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Long-Term Outcomes of Colon Cancer Patients Undergoing Standardized Technique Operation With Curative Intent

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There is no defined standard surgical technique accepted worldwide for colon cancer, especially on the extent of resection and lymphadenectomy, resulting in technical variations among surgeons. Nearly all analyses employ more than one surgeon, thus giving heterogeneous results on surgical treatment. This study aims to evaluate long-term follow-up results of colon cancer patients who were operated on by a single senior colorectal surgeon using a standardized technique with curative intent, and to compare these results with the literature. A total of 269 consecutive patients who were operated on with standardized technique between January 2003 and June 2013 were enrolled in this study. Standardized technique means separation of the mesocolic fascia from the parietal plane with sharp dissection and ligation of the supplying vessels closely to their roots. Patients were assessed in terms of postoperative morbidity, mortality, disease recurrence, and survival. Operations were carried out with a 99.3% R_0 resection rate and mean lymph node count of 17.7 nodes per patient. Surviving patients were followed up for a mean period of 57.8 months, and a total of 19.7% disease recurrence was recorded. Mean survival was 113.9 months. The 5- and 10-year survival rates were 78% and 75.8% for disease-free survival, 82.6% and 72.9% for overall survival, and 87.5% and 82.9% for

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cancer-specific survival, respectively. R_1 resection and pathologic characteristics of the tumor were found to be the most important prognostic factors according to univariate and Cox regression analyses. Standardization of surgical therapy and a dedicated team are thought to make significant contributions to the improvement of prognosis.

Key words: Colon cancer – Standardized surgery – Recurrence – Survival

Colorectal cancer (CRC) is an international health problem with increasing frequency. Approximately 1 million new patients receive a diagnosis worldwide, and 529,000 patients die of the disease annually.[1] CRC is the second most frequent malignancy in females and the third most common in males, according to data from the Ministry of Health in Turkey.[2]

Despite the increase in its frequency, operative morbidity has been decreasing during the last 20 years, and disease-free survival (DFS) and overall survival (OS) rates are gradually increasing.[3–5]

There are various reasons for the increase in successful outcomes. Early diagnosis and treatment, more effective staging, advancements in surgical techniques, development of more efficient adjuvant therapy options, better selection of patients for adjuvant therapy, developments in postoperative care, and multidisciplinary approach can be named among these reasons.[6] It is important to specify the surgeon as one of the most crucial factors for success, because the main therapy for CRC is surgery. Many studies indicate that surgeons affect outcomes, and they emphasize the fact that a dedicated colorectal surgeon is an important prognostic factor positively affecting survival in CRC treatment.[6–8] However, there is no defined standard surgical technique accepted worldwide, especially on the extent of resection and lymphadenectomy for the treatment of colon cancer (CC). Moreover, there are technical variations even among colorectal surgeons.[9–11] Because of these conditions, nearly all of the studies on morbidity, mortality, recurrence, and survival analyses employ more than one surgeon, thus giving heterogeneous results on surgical treatment. Therefore, aiming to provide more homogenous data, we represent our long-term results of a patient group operated on by a single senior colorectal surgeon (E.A.). The aim of the study was to evaluate outcomes of the patients who were operated on with curative intent because of CC.

Patients and Methods

After the study was approved by the institutional local ethics committee, prospectively collected medical recordings of 487 CC patients who underwent the standardized technique operation with curative intent between January 2003 and June 2013 were retrospectively analyzed. Medical treatment of the patients was carried out by a senior medical oncologist (B.K.). Patients were carefully followed up in the first 30 days for possible complications or mortality (postoperative morbidity-mortality), which was documented in detail when it occurred. Periodic follow-up after first 30 days was supervised by E.A. in the Department of General Surgery and/or by B.K. in the Department of Medical Oncology. The study was ended in May 2014. A total of 292 patients meeting the criteria of the study were included. A total of 23 patients who were lost to follow-up were excluded. Eventually, 269 patients were enrolled in the study (Fig. 1).

All patients underwent mechanical bowel preparation (90 mL orally and 135 mL enema Na phosphate) 1 day prior to surgery, and antibiotic prophylaxis 30 minutes before the incision. Operations were carried out in Lloyd-Davis position. Following general abdominal exploration, tumors were mobilized first laterally and then medially.

