

Original Article

Recurrence Factors In Stage II Colon Cancer

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Abstract

Objective and Methods: For evaluating recurrence factors in Stage II colon adenocarcinoma a clinical, non-experimental, longitudinal and retrospective study was done in the Department of Abdomen of INEN from January 1, 1990 to December 31, 2000. **Results:** In 200 eligible patients 20 (10%) recurrence cases were observed that appeared in an average 2.3 years after surgery. The main site of recurrence was local-regional (5.5%), pulmonary (2.5%), hepatic (1%), and peritoneal (1%). The following factors were considered: age, sex, CEA level, type of operation (elective or emergency), site of the primary injury, invasion (T3 or T4), lymphatic vessel invasion, histologic differentiation, and synchronous carcinoma. We found that patients more than 70 years old ($p=0.0305$) have a lesser disease-free time. Be more than 70 years old was the only recurrence-related factor; this group has 2.56 times more risk of recurrence. No other studied variable was related to recurrence.

Key words: Colon. Adenocarcinoma. Risk factors. Recurrence.

Introduction

Colorectal cancer is the third most common neoplasia diagnosed in both sexes, with 150,000 new cases in 2003, being the second cause of death by cancer, with near 55,000 deaths annually in the United States.¹ About 30% of all the patients with colorectal cancer have metastasis at diagnostic and 50% of the early clinical stages in the course of the disease can develop metastases or advanced disease.²

In Peru according to the data of the Registry of Cancer of Metropolitan Lima, colorectal cancer is the 8th most frequent neoplasia and is the 2nd of the digestive tract, after gastric cancer, being also the 10th cause of death by cancer.³

Colorectal cancer 5-year survival rate is 80% to 90% for disease located in the intestinal wall, 40% to 60% for regional disease, and is less than 5% for metastatic disease.¹ From all patients with colon cancer, the incidence of Stage II is from 40% to 45%; and 80% of patients with Stage II cancer colon are disease free after

five years, submitted to surgical treatment with curative intention (standard treatment) and about 20% develop recurrence within the first five years.⁴

Standard treatment for Stage II colon cancer is surgery with no adjuvant treatment; chemotherapy as adjuvant treatment is still controversial for clinical stage II,⁵ but some series recommend complementary chemotherapy for patients with clinical pathological prognostic factors of recurrence.

In Stage III, chemotherapy as adjuvant treatment to surgery improved survival.⁶

No remarkable additional benefit was observed in studies about Stage II, or Dukes B, colon cancer treated by

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surgery and adjuvant chemotherapy in relation to those treated only surgically.⁶⁻⁷ With the purpose of identifying what patients have greater risk of recurrence in Stage II colon cancer, clinical-pathological prognostic factors are evaluated that can predict recurrence⁸⁻¹² which could benefit from adjuvant chemotherapy.⁶⁻⁷

Patients and Methods

We conducted a non-experimental, longitudinal and retrospective clinical study of all patients submitted to curative resection of stage II colon adenocarcinoma, with surgery performed in INEN from January 1, 1990 and December 31, 2000. Inclusion criteria were: 1) colon adenocarcinoma. 2) stage II, according to AJCC, 6th ed. Classification;¹³ pT3 or pT4 with negative ganglia and without distant metastasis. 3) no residual disease or compromised edges. 4) no adjuvant chemotherapy. Exclusion criteria were: 1) patients operated in other institutions. 2) patients submitted to non-curative surgery. For evaluating recurrence, follow-up time was from the day of the operation to the last follow up.

The studied sample is formed by 207 patients Stage IIa and IIb, submitted to curative resection for colon adenocarcinoma. Seven patients were excluded (3.4%) with non-curative surgery. Finally 200 patients were selected that met inclusion criteria.

The present study uses INEN databases, where are registered all patients treated for colon adenocarcinoma in the period of study. This information was complemented by the following variables: date of recurrence, site of recurrence and date of death. A follow-up work was done to reduce the number of patients lost, by means of location by the telephone, and life verification with the Registro Nacional de Identificación e Estado Civil (RENIEC), that registers all living people.

