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Gastrointestinal Tract

Significance of selected morphological and histopathological parameters of colon tumors as prognostic factors of cancer spread

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ABSTRACT

Background/Aims: The identification of prognostic factors of metastatic development is one of the most important issues in colorectal cancer (CRC) research. The aim of this study was to determine the usefulness of colon tumor characteristics, including location, circumferential location, histological type, and histological grade, as predictors of metastases.

Materials and Methods: To identify potential predictors of CRC spread, we analyzed data of 191 patients who had undergone surgery for colon tumors. We searched for potential associations between the location in the right or left colon, circumferential location, histological type, and histological grade (G-parameter) of colon tumors and the incidence of lymph node and distal metastases. The analysis was based on Pearson's chi-square (χ^2) test with a statistical significance of $p<0.05$.

Results: Lymph node metastases were found in 100 patients, including 44 patients with synchronous liver metastases. Lymph node involvement was detected in 43 (52.4%) patients with right-sided and in 57 (52.3%) patients with left-sided tumors (p=0.984). Liver metastases were detected in 19 (23.17%) patients with right-sided colon tumors and in 25 (22.9%) patients with left-sided tumors (p=0.969). Lymph node and liver metastases were found in 60 (47.6%) and 24 (19.0%) patients with annular tumors, respectively (p=NS), and these were found on the mesenteric side in 75.0% (n=30) and 20.0% (n=8) patients (p=0.004) and on the antimesenteric side in 47.6% (n=10) and 48.0% (n=12) patients (p=0.044), respectively.

Conclusion: The circumferential location of primary colon tumors is a significant predictor of their metastatic potential. The mesenteric location of the tumor is predisposed to lymphatic spread, whereas the antimesenteric location predicts hematogenous spread.

Keywords: Colorectal cancer, liver metastases, mesenteric location, lymph node metastases, circumferential location, prognostic factors

Original Article

INTRODUCTION

Colorectal cancer (CRC) is the second and third most frequent cause of mortality in male and female cancer patients, respectively. A total of 15,900 new cases of CRC have been diagnosed in Poland in 2013, and the incidence of this malignancy is ca. 1.4 million worldwide (1,2). The high and sustained increase in morbidity of CRC constitutes a crucial clinical problem and suggests the need for extensive multidisciplinary research on the biology of this malignancy.

One direction for this research is the identification of prognostic factors linked to the outcome of CRC. These factors can be grouped into four categories (3,4). Category I includes widely accepted and routinely used factors whose prognostic significance has been confirmed in numerous independent studies, i.e., local advancement of the tumor (T-parameter), regional lymph node involvement (N-parameter), presence of distant metastases (M-parameter), residual tumor following surgery with curative intent (R-parameter), and preoperative

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serum level of carcinoembryonic antigen (5). Category II includes factors that are neither widely accepted nor routinely used despite having prognostic value in most clinical studies. This group includes factors such as histological grade (G-parameter), radial resection margin, host lymphoid response to the tumor, and expression of oncogenes (3,6). Category III comprises factors whose prognostic value has not been confirmed yet by a sufficient number of clinical trials, and these include some structural alterations in DNA and the expression of epidermal growth factor receptor (7,8). Category IV includes factors that, despite being the subject of extensive independent clinical trials, have not shown prognostic significance, e.g., tumor volume (9,10).

The aim of the study was to verify the usefulness of four characteristics of colon tumors as predictors of lymph node and distant metastases: right- or left-sided location, circumferential location, histological type, and histological grade (G-parameter).

MATERIALS AND METHODS

A total of 240 patients had undergone surgery for colon cancer in 2007-2012, and eventually, 191 individuals with resectable cancers qualified for further analysis.

Ethical approval was obtained from the local bioethics committee at the Medical University of Bialystok (resolution no. R-I-002/84/2014 on 03-27-2014). The study was performed with the written consent of each patient who underwent therapeutic procedures under the National Health Fund in the Second Clinic of General and Gastroenterological Surgery at the University Hospital of Bialystok. The experiment was performed in accordance with the Declaration of Helsinki and Guidelines for Good Clinical Practice.

The remaining patients satisfied one of the following exclusion criteria: 1) acute obstruction of the large bowel requiring salvage surgery (n=15), 2) spread of cancer from its primary site and resultant impossibility of radical resection (n=27), and 3) presence of poorly differentiated cancer (n=7).

Preoperative evaluation comprised endoscopic examination and abdominal computed tomography. Surgical resection included primary tumor and regional lymph nodes. Patients who presented with resectable liver metastases were additionally subjected to anatomical or non-anatomical resection of the liver. Depending on the nature of the surgical procedure, neoplasms of the transverse colon were considered to be located in the hepatic or splenic flexure and were classified as right- or left-sided tumors, respectively. Tumor specimens as well as resected lymph nodes and liver metastases were subjected to histopathological evaluation. The presence of lymph node metastases was considered to be a marker of lymphatic spread and the presence of liver metastases was considered to be a marker of hematogenous spread of colon cancer.