1. Step 1. While the colon was retracted medially during lateral mobilization, lateral peritoneum was opened, and anatomic mobilization was achieved by sharply (using electrocautery) dissecting through mesocolic plane (loyally following embryonic planes). For right colectomy, we performed the procedure by lateral-to-medial dissection, up to the lateral border of the superior mesenteric vein, exposing the third portion of the duodenum (by Kocher maneuver). For left colectomy, splenic flexure was mobilized from lateral-to-medial dissection, up to the entire mesocolon of the descending and sigmoid colon dissected off of the visceral fascia. The greater omentum was detached from the transverse colon for exposure of the lesser sac and subsequent division of the mesocolon.

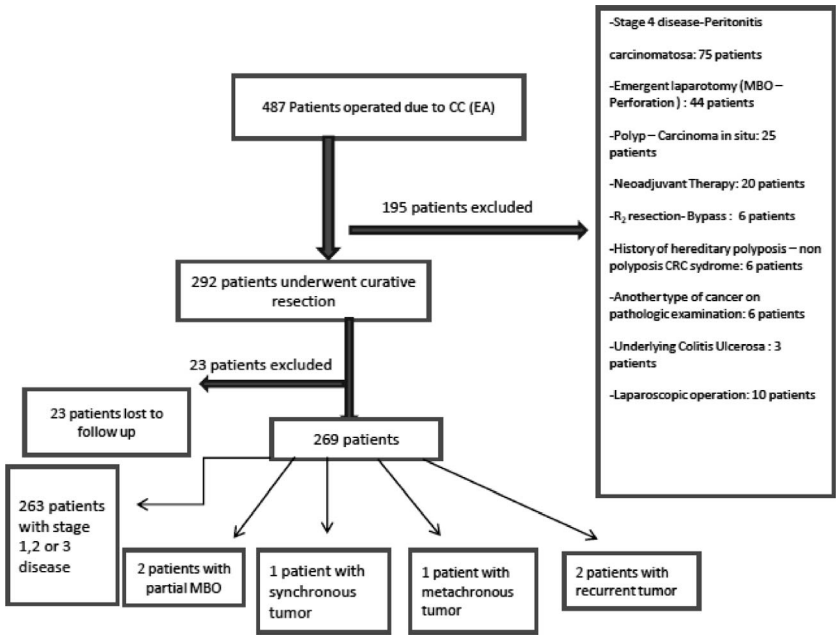

Fig. 1 Inclusion algorithm.

2. Step 2. After full mobilization, while the colon was retracted upward, we could easily identify superior and inferior mesenteric vessels (from a medial aspect) by using transillumination. Subsequently, mesocolon was incised from medial plane just over the main root, and vessels harboring the relevant segment were ligated and transected as close as possible to it. For cecum and ascending colon cancers, the ileocolic vessels, the right colic vessels (if present), and the right branch of the middle colic vessels were transected as close as possible from the superior mesenteric vessels (right hemicolectomy). If the tumor was located at the hepatic flexure and proximal transverse colon, the middle colic vessels were ligated as close as superior mesenteric vessels' root (extended right hemicolectomy). For cancer located at the descendent colon or sigmoid colon, the root of the inferior mesenteric artery and vein below the pancreas were divided (left hemicolectomy).

3. Step 3. Eventually, segmentary resection with intact mesocolon and adequate lymph node dissection was achieved. Despite similarities, the described technique differs from the technique described by Bokey *et al*[11] in 2003, by means of isolation of vessels, their ligation, and lymph node dissection. Special attention was paid not to perforate the tumor, and the least possible amount of manipulation was applied to the tumor during dissection. In all cases with visible tumor invasion to adjacent organs (clinical T_4 tumor), adhesions were left intact, and meticulous dissection was performed to achieve *en bloc* R_0 resection (multivisceral resection). All of the anastomoses were performed by hand-sewn technique, except the reconstructions of total colectomies and sigmoidectomies, which were performed using the double-stapler technique.

All patients were staged based on the seventh edition of the American Joint Commission on Cancer (AJCC/UICC) TNM staging system.[12] Histologic evaluation was done by 2 gastrointestinal tract–dedicated pathologists. The histologic classification proposed by the World Health Organization (WHO) was used for tumor typing.[13] The staging was done and reevaluated for controversial issues as peritumoral deposits or satellite nodules according to the guidelines of the College of American Pathologists and the AJCC/UICC TNM classification, seventh edition.[14]

Patients were evaluated by means of average age, sex, mean follow-up time, tumor localization, type of operation, coexisting pathologies, histopathology results, morbidity, locoregional recurrence (LR), distant metastasis, DFS, cancer-specific survival (CSS), OS, and prognostic factors affecting these parameters.

