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LOCALLY ADVANCED COLORECTAL CANCER: results of surgical treatment and prognostic factors

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ABSTRACT – ***Objectives*** - To evaluate the incidence surgical results and prognostic factors of locally advanced colorectal cancer. ***Methods*** - Cohort study including 679 colorectal cancer patients treated from 1997 to 2007. Clinical, surgical and histological data were analyzed. ***Results*** - Ninety patients (females 61%; median age 59 years) were treated for locally advanced carcinomas (13.2%), either in the colon (66%) or rectum (34%). Extended resections most commonly involved the small bowel (19.8%), bladder (16.4%), uterus (12.9%) and ovaries (11.2%). Postoperative morbidity and mortality occurred in 23 (25.6%) and 3 (3.3%) patients, respectively. Survival and recurrence analysis among 76 R0 (84.4%) procedures revealed a 60% 5-year survival and 34% local recurrence rates. Survival curves demonstrated reduced rates for rectal location (45% vs 65%), tumor depth (50% for T4 vs 75% for T3), vascular/lymphatic/perineural invasion (35% vs 80%) and lymph node metastasis (35% vs 80%). ***Conclusions*** - Locally advanced carcinomas were found in 13.2% of patients. Survival rates were negatively affected by rectal location and adverse histological features. Number of involved organs and neoplastic adhesions did not influenced chances of survival. A radical R0 extended resection was achieved in a high proportion of cases, resulting in a 60% cancer-free survival under acceptable operative risks.

HEADINGS – Colorectal neoplasms, surgery.

INTRODUCTION

Colorectal cancer (CRC) is nowadays one of the most frequent malignant tumors in the Western world, leading to local invasion or adhesion to surrounding organs in 5% to 20% of the patients[4, 18, 20, 21, 28]. Such a situation may demand different operative strategies and technical skills from the surgical team[2, 17].

Within this context, a proper oncologic approach includes an en-bloc multivisceral resection of all organs and/or structures involved. Since distinction between inflammatory or neoplastic adhesions can only be achieved through pathological assessment, separation of the affected organs is not advised to prevent dissemination of malignant cells and tumor perforation[40]. Although locally advanced colorectal lesions were considered non-resectable just some decades ago[42], the performance of a more extensive procedure is nowadays the only chance for cure, besides a potential greater operative risk.

Several adverse prognostic factors have been implicated with multivisceral resections, such as tumor location and depth, tumoral adhesions, number of positive lymph nodes, blood transfusion, histological features and number of resected organs[45].

The aims of the present study were to estimate the incidence of locally advanced CRC in a consecutive group of patients, to evaluate complication rates in this setting and to analyze the benefits of multivisceral resections in terms of survival, considering the influence of several clinical, pathological and operative variables.

METHODS

This prospective study was approved by and followed all ethical standards of the Gastroenterology Department Ethics Committee in our hospital. There were analyzed 679 records from patients with CRC treated at the Colorectal Unit (University of São Paulo Medical School, São Paulo, Brazil) from 1997 to 2007 under the same oncological principles by laparotomy.

Clinical and tumoral data from patients undergoing en-bloc resections of locally invasive T3 and T4 tumors were prospectively collected. Information concerning cancer location, affected organs and tumoral dissemination were retrieved from medical records, colonoscopy, radiological exams and surgical description. We classified R0 resections all the radical

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procedures where the surgeon considered there was not any microscopic or macroscopic tumor left behind. Complementary histological data (histological type, differentiation degree, perineural and/or lymphatic and vascular embolization and lymph node involvement, nature of adhesions) were also collected. Tumors were staged according to the TNM/AJCC classification[1].

There was also recorded information concerning blood transfusion, early and late postoperative complications, surgical mortality and oncological outcome during follow-up. Adjuvant chemotherapy was indicated only for stage III patients.

Patients were schedule to medical appointments every 4 months (first 2 years), 6 months (3rd year) and annually (5th year). During this period, they underwent CEA dosage, abdominal and pulmonary tomography (each 6 months), colonoscopy (1st and 5th years) and other exams depending on symptoms and other findings. Factors potentially affecting prognosis were then confronted with survival and recurrence rates.

