

research article

Standard and multivisceral colectomy in locally advanced colon cancer

Artur M. Sahakyan^{1,2}, Andranik Aleksanyan^{1,3}, Hovhannes Batikyan¹, Hmayak Petrosyan², Mushegh A. Sahakyan^{1,4}

¹ Department of Surgery ,N1, Yerevan State Medical University after M.Heratsi, Yerevan, Armenia

² Department of General and Abdominal Surgery, ArtMed MRC, Yerevan, Armenia

³ Clinic of Surgery, Mickaelyan Institute of Surgery, Yerevan, Armenia

⁴ The Intervention Center, Oslo University Hospital Rikshospitalet, Oslo, Norway

Radiol Oncol 2020; 54(3): 341-346.

Received 21 February 2020
Accepted 30 April 2020

Correspondence to: Mushegh A. Sahakyan, M.D., Ph.D., The Intervention Center, Oslo University Hospital Rikshospitalet, Sognsvannsveien 20, 0424 Oslo, Norway; E-mail: sahakyan.mushegh@gmail.com

Disclosure: No potential conflicts of interest were disclosed.

Background. Management of locally advanced colon cancer (LACC) is challenging. Surgery is the mainstay of the treatment, yet its outcomes remain unclear, especially in the setting of multivisceral resections. The aim of the study was to examine the outcomes of standard and multivisceral colectomy in patients with LACC.

Patients and methods. Patients demographics, clinical and perioperative data of patients operated within study period 2004–2018 were collected. LACC was defined as stage T4 colon cancer including tumor invasion either through the visceral peritoneum or to the adjacent organs/structures. Accordingly, either standard or multivisceral colectomy (SC and MVC) was performed.

Results. Two hundred and three patients underwent colectomy for LACC. Of those, 112 had SC (55.2%) and 91 (44.8%) had MVC. Severe morbidity and mortality rates were 5.9% and 2.5%, respectively. MVC was associated with an increased blood loss (200 ml vs. 100 ml, $p = 0.01$), blood transfusion (22% vs. 8.9%, $p = 0.01$), longer operative time (180 minutes vs. 140 minutes, $p < 0.01$) and postoperative hospital stay (11 days vs. 10 days, $p < 0.01$) compared with SC. The complication-associated parameters were similar. Male gender, presence of ≥ 3 comorbidities, tumor location in the left colon and perioperative blood transfusion were associated with complications in the univariable analysis. In the multivariable model, the presence of ≥ 3 comorbidities was the only independent predictor of complications.

Conclusions. Colectomy with or without multivisceral resection is a safe procedure in LACC. In experienced hands, the postoperative outcomes are similar for SC and MVC. Given the complexity of the latter, these procedures should be reserved to qualified expert centers.

Key words: colectomy; colon cancer; locally advanced; multivisceral; morbidity

Introduction

Colon is the second most common site for cancer both in men and women.^{1,2} Significant advances in its treatment have been achieved over the last decades due to the improvements in surgical technique, chemotherapy, targeted therapy and examination of tumor biomarkers.^{3,4} Unfortunately, many of these patients are diagnosed relatively late presenting with locally advanced colon cancer

(LACC), which is challenging to manage.⁵ The definition of LACC is controversial as no uniform approach exists in the literature to date. Some authors qualify stage T3 cancer with extramural invasion ≥ 5 mm and T4 as locally advanced, while others define LACC as stage T4 cancer solely.^{6,7}

Multimodal treatment is the standard approach for LACC, although surgery remains its cornerstone. Microscopically complete resection provides satisfactory oncologic outcomes, however,

complex multiorgan resection may be required in these patients.⁸ The latter is associated with postoperative complications, prolonged hospital stay, increased treatment-associated costs and later start of adjuvant chemotherapy, which may ultimately increase the risk of tumor recurrence.⁹ Thus, po-

tential improvement in survival after surgery for LACC should outweigh the aforementioned risks.

This study explores the outcomes of colectomy in patients with LACC. The impact of surgical approaches on postoperative results as well as potential risk factors for complications were evaluated.

