence of lymph node and vascular invasion. According to the obtained results, the presence of metastases increases the risk of vascular invasion by 6 times with a 5-fold risk of lymphatic invasion. Histologic type and number of

Table V: Parameters Estimated in ROC Curve Analysis.

Area Under the Curve					
Test Result Variable(s)	Area Under the Curve (AUC)	Std. Error	Asymptotic Sig.[b] (p)	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Tumor volume	0.594	0.096	0.484	0.406	0.782

[b]Null hypothesis: true area = 0.5

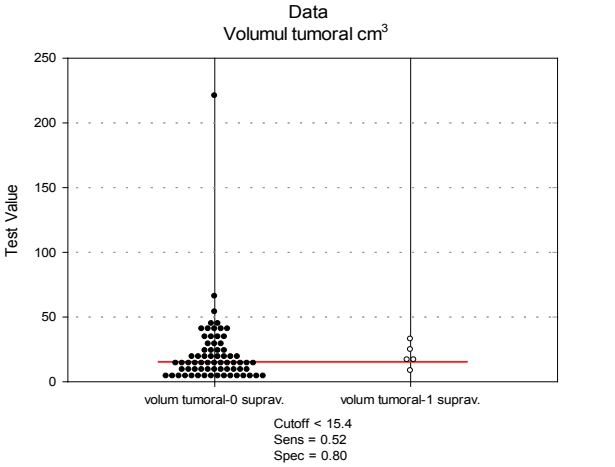

Figure 4: Point-Pair Histogram for Tumor Volume Cut-off Values vs. Survival.

positive lymph nodes were analyzed and they proved to be important factors influencing the maximum tumor diameter. Tumor volume was influenced by male gender, type of invasion, and tumor stage. To use tumor volume and maximum tumor diameter as predictive factors, their cutt-off values were calculated. The obtained statistical results were insufficient for predicting overall survival of the study cohort.

The short follow-up period represents a disadvantage of our study as it did not allow the obtaining of disease-free survival curves. As a perspective of our study is an enlarge cohort with a follow-up according to the international guidelines recommendations with a review of statistical analysis.

Conclusions

Prognostic factors in colon cancer are numerous, but number of lymph nodes is the most powerful in predicting clinical evolution. Tumor dimensions are not included yet in the category of prognostic factors. Nevertheless tumor parameters represent the characteristics that may be used to evaluate tumor aggressiveness. In order to be considered factors with prognostic value, these parameters should be analyzed and validate in larger prospective studies.

Conflict of interests

The authors have no conflict of interests to declare.

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