A descriptive statistical analysis was performed for all variables, considering the confidence interval of 95% ($P<0.05$). χ^2 test and Fisher exact test[13], proportional Cox risks model[8, 44] and Kaplan-Meier curves[25] were selectively used to study qualitative/quantitative variables and survival rates.

RESULTS

Among the 679 CRC patients analyzed, 90 (13.2%) were considered to have locally advanced tumors and therefore were managed through extended resections (including viscera or anatomical structures). In this group, average age was 59 years (24-88) and women [55 (61.1%)] prevailed over men [35 (38.9%)]. Thirty-one tumors (34.5%) were primarily located in the rectum (distal 15 cm from the promontory) and 59 (65.5%) affected colonic segments. While rectal tumors (24; 77%) were more common among women, colonic lesions were equally distributed in both genders [31 women (53%) vs 28 men (47%)].

Surgical data

Seventy-six procedures (84.4%) were considered curative (R0 resections, without residual tumor) and 14 (15.6%) were palliative (R1 resections, with microscopic residual tumor or R2 resections, with macroscopic residual tumor).

Surgical procedures are listed on Table 1. Operative length varied from 150 to 590 minutes (average of 304.4 minutes) and 41 patients (45.6%) required perioperative blood transfusion. Colostomies were necessary in 17 patients (18.9%), 15 after abdominoperineal excision and 2 due to operative complications. Ileostomies were performed in 6 (6.7%) patients after low anterior resection. According to the Department's protocol[15], neoadjuvant chemoradiation (5400 Gy, 5-Fluoracil and leucovorin) was only indicated to mid or distal rectal tumors (17/31 rectal tumors; 54.8%). Techniques of proctectomy included total mesorectal excision.

Table 2 shows a list of organs and structures simultaneously resected. Small bowel (19.8%), bladder (16.4%), uterus (12.9%) and ovaries/fallopian tubes (11.2%) were the most commonly affected organs. It was necessary to remove one, two, three or more additional organs in 57%, 29% and 14% patients, respectively (Figure 1).

TABLE 1. Surgical procedures performed in 90 patients with locally advanced colorectal cancer

Procedures	Number	Percentage (%)
Anterior resection	39	43.3
Right colectomy	17	18.9
Abdominoperineal excision	15	16.7
Left colectomy	8	8.9
Total colectomy	6	6.7
Transverse colon resection	3	3.3
Subtotal colectomy	1	1.1
Pelvic exenteration	1	1.1

TABLE 2. Organs and structures simultaneously removed with the primary colorectal tumor

En-bloc resection	Number	Percentage (%)
Small intestine	23	19.8
Bladder	19	16.4
Uterus	15	12.9
Ovary/Fallopian tube	13	11.2
Vagina wall	11	9.5
Abdominal wall	6	5.2
Spleen	5	4.3
Another colon segment and ureter	4	3.5
Stomach, gall bladder	3	2.6
Part of liver lobe	2	1.8
Kidney, pancreas, part of diaphragm, seminal vesicle and ductus deferentes	1	0.8

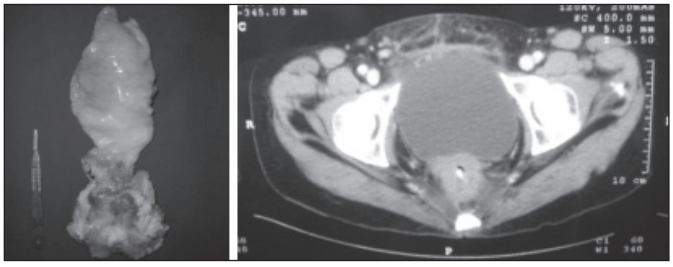

FIGURE 1. Specimen from an abdominoperineal excision and total cystectomy (left). Computed tomography (right) shows invasion of rectal cancer into bladder

After treatment, 23 patients (25.6%) developed complications (Table 3), the most common being surgical site infection (6.7%), prolonged ileus (4.4%) and anastomotic dehiscence (3.3%). Reoperation was necessary in two patients due to intestinal occlusion and pelvic abscess. Three patients (3.3%) died from operative complications. Average hospital length of stay was 21 days (3 to 63 days).

