

ORIGINAL RESEARCH

PROGNOSTIC FACTORS IN LOCALLY ADVANCED COLON CANCER TREATED BY EXTENDED RESECTION

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The impact of clinical, pathologic, and surgical variables on the postoperative morbidity, mortality, and survival of patients undergoing extended resections of colon carcinoma were evaluated.

METHODS: The medical records of 95 patients who underwent extended resections for colon carcinoma between 1953 and 1996 were reviewed. In all cases, in addition to colectomy, 1 or more organs and/or structures were resected en bloc due to a macroscopically based suspicion of tumor invasion. The clinical, pathologic, and surgical parameters were analyzed. Overall survival rates were analyzed according to the method of Kaplan and Meier. Multivariate analysis was performed using the Cox proportional hazards model.

RESULTS: Eighty-six patients were treated by curative surgeries and the remaining by palliative resections. Invasion of the organs and/or adjacent structures and regional lymph nodes was found microscopically in 48 and 31 patients, respectively. The median follow-up without postoperative mortality was 47.7 months. The 5-year overall survival rates was 52.6%. The 5-year overall survival rates for patients undergoing curative and palliative surgeries was 58.3% and 0%, respectively. The mean survival time in the palliative surgery group was 3.1 months. Multivariate analysis showed that Karnofsky performance status was strongly related to the risk of postoperative complications ($P = .01$), and postoperative deaths were associated with the type of surgery and Karnofsky performance status at the time of admission ($P = .001$).

CONCLUSIONS: Some patients with locally advanced colon adenocarcinomas undergoing extended resections have a 5-year overall survival rates of 58.3%. Patients could benefit from palliative-intent procedures, but these measures should cautiously be indicated and avoided in patients with low Karnofsky performance status due to high rates of postoperative mortality and poor survival.

KEYWORDS: Extended surgery. En bloc resection. Colon cancer. Morbidity. Mortality. Prognosis.

The term, locally advanced colorectal cancer, refers to tumors infiltrating or adherent to adjacent organs and/or structures in patients without distant metastases. Frequently considered an incurable disease, locally advanced colorectal cancer represent 5% to 22% of all colorectal carcinomas.¹⁻⁵

In the USA, there are an estimated nearly 130,000 new cases per year of colorectal carcinoma, and 6,500 cases are locally advanced.⁶ Surgery still re-

mains the only curative treatment for colon cancer. Radiation and chemotherapy do not cure locally advanced colon cancer.⁷

Extended or multivisceral resection is the type of procedure in which, in addition to the standard operation,

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adherent organs and/or structures are resected en bloc.⁸ The rationale for multivisceral resections is that microscopic infiltration of the organs and/or adjacent structures can not be ascertained preoperatively or even intraoperatively.⁹ Furthermore, the dissection between the colonic tumor and the adjacent structures can seed neoplastic cells in the peritoneal surface, resulting in a poor prognosis.^{1,2,11,12} Thus, this practice should be avoided.

Extended surgeries are recommended because good local control of colorectal cancer can be achieved with results for 5-year survival of rates of 33% to 79% in different series.^{2,8,11,13,14} Despite the good survival rates, patients undergoing extended resections experience considerable postoperative mortality and morbidity.^{3,13,15} With the improvement of postoperative care and surgical technique, postoperative mortality and morbidity rates have decreased and are comparable to the rates achieved with standard or nonextended resections.^{11,16}

The aim of this study was to evaluate the clinical, pathologic, and surgical prognostic factors in patients with locally advanced colon cancer treated with surgery.

PATIENTS AND METHODS

The medical records of 95 patients with locally advanced colon carcinoma undergoing extended resections from 1953 to 1996 were reviewed. Extended resection was defined as an en bloc surgery of the primary colon tumor together with 1 or more organs and/or structures that are macroscopically adherent to the tumor-bearing bowel segment. The presence of macroscopic residual tumor (R2 resection), positive microscopic margins (R1 resection), or abdominal or systemic disease indicated the palliative-intent procedures. The absence of these elements (R0 resection) indicated the curative-intent surgeries.

Clinical and laboratory variables were studied, including age, gender, Karnofsky performance status at admission, tumor location, preoperative serum albumin, and hemoglobin level.