Adjuvant therapy

Chemotherapy regimens based on 5-FU were administered to patients with stage III disease between 2003 and 2006. After 2006, oxaliplatin-

fluoropyrimidine regimens were administered to patients who were younger than 75 years and who did not have significant comorbidities. Capecitabine-based regimens were reserved for patients older than 75 years and who had severe comorbidities, and were administered for 6 months. A total of 92 of 105 patients (87%) with stage III disease received chemotherapy.

No chemotherapy was administered to patients with stage II disease who were older than 75 years or who had severe comorbidities. Chemotherapy was reserved for high-risk patients with poorly differentiated tumors, T_4 tumors, lymphovascular invasion (LVI), or who had fewer than 12 nodes on the specimen. A total of 52 of 132 patients (39.4%) received fluoropyrimidine-based regimens.

Eventually, 144 patients of a total of 269 patients (53.2%) received adjuvant chemotherapy.

Definitions

Tumors included in the present study were primary adenocarcinomas of the large bowel that arose anywhere between the cecum and distal sigmoid colon from 17 cm above the anal verge.

The operation was defined as palliative if macroscopic tumor remained at the end of the surgical procedure (R_2 resection) and radical (R_0 or R_1 resection) if no macroscopic tumor remained. An R_0 resection was defined by a microscopically negative margin, and an R_1 resection by a microscopically positive margin.

Metachronous cancer was defined as tumors as that developed at a site remote from the primary tumor, which were histologically separate and occurred 12 months or more after surgery in the colon.

Synchronous cancer was defined as more than 1 primary adenocarcinoma in the colon at the time of resection or within 12 months.

Tumors were classified as clinical T_4 (T_{4a}) when multivisceral resection was performed in doubt of invasion but pathologic examination proved negative, and as pathologic p_{T4} (T_{4b}) if invasion was detected under the same circumstances.

LR was defined as the presence of recurrent tumor on anastomosis line, in the abdomen (abdominal wall and retroperitoneum, mesenterium, lymph nodes), or in the pelvis, as suggested by Harji *et al*.[15]

Disease recurrence was defined as tumor recurrence at the LR site, or in the peritoneum or distant organs.

DFS was defined as the time from the date of the operation to the date of first recurrence.

CSS was defined as the time from the date of the operation to the date of death from CC.

OS was defined as the time from the date of the operation to the date of death from any cause.

Statistical analysis

Statistical analysis was performed by SPSS (version 21.0, SPSS, Chicago, Illinois). Survival curves were obtained with the Kaplan-Meier method. Effects of categoric covariates on survival rates were analyzed with the log-rank test, whereas effect of numeric covariates was done using Cox regression analysis in univariate analysis. Finally, forward likelihood ratio method was applied on variables that were significant in univariate analysis, for multiple Cox regression analysis. All hypothesis controls were performed at a $P = 0.05$ significance level.

Results

Of 269 patients, 158 were male (58.7%) and 111 were female (41.3%). Average age was 63.3 years.

Characteristics of patients, tumors, and histopathologic results are expressed in detail in Tables 1 and 2.

Synchronous tumor was present in 14 patients (7%). One of these patients was operated on elsewhere 11 months ago. In 6 of the remaining 13 patients, tumors were located on 2 different segments, 5 patients had tumors on the same segment, and 2 patients had tumors on colon and distal rectum. Total colectomy and reconstruction with ileorectal anastomosis was performed on 21 patients (8%). Indication for total colectomy was accompanying polyps in 12 patients, synchronous tumor in 6 patients, recurrent tumor in 1 patient (operated on elsewhere), metachronous tumor in 1 patient (operated on elsewhere), and sigmoid tumor invading cecum in 1 patient. In addition, 1 patient underwent right hemicolectomy and anterior resection because of synchronous tumors of cecum and sigmoid colon (Table 1).