Table 4 presents the results of clinical and surgical data in relation to survival.

TABLE 3. Incidence and causes of operative complications

Complications	Number	Percent (%)
Surgical site infection	6	6.7
Prolonged ileus	4	4.4
Anastomotic dehiscence	3	3.3
Urinary fistula and hematuria	2	2.2
Vaginal fistula	1	1.1
Pancreatic fistula	1	1.1
Biliary fistula	1	1.1
Hemorrhagic shock	1	1.1
Septic shock	1	1.1
Intestinal obstruction	1	1.1
Bronchopneumonia	1	1.1
Pelvic abscess	1	1.1
Total number	23	25.6

TABLE 4. Number and percent of clinical and surgical data. Results of statistical analysis comparing survival for each variable

Clinical and surgical data	Number	Percent	5-year survival	*P*
Colon tumor	59	65.5%	65%	0.01
Rectum tumor	31	34.5%	47%	
R0 resection	76	84.4%	64%	<0.001
R1-R2 resection	14	15.6%	0	
With blood transfusion	41	45.6%	51%	0.13
Without blood transfusion	49	54.4%	59%	
Extracted organs (1)	51	57%	58%	0.8
Extracted organs (>2)	39	43%	53%	

Histological features

Histological features and survival are presented in Table 5. According to the depth of penetration, 28 (42.2%) tumors were staged as T3 and 52 (57.8%) as T4 lesions. Most adenocarcinomas were classified as tubular (68; 75.5%), but there were also found epithelial (mucinous and mucocellular, signed-ring cells) in 14 (15.6%) and tubulovillous in 8 patients (8.9%). A moderate degree of cellular differentiation was detected in the great majority of lesions (74, 82.2%). In a lesser proportion, poor and well-differentiated tumors were found in eight cases each (8.9%).

Lymph node involvement was detected in 52 patients (58%), 27 (30.2%) of them showing 1-3 and 25 (27.6%) with more than four positive lymph nodes. Vascular, lymphatic or perineural invasion was similarly detected in 42 patients. Inflammatory and tumoral adhesions among the resected organs were found in 37 (41.1%) and 53 (58.9%) patients, respectively.

Survival and recurrence

Length of follow-up among all patients varied from 16 to 114 months (average 36), and there was not statistical difference between colon and rectal lesions.

During this period 25 (27.8%) late deaths were registered, most of them (23; 25.6%) due to disease recurrence. Other causes were hepatic failure and septic shock in one patient each (1.1%). Survival and recurrence analysis was performed for all patients. The group of 76 patients (84.4%) who underwent R0 resections presented a 64% survival rate, while there was no 5-year survival after a R1-2 resection (Figure 2).

TABLE 5. Influence of histological features on survival outcome after resection of locally advanced colorectal carcinoma

Histological features	Number	Percent	5-year survival	*P*
T3	38	42.2%	75%	0.02
T4	52	57.8%	50%	
N0	38	42.2%	79%	0.003
N+	52	57.8%	37%	
M0	76	84.4%	61%	<0.001
M1	14	15.6%	0	
V-L-P* invasion -	48	46.7%	75%	0.02
V-L-P* invasion +	42	53.3%	38%	
Inflammatory adhesions	37	41.1%	62%	0.6
Neoplastic adhesions	53	58.9%	55%	