Surgical records were searched for type of surgery (curative or palliative), date of the procedure, previous laparotomy, operative time, number of resected organs and/or structures, hos-

pital stay, and decade of the surgery. Data related to postoperative complications, as well as the date and cause of death were also collected. All slides were reviewed by the same pathologist.

Histological subtypes, tumor grade, microscopic margins, clinical and pathological stages (pTNM-1997), primary tumor penetration (pT), lymph node status (pN), perineural infiltration, and lymphatic and vascular embolization were evaluated. The outcome was classified as follows: alive with no evidence of disease; dead by cancer or related causes, including treatment; dead without cancer (causes not related); and lost to follow-up. The specific cancer mortality was evaluated. The survival analysis began on the date of the surgery and finished on June 30th 1999.

Postoperative deaths were those occurred during the hospitalization or readmission due to short-term complications. We considered the case lost to follow-up when the patient did not return within a time equal or longer than 2 times the recommended time interval.

Statistics

The chi-square and Fisher exact tests were used to compare variables. The multiple logistic regression model was used to evaluate complications and postoperative death risk. The actuarial survival estimates were calculated according to the Kaplan & Meyer method, and the multifactorial relative risk of death was analyzed with the Cox proportional hazards model using a significance level of $P < .05$. A variable was selected for multivariate analysis when $P < .10$. Postoperative mortality was not excluded from the analysis. The SPSS[®] program for Windows[™] 8.0 was used.

RESULTS

Five patients who had surgery dur-

ing the 1950s were evaluated, 7 with surgery in the 1960s, 21 in 1970s, 35 in 1980s, and 27 in 1990s. Patient ages ranged from 15 to 84 years (median = 56 years). Of the total of 95 patients, 48 were male and 86 were Caucasian. The disease evolution time ranged from 1 day, for a patient with an acute abdomen, to 60 months (mean = 11.1 months). The cecum and sigmoid were the most frequent tumor locations.

The most common signs and symptoms were pain (71), weight loss (69), rectal bleeding (38), change in bowel habits (52), tumor (53), mucorrhea (9), fever (9), fistula (7), vaginal bleeding (4), and pneumaturia (3). A palpable tumor at the physical examination was found in 57 patients. Seventy-one patients had no previous treatment, and 24 had been already undergone laparotomy, with the tumor considered unresectable. Curative surgery (R0) was performed in 86 cases. The operative time ranged from 2 to 12.2 hours (mean = 6 hours). Intra-operative blood transfusion was necessary in 79 patients (mean = 900 mL). The hospital stay ranged from 1 day (1 patient who died during the surgery) to 70 days (mean = 15.5; median = 11 days). The number of organs and/or structures resected en bloc was 1 (40 patients), 2 (38 patients); 3 (11 patients); 4 (5 patients), and 5 (1 patients). Abdominal wall muscles were the most frequently resected structures (36), followed by the small bowel (29) and bladder (18).

Regarding the types of tumors found, 61 patients had pure adenocarcinoma, 27 mucinous, and 7 other histologic subtypes. Regarding tumor differentiation, 21 were well differentiated; 54 moderately differentiated, and 20 poorly differentiated.

Microscopic involvement of adjacent organs and/or structures occurred in 48 patients. In 1 case, it was not possible to differentiate inflammatory adhesion from tumor infiltration. The

Table 1 - Tumor penetration and lymph node status in patients undergoing extended resections due to colon cancer.

Tumor Penetration (pT)	Lymph node status (pN0)	Lymph node status (pN1)	Lymph node status (pN2)	Lymph node status (pNx)	Lymph node status (pN+)	Total
pT2	3	-	-	-	-	3
pT3	27	11	5	-	16	43
pT4	28	7	8	5	15	48
pTx	-	-	-	1	-	1
Total	58	18	13	6	31	95

number of dissected lymph nodes ranged from 3 to 72 nodes (mean = 21.4 nodes). In 6 cases, the lymph node status could not be established. In 58 patients, lymph node metastasis was absent (pN0).

The tumor penetration (pT) and lymph node status (pN) parameters are listed in Table 1. Table 2 shows the relationship between resected organs and/or structures and the histologic infiltration.