Statistical Analysis

We analyzed associations between the left- or right-sided location, circumferential location (annular carcinoma vs. tumors located on the mesenteric or antimesenteric side), and the histological type and grade (G-parameter) of colon cancer and the incidence of lymph node and liver metastases. The analysis was based on Pearson's chi-square (χ^2) test, with a statistical significance set at $p<0.05$.

RESULTS

The study included 85 females and 106 males aged between 26 and 95 years (mean age of 66.5 years). Majority colon cancers were located in the sigmoid colon. The distribution of the analyzed tumors according to their anatomical location is presented in Table 1.

Of all patients, 82 (42.9%) presented with right-sided colon cancer, whereas 109 (57.1%) presented with left-sided colon cancers. Depending on their anatomical location, the tumors were removed by means of sigmoid resection (n=89) or right- (n=82) or left-sided hemicolectomy (n=20). Lymph node metastases were found in 100 patients, and synchronous liver metastases in 44 cases. The latter group included 24 (54.5%) patients who were subjected to synchronous metastasectomy and 20 (45.5%) individuals with non-resectable liver metastases.

Right- or Left-Sided Location

The incidence of lymph node and liver metastases were similar irrespective of the tumor location. Statistical analysis did not reveal significant associations between the right- or left-sided location of the primary tumor and the incidence of locoregional or distant metastases. Detailed data are shown in Table 2.

Mesenteric and Antimesenteric Location

The mesenteric location of the primary tumor was associated with significantly higher incidence of lymph node metastases

Table 1. Distribution of analyzed tumors according to their anatomical location in patients

	Right-sided location				Left-sided location			
Location of colon cancer	**Cecum**	**Ascending colon**	**Hepatic flexure**	**All**	**Splenic flexure**	**Descending colon**	**Sigmoid colon**	**All**
The number of patients n/(%)	30 (15.7%)	27 (14.1%)	25 (13.0%)	82 (42.9%)	8 (4.18%)	12 (6.28%)	89 (46.5%)	109 (57.1%)

Table 2. Incidence of lymph node and liver metastases according to different features of the tumor

		Lymph node metastases (n=100) n (%)	Liver metastases (n=44) n (%)
Primary location of the tumor	Right-sided location (n=82)	43 (52.4)	19 (23.2)
	Left-sided location (n=109)	57 (52.3)	25 (22.9)
	p*	0.984	0.969
Primary location of the tumor	Mesenteric location (n=40)	30 (75.0)	8 (20.0)
	Antimesenteric location (n=25)	10 (40.0)	12 (48.0)
	Annular infiltration (n=126)	60 (47.6)	24 (19.0)
	p*	0.004	0.044
Histological type of colon cancer	Tubular carcinoma (n=148)	82 (55.4)	36 (24.3)
	Mucinous carcinoma (n=43)	18 (41.9)	8 (18.6)
	p*	0,117	0.433
Grade of the colon cancer	Grade 2 (n=176)	91 (51.7)	41 (23.3)
	Grade 3 (n=15)	9 (60.0)	3 (20.0)
	p	0.904	0.383

*chi-square test (χ^2)

(p=0.004). In contrast, liver metastases were found significantly more often in patients with colon cancers located on the antimesenteric side (p=0.044). Annular carcinoma was the most common morphological form of colon cancer found in our data. The incidence of lymph node metastases in patients with this morphological variant was similar to the incidence of liver metastases. Data on the incidence of lymph node and liver metastases in patients with different locations of primary tumors are presented in Table 2.

Histological Type

We did not find significant associations between the histological type of colon cancer and the incidence of lymph node and liver metastases. Data on the incidence of lymph node and liver metastases in patients with various histological types of colon cancer are presented in Table 2.

Cellular/Nuclear Pleomorphism

Our patients significantly more often presented with G2 tumors than with G3 tumors. However, statistical analysis did not confirm significant effects of cellular/nuclear pleomorphism on the incidence of lymph node or liver metastases (Table 2).