There was clinical suspicion of adjacent organ invasion (clinical T_4 tumor) in 29 patients (10.7%). *En bloc* multivisceral resection was performed on all of these patients to achieve R_0 resection. True microscopic invasion (pT_4) was present in 17 patients (58%) on pathologic examination. More than one organ was involved in some of the patients, consequently raising the rate of pT_4 to 75%. A

Table 1 Characteristics of patients and tumors (n = 269)

		n (%)
Sex		
Male		158 (58.7)
Female		111 (41.3)
Age, y, mean/median (range)		63.3/64 (26–94)
Primary site		
Sigmoid		122 (44)
Right colon (cecum, ascending colon, hepatic flexure)		100 (37)
Left colon (splenic flexure, descending colon)		25 (9)
Transverse colon		8 (3)
Synchronous		14 (7)
Operation		
Anterior resection		116 (43)
Right (extended) hemicolectomy		95 (35)
Left (extended) hemicolectomy		24 (9)
Transverse colectomy		8 (3)
Anterior resection + stoma		2 (0.8)
Total proctocolectomy + end ileostomy		2 (0.8)
Right hemicolectomy + anterior resection		1 (0.4)
Total colectomy + ileorectal anastomosis		21 (8)
Multivisceral resection		29 (10.7)
Clinical T_4		12 (42)
pT_4 (true invasion)[a]		17 (58)
Small bowel (5)	Resection (3)	
Abdominal wall (4)	Partial excision (4)	
Liver (2)	Wedge, segmentectomy	
Uterus-ovaries (2)	TAH + BSO	
Duodenum (2)	Wedge, partial resection	
Spleen (1)	Splenectomy	
Stomach (1)	Wedge resection	
Colon (1)	Total colectomy	
Kidney (1)	Partial nephrectomy	
Appendix (1)	Appendectomy	

TAH + BSO, total abdominal hysterectomy + bilateral salpingo-oopherectomy.

[a]pT_4: 20 procedures were performed in 17 patients, because some patients had more than one organ involvement.

Table 2 Histopathologic results

	n (%)[a]
Sufficient lymph node dissection (≥12)	212 (78.8)
No of lymph node examined per patient (except total colectomy), mean (median; range)	17.7 (16; 0–61)
R classification	
R_0	267 (99.3)
R_1	2 (0.7)
pT category	
pT_1	17 (6.3)
pT_2	19 (7.1)
pT_3	188 (69.9)
pT_4	45 (16.7)
pN category	
pN_0	165 (61.3)
pN_1	70 (26)
pN_2	34 (12.6)
Stage	
Stage I	32 (11.9)
Stage II	132 (49.1)
IIA	99 (36.8)
IIB	23 (8.6)
IIC	10 (3.7)
Stage III	105 (39.1)
IIIA	4 (1.5)
IIIB	69 (25.7)
IIIC	32 (11.9)
Differentiation	
Well differentiated	35 (13)
Moderately differentiated	192 (71.4)
Poorly differentiated	17 (6.3)
Mucinous	23 (8.6)
Signet ring cells	2 (0.7)
PNI	
Present	35 (13)
Absent	234 (87)
LVI	
Present	42 (15.6)
Absent	227 (84.4)
Peritumoral deposit (satellite nodule)	
Present	16 (5.9)
Absent	253 (94.1)

PNI, perineural invasion.

[a]N = 269.

summary of involved organs and performed operations is shown on Table 2.

According to TNM staging system 32 patients (11.9%) were staged as stage I, 132 (49%) were stage II, and 105 (39.1%) were stage III. There were 12 or more lymph nodes dissected in 78.8% of the patients, and mean dissected lymph node count per patient was 17.7 (range, 0–61). Patients who underwent total colectomy were excluded while mean lymph node count was calculated (Table 2). Our R_0 resection rate was 99.3%, with only 2 patients (0.7%) reported to have a radial margin less than 1 mm (R_1 resection; Table 2).

There were 18 different complications detected in the early postoperative period in 18 patients (6.7%) and 22 in 21 patients (8.2%) in the late postoperative period. There were 3 postoperative mortalities (1.1%). Those were the patients with pulmonary embolism, myocardial infarction, and cerebrovascular event. An additional 2 patients died of chemotherapy toxicity on the 45th postoperative day (Table 3).

