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Original Article

The Relationship between Size of Adenocarcinoma of Colon and Lymph Node Involvement

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ABSTRACT

Background and Objectives: Involvement of lymph nodes is an important prognostic factor in the most cancers, including colorectal cancer. In the recent years, invasion to blood and lymphatic vessels has been shown to predict involvement of lymph nodes and the number of involved nodes has been less studied issue. The aim of this study was determination of the relationship between the size of colorectal adenocarcinoma and lymph node involvement.

Materials & Methods: In this cross-sectional study, 116 patients were enrolled with colorectal cancer from Rasoul-e-Akram and Mehr Hospitals in 2002-2008. Data analysis was performed by SPSS-15 software. Results were expressed as frequency, percent, and mean ±SD. We used Chi2, student *t*-test and correlation tests for statistical analysis.

Results: 54.3% of patients were male and 45.7% were female. Mean age of them was 59.4± 12.9 years. Mean of tumor size (longest diameter) was 5.4± 2.2 (range: 1.5 to 12) cm. Mean number of involved lymph nodes was 4.9± 3.5(range: 1-14). There was no correlation between number of lymph node involvement and tumor size. There was no correlation between lymph node involvement and tumor and age group, sex, location and depth of tumor. Poorly differentiated tumor significantly correlated to lymph node involvement (P=0.001).

Conclusion: There is no correlation between tumor size and number of involved lymph node in colorectal cancer. However, poor histopathologic grade is associated with lymph node involvement.

Keywords: Adenocarcinoma, Colon, Tumor Burden, Lymphatic Metastases

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Introduction

The prognostic significance of tumor size and lymph node status has served as the basis for staging system in the majority of solid tumor (TNM) (1, 2). The relationship between tumor size and prognosis has been perceived to indicate that the smaller the tumor the greater the likelihood of prolonged control with operative extirpation (3). Moreover, a direct relationship between tumor size and regional lymph node metastases has been assumed in numerous solid tumors (4-7), and the data available in breast cancer have been utilized to illustrate an association between these two variables (3), although results contradicting such a relationship have appeared (8). The various staging schemes available for colorectal cancer are exceptional in that tumor penetration rather than tumor size is utilized as a predictive index of prognosis.

The inherent implication in these colorectal classifications is that tumor size is predictive of neither prognosis nor regional lymph node status suggesting a unique biological situation (3). In an effort to explore the relationship between tumor size and regional lymph node statue, the national surgical adjuvant project for breast and bowel cancer (NSABP) was carried out and analysis obtained from an initial cohort of 924 patients with colorectal cancer. The result indicated that tumor size was unrelated to regional lymph node status. Moreover, the relationship between tumor size and number of the positive nodes was not addressed (3).

Involvement of lymph node is a relevant prognostic parameter, which determines the duration of survival in patients with colonic and rectal adenocarcinoma (9). Presence of involved lymph nodes necessitates adjuvant chemotherapy after surgery (10, 11). In the recent years, invasion the blood and lymphatic vessels has been shown to predict involvement of lymph node (12). However, the issue that the size of tumor can be used for prediction of lymph node was less studied. The number of involved lymph nodes is an important factor in determination of patient's survival (12-14). Thus, finding a relationship between tumor size and number of involved lymph nodes will help us to predict the number of metastatic lymph nodes (and thereby survival of patients) based on tumor size.

If such relationship is confirmed in other studies, we can use tumor size as a major prognostic marker in predicting lymph node involvement and risk stratification in particularly stage IIA rectal cancers.

Our aim in this study was to determine the relationship between size of adenocarcinoma of colon and lymph node involvement and number of involved nodes.

Materials and Methods

In this cross-sectional study, 116 consecutive patients were enrolled with colorectal cancer in Rasoul-e-Akram and Mehr hospitals in 2002-2008. After identifying the patients, we collected our data (demographic and pathologic data) from the samples by means of a checklist. All pathologic examinations were done by one pathologist.

Statistical analysis

We used SPSS-15 software for data and chi2, student *t*-test and person correlation for statistical analysis to compare frequencies, comparison of means and to assess correlations, respectively.

Results

Male to female ratio was approximately 1.2:1. 54.3% of patients were male and

45.7% were female. Age of patients ranged from 27 and 87 years and mean age of them was 59.4±12.9 years. 57.9% of patients were above 50 years old and only two patients (1.7%) were under 30 years.

Frequencies of location of tumor in Rt. colon, Lt. colon, sigmoid and rectum were 35.3%, 8.6%, 15.5%and 40.5%, respectively. 56.9% of tumors were well differentiated, 25% were moderately differentiated, and 18.1% were poorly differentiated. Tumor size ranged from 1.5 to 12 cm and mean of tumor size (maximum diameter) was 5.4±2.2 cm.