Twenty-two deaths occurred, and morbidity related to extended resections was observed in 53 patients. The main complications were cardiovascular (18), wound infection (16), intestinal fistula (6), sepsis (6), deep venous thrombosis (3), wall dehiscence (3), urinary fistula (2), and hernia (2). Table 3 shows the relative risk of complication and death according to selected variables. Karnofsky performance status ($P = .02$) and type of surgery (curative vs

palliative) ($P = .004$) were independent prognostic factors for postoperative death rates in the multivariate analysis ($P = .001$) (Table 3).

Patients treated after 1980 had 39% fewer postoperative complications. Postoperative mortality de-

creased from 42.9% in the 1950s to 7.4% in the 1990s ($P = .09$). The postoperative death risk decreased 57% for patients treated after 1980.

Patients who underwent palliative surgeries had higher complication rates (77.8% vs 53.5%) and postopera-

Table 2 - Resected organ and/or structure, tumor penetration, and 5-year overall survival rates in patients undergoing extended resections due to colon cancer.

Resected organ and/or structure	Number of patients	Tumor penetration staging (pT4)	5-year survival (%)
Abdominal wall	36	18	57.7
Small bowel	29	10	57.7
Bladder	18	6	54.2
Ovary	12	3	41.7
Uterus	10	6	37.5
Duodenum	8	2	56.2
Stomach	10	2	56.2
Kidney	6	2	83.3
Gonadal vessels	4	2	100.0
Pancreas	3	1	100.0
Liver	3	2	66.7
Prostate	1	0	0
Ureter	1	0	0
Total	95	48	-

Table 3 - Relative risk of postoperative complication and death according to selected variables in patients undergoing extended resections due to colon cancer.

Variable	Category	Number of patients	Odds ratio	Complication confidence interval	P	Odds ratio	Death confidence interval	P
Karnofsky performance status	80 to 100	41	1.00	ref	.01	1.00	ref	.02
	60 to 70	48	2.82+	1.22-6.54		1.44	0.50-4.15	
	< or = 50	6				9.71	1.48-63.80	
Albumin*	>or =3.5g%	23	1.00	ref	.05	1.00	ref	.82
	<3.5g%	71	2.53	0.96-6.65		1.13	0.36-3.51	
Pre-operative Hemoglobin	>= 10g%	54	1.00	ref	.19	1.00	ref	.08
	<10g%	41	1.73	0.76-3.97		2.32	0.88-6.14	
Surgical status on admission	Intact	71	1.00	ref	.21	1.00	ref	.80
	Previous laparotomy	24	1.84	0.67-4.84		1.15	0.39-3.37	
Type of surgery	Curative	86	1.00	ref	.18	1.00	ref	.004
	Palliative	9	3.04	0.60-15.50		8.75	1.97-38.76	
Number of resected organs	1	40	1.00	ref	.77	1.00	ref	.71
	2 to 5	55	0.88	0.39-2.02		0.84	0.32-2.20	

*Cases without information were excluded from analysis; + fair and bad association; ref = reference.

tive death (66.7% vs 18.6%) compared to curative procedures. The univariate analysis showed that cardiopulmonary complications ($P = .001$) and anastomosis dehiscences with sepsis ($P = .009$) were also related to high rates of postoperative mortality.

The follow-up ranged from 1 to 295.2 months (mean = 53.9; median = 24.3 months). Excluding the postoperative deaths, the mean and median follow-up were 69.7 and 47.7 months, respectively. The status at the end of the study was: 29 (30.5%) alive without cancer, 26 (27.4%) deaths due to cancer, 22 (23.2%) postoperative deaths, 6 (6.3%) deaths due to causes not related to cancer, 1 (1.1%) alive with cancer, 1 (1.1%) death due to cause not reported, and 10 (10.5%) were lost to follow-up, with 2 of them having recurrent disease. Thirty patients experienced recurrent disease that was local (10), distant (17), or local and distant (3). Eighty percent of

the recurrences occurred within the first 2 years after surgery.