Surviving patients were followed up for a mean period of 57.8 months and a median 53.5 months (range, 11–137 months). Follow-up mean time was

Table 3 Postoperative morbidity, early mortality

	n (%)
Early complication	18 (6.7)
Wound infection	4
Intraabdominal abscess (PD)	1
Urinary leakage (double J)	1
Prolonged postoperative ileus	1
Atelectasis	3
Pneumonia	1
Pulmonary embolism	1–exitus
Atrial fibrillation	2
MI	1–exitus
CVE	1–exitus
USI	1
Prerenal azotemia	1
Early mortality	5 (1.9)
Postoperative mortality	3
Chemotherapy toxicity	2
Late complication	22 (8.2)
Incisional hernia	16
MBO	5
Splenic artery thrombosis	1

CVE, cerebrovascular event; MBO, mechanical bowel obstruction; MI, myocardial infarction; PD, percutaneous catheter drainage; USI, urinary system infection.

54.5 months (range, 6–137 months) for all patients. Metachronous cancer was detected in 3 patients (1%), and they underwent total colectomy. One of these 3 patients developed advanced metastatic disease (liver, lung, peritoneal metastases) and is still alive with disease; the other 2 patients are alive and free of disease.

Recurrent disease was detected in 52 patients (19.7%). Reoperation was performed on 27 of these. Curative resections were achieved in 22 patients (42.3%). A total of 15 of these patients had isolated LR, and 7 had isolated distant metastases. Palliative operations (3 mechanical bowel obstruction (MBO), 1 perforation, and 1 rectovaginal fistula) were performed on the remaining 5 patients.

Mean survival time was 113.98 months according to survival analyses [95% confidence interval (95% CI), 107.52–120.39 months]. Survival dropped to a mean of 56.4 months in patients with recurrent disease (95% CI, 45.16–67.64 months) but rose to 126.49 months in patients without recurrence (95% CI, 120.91–132.10 months).

Average 5- and 10-year DFS was 78% and 75.8%, respectively. Stage-dependent survival rates are shown in Fig. 2. Prognostic factors affecting DFS in univariate analysis were stage ($P < 0.001$), N status ($P < 0.001$), T status ($P = 0.01$), presence of LVI ($P = 0.008$), coexistence of LVI and PNI ($P = 0.03$), and R_1 resection ($P < 0.001$). When Cox regression analysis was applied on these factors, only N_2 nodal status [$P < 0.001$; hazard ratio (HR), 6.03; 95% CI, 3.19–11.37] and R_1 resection ($P = 0.01$; HR, 6.36; 95% CI, 1.45–27.88) were found to be significant (Fig. 2).

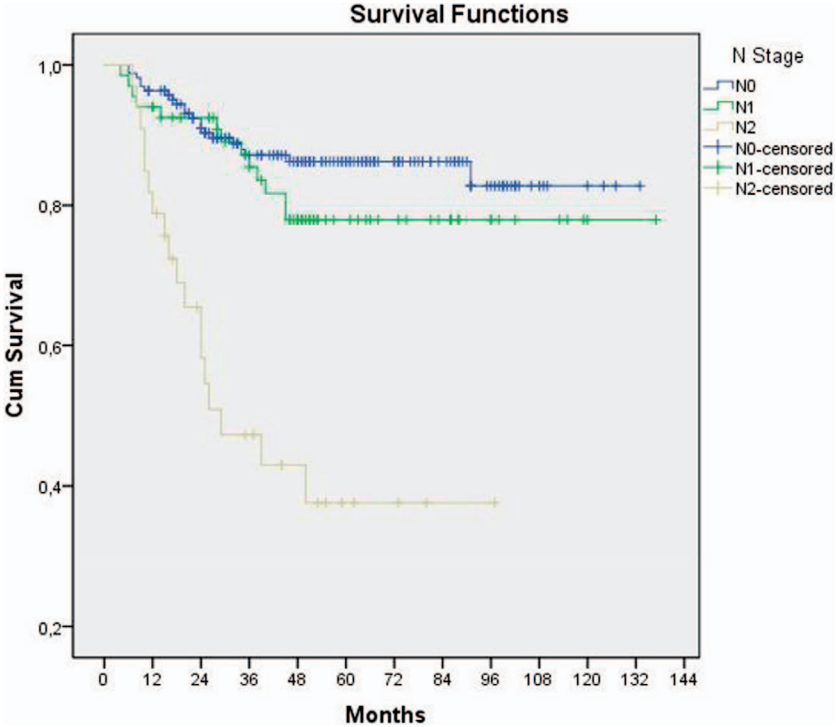

Fig. 2 DFS curves according to N status.