TABLE 1. Patient characteristics and perioperative outcomes in patients with T4 colon cancer undergoing colectomy

Variables	(n = 203)
Age, years, mean (± SD)	63.1 (11.6)
Body mass index, kg/m ² , mean (± SD)	27 (4.9)
Female gender, n (%)	87 (42.9%)
Comorbidities, n (%)	21 (10.3%)
ASA score > III, n (%)	5 (2.4%)
Colonic obstruction, n (%)	82 (40.4%)
Hemoglobin, mean (± SD)	111 (29)
Total protein, mean (± SD)	72 (6)
Albumin, mean (± SD)	40 (6)
Tumor location, n (%)	
Right	68 (33.5%)
Left	118 (58.1%)
Transverse colon	17 (8.4%)
T stage, n (%)	
T4a	79 (38.9%)
T4b	124 (61.1%)
N stage, n (%)	
N0	83 (40.9%)
N1	46 (22.7%)
≥ N2	74 (36.4%)
M stage, n (%)	
M0	145 (71.4%)
M1	58 (28.6%)
Tumor size ≥ 6cm, n (%)	169 (83.3%)
Operative time, min, median (range)	160 (60–480)
Estimated blood loss, ml, median (range)	175 (50–900)
Red blood cell transfusion, n (%)	30 (14.8%)
Morbidity (≥ II C–D), n (%)	25 (12.3%)
Severe morbidity (≥ IIIa C–D), n (%)	12 (5.9%)
Anastomosis leakage, n (%)	10 (4.9%)
Relaparotomy, n (%)	10 (4.9%)
Mortality, n (%)	5 (2.5%)
Postoperative stay, days, median (range)	11 (5–44)

ASA = American Society of Anesthesiologists; SD = standard deviation

Patients and methods

Study design and patients

This retrospective observational study included patients with LACC operated at a single surgical unit between 2004 and 2018. Retrospective study was approved by the accredited Institutional Review Board for medical Ethics. LACC was defined as stage T4 (T4a and T4b) colon cancer confirmed on final pathology. Tumor stage was determined and classified based on the criteria suggested by the 8th edition of American Joint Committee on Cancer.¹⁰ Given the diversity of T4a and T4b colon cancers, patients underwent either standard colectomy (SC) or multivisceral colectomy (MVC). Patient demographics, clinical characteristics, imaging findings, lab tests, perioperative and pathology work-up data were prospectively collected and registered in the database. Surgical outcomes and risk factors for postoperative complications were examined. Comparisons were drawn between the outcomes of SC and MVC. Patients diagnosed with tumors other than adenocarcinoma were excluded from the analysis.

The selection criteria for surgery did not change throughout the study period. Normally, all functionally fit patients with no preoperative signs of distant metastases were referred to surgery. However, some patients with metastatic LACC were operated due to life-threatening conditions, such as

TABLE 2. Organs and structures resected during multivisceral colectomies (n = 91) for locally advanced colon cancer

Small bowel	18
Stomach	13
Uterus and/or ovaries	13
Kidney/Ureter/Urinary bladder	11
Liver	11
Gallbladder	3
Pancreas	1
> 1 organ/structure	21
Total	91

colon obstruction or bleeding. Of note, colon stenting was not available at our institution during the study period, hence surgery was the only available option. None of the patients had received neoadjuvant chemotherapy. D2 lymphadenectomy was performed routinely. All anastomoses were performed using a hand-sewn uninterrupted suture. Following surgery, the patients were mobilized on a next day. Nasogastric tube was removed on postoperative day 3 and the enteral feeding was started.

Definitions

Tumor size was defined as the largest dimension of the tumor measured microscopically at the pathology work-up. Resection radicality was regarded as R1 if microscopic presence of tumor or tumor involved lymph node was found within 1mm of the resection margin. R2 resection included at least one of the following: macroscopic tumor at the resection margin, distant metastases or peritoneal carcinomatosis.

Postoperative complications were defined and graded according to the classification system suggested by Clavien and Dindo.¹¹ Complications that were grade II and higher were registered. Grade \geq III complications were defined as severe. The Comprehensive Complication index was used for a comprehensive assessment of postoperative complications.^{12,13} Mortality included all cases of death within 30 days of surgery.