*V-L-P = vascular, lymphatic or perineural invasion

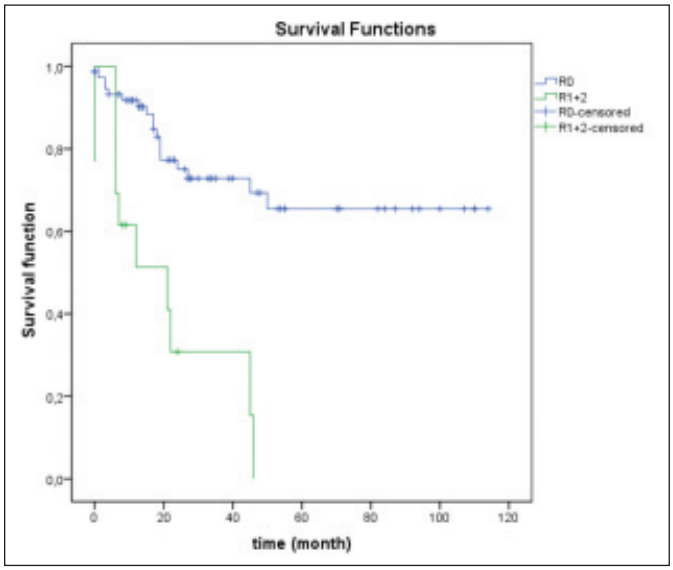

FIGURE 2. Survival curves showing a clear survival difference (*P*<0.001) after R0 or R1+2 resections

Tables 4 and 5 present clinical, surgical, histological data and statistical analysis focusing survival. Survival rates were negatively affected by rectal location, type of resection and adverse histological features such as TNM and vascular, lymphatic or perineural invasion. On the other hand, factors such as tumor vs inflammatory adhesions ($P = 0.6$), blood transfusion ($P = 0.13$), number of resected organs ($P = 0.8$), tumor differentiation ($P = 0.14$) and histological type ($P = 78$) did not influence survival.

Recurrences were detected in 26 patients (34.2%) within an average period of 6.4 months (3.8 to 8.8 months). Location of

tumor recurrences is presented in Table 6. Recurrences were mostly detected as distant lesions (14); in a lesser proportion, they occurred as local (8) or carcinomatosis (4).

TABLE 6. Number and location of tumoral recurrences after R0 resections

Local of recurrence	Number (%)	Percent of all recurrences
Pelvic	8 (10.5)	30.8
Liver	7 (9.2)	27.0
Carcinomatosis	4 (5.3)	15.4
Liver and lung	3 (4.0)	11.5
Lung	2 (2.6)	7.7
Others	2 (2.6)	7.7
TOTAL	26 (34.2)	100

DISCUSSION

The present survey of 679 patients treated during a 10-year period, 90 (13.2%) showed T3 or T4 colorectal tumors adhered to adjacent organs and/or structures. This incidence confirms that this is not a rare event[10, 16, 19, 26], emphasizing the need for a well-trained surgical team capable of dealing with such a situation by performing a multivisceral instead of a standard resection[9, 14, 23].

As others[15, 22, 29], we also found a female prevalence (61.1% vs 38.9%), finding that is probably due to the proximity of genital and urinary organs to the sigmoid and rectum inside the pelvis. Regarding tumor topographic distribution, most series reveal rectal or sigmoid tumors in 2/3 of the cases[6], while others reported a higher proportion of advanced primary tumors in the right colon[29].

When facing a locally advanced lesion, efforts should be driven to achieve a radical resection under acceptable operative risks. Similarly to others[10, 33], we achieved a R0 resection in 85%, leading to a 60% survival rate. On the other hand, we found no 5-years survivors among palliative procedures, confirming the idea that residual tumor is a significant predictor for survival.

In this setting, an en-bloc resection must remove all tumor-bearing tissue while avoiding tumor cells spreading. As it is impossible to distinguish the true nature of the adhesions during the procedure, the adherent organ/structure should not be separated from the primary tumor in order to leave no residual tumor[16, 41]. The imposition to perform an extended resection has been recognized as an effective measure since Butcher and Spjut[6] reported a significantly smaller survival (5% vs 33%) in patients undergoing limited resections in 1959. In another comparative study[22], standard colectomy, extended resection and colectomy with separation of the adhered organs led to survival rates of 55%, 61% and 23%, respectively.

