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Risk factors for recurrence of stage I/II (TNM) colorectal adenocarcinoma in patients undergoing surgery with curative intent☆

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ABSTRACT

Objective: Evaluate risk factors for colorectal cancer recurrence after surgical treatment.
Methods: Sixty-five patients with colorectal adenocarcinoma, stage I and II (TNM), undergoing curative-intent surgery and followed for five years were studied. Presence of adjuvant/neo-adjuvant therapy, tumor differentiation degree, lymphatic and venous vascular infiltration, depth of tumor invasion, and disease staging was analyzed, using recurrence relative risk ratios for each parameter calculated at two years, after two years and five years of follow up.
Results: At five years, recurrence was 21.4% (14/65), with equal incidence (10.7%) for the separated periods. Only lymphatic and venous vascular infiltration showed statistically significant association with recurrence during times analyzed. Relative risk (RR) of recurrence was significantly related to the presence of lymphatic infiltration [RR = 6 (1.3 – 28.5) p = 0.01] and venous infiltration [RR = 9.5 (2.6 – 34.9) p < 0.001] after two years of follow-up. At five years follow-up, only venous infiltration remained with significant relative risk for recurrence [RR = 3.9 (1.8 – 8.8) p < 0.001]. In a multivariate analysis, only venous vascular infiltration was associated with recurrence [accuracy 81.5% (p < 0.001)].
Conclusion: In this series, the factors associated with risk of colorectal cancer recurrence were the presence of lymphatic and venous vascular infiltration.

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Fatores de risco para recidiva em pacientes com adenocarcinoma colorretal estádio I e II (TNM) submetidos à cirurgia com intenção curativa

Palavras-chave:
Invasividade neoplásica
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RESUMO

Objetivo: Analisar fatores de risco para recidiva de câncer colorretal após tratamento cirúrgico.

Método: Avaliou-se 65 pacientes com adenocarcinoma colorretal, estadio I e II (TNM), submetidos à cirurgia com intenção curativa, acompanhados por cinco anos após a operação. Analisou-se presença de tratamento adjuvante/neoadjuvante, grau de diferenciação do tumor, infiltração vascular linfática e venosa, profundidade de invasão tumoral e estadiamento da doença, estabelecendo-se para cada um o risco relativo de recidiva aos dois anos, após dois anos e aos cinco anos de seguimento.

Resultados: Recidiva global em cinco anos foi 21,4% (14/65), com idêntica incidência (10,7%) nos períodos separados. Somente as infiltrações vasculares linfáticas e venosas apresentaram associação estatisticamente significativa com a recidiva nos períodos de análise. Encontrou-se risco relativo (RR) estatisticamente significativo após dois anos relacionados à presença de infiltração linfática [RR = 6 (1,3 – 28,5) p = 0,01] e infiltração venosa [RR = 9,5 (2,6 – 34,9) p < 0,001]. Após cinco anos, apenas a infiltração venosa manteve a significância estatística, com risco relativo elevado para ocorrência de recidiva [RR = 3,9 (1,8 – 8,8) p < 0.001]. Na análise multivariada apenas a presença de infiltração vascular venosa com 81,5% de acerto foi associada à recidiva (p < 0.001).

Conclusão: Nesta série, os únicos fatores associados com risco de recidiva do câncer colorretal foram a presença de infiltração vascular linfática e venosa.

Introduction

Colorectal cancer (CRC) ranks second in mortality in the U.S. and in Brazil, second only to lung cancer. The National Institute of Health reported 141,210 new cases and 49,380 deaths in the year 2011.[1] In Brazil, according to the National Cancer Institute (INCA) data, 30,140 new cases of colon and rectum cancer are expected for the year 2012, with a slightly higher incidence in women.[2]

Although there has been progress in understanding the genesis of colorectal tumors, CRC-related deaths are still high, with great impact on public health programs.[2] The overall median survival at 5 years is around 55% in developed countries and 40% in developing countries, and can reach higher rates.[2]

Currently, colorectal cancer staging is based on clinicopathological staging proposed by the International Union Against Cancer (TNM staging system), i.e., depth of tumor invasion into the colon wall, presence of lymph node and distant metastases. However, patients with the same stage may have different clinical outcomes, indicating that the currently used staging may not reflect the actual aggressiveness of each individual tumor.[3,4]

Several efforts have been made regarding the identification of the colorectal cancer prognostic factors. This study objective was to analyze in a case series of colorectal cancer (TNM staging I-II) the relationship between the specific clinicopathological factors and recurrence after surgical treatment with curative intent.

Methods

This study was approved by the Human Research Ethics Committee of the Hospital de Clínicas (HC), Universidade Federal do Paraná (UFPR), and registered under the No 82.001/2003-01.

Patients: After reviewing 550 cases of colorectal cancer treated at the General Surgery and Digestive Surgery centers (HC–UFPR), from September 1995 to January 2003, 65 patients with neoplasia, classified as TNN clinical stage I and II and underwenting curative surgical treatment were selected. Exclusion criteria were familial adenomatous polyposis, inflammatory bowel disease, and postoperative death.