Statistics

Continuous data were presented as mean (\pm standard deviation) or median (range) depending on data distribution. The two-sample T-test was used to compare means, and the Mann-Whitney *U* test was used for medians. The categorical variables were presented as frequencies (percentages). The Chi-square test or Fisher's exact test were used to compare the categorical data. P-value $<$ 0.05 was considered statistically significant. The aforementioned tests were used in the univariable analysis of risk factors for postoperative complications. Variables significant at p-value $<$ 0.1 were added to the binary logistic regression model to determine the independent predictors of complications.

Results

A total number of 474 patients with colon cancer underwent surgery throughout the study period. Of those, 203 (42.8%) were operated for LACC.

TABLE 3. Outcomes of colectomy for locally advanced colon cancer depending on the type of resection (standard and multivisceral)

Variables	Standard (n = 112)	Multivisceral (n = 91)	p-value
Age, years, mean (\pm SD)	63.5 (11.7)	62.5 (11.3)	0.57
Body mass index, kg/m ² , mean (\pm SD)	27.5 (5.3)	26.2 (4.2)	0.41
Gender, n (%)			0.78
Male	63 (56.2%)	53 (58.2%)	
Female	49 (43.8%)	38 (41.8%)	
Comorbidities, n (%)	98 (87.5%)	84 (92.3%)	0.26
Number of comorbidities, mean (\pm SD)	2.6 (0.9)	2.6 (1.0)	0.62
Type of comorbidities, n (%)			0.55
Cardiovascular	66 (58.9%)	56 (61.5%)	
Diabetes mellitus	9 (8 %)	3 (3.3%)	
Thrombophlebitis	13 (11.6%)	9 (9.9%)	
ASA score $>$ III, n (%)	1 (0.9%)	4 (4.4%)	0.07
Colonic obstruction, n (%)	54 (48.2%)	28 (30.8%)	0.16
Hemoglobin, g/dl, mean (\pm SD)	114 (28)	107 (29)	0.11
Total protein, g/dl, mean (\pm SD)	69 (14.9)	72.8 (5.9)	0.045
Albumin, g/dl, mean (\pm SD)	40.1 (6.2)	39.2 (6.2)	0.6
CEA, ng/ml, median (range)	3.0 (0.7–267)	7.5 (0.8–1155)	0.52
CA 19-9, U/ml, median (range)	8.6 (0.6–13444)	7.7 (2–2147)	0.96
Tumor location, n (%)			0.07
Right	45 (40.2%)	23 (25.3%)	
Left	60 (53.6%)	58 (63.7%)	
Transverse colon	7 (6.2%)	10 (11%)	
T stage, n (%)			$<$ 0.01
T4a	74 (66.1%)	5 (5.5%)	
T4b	38 (33.9%)	86 (94.5%)	
N stage, n (%)			0.2
N0	45 (40.2%)	38 (41.8%)	
N1	21 (18.8%)	25 (27.5%)	
\geq N2	46 (41.1%)	28 (30.8%)	
M1 stage, n (%)	35 (31.2%)	23 (25.3%)	0.35
Tumor size \geq 6cm, n (%)	91 (81.2%)	78 (85.7%)	0.4
Operative time, min, median (range)	140 (60–480)	180 (85–390)	$<$ 0.01
Estimated blood loss, ml, median (range)	100 (50–900)	200 (100–600)	0.01
Red blood cell transfusion, n (%)	10 (8.9%)	20 (22.0%)	0.01
Morbidity (\geq II C-D), n (%)	15 (13.4%)	10 (11%)	0.6
Severe morbidity (\geq IIIa C-D), n (%)	8 (7.1%)	4 (4.4%)	0.41
CCI, median (range)	33.7 (20.9–100)	29.6 (20.9–100)	0.33
Anastomosis leakage, n (%)	5 (4.5%)	5 (5.5%)	0.76
Relaparotomy, n (%)	5 (4.5%)	5 (5.5%)	0.76
Mortality, n (%)	2 (1.8%)	3 (3.3%)	0.66
Postoperative stay, days, median (range)	10 (5–44)	11 (7–44)	0.04