One used the Chi-square test to establish the association between studied factors and recurrence, recurrence ratio was calculated by Kaplan – Meier method and Cox multivariate analysis was used for selecting prognostic factors for recurrence. Codification and analysis were done with SPSS 12.0 statistic program.

Results

Location of recurrence in Stage II colon cancer

Recurrence developed in 20 (10%) of the 200 eligible patients. The mean time for recurrence was 2.3 years after surgery with curative intention, with a time interval from 2.5 months to 8.5 years. Eleven patients

(5.5%) had local-regional recurrence from 5 months to 6.7 years, and a mean time of recurrence of 2.4 years; among them six patients (3%) had local recurrence at the surgical table from 8 months to 4.6 years, and a mean time of recurrence of 2.3 years; and three patients (1.5%) had local recurrence in the anastomosis from 5 months to 6.7 years, and an average time of recurrence of 6.4 months. Five patients (2.5%) had pulmonary recurrence from 1 to 8.5 years, with a mean time of recurrence of 2.6 years. Two patients (1%) had hepatic recurrence in a 7- to 20-month interval, with a mean time of 14 months. Two patients (1%) had peritoneal recurrence from 2.5 months to 6.5 months, with a mean time of recurrence of 4.6 months (Table 1).

Table 1 - Recurrence in 200 Stage II Colon Cancer patients

Recurrence	N	%	Time	Mean
Local-regional	11	5.5	5m-6.7y	2.4y
Pulmonary	5	2.5	1y-8.5y	2.6y
Hepatic	2	1.0	7m-20m	14m
Peritoneal	2	1.0	2.5m-6.5m	4.6m

m = months; y = years

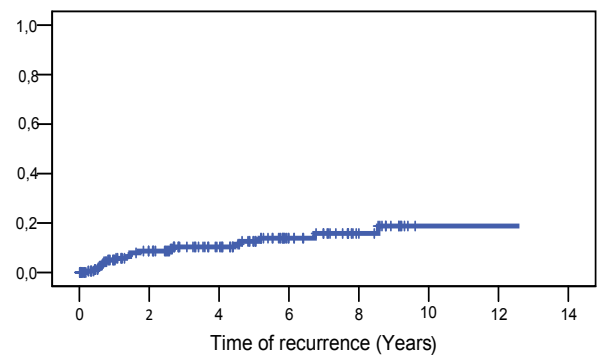


Figure 1 - Recurrence in 200 patients with Stage II colon cancer

Time of global recurrence and factors associated to recurrence in Stage IIA and IIB colon adenocarcinoma

The disease-free mean time was 10.91 years, with a SD 0.35 CI 95% 10.22 – 11.60. The ratio of patients with recurrence in five years was estimated in 0.1257, with a standard deviation of 0.0294. The last case of recurrence occurred 8.55 years after diagnosis and the ratio of

patients with recurrence is considered at that moment in 0.1878. (Figure 1). Age did not have a significant association with the recurrence ($p = 0.096$) (Table 2).

Table 2 - Univariate analysis of 20 cases of recurrence

Variable	N	Recurrence (N)	Recurrence (%)	p
Age				
>70 years	58	9	45	0.096
Sex				
Male	87	10	50	0.537
Female	87	10	50	
CEA				
High	36	4	40	0.801
Type of operation				
Elective	185	15	20	0.179
Emergency	15			
Intestinal Obstruction				
Yes	12			
Site				
Unknown	18			
Ascending colon	59	8	40	0.278
Hepatic flexure	23	2	10	0.625
Transverse colon	26	2	10	0.674
Splenic flexure	6	0	0	
Descending colon	15	1	5	0.655
Sigmoid	62	7	35	0.683
Invasion				
T3/Stage IIA	170	17	85	1.000
T4/Stage IIB	30	3	15	
Lymphatic vessels	18	3	15	0.323
Venous invasion	4	1	5	0.312
Classification				
Differentiated	177	16	80	0.209
Undifferentiated	23	4	20	0.700
Synchronous Tumor				
Yes	7	1	5	0.700

Prognostic Factors

Results show patients more than 70 years old have a significantly shorter disease-free time ($p = 0.0305$) (Figure 2). No other factor turned out to be significant

