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ORIGINAL ARTICLE

Prognostic significance of histological features and biological parameters in stage I (pT1 and pT2) colorectal adenocarcinoma

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Abstract

Patients with stage I colorectal cancer have a good prognosis, however, a small fraction of them die of local or distant recurrence after curative resection. The aggressive behavior reflects some biological properties of these tumors. In this study, we evaluated the prognostic role of some histopathological and biological parameters in stage I colorectal carcinomas. From the Colorectal Cancer Registry of Modena, we selected two series of patients; the first included all patients who had died of disease progression, the second included patients with a favorable outcome. The histopathological parameters assessed were grade of differentiation, growth pattern at the invasive tumor front, peritumoral lymphocytic infiltration, tumor budding and vascular invasion. The biological variables were proliferative activity (using Ki-67 nuclear antigen), overexpression of p53 protein and altered expression of the mismatch repair proteins (MLH1 and MSH2).

The results showed that an infiltrating growth pattern, absent or sparse peritumoral lymphocytic infiltration, the presence of tumor budding and vascular invasion are significantly related to the risk of recurrence. Among the biological parameters, p53 overexpression was significantly correlated with a poor clinical outcome. Our study showed that the histopathologial features are relevant prognostic indicators and might be used as markers for an appropriate treatment strategy in patients with stage I carcinomas.

Keywords: Stage I colorectal carcinoma; Prognostic parameters; Tumor budding; Vascular invasion; P53 overexpression

Introduction

Patients with stage I (pT1N0M0, confined to submucosa or pT2N0M0 limited to the muscularis propria) or Dukes A colorectal cancer have a good prognosis, with a 5-year survival of 80–90% [10–12,41]. However, rather surprisingly, a small fraction of stage I tumors show a poor outcome even after a curative resection,

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and this suggests that the aggressive behavior may reflect some biological and morphological properties of these neoplasms.

Several parameters have been investigated as potential indicators of adverse outcome in colorectal malignancies. Among morphological variables, a low degree of differentiation and lymphovascular invasion have been considered possible risk factors of lymph node metastasis in apparently limited and resectable colorectal cancers [5,8,18,30]. Some studies have also shown that "tumor budding" is a predictive marker of nodal status involvement in pT1 or pT2 cancer [18–20,31,40]; in addition, the pattern of tumor growth and peritumoral lymphocytic infiltration have been considered potential indicators of prognosis in these patients [22,25,37].

Relatively little is known about the molecular features of colorectal cancer that might explain the biological reasons for the different behavior of tumors appearing so similar on a clinical basis. Several investigations of colorectal carcinomas of different stages suggest that overexpression of the p53 tumor suppressor gene could be a negative prognostic factor [1,4,16]; other studies tried to evaluate the correlation between cell proliferation and clinical behavior, but the conclusions were frequently equivocal [1,2,17,21,35,36,38]. More recently, various studies have reported that microsatellite instability evaluated either by immunohistochemistry analysis of the mismatch repair (MMR) proteins expression or by PCR [3,7,26,34] is often associated with a more favorable outcome when compared with microsatellite stable tumors.

In this study, we tried to find out whether a careful evaluation of some morphological and molecular indicators might give an answer to the question of why a subgroup of patients with tumors limited to the bowel wall and completely resected (two factors which assure long-term survival in the great majority of these patients) showed a dismal prognosis.

Materials and methods

The colorectal cancer registry

This study could be carried out owing to the existence of the Colorectal Cancer Registry of Modena, instituted in 1984, whose main purposes have been described in detail in other reports [32,33]. During the period 1984–1998, a total of 2,529 carcinomas were diagnosed in 2,400 patients (the crude incidence rate ranged between 58 and 69 new cases/100,000 residents/year). Among these, there were 295 patients with stage I lesions (155 males, 140 females, mean age 67.9 years): 150 individuals had tumors infiltrating the muscular wall (T2), and 145 had neoplasms limited to the submucosa (T1). All patients with stage I colorectal carcinoma in the whole series (or their relatives) were contacted so that a complete 5-year follow-up could be traced [11].

The clinical charts and the pathological records revealed that 22 patients had died of colorectal cancer, while the others showed a favorable outcome without progression of disease.

Cohort definition

From the Colorectal Cancer Registry, we identified all the 22 stage I patients who had died of colorectal cancer. This series of patients with an unfavorable prognosis was compared—matching for sex, age, location of tumors, type of resection and extension (T1 or T2) of the disease—with a series of 96 stage I patients that showed a favorable outcome (Table 1). The colonoscopic records, biopsy results and number and types of recurrences were recorded for each patient. The presence of recurrence disease was confirmed by histology. Locoregional recurrence was defined as a disease related to anastomosis or in the adjacent mesentery and peritoneum; tumor recurrence at other sites was labeled as distant metastasis.

Histopathological parameters

We evaluated the following histopathological parameters: grade of differentiation (classified as well, moderate and poor), growth pattern at the invasive front of the tumor (subdivided in expanding and infiltrating), peritumoral lymphocytic infiltration (scored as absent, little, moderate or marked), vascular

Table 1. Clinicopathological features in the two groups of stage I colorectal carcinoma patients

	Alive (96)	Deceased (22)
Sex		
Male	46	11
Female	50	11
Age at diagnosis (mean ± SD)	64.35 ± 9.90 years	67.64 ± 8.9 years
Range	(43–85 years)	(48–81 years)
Tumor site		
Proximal colon	10	1
Distal colon	36	6
Rectum	50	15
Type of surgery		
Resection	94	21
Polypectomy	2	1
Staging (pT)		
T1	8	3
T2	88	19