ASA = American Society of Anesthesiologists; CA 19-9 = Carbohydrate antigen 19-9; CEA = Carcinoembryonic antigen; CCI = Comprehensive Complication Index

TABLE 4. Univariable analysis of factors associated with postoperative complications

Variables	Complications (n=25)	No complications (n=178)	p-value
Age ≥ 65 years, n (%)	15 (60%)	98 (55.1%)	0.68
Body mass index ≥ 30 kg/m ² , n (%)	2 (8%)	36 (20.2%)	0.44
Male gender, n (%)	18 (72%)	98 (55.1%)	0.09
Comorbidities, n (%)	1 (4%)	20 (11.2%)	0.48
Number of comorbidities ≥ 3, n (%)	7 (28%)	18 (10.1%)	0.02
Cardiovascular disease n (%)	15 (60%)	107 (60.1%)	0.85
ASA score > III, n (%)	1 (4%)	4 (2.2%)	0.51
Colon obstruction, n (%)	12 (48%)	70 (39.3%)	0.78
Hemoglobin, g/dl, mean (±SD)	111 (27)	111 (28)	0.94
Total protein, g/dl, mean (±SD)	73.3 (5.5)	72.1 (6.2)	0.27
Albumin, g/dl, mean (±SD)	38.5 (4.7)	39.8 (6.5)	0.55
Tumor location, n (%)			0.05
Right	5 (20%)	63 (35.4%)	
Left	20 (80%)	98 (55.1%)	
T stage, n (%)			0.23
T4a	7 (28%)	72 (40.4%)	
T4b	18 (72%)	106 (59.6%)	
N+ disease, n (%)	17 (68%)	103 (57.9%)	0.6
M1 stage, n (%)	9 (36%)	49 (27.5%)	0.38
Tumor size ≥ 6cm, n (%)	21 (84%)	148 (83.1%)	1.0
Estimated blood loss, ml, median (range)	200 (50–900)	100 (100–500)	0.12
Red blood cell transfusion, n (%)	7 (28%)	23 (12.9%)	0.07
≥ 2 organs resected, n (%)	3 (12%)	18 (10.1%)	0.73
Single-layer anastomosis suture, n (%)	15 (60%)	136 (76.4%)	0.13
End-to-end anastomosis, n (%)	9 (36%)	53 (29.8%)	0.57

ASA = American Society of Anesthesiologists

TABLE 5. Multivariable analysis of risk factors for postoperative complications

Variables	Odds ratio (95% confidence interval)	p-value
Male gender	1.88 (0.7–5.04)	0.21
Number of comorbidities ≥ 3	3.1 (1.1–9.2)	0.04
Left-sided tumor	2.2 (0.74–6.48)	0.16
Red blood cell transfusion	1.94 (0.67–5.64)	0.22

Patient characteristics, perioperative data and pathology findings are presented in Table 1. The most common location of LACC was the left colon (58.1%), while 82 (40.4%) patients had colon obstruction. More than one-fourth of the patients (28.6%) had distant metastases at surgery. In pa-

tients with non-metastatic LACC (n = 145), the rate of curative resections (R0) was 97%. Morbidity and mortality rates were 12.3% and 2.5%, respectively. Median length of stay was 11 (5–44) days.

SC was performed in 112 (55.2%) patients and MVC in 91 (44.8%). The latter included resections of one (n = 70) or ≥ 2 organs/structures (n = 21) (Table 2). In patients with ≥ 2 organs/structures resected the resection of the small bowel, stomach and pancreas was most often carried out.

A comparative analysis between the outcomes of MVC and SC was performed (Table 3). Preoperative parameters were similar except the significantly higher total protein levels in the MVC group. The latter was almost always performed in patients with T4b adenocarcinoma (94.5% vs. 33.9%, p < 0.01). Operative time was significantly longer for MVC (180 minutes vs. 140 minutes, p < 0.01) and so was the median blood loss (200 ml vs. 100 ml, p = 0.01). The red blood cell transfusion rate was significantly higher for MVC - 22% vs. 8.9%, p = 0.01. Microscopically complete resection was achieved in a similar number of patients (98.5% vs. 95.3%, p = 0.56). Proportions of postoperative complications and their types were comparable between the groups. The length of stay after surgery was longer following MVC (11 days vs. 10 days, p = 0.04).