The overall survival rate (OSR) at 5 and 10 years was 52.6% and 47.4%, respectively (Figure 1). The mean and median survival time for all the patients was 133.6 and 68.5 months respectively. The mean survival time for patients with vascular embolization was 9.2 months (Figure 2). The 5-year OSR for patients undergoing curative surgeries was 58.3% (Figure 3). The Table 4 shows the OSR according to selected variables.

DISCUSSION

Colorectal carcinoma (CRC) is one of the main causes of death in the United States.⁶ Despite advances in management, the rate of early diagnosis has not changed.¹⁷ Approximately 10% to 20% of CRC are advanced at the time of diagnosis.¹³

Radiation and chemotherapy do not cure CRC after incomplete resection.⁷ Surgery for recurrent CRC is rarely successful. The failure in the treatment of advanced CRC could be avoided if extended resection were considered in the first approach.^{15,19,20,21}

Preoperative image tests could help in predicting the absence or presence of malignant invasion of contiguous structures; however, these methods should not be employed to contraindicate laparotomy for advanced colon cancer.^{10,14}

Moynihan first reported in 1926 an extended resection for locally advanced CRC.²² The survival rates achieved with en bloc resections are significantly higher than those obtained with operative separation of adhesions.^{1,2,12} During the exploration of the abdominal cavity, it is difficult to differentiate inflammatory adhesions from carcinomatous infiltration.²³ Biopsies and manipulation of adhesions

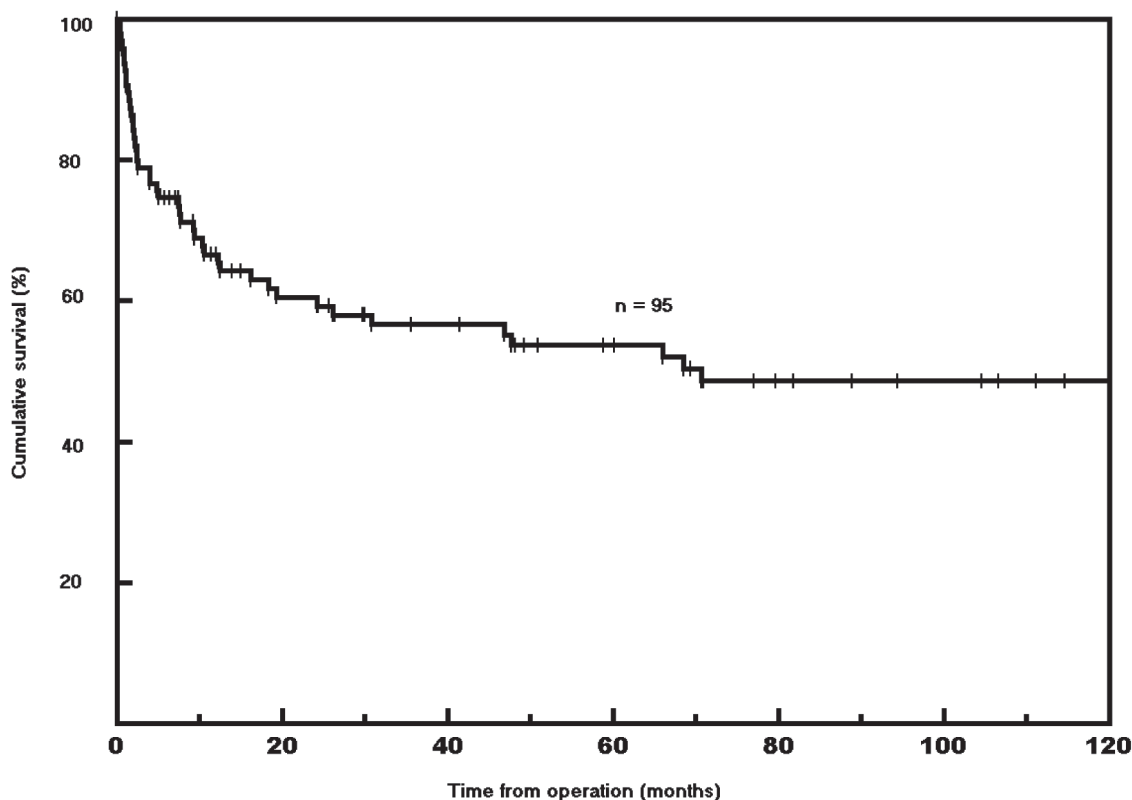


Figure 1 - Overall survival rate of patients with colon cancer undergoing extended resection.