Reactive lymph nodes were seen in all patients. Lymph nodes were involved by tumor in 56 patients (48.3%). Mean number of involved lymph nodes was 4.9±3.5 (range: 1-14).

Tumor stages were in a scale from I to IV; the most common stage was stage II A with frequency of 33.6%.

There was not any significant difference between two groups of patients with involved lymph nodes and those without involved lymph nodes as regards age, tumor size, and depth of tumor (T). Furthermore, there was no relation between number of lymph node involvement and tumor size. Mean number of involved lymph nodes in patients with tumor size 5cm was not different from patients with tumor size>5cm (4.53± 3.4vs 5.32± 3.7). There was no correlation between lymph node involvement and age group, sex and location of tumor. Grade of tumor significantly correlated to lymph node involvement (*P*=0.001). These results are summarized in Table1.

Table 1: Comparison of characteristics of patients with colorectal cancer with involved lymph nodes and those without involved lymph nodes

		LN involvement		*P* value
		Neg.	Pos.	
Sex	Male	27(42.9%)	36(57.1%)	>0.05
	Female	29(54.7%)	24(45.3%)	
Location of tumor	Rt. colon	18(43.9%)	23(56.1%)	>0.05
	Lt. colon	6(60.0%)	4(40.0%)	
	Sigmoid	11(61.1%)	7(38.9%)	
	Rectum	21(44.7%)	26(55.3%)	
Tumor depth (T)	T2	12(70.6%)	5(29.4%)	>0.05
	T3	34(45.3%)	41(54.7%)	
	T4	10(43.5%)	13(56.5%)	
Age group	<30yr	0(.0%)	2(100.0%)	>0.05
	30-50yr	11(42.3%)	15(57.7%)	
	>50yr	45(51.1%)	43(48.9%)	
Grade(differentiation)	Well	40(60.6%)	26(39.4%)	>0.001
	Moderate	13(44.8%)	16(55.2%)	
	Poor	3(14.3%)	18(85.7%)	
Tumor size	<=5cm	36(53.7%)	31(46.3%)	>0.05
	>5cm	20(40.8%)	29(59.2%)	
Mean age (yr)		60.6±11.6	58.2±13.9	>0.05
Mean tumor size		5.07±2.3	5.7±2.04	>0.05
Mean depth of tumor (T)		2.96±0.63	3.2±0.6	>0.05

Discussion

Tumor staging systems characterize the extent of neoplastic dissemination. Each tumor class is defined by a number of features invariably based upon specific morphological properties of the particular tumor.

In order to classification scheme to be clinically useful, each defined category must serve as a marker for a specific tumor subset with discrete biological features, as well as unique natural history characteristics and prognosis.

Patient prognosis is the function of clinical and histopathological stage of colon cancer at diagnosis. In addition to the well-established significance of standard pathological features such as depth of bowel wall penetration (T), the number of regional lymph nodes involved (N), and presence of extracolonic metastases (M), several other factors have been proven to be of importance. These include number of harvested and processed lymph node, histologic grade, and evidence of lymphvascular as well as perineural invasion. The most of previous studies have evaluated the relationship between factors such as tumor histological grade and lymph vascular invasion and lymph node involvement (15-17).However, studies assessing relationship between tumor size and number of involved lymph node are lacking.

Bjelovic *et al*. (1998) in the survey in the institute of digestive disease, clinical center of Serbia, evaluated a correlation between the macroscopic (size and consistency) and microscopic characteristics of the regional lymph node (type of involvement in tumor tissue, state of the capsule, adherence of the lymph nodes, etc) in patient with colorectal carcinoma.

In this prospective study, 46 patients with rectal and sigmoid adenocarcinoma were studied through randomized selection. From the resected specimens, a total of lymph nodes were identified (average 15.66 per patient), with the precise location determine according to Enker and Philiphsken.

The macroscopic characteristics of each lymph node were identified. Within the group of "small" lymph nodes, 17.18% were malignant. Additionally, of all the malignant lymph nodes, 46.23% were less than 5 mm in diameter. Although the malignant lymph nodes were diffusely involved within the tumor tissue, 19.50% were focally involved within the tumor tissue, of which 48.38% were "small" lymph nodes, which are commonly non-palpable. These authors concluded that size and consistency of the lymph nodes were not dependable parameter for appraisal of lymph node involvement in tumor tissue, the state of the lymph node capsule, and the interrelation among the lymph nodes. As in the case of the primary tumor local tumor aggression in the lymph nodes is conditional by the grade of differentiation, i.e. histologic immaturity, rather than by tumor size (9).