Many factors may affect survival and risk of recurrence after extended resections. In this scenario, a reduced size of primary tumor, smaller number of involved organs, tumor-free resection margins, inflammatory adhesions and absence of lymph nodal involvement (or small number of positive ones) have been identified as favorable prognostic values[35]. Besides a radical resection, other important factors may affect survival rates, such as location of primary tumor, need for transfusion and histological parameters. Thus, the recognition of risks factors associated with prognosis may influence surgical and postoperative decisions.

Regarding tumor location, rectal lesions presented worse outcomes when compared to the colonic ones (39% against 61%; $P = 0.01$). This different outcome is reasonably explained by the technical difficulties during resection of a locally advanced rectal lesion inside the pelvis and the worse prognosis associated with lesions below the peritoneal reflexion (when compared to the upper rectum lesions). Among our rectal tumor patients, more than half (54%) were extraperitoneal. Otherwise, other publications did not find such a survival disadvantage[15, 27]. T3 and T4 extraperitoneal lesions received neoadjuvant therapy as a routine, despite their condition of local invasiveness. This treatment did not add technical difficulties to the procedure.

Surprisingly, survival rates were not affected by the number of resected organs or by the implementation of blood transfusion in the present series. Besides this, a recent publication about 53 CRC en-bloc resections showed blood transfusion to be the worst prognostic factor among others (tumor size, invasion depth, operation length)[33].

Similarly to other publications[12, 34, 39], the confrontation of histological variables with survival rates showed worse figures for deeper wall lesions, node involvement and vascular, lymphatic or perineural invasion. On the contrary, histological types, cellular differentiation grades and character of adhesions had not impact on survival, as corroborated by previous reports[4, 27, 45, 46].

Neoplastic adhesions among organs vary widely from 40% to 80% in the literature[5, 37, 42]. Although reduced survival rates may be expected in this situation[27, 40], we believe that the nature of the adherence may not affect outcome once a complete oncological excision is performed including the affected organs.

Regarding the presence of vascular and lymphatic embolization and perineural invasion by tumor cells, our results displayed a negative influence on survival mainly when lymphatic embolization was detected (36.7% vs 63.3%, $P = 0.02$). Similar data (28% vs 60% survival) have already been published[27]. By crossing this data with tumor depth, we discovered that 73% of patients with lymphatic invasion had T4 tumors, fact that explains the bad prognosis in this group.

The presence of lymph node involvement has been widely accepted as an independent prognostic factor either after standard or multivisceral resections[9, 11, 27, 28, 36]. Indeed, this variable showed the most significant statistical difference in our study, leading to a negative impact on survival of 52 patients (57.8%) with positive nodes (29% vs 70%). Furthermore, the majority of these patients (32; 61.5%) also presented tumoral adhesions and was classified as T4 lesions (33; 63.5%). Among those with T4 tumors and neoplastic lymph node, the number

of resected organs with the primary tumor was one in 18 patients (54.5%), two organs in 9 (27.3%) and three or more organs in 6 (18.2%).

Along with these prognostic variables, the decision to perform an extended procedure should address morbidity risks and individual chances for cure[7, 38, 42]. Complications and mortality occurred in 25.6% and 3.3% of our patients, respectively. In the consulted literature, postoperative complication rates vary from 20% to 42%[11] (average 30%), and mortality has been reported to occur in 1.7% to 13%[24]. Especially in elderly patients, these procedures are generally associated with higher morbidity rates when compared to standard colorectal resections[23, 30, 31]. In our series, 10 (43.5%) out of 23 patients presenting complications were older than 65 years. This issue was addressed in a prospective multicenter study involving 3756 patients in Germany[30]. These authors found increasing rates of morbidity according to age: 21.5% for patients with less than 64 years, 28.6% at 65-79 years and 41.2% for those older than 80 years. They justify these results by the greater proportion of more advanced tumors that were found in older patients.