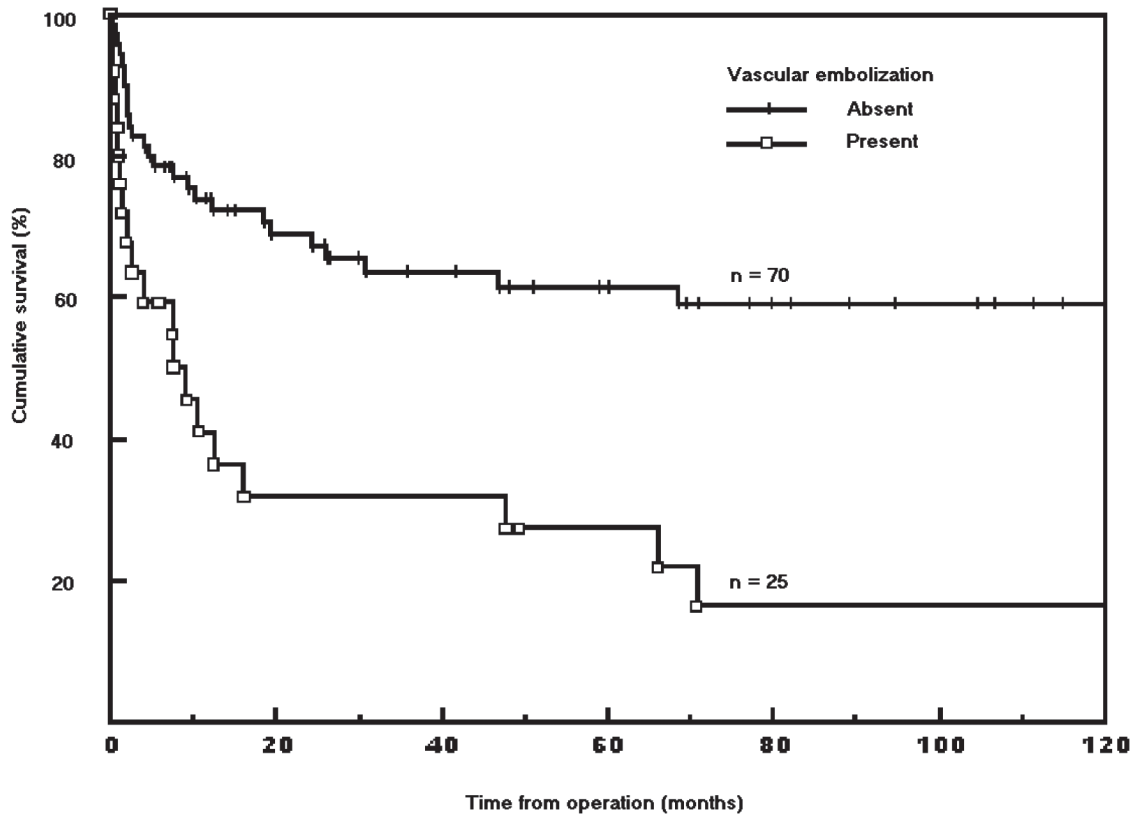


Figure 2 - Overall survival rate according to vascular embolization (absent vs present) in patients undergoing extended resection for colon cancer.