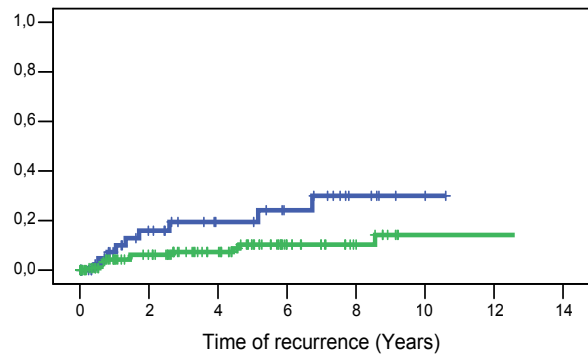


Figure 2 - Recurrence according to age (blue line - younger than 70 years; green line - 70 years or older)

(Table 3). Cox regression showed that patients more than 70 years old have 2.56 times more risk of recurrence (Table 4), that is, be more than 70 years is a factor determining recurrence.

Discussion

World literature have few studies on risk factors for recurrence in Stage II colon cancer, and some take into consideration clinical findings such as type of presentation by emergency, be it by obstruction or perforation, site, CEA etc. and others consider pathological results such as histologic type, depth, differentiation, vascular and lymphatic invasion, etc; or else a combination of these,^{8,10,12,14-15} demonstrating in some cases a certain relation with recurrence where a benefit would be gained from adjuvant treatment.⁶⁻⁷

In this study no evaluated factor had relation with this event, except age: patients more than 70 years old had a greater risk of recurrence, up to 2.56 times. In no study here mentioned was age a recurrence prognostic factor, and one would have to individualize patients according to their general clinical condition and comorbidity, analyzed the disadvantages and limitations of adjuvant treatment, since in our society average life expectancy is less than 70 years.

The incidence of Stage II colon cancer was compatible with world rates, around 40%, and recurrence percentage was 10%, half of the reported world average.⁴ Nevertheless, around 30% of cases did not have the minimum follow-up time of two years; if we excluded patients about whom there is no certainty on their being disease free, the recurrence rate would rise to 15%.

In spite of the recommendations of ASCO, namely to consider the possibility of using adjuvant chemotherapy

Table 3 – Kaplan - Meier analysis in 20 cases of recurrence.

Variable	Disease-free time	Standard Deviation	CI 95%	Log Rank Test	p
Age					
<70 years	8.31	0.66	7.01-9.61	4.68	0.0305
>70 years	11.36	0.36	10.66-12.06		
Sex					
Male	9.71	0.45	8.83-10.59	0.09	0.7612
Female	11.09	0.45	10.21-11.97		
CEA					
High	8.51	0.54	7.44-9.57	0.17	0.6791
Type of surgery					
Elective	10.38	0.35	9.69-11.07	1.55	0.2136
Site					
Unknown					
Ascending colon	9.85	0.71	8.47-11.23	1.37	0.2426
Hepatic flexure	9.46	0.76	7.97-10.95	0.08	0.7748
Descending colon	9.85	0.89	8.12-11.59	0.27	0.6046
Sigmoid	10.58	0.70	9.21-11.96	0.47	0.4918
Invasion					
T3/Stage II A	10.87	0.39	10.11-11.63	0.00	0.9670
T4/Stage II B	8.64	0.56	7.55-9.73		
Lymphatic vessels	5.35	0.80	3.78-6.92	2.81	0.0934
Venous invasion	2.38	0.27	1.85-2.91	1.69	0.1941
Classification					
Differentiated	11.08	0.36	10.38-11.78	2.10	0.1471
Undifferentiated	9.04	1.26	6.57-11.51		
Synchronic Tumor					
Yes	7.22	1.89	3.52-10.93	0.58	0.4466

for patients who have as pathology results T4, lymphatic, vascular, or neural invasion, or else are operated due to perforation, less than 13 resected lymph nodes, this study demonstrated no statistical significance of these variables as regards recurrence.