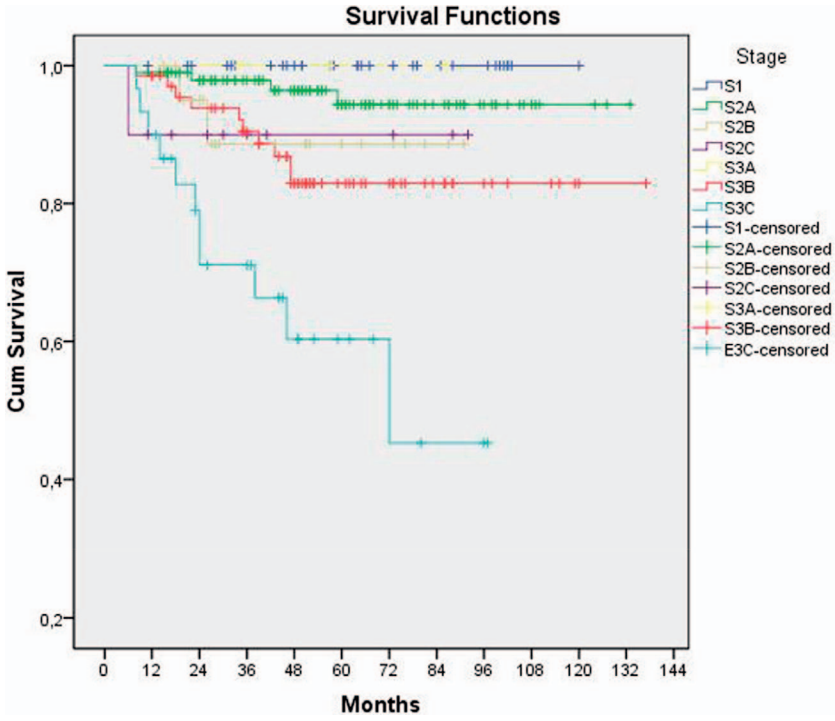

Fig. 3 CSS curves according to stages.

Our 5- and 10-year CSS rate was 87.5% and 82.9%, respectively. Stage-adjusted CSS rate was 100% for stage I, 94.4% for stage IIA, 88.7% for stage IIB, 90% for stage IIC, 100% for stage IIIA, 82.9% for stage IIIB, and 60.3% for stage IIIC for 5 years. CSS with respect to stage is expressed in Fig. 3. Factors significantly affecting CSS in univariate analysis were stage ($P < 0.001$), N status ($P < 0.001$), T status ($P = 0.04$), presence of LVI ($P = 0.03$), presence of satellite nodule ($P = 0.03$), R_1 resection ($P < 0.001$), LR ($P < 0.001$), and distant metastasis ($P < 0.001$). Among these, only the presence of distant metastasis ($P < 0.001$; HR, 105.71; 95% CI, 24.924–448.265) and R_1 resection ($P = 0.02$; HR, 5.876; 95% CI, 1.312–26.313) were found to be significant on Cox regression analysis (Table 4 and Figs. 3–5).

OS rates at 5 and 10 years were 82.1% and 72.9%, respectively. OS with respect to stage is expressed in Fig. 6. Significant factors affecting OS are expressed in detail in Table 5.

The latest conditions of our 269 patients are summarized in Table 6.

Discussion

Our study scrutinizes the follow-up outcomes, for a mean of 58 months, of 269 CC patients who underwent operation with a standardized technique by a single colorectal surgeon, whose tumors were evaluated by 2 dedicated senior gastrointestinal system pathologists, and who were administered adjuvant therapy by a single senior medical oncologist. Results are considered rather successful by means of surgical radicality (R_0 resection rate 99.3%, mean dissected number of lymph nodes 17.7 per patient), postoperative mortality-morbidity (1.1%–6.7%), disease recurrence (19.7%), and survival rates (DFS, CSS, OS). DFS was 75.8%, OS was 72.9%, and CSS was 82.9% at 10 years, and average survival was 113.98 months. Even though all of these good results cannot be attributed solely to standardization of surgical technique and experienced team, their significance cannot be overlooked.