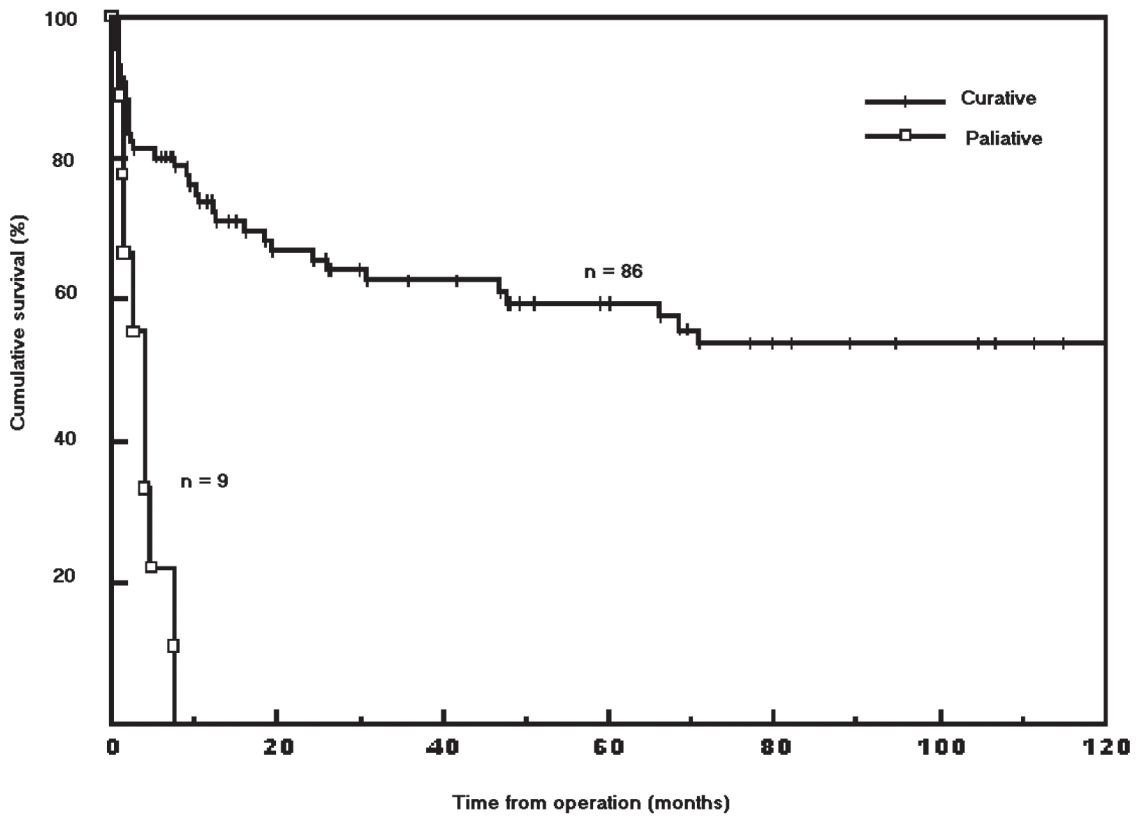


Figure 3 - Overall survival rate according to the type of surgery (curative vs. palliative) in patients undergoing extended resection for colon cancer.

Table 4 - Five year overall survival rate according to selected variables in patients undergoing extended resection due to colon cancer.

Variable	Category	No. of patients	5-year overall survival rates (%)	P
Type of surgery	Curative	86	58.3	<.001
	Palliative	9	0	
pT stage*	pT2+3	46	63.4	.02
	pT4	48	41.3	
Lymph node metastasis	Absent	58	57.5	.72
	Present	31	44.1	
	Ignored	6	44.4	
EC (TNM)	I + II	55	57.6	.16
	III	26	52.8	
	IV	7	14.3	
	Ignored	7	53.2	
Differentiation	Well	21	42.6	.33
	Moderate	54	57.7	
	Poor	20	47.5	
Adenocarcinoma subtype	Pure	61	61.2	.08
	Mucinous	27	39.4	
	Other	7	28.6	
Vascular embolization	Absent	70	61.6	.0002
	Present	25	27.4	
Lymphatic vessel embolization	Absent	59	60.0	.04
	Present	36	40.2	
Perineural infiltration	Absent	75	55.9	.07
	Present	20	40.4	

* = one case excluded for analysis.

can lead to intraperitoneal seeding of tumoral cells. Hunter et al. had 69% with local recurrence following resections with separation of adhesions and 18% following en bloc resections.¹

The good results achieved in different studies regarding local control of CRC and survival rates confirm that en bloc multivisceral resections should be the standard treatment of locally advanced colon cancer for a selected group of patients. Some studies comparing extended and classic surgeries found that the presence of positive margins was associated with poor survival rates.^{8,16,24} There is no 5-year survival when palliative surgery is performed.^{3,5,11,14,16}