Univariable analysis of factors associated with postoperative complications was performed (Table 4). Male gender, presence of ≥ 3 comorbidities, tumor location in the left colon and red blood cell transfusion were associated with grade ≥ II complications. These factors were analyzed together in the multivariable model (Table 5). The latter demonstrated that only presence of ≥ 3 comorbidities was associated with grade ≥ II morbidity. Specifically, their risk increased more than three times in these patients - OR 3.1 (1.1–9.2), p = 0.038.

Discussion

Our findings indicate that colectomy in patients with LACC is a safe procedure providing satisfactory surgical outcomes when performed in a specialized surgical unit. This is applicable to both SC and MVC. In the literature, postoperative morbidity and mortality rates following surgery for LACC are 25–38% and 3.3–6.9%, respectively.^{5,14–17} Hoffman *et al.*, demonstrated that morbidity rate may increase with the use of multiorgan resections.¹⁸ In this series, postoperative morbidity rate was 12.8% including 7.4% severe complications. Although MVC was associated with an increased

blood loss, need for blood transfusion, as well as with longer operative time and hospital stay, postoperative morbidity-associated parameters and mortality were comparable to those of SC.

Severe complications were mostly caused by the anastomotic leakage (4.9%), which is consistent with the data in the literature.^{14,19} Multiple parameters are found to be associated with the risk of leakage including patient-specific variables, intraoperative complications, surgeon- and technique-related factors. In this report, such analysis was not possible due to the small number of cases. However, when analyzing risk factors for complications technical parameters such as single-layer anastomosis suture or its end-to-end type did not increase the rate of complications. We believe that single-layer suture is a simple technique that significantly expedites the procedure, while the end-to-end anastomosis avoids the need for additional closure of the intestinal stumps on the proximal and/or distal loops. The effectiveness of this technique was reported also by Liu *et al.*²⁰ Our results do not confirm the association between the postoperative results and blood transfusion suggested by Marinello *et al.*¹⁴ Despite being a significant predictor in the univariable analysis, blood transfusion was not an independent predictor of complications in the multivariable model.

According to the literature, MVC is performed in only 1.2–12% of patients with colon cancer.^{14,15,21,22} In our study, MVC was performed in 44.8% of patients with LACC, which accounts for 19.2% of a total number of colon resections for cancer. Higher incidence of MVC in our series can be attributed to strict selection criteria in the aforementioned studies, as well as to a significantly higher proportion of late diagnosed patients in our population. This is confirmed also by the fact that nearly 40% of our patients presented with partial or total colon obstruction prior to surgery.

Intraoperatively, it is not always possible to assess whether or not colectomy will be curative, thus the main goal is to achieve a complete resection of the primary tumor and suspicious adjacent tissues if these are found at surgery.⁹ According to the literature, the most common invasion sites for T4b colon cancer are the small bowel, urinary bladder and abdominal wall.¹⁵⁻¹⁷ In this series, most often these patients had tumor ingrowth into ≥ 2 organs, predominantly to the small bowel, distal pancreas and stomach. Tumor invasion into adjacent structure(s) was verified by the pathology examination in about 95% of patients who had undergone MVC. Given that this parameter ranges

from 44% to 72.5% in the literature^{5,9,15,16}, the choice of surgical approach was adequate in this series.

This report has several limitations, including retrospective design with its inherent biases. Furthermore, we did not register grade I complications (according to Clavien-Dindo)¹¹, which somewhat limits the information on postoperative results of colectomy for LACC. It is also worth mentioning that our data are based on an experience of a specialized center of colorectal surgery, thus the reproducibility of our results is limited and surgical outcomes should be interpreted with caution.

Conclusions

In conclusion, colectomy including MVC is a safe procedure in the setting of LACC. In experienced hands, the postoperative outcomes are acceptable showing no differences between the SC and MVC. However, their oncologic benefits require further investigation. Given the complexity of MVC, these procedures should be reserved to qualified expert centers that are familiar with colorectal procedures as well as with the surgery of other organ systems.

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