DISCUSSION

Right- or Left-Sided Location

Based on their anatomical location, colon cancers are classified as right-sided (proximal) tumors, i.e., those located between the cecum and splenic flexure, and as left-sided (distal) tumors, involving the segment from the splenic flexure up to the sigmoid colon. Colon cancers are more often located in the distal part of the colon than in the proximal part. The sigmoid colon (46.5%) was the most frequent location of colon cancer in our data, and left-sided tumors were rarely found in other anatomical locations. Of all patients, 42.9% presented with right-sided tumors and these were equally distributed among various anatomical parts of the proximal colon. Data published during the last three decades have documented an increase in the incidence of tumors located in the proximal colon (11,12). In a retrospective study of 600 cases, the incidence of CRC in the right colon amounted to 15% in 1978-1982 and to 21.4% in 1983-1987 (13). Results of recent studies point to the potential prognostic value of tumor location. However, our patients with right- and left-sided colon cancers did not differ significantly in terms of the incidence of lymph node or liver metastases. These findings suggest that the location of the tumor within the right or left colon probably has no value as a predictor of its spread. Similar observations were previously reported by Derwinger and Gustavsson (14) who analyzed a group of 1,588 patients who underwent surgery for CRC. However, according to many authors, the location of a tumor in the right or left colon is associated with its specific biology and clinical phenotype (15,16). Previous studies showed that the anatomical location of colon cancer is age- and sex-specific (17,18).

Proximally located tumors have been shown to be more prevalent among younger patients and in men, whereas distally located malignancies are more frequently observed in women and older individuals (18). However, a relationship between the location of cancer in the right or left colon and the prognosis raises some controversies. One potential explanation for different clinical phenotypes of the right- and left-sided tumors is the presence of microsatellite instability, i.e., changes in the length of repeated sequences of DNA (microsatellites) resulting from impaired DNA mismatch repair, usually due to inactivation of one of the following mismatch repair genes: *MSH2*, *MLH1*, *MSH6*, or *PMS2* (19). Tumors presenting with microsatellite instability were more often located in the right colon. Such tumors are typical in familial CRC syndromes and are associated with better prognosis than tumors with stable microsatellites, which are more prevalent in the left colon and are usually sporadic malignancies (20). However, according to many authors, tumors located in the right colon are associated with poorer prognosis. Shorter overall and progression-free survival are likely observed because right-sided tumors are usually flat,

rather than polypous, and together with a wider lumen and more liquid contents of the right colon, this leads to delayed diagnosis of proximal tumors until more advanced clinical stages. Furthermore, flat tumors can be overlooked during colonoscopy (21). In turn, tumors located in the left colon give earlier signs of sub-obstruction that lead to the performance of appropriate diagnostic tests.

Mesenteric and Antimesenteric Location

The mesenteric and antimesenteric location of colorectal tumors has not been frequently analyzed as a potential prognostic factor of lymph node involvement and distant metastases. One premise for such research is the hypothesis tumors with higher metastatic potential and more aggressive phenotypes are located on the mesenteric side. This location of the primary tumor is associated with close proximity to blood and lymphatic vessels (22). In our study, the incidence of lymph node metastases was significantly higher in the case of tumors located on the mesenteric side than in those located on the antimesenteric side (75% vs. 40%). A different situation has been reported in Posner's study of the case of distant metastases, with significantly more frequent occurrence in the case of tumors located on the antimesenteric side than in those located on the mesenteric side (48.0% vs. 20.0%) (22). Animal experiments conducted by Boni et al. (23) showed that the kinetics of tumor growth is determined by the circumferential location of the lesions. Neoplastic cells injected at the mesenteric side of the large intestinal wall showed a tendency for locoregional spread via the lymphatics. Conversely, the cells injected at the antimesenteric side were more likely to form diffuse peritoneal carcinomatosis. This phenomenon can be explained by differences in the vascular patterns of the mesenteric and antimesenteric side, namely the presence of minute blood vessels with lower density and higher permeability on the antimesenteric side. The results of experimental studies suggest that the metastatic potential of colon tumors differs depending on their circumferential location. Benevento et al. (24) confirmed this hypothesis in a study on patients with CRC. Lymph node involvement was documented in 101 of 255 patients with tumors located on the mesenteric side and in only 5 from 37 individuals with tumors located on the antimesenteric side. Tumors with mesenteric location were shown to be slightly more prevalent than tumors located on the antimesenteric side. Boni et al. (23) showed that the mesenteric location of a tumor is associated with a higher incidence of lymph node metastases but greater likelihood of 5-year survival. Our findings are consistent with the above-mentioned data. Therefore, we confirmed the significance of mesenteric and antimesenteric location of colon cancer as an independent prognostic factor of its spread. Importantly, the above-mentioned characteristic pattern of metastasis formation was not observed in the case of annular carcinomas. To the best of our knowledge, this issue was addressed by only one previous study. Based on the analysis of 43 patients with annular carcinoma of the colon, McCarthy showed that this cancer phenotype is characterized by higher incidence of both lymph node and liver metastases (25).