In our study, there was no correlation between number of lymph node involvement and tumor size. The mean number of involved lymph nodes in patients with tumor size <5cm was not different form patient with tumor size >5cm. Other studies reported that no correlation was found between lymph node involvement and tumor size, but numbers of involved lymph nodes were not considered. Wolmark *et al.* (2006) in a study explored the relationship between tumor size and regional lymph node involvement in patients with Dukes' B and C colorectal cancer in the randomized prospective clinical trials.

Overall, 670 patients with colon cancer, and 236 patients with carcinoma of the rectum were available for analysis. The result indicated that there was no correlation between

the longest diameter of the primary tumor and the status of regional lymph nodes for either colon or rectal cancer. Moreover, this lack of association was evident throughout the distribution. These finding underscore the unique biological behavior of colorectal cancer and emphasize the function of the current generation of randomized prospective trials in providing natural history information (18).

The lack of correlation between tumor size and regional lymph node involvement has received sporadic attention for many years. In 1938, Gilchrist and David (19) proclaimed that the size of a tumor was of little value in determining the presence or the absence of lymph node metastases and in 1940 Coller *et al.* (20) described 52 rectal lesions and concluded that there was no relationship between the size of the lesion and the presence of regional metastases. These authors specifically noted that the incidence of metastases was the same for the smallest and largest lesions. A relationship was noted between tumor configuration and regional node involvement with sessile tumors demonstrating the highest percentage and "excavating" tumors the lowest. Coller and colleagues (21) not only reaffirmed that their initial conclusions related to tumor size but also suggested that the incidence of metastasis was actually higher in tumors of small surface area. Reports by Steams and deddish (22) and Spratt and Ackerman (23) revealed that the size of a rectal cancer bore no relation to the penetration of the bowel and frequency of lymph node involvement. The latter report analyzed 226 consecutive patients with carcinoma of the colon or rectum who underwent tumor resection. In a subsequent analysis in 1962, (24), reaffirmed that tumor morphology was an important predictive index in that pedunculated cancers were far less likely to be associated with lymph node metastasis than were ulcerated lesions of similar size. There is a considerable interest in chance of lymph metastases from visible cancer <2 cm was statistically the same as larger lesion and small-ulcerated cancer were the most infiltrating of all.

In another study, miller *et al*. analyzed the relationship of tumor size to regional and system metastasis and to survival according to stage of disease. Colon cancers (391 cases) that were treated surgically at M.D. Anderson Hospital from 1955 to 1975 were reviewed. Staging of disease was based on the astler-coller modification of Dukes' staging classification. The mean diameters (cm±s.e.m.) of Dukes' B1, B2, C2 and D tumor were 4.47±0.34 (n = 46), 6.61±.029 (n = 147), 5.39±0.23 (n= 71) and 5.78±0.24 (n= 120), respectively. The mean diameter of Dukes' B2 tumor was significantly greater than C2 (P<0.001) and D (P<0.05) tumors. Within stage B and C, there was no relationship between the size of the primary tumor and the 5-year adjusted survival. These finding suggest that colon carcinoma metastasis and survival are independent of tumor size. Because tumor burden dose nit account for distant disease, specific tumor cell phenotypes and biological processes are probably more important in determining metastatic disease (24).

In our study, histopathologic grade of tumor is significantly correlated to lymph node involvement. This is similar to Miller study (11).

In the statistical analysis, there was no significant correlation between lymph node involvement and location of tumor or depth to tumor (T). Depth of tumor penetration in colon wall has been reported to be associated with lymph node involvement; Wolmark *et al*., examined the interrelationship of depth of penetration, tumor size, and the number of positive nodes in Dukes C colo-

rectal cancer. The result indicated that depth of tumor penetration was related to both tumor size and the number of positive regional lymph nodes. Tumors with positive nodes, which failed to penetrate the muscularis propria (C1), were smaller, and were associated with fewer positive nodes as compared to tumors penetrating all coats of the bowel (C2). Although tumor penetration was related to tumor size and the number of positive nodes, no correlation was evident between tumor size and the number of positive nodes within the C1 and C2 patient subsets. The data underscore the biological significance of depth of tumor penetration and militate against tumor size as a prognostic discriminate in patients with colorectal cancer. The finding represents a contradiction to the prevailing biological concept related to the behavior of solid tumors as reflected in the TNM classification scheme (3).

Conclusion

This study indicates that there is no correlation between tumor size and number of involved lymph node in colorectal cancer. However, Histopathologic grade is associated with lymph node involvement.

Acknowledgment

The authors declare that there is no conflict of interests.

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