The single most important step in a successful therapy is a curative resection. No adjuvant therapy is capable of undoing the harm of insufficient surgery. Our achieved R_0 resection rate was 99.3%, a considerably high rate compared with the literature. Only 2 patients had R_1 resection; LR and death occurred in both. Thus, R_1 resection emerged as an important prognostic factor negatively affecting all survival univariate and multivariate analyses, and promoting development of LR. Achieving R_0 resection is crucial for both primary cancer cases and recurrences, and multivisceral resections should not be avoided if necessary. However, this approach is not sufficiently practiced in many cases, even as suggested by the guidelines of National Cancer

Table 4 Statically significant clinicopathologic characteristics of CC patients, according to CSS

Grand average	Cancer-specific mortality, n (%) 10.40%[a]	CSS		Univariate analysis (*P* value)	Cox regression analysis		
		5 y, % 87.50%[b]	10 y, % 82.90%[b]		*P*	HR	95% CI
Stage				<0.001		NS	
I	0	100	100				
IIA	4 (14.3)	94.40	94.40				
IIB	2 (7.1)	88.70	NA				
IIC	1 (3.6)	90	NA				
IIIA	0	100	100				
IIIB	10 (35.7)	82.90	82.90				
IIIC	11 (39.3)	60.30	NA				
N status				<0.001		NS	
N_0	7 (25)	95.80	94.50				
N_1	8 (28.6)	85.70	85.10				
N_2	13 (46.4)	57.40	NA				
T status				0.04		NS	
T_1	0	100	100				
T_2	0	100	100				
T_3	20 (71.4)	87.10	84.40				
T_4	8 (28.6)	78.90	NA				
LVI (+)	8 (28.6)	76.70	NA	0.03		NS	
Satellite nodule (+)	4 (14.3)	79.40	NA	0.03		NS	
R_1 resection	2 (7.1)	0	0	<0.001	0.02	5.876	1.312–26.313
LR (+)	6 (21.4)	61.20	NA	<0.001		NS	
Distant metastasis (+)	26 (92.9)	29.10	NA	<0.001	<0.001	105.71	24.924–448.265

NA, not available; NS, not significant.

[a]n = 28.

[b]87.50% and 82.90% are the Cancer Specific Survival (CSS) rates of 5 years and 10 years, respectively, according to the Kaplan Meier Statistical Method.

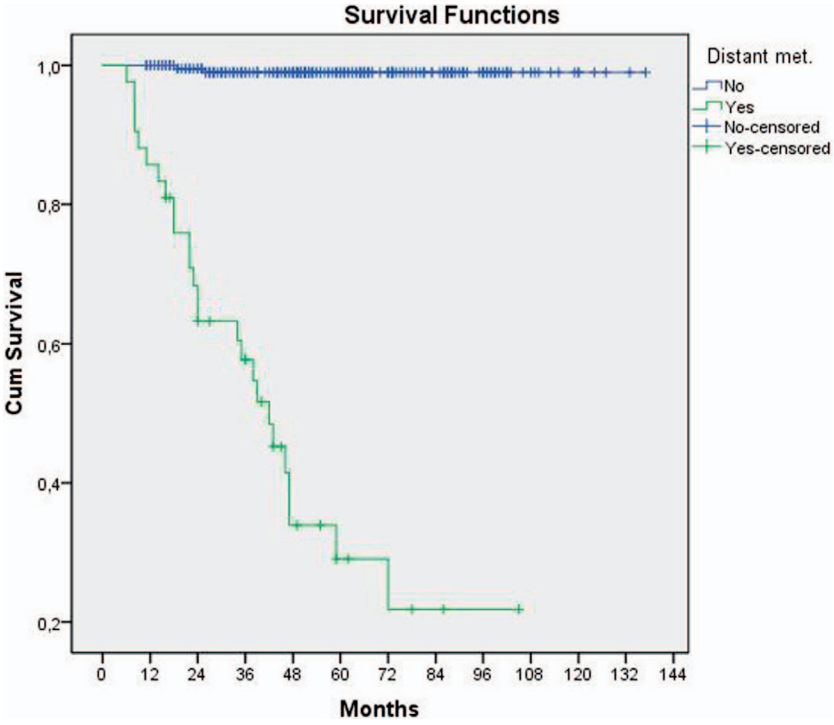

Fig. 4 CSS curves according to distant metastasis.