Follow-up: After surgery, patients were followed-up for at least five years, according to the following protocol: clinical history, physical examination, measurement of blood carcinoembryonic antigen (CEA), chest X-ray, abdominal ultrasound, chest and abdominal CT scans, and colonoscopy. In the first year after surgery, follow-up visits were quarterly and colonoscopy semiannually; from the second year onward, the visits were semiannual and colonoscopy annual. CEA blood test, chest X-ray, and abdominal ultrasound were performed every three months for the first year and every six months after the second year. Chest and abdominal CT scan was performed every six months in the first year and annually from the second year onwards.

Study parameters: Data regarding anatomopathological parameters, histology, tumor differentiation degree, angiolymphatic and angiovenous invasion, depth of tumor invasion into the colon wall, in addition to adjuvant/neoadjuvant

therapy used were correlated with the incidence of relapse when detected up to two years, after two years, and at five years of follow-up.

Statistical Analysis: The measures of central tendency considered were average, standard deviation, and 95% confidence interval for continuous variables and absolute frequencies and percentages for categorical variables. The estimated risk was performed by calculating the relative risk for variables with three levels of classification, always comparing the second level with the first, then the third level with the first, and finally both levels with the first. Multivariate logistic regression and discriminant analysis models were used to assess the predictive power for disease recurrence. To estimate the difference between variables, Student's t-test was used for continuous variables and chi-square test and Fisher's exact test for categorical variables; p values < 0.05 were considered statistically significant.

Table 1 – Frequency of presented parameters and recurrence in the study patients.

Characteristics	Values
Adjuvant/neoadjuvant therapy	Chemotherapy and/or radiotherapy: 29 cases (44.6%)
Grade of histological differentiation	Grade I: 45 cases (69.3%) Grade II: 9 cases (13.8%) Grade III: 11 cases (16.9%)
Vascular infiltration	Lymphatic: 19 cases (29.2%) Venous: 8 cases (12.3%) Lymphatic and venous: 6 cases (9.2%)
Depth of tumor invasion	T1: 1 case (1.5%) T2: 22 cases (33.9%) T3: 42 cases (64.6%)
TNM staging	Stage I: 23 cases (35.4%) Stage II: 42 cases (64.6%)
Recurrence	Present: 14 cases (21.4%) Liver: 6 cases (9.2%) Pelvic region: 6 cases (9.2%) Anastomotic line: 1 case (1.5%) Lung: 1 case (1.5%) Time of recurrence: Up to two years: 7 cases (10.7%) After 2 years: 7 cases (10.7%) At 5 years: 14 cases (21.4%)

Results

Patient's mean age was 58.5 ± 12.6 years (24-79 years), with a slight predominance of male (53.3%). Rectal neoplasm accounted for 40% of cases (26), with 40% represented by other lesions in the left colon and the remaining 20% (13) located in the right colon. Surgical treatment consisted of anterior rectosigmoidectomy or sigmoidectomy in 29 cases (44.7%). Abdominoperineal excision of rectum was performed in 17 patients (26.1%). Fifteen patients (23.1%) underwent right colectomy and four patients (6.1%) were treated for left colectomy.

Table 1 shows the frequency of the analyzed parameters and recurrence occurred during the follow-up times. Adjuvant/neoadjuvant therapy was used in 44.6% of cases. Grade 1 histology was predominant (69.3%). Lymphatic infiltration overcame venous infiltration (29.2% vs 12.3%), while T3 tumor depth and TNM stage II predominated (64.6%).

Recurrence was observed in 14 patients over the five year of follow-up (21.4%), divided equitably (seven cases, 10.7%) between times up to two years and after two years. Topographically, the locations with the highest frequency of recurrence were the liver and pelvic region, with six cases each (9.2%). Recurrence was also seen in the lung and anastomotic line in one case each (1.5%) (Table 1).

Regarding relative risk of relapse according to the studied parameters, there were no statistically significant differences between any of the times studied and the adjuvant/neoadjuvant therapy used, tumor differentiation degree, depth of tumor invasion, and disease stage (Table 2).

Presence of lymphatic and venous infiltration was associated with a statistically significant relative risk of recurrence after two years of follow up. The risk of recurrence after two years of follow-up was six times higher with lymphatic infiltration (95% CI = 1.3 – 28.5) than without lymphatic involvement. Similarly, the risk of tumor recurrence after two years of follow-up was 9.5 times higher (95% CI = 2.6 – 34.9) with venous infiltration than without venous vascular invasion. The latter persisted with statistical significance for increased risk of recurrence also when analyzing the total follow-up time (five years), with a risk of recurrence 3.9 times higher (95% CI = 1.8 – 8.8) (Table 2).

Table 2 – Relative risk of relapse according to the study parameters.