In this series we found several pathological characteristics that were related to a better prognosis for CRC, such as 48.4% of inflammatory adhesions; 61.1% of non metastatic lymph nodes; 78.9% of grade I and II tumors; 73.7% of absence of vascular embolization; 78.9% of absence of perineural infiltration and 62.1% absence of lymphatic embolization. Tumor penetration (pT) and the lymph node status (pN) are the most evaluated prognostic factors in several reported series of locally advanced CRC. Lymph node metastasis^{4,10,25} and adjacent organ infiltration^{4,5} have been identified as poor prognostic factors; however, there is not a consensus on this finding.^{15,16} On the other hand, there is

consensus that positive surgical margins^{24,26,27} and nonextended resections for patients with pT4 tumors^{11,16,27} are strongly related to a poor prognosis.

The survival analysis based on each resected organ (Table 2) is difficult due to the high degree of association of resected organs and/or structures,⁴ but there was no statistically significant difference in the survival of patients undergoing en bloc resection of 1 organ compared to those that had 2 or 5 resected organs, showing as in other series that the involvement of several organs should not be a contraindication for surgery.¹¹

The significant decrease of postoperative complications and death rates from the 1950s to 1990s could be attributed to the improvement in staging methods, preoperative and postoperative care, intensive care, and the experience of surgical team. Patients undergoing surgery after 1980s had a more than 50% decrease in the chance of death related to the procedure as compared to those undergoing surgery in the early 1950s. Our data support that the experience gained with extended resections plays an important role in the outcome of patients with locally advanced CRC.

Curative extended resections are the best treatment for patients with locally advanced colon cancer. Some patients could benefit from palliative-intent procedures, but these should cautiously be indicated in patients with low Karnofsky performance status due to high rates of postoperative mortality and poor survival.

RESUMO

VIEIRA RAC e col. Fatores prognósticos em câncer de cólon localmente avançado tratado com ressecção extendida. *Rev. Hosp. Clín. Fac. Med. S. Paulo* 59(6):361-368, 2004.

Foi avaliado o impacto de variáveis clínicas, patológicas e cirúrgicas na morbidade e mortalidade pós operatórias de pacientes submetidos à ressecção extendida de carcinoma do cólon.

MÉTODOS: Prontuários médicos de 95 pacientes submetidos à ressecção extendida de carcinoma de cólon entre os anos de 1953 e 1996 foram revisados. Em todos os casos, além de

colectomia, um ou mais órgãos e/ou estruturas foram ressecados em bloco devido à suspeição de invasão tumoral macroscópica. As variáveis clínicas, patológicas e cirúrgicas foram analisadas. As taxas de sobrevida global foram analisadas de acordo com o método de Kaplan and Meier. A análise multivariada foi realizada empregando-se o modelo de risco proporcional de Cox.

RESULTADOS: Oitenta e seis pacientes foram tratados com cirurgia curativa e o restante com ressecção paliativa. Invasão microscópica de órgãos e/ou estruturas adjacentes e linfonodos regionais foi encontrada em 48 e 31 pacientes respectivamente. O tempo de

seguimento mediano, sem mortalidade pós operatória, foi de 47.7 meses. A taxa de sobrevida global em 5 anos foi de 52.6%. A taxa de sobrevida global para pacientes submetidos à cirurgia curativa e paliativa foi de 58.3% e zero, respectivamente. A sobrevida mediana no grupo de pacientes com cirurgia paliativa foi de 3.1 meses. A análise multivariada mostrou que a performance status de Karnofsky fortemente correlacionou com risco de complicações pós operatórias ($p=0.01$), e que o risco de morte pós operatória estava associada com o tipo de cirurgia e a performance status de

Karnofsky na admissão ($p=0.001$)

CONCLUSÕES: Pacientes com adenocarcinoma de cólon localmente avançados submetidos à ressecção estendida têm taxa de sobrevida global em 5 anos de 58.3%. Este tipo de cirurgia pode ser empregada com intuito paliativo, mas deve ter indicação criteriosa e ser evitada em pacientes com baixa performance status de Karnofsky devido às altas taxas de mortalidade pós operatória e baixa sobrevida.

UNITERMOS: Cirurgia estendida. Ressecção *en bloc*. Câncer do colon. Mortalidade. Prognóstico.

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