Our study demonstrated that the most important prognostic factor for colon cancer is the presence of lymph nodes affected by the disease and that the main distant recurrences are the hepatic and the pulmonary one, but for patients with colon cancer without linfonodes

(Stage II), one has not data for pointing out the most important prognostic factors, and our study showed a local-regional recurrence rate of 5.5% from the 10% cases, and thus surgery plays for these patients a very important role.¹⁸

Due to the great heterogeneity of Stage II colon tumors, the role of adjuvant chemotherapy is very controversial, since patient with tumors of the same clinical stage present different results, mainly related to recurrence. This way, the standard procedure is unable to exactly

Table 4 – Recurrence-related variable according to Cox multivariate analysis

Category	SD	Wald	p	RR	CI95%
Age					
>70 yrs	0.45	4.35	0.0370	2.55	1.06-6.19

predict this neoplasia prognosis and makes necessary the identification of specific molecular characteristics of each tumor that can predict a better response to chemotherapy, intending to significantly reduce recurrence rates in Stage II. For identifying the groups of patients who can need adjuvant treatment, the correlation of molecular analysis and clinical data would be very helpful.

The course of colon cancer, many genetic changes accumulate that frequently cause a kind of genomic instability. The two better known mechanisms of genomic instability are chromosomal instability (CIN) and microsatellite instability (MSI). CIN phenotype is found in about 85% of sporadic tumors and is characterized by aneuploidies, manifold chromosomal rearrangements and the accumulation of somatic mutations in KRAS oncogene and in tumor-suppressor genes TP53 and APC.¹⁶⁻¹⁸ MSI phenotype is associated with small insertions and deletions, mainly in repetitive sequences (microsatellite), and is found in approximately 15% of the cases. MSI is caused by defects in DNA repair system, including repair errors during DNA replication.

This instability is related to patients' prognosis and response to chemotherapy,¹⁹ being frequently referred as high-frequency MSI (MSI-H). Diverse theories were postulated to explain why tumors with MSI-H present a better prognosis in spite of unfavorable histologic characteristics. One theory suggests that accumulation of genetic abnormalities causes aberrant protein expression, recognized by the immune system and triggering the destruction of tumor-like cells. Another theory relates the defect of the repair system to a better survival, since several mutations are not repaired during the replication and their accumulation becomes incompatible with cellular life.

Mutations in *TP53* gene are associated to tumors' aggressive growth and to reduced survival rates, whereas MSI-H seems to be related to a favorable prognosis of the disease.¹⁶ Associations between somatic genetic alterations and the clinical behavior of colorectal tumors are rare.

Recent studies associated to tight-junction proteins key molecular components in cellular proliferation

and neoplastic signaling, due to their double function of intracellular-extracellular signaling and cytoskeleton. Therefore, neoplastic cells show structural and functional deficiencies in "tight junction". Claudina-1, one of the proteins that comprise "tight junction", has a low expression in Stage II colorectal cancer and is a strong indicator of recurrence and poor survival for Stage II patients.²⁰

Another cellular-adhesion molecules involved in the progression of colorectal cancer is E-cadherin, which would help to identify sub-groups of high-risk patients which can need an appropriate and continuous therapeutic strategy.²¹

Although this study intends to avoid adjuvant treatment for Stage II colon cancer patients submitted to surgical treatment with curative intention (an adequate oncologic operation), it is crucial to understand that colorectal cancer is a multiple-route disease that includes/understands clinical, pathological characteristics and molecular individuals and that the present idea of carcinogenesis routes simplification has been the main process negatively affecting the identification of risk factors for colorectal cancer.²²

Based on these molecular antecedents, the immunohistochemical study of TP53, K-RAS and APC, as well as the analysis of microsatellite instability and the sequencing of these genes in patients with Stage II colorectal cancer is suggested.²³⁻²⁴

Conclusions

Five-year recurrence of patients curatively operated for Stage II colon adenocarcinoma in the Institute of Neoplastic Diseases "Dr Eduardo Cáceres Graziani" from January, 1 1990 and December 31, 2000 has been 0.1257 with a standard deviation of 0.0294.

The only factor related to recurrence has been age: patients with more than 70 years at the time of the main surgery ($p = 0.0305$), had a risk of recurrence 2.56 times greater. No other studied factor has relation to recurrence. It is suggested molecular profile should be performed in stage II colon cancer patients.

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