Study parameters	Recurrence					
	Up to 2 years		After 2 years		At 5 years	
	Relative risk	p	Relative risk	p	Relative risk	p
Adjuvant/ neoadjuvant therapy	1.6 (0.4 – 6.8)	0.69	3.1 (0.6 – 14.8)	0.22	2.2 (0.8 – 5.9)	0.13
Degree of tumor differentiation	3.6 (0.9 –14.2)	0.08	0.6 (0.1 – 4.7)	0.59	1.3 (0.1 – 4.0)	0.69
Lymphatic infiltration	1.0 (0.2 – 4.5)	1.00	6.0 (1.3 – 28.5)	0.01	2.4 (1.0 – 6.0)	0.09
Venous infiltration	1.2 (0.2 – 8.6)	1.00	9.5 (2.6 – 34.9)	< 0.001	3.9 (1.8 – 8.8)	< 0.001
Depth of tumor invasion	0.2 (0.01 – 0.09)	1.00	0.2 (0.01 – 0.09)	1.00	0.4 (0.1 – 1.8)	1.00
Disease stage	1.4 (0.3 – 6.5)	1.00	3.5 (0.4 – 27.1)	0.05	3.3 (0.8 – 13.4)	0.11

Considering relapse as dependent variable, discriminant analysis showed that the studied parameter selected with the highest discrimination power was the presence of venous vascular infiltration, with 81.5% of correct classification ($p < 0.001$).

Discussion

In the present study, as often observed in the literature,[1,5] the most frequent tumor location was in the left colon and rectum; histological type was adenocarcinoma; and grade of histological differentiation was Grade I.

There was no recurrence in 78% of patients, which can be explained by the early clinical stage of tumors (I-II). Recurrence was more frequent in the liver and pelvic region, which is consistent with literature reports.[6,7]

Diagnosis and treatment of colorectal cancer have evolved considerably in recent years, particularly with regard to decisions on limited or complete resection and the type and indication of the adjuvant therapy used. In both situations, decisions are mainly based on the histopathological findings of the resected specimen.[8-10] The indication of adjuvant therapy in clinical stages I and II patients remains controversial in the literature because, besides the possibility of not increasing the survival of these individuals, it has a high cost and may expose them to the adverse effects of QT and RT.[8,11]

In our series, the evaluation of adjuvant or neoadjuvant therapy as a prognostic factor for recurrence showed no significant association. This may be evidence that in patients with early clinical stage disease the use of adjuvant or neoadjuvant treatment does not change the course of disease.

Although adjuvant chemotherapy is indicated for patients with colorectal cancer with lymph nodes positive for malignancy, a small proportion of patients with negative nodes have an unfavorable clinical course, and thus adjuvant therapy could be beneficial for these patients, justifying costs and adverse effects.[8,12] Therefore, identification of patients at higher risk for local, lymph node, and distance metastasis recurrence is critical, regardless of the information obtained by the application of the current pathological TNM staging system.

Contrary to what literature often reports, in this series we found no association between frequency of tumor recurrence and degree of differentiation, depth of tumor invasion, and staging.[13,14] Coincidentally, the classification of these parameters evaluated in this study whose classification could not be categorized in a dichotomous (present/absent), requiring two (TNM staging) or three classes (grade of histological differentiation and depth of tumor invasion), subdividing the number of patients prior to statistical analysis. Unfortunately, we cannot discard definitively that the analysis of these parameters for the associations estimated as non-significant may have been a type II error due to the sample size.

The presence of lymphatic and venous vascular infiltration by neoplastic colorectal cells is described in literature as a prognostic factor indicative of more aggressive neoplasm.[7,15-18] In this study, 29% of patients had lymphatic vascular infiltration and 12% had venous infiltration. Moreover, there was a statistically significant association between venous or lymphatic infiltration and tumor recurrence rate measured at follow-up.

When we stratified the time of global recurrence, assessed at five years follow-up in two different times (up to two years and after two years recurrence), we found similar behavior of lymphatic and venous infiltration according to the sub-period analyzed (Table 2). Both parameters (venous and lymphatic infiltration) did not reach statistical significance when studied for association with early relapse within two years. On the other hand, both parameters were significantly associated with tumor recurrence after the third year of follow up. We believe that this fact has important clinical implications relevant to current and future strategies of postoperative follow-up of patients undergoing colorectal cancer surgery. We could ask, for example, to patients at follow-up (with known high risk of recurrence) the reasons for the infrequency, except from the third year of follow up. Are frequency and the means currently available to detect recurrences suitable for the earlier periods of follow-up? Is there a different clinical profile among patients with early recurrence compared to others?

In this series, the predictive factors of recurrence in multivariate analysis revealed vascular venous infiltration as the only factor capable of predicting recurrence alone with statistical significance ($p < 0.001$).

Currently, the biological behavior of malignant colorectal neoplasm still surpasses the ability to predict recurrence parameters of known value and used for evaluation and characterization of clinical placements.

Conclusion

In this work, it was possible to concluded that among the clinicopathological factors analyzed, the ones associated with risk of recurrence were lymphatic and venous vascular infiltration by tumor cells; nevertheless, only after two years of follow-up.

Further studies with new criteria to predict early relapse are still needed in order to have an even better performance in colorectal cancer follow-up.

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