Histological Type

According to the World Health Organization classification, colorectal tumors represent a few histological types, namely mucinous, signet ring, squamous cell, small-cell, and undifferentiated adenocarcinomas. Extracellular mucus represents more than 50% of the mucinous adenocarcinoma mass, and signet ring adenocarcinomas are characterized by a high intracellular content of mucus that pushes the nucleus to the periphery (26). Most previous studies did not confirm an association between the histological type of CRC and incidence of locoregional and distant metastases. The only exception pertains to less favorable prognosis in the case of poorly differentiated tumors, i.e., undifferentiated and signet ring adenocarcinomas. However, these two histological types of CRC are extremely rare, representing only 1%-2.4% and <1% of all the cases, respectively (27). Because the incidence of mucinous and signet ring adenocarcinomas in our data was low [3 (1.25%) and 4 (1.67%) cases, respectively], these histological types of colon cancer were excluded from further analysis. We did not observe a significant association between the histological type of colon cancer and incidence of metastases. This question has not been frequently dealt with in the available literature. A few previous studies showed that mucinous adenocarcinoma represents a more aggressive phenotype than other types of adenocarcinoma, but only if present in the sigmoid colon or rectum and in individuals younger than 45 years (28,29). Goldstein and Hart (30) confirmed mucinous adenocarcinoma as an unfavorable prognostic factor. However, their study included only patients with tumors obstructing the large intestinal lumen, which *per se* represents an unfavorable prognostic factor. In contrast, Purdie and Piris (31) analyzed a group of 255 patients with CRC and did not show a significant association between the histological type of a tumor and incidence of metastases.

Cellular/Nuclear Pleomorphism (G-Parameter)

Many years of research have shown that the ability to form tubules is the most accurate measure of tumor differentiation. Tumors with a low percentage of tubules in their architecture are considered to be poorly differentiated, and thus associated with worse prognosis (32). The fact that high histological grade is associated with greater local invasiveness and higher incidence of locoregional and distant metastases was confirmed in many previous studies and raises no controversies (33). However, the tumor grade is still classified as a category II prognostic factor (34). This is likely because this parameter is rarely considered in routine surgical practice. Currently, the degree of tumor differentiation can be assessed with a few different scales. Although all of the scales are based on the percentage of tubular structures within the tumor, some of them include additional

parameters such as nuclear polymorphism or alterations of nuclear structures. However, the two most popular scales are based solely on the ability to form tubules. The first scale, recommended by the College of American Pathologists, has two grades- well-differentiated tumors, in which tubular structures constitute >50% of the area, and poorly differentiated tumors, with <50% of the area being formed by tubular structures. The second scale has three grades-G1, in which >95% of the tumor area represents tubular structures, G3, in which < 49% of the tumor area is formed by tubular structures, and G2, which is an intermediate type between G1 and G3. Tumors that do not contain tubular structures are by default classified as poorly differentiated (35).

We observed lymph node metastases in 51.7% of patients with G2 tumors and in 53.3% of patients with G3 malignancies. Liver metastases were found in 45.0% and 33.3% of G2 and G3 tumors, respectively. Although none of these differences were statistically significant, this might result from too small a number of patients with G3 tumors. Ueno et al. (36) used the same scale of nuclear/cellular pleomorphism to analyze the incidence of lymph node metastases in patients with G1/G2 and G3 CRCs. Lymph node involvement was documented in 3.7% and 37% of patients with G1/G2 and G3 malignancies, respectively. Our findings suggest that prognosis in moderately well and poorly differentiated tumors is similar. Due to a lack of well-differentiated (G1) tumors in our data, we were unable to determine their aggressiveness and metastatic potential. However, according to most authors, G1 grade represents a favorable prognostic factor in cancer patients (37). Both the results of this study and the literature data suggest that except for tumors located on the antimesenteric side, lymphatic vessels, rather than blood vessels, constitute the predominant route of colon cancer spread. These findings point to regional lymphadenectomy as a vital component of surgical treatment of colon cancer.

In the present study, the circumferential location of primary colon tumors is a significant predictor of their metastatic potential. In contrast, location in the right or left colon, histological type, and degree of nuclear/cellular polymorphism should not be considered as predictors of metastasis in colon cancer patients. Moreover, while mesenteric location of colon tumors predisposes to their spread via the lymphatics, antimesenteric location predicts their hematogenous spread. Preoperative identification of primary colon tumor located on the antimesenteric side necessitates evaluation for the presence of liver metastases and careful postoperative monitoring.

Ethics Committee Approval: Ethics committee approval was received for this study from the Local Bioetics Committee at Medical University of Białystok (Decision Date: 27.03.2014/Decision No: R-I-002/84/2014).

Informed Consent: Written informed consent was received from patients who participated in this study.

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