Otherwise, others think that en-bloc resections are not associated with greater morbidity when compared to standard operations. Andreoni et al.[3] reported no statistical difference between those groups (37.5% vs 41.1%, $P = 0.44$), although extended resections required more blood transfusions (16.3% vs 10%, $P = 0.03$).

In an attempt to evaluate the clinical outcome after extended resections, Yun et al.[46] reviewed 84 (6.5%) out of 1288 patients with T3-4 colon cancers. The authors used the Clavien et al.[7] classification in both multivisceral and standard resection groups aiming to determine the clinical importance of morbidity. Their results showed that although major morbidity (above the grade II) was similar (2.4% vs 0.9%; $P>0.05$), minor morbidity (grade I) was more frequent after multivisceral resections (10.8% vs 1.9%; $P<0.001$). In spite of that, they considered multivisceral resections safe and effective for treating locally advanced tumors.

It has been recognized that extended resections poses a greater risk of loco-regional recurrences (26% vs 13%) when compared to standard procedures[43, 32]. And besides the aid of multimodal neoadjuvant or adjuvant therapy in selected cases, the high levels of local recurrence rates after extended resections, especially for the treatment of rectal tumors, still remain a problem to be solved.

We detected tumor recurrence in 32.4% of our cases, similarly to the rate of 30% reported by the Mayo Clinic series[43]. As described by others[39], recurrence was mostly detected as distant metastasis in about 70% (18 out of 26 cases).

Locally advanced colorectal tumors are therefore a distinct group of lesions that are suitable for curative resections, regardless of their local invasive features and the number of involved organs. Besides the potential risks associated with complex procedures, many literature series and comparative studies have demonstrated acceptable operative outcome in this situation.

Thus, the liberal indication of multivisceral resections for the surgical treatment of colorectal carcinomas involving neighboring organs is an effective way to provide symptomatic relief and survival benefit even in palliative cases. Moreover, a R0 resection is achieved in a high percentage of cases, allowing long-term control of the disease even in this adverse scenario.

Campos FG, Calijuri-Hamra MC, Imperiale AR, Kiss DR, Nahas SC, Cecconello I. Câncer colorretal localmente avançado: resultados do tratamento cirúrgico e fatores prognósticos. Arq Gastroenterol. 2011;48(4):270-5.

RESUMO – ***Objetivos*** - Avaliar a incidência, os resultados operatórios e os fatores prognósticos relacionados aos tumores colorretais localmente avançados. ***Métodos*** - A população deste estudo foi constituída por 679 pacientes com câncer colorretal tratados entre 1997 e 2007. Dados clínicos, cirúrgicos e histológicos foram analisados. ***Resultados*** - Noventa pacientes (mulheres 61%; idade media 59 anos) foram tratados por câncer colorretal localmente avançados (13.2%) no cólon (66%) ou no reto (34%). As ressecções alargadas mais frequentemente envolveram o intestino delgado (19.8%), bexiga (16.4%), útero (12.9%) e ovários (11.2%). Houve morbidade e mortalidade pós-operatórias em 23 (25.6%) e 3 (3.3%) pacientes, respectivamente. Análise de sobrevida e recidiva entre 76 ressecções R0 (84.4%) mostraram sobrevida de 5 anos em 60% e índice de recidiva local em 34%. As curvas de sobrevida demonstraram índices menores para localização retal do tumor (45% vs 65%), grau de penetração (50% para T4 vs 75% para T3), invasão vascular, linfática ou perineural (35% vs 80%) e metástases linfonodais (35% vs 80%). ***Conclusões*** - Carcinomas localmente avançados foram diagnosticados em 13.2% dos pacientes. Os índices de sobrevida foram negativamente afetados pela localização retal e fatores histológicos adversos. O número de órgãos envolvidos e aderências neoplásicas não influenciaram as chances de cura. Foi possível realizar ressecções alargadas R0 em grande proporção de casos, resultando em sobrevida livre de doença em 60% dos doentes, em condições de risco cirúrgico aceitável.

DESCRITORES – Neoplasias colorretais, cirurgia.

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