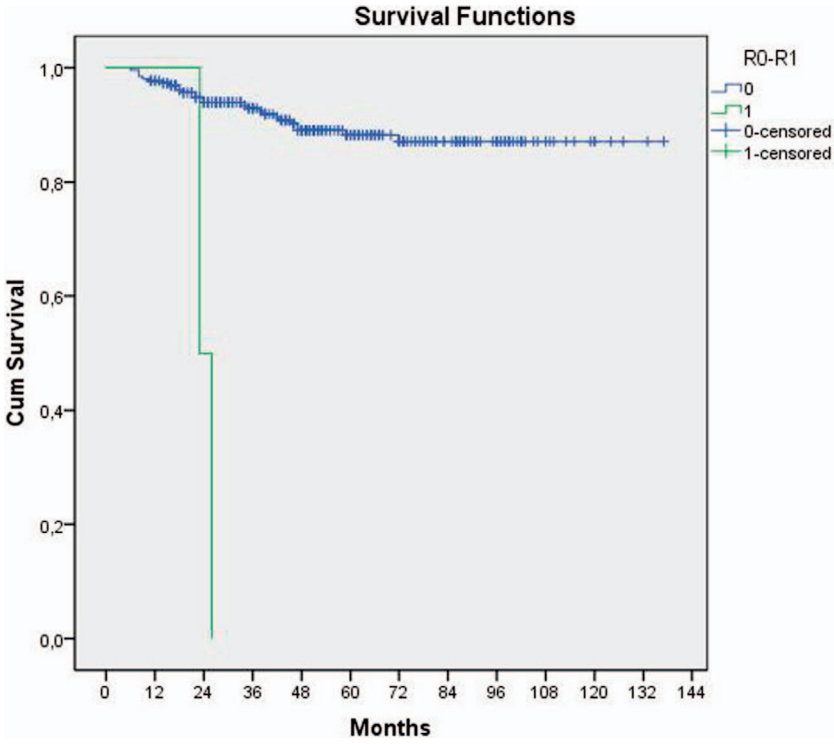

Fig. 5 Cancer-specific survival curves according to R status.

Institute[16] and the American Society of Colon and Rectal Surgeons,[17] possibly in favor of reducing operative morbidity and mortality rates.[18] Multivisceral resections owing to clinical suspicion of adjacent organ invasion were performed on 29 patients (10.7%) in our series, and R_0 resection was achieved for all. Pathologic examination revealed true invasion (pT_4) in 17 patients (58%). Literature

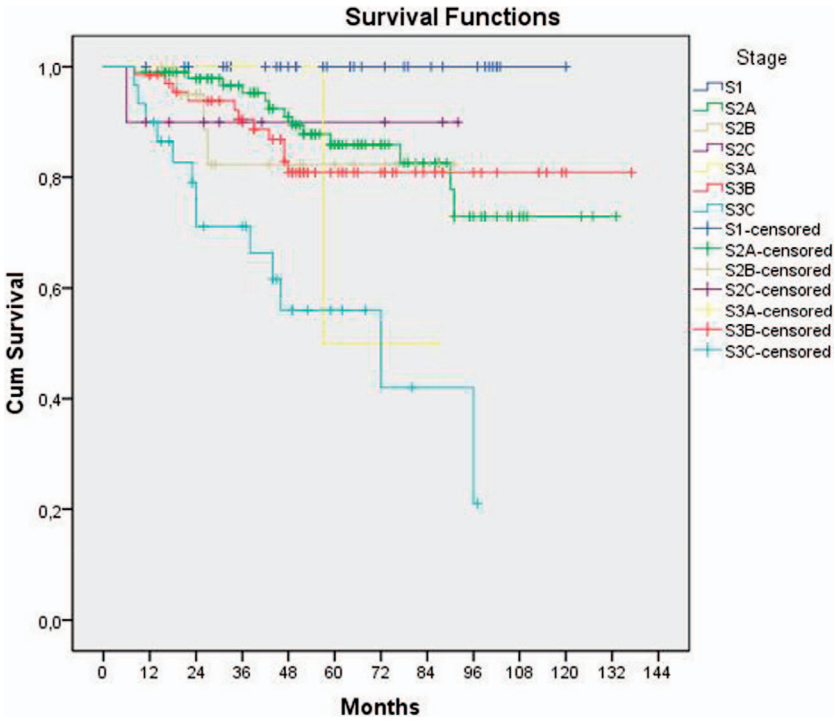

Fig. 6 Overall survival curve according to stages.

Table 5 Statistically significant clinicopathologic characteristics of colon cancer patients, according to overall survival (OS)

		Overall survival			Cox regression analysis		
Grand average	Total mortality (n = 47), 17.5%	5 y (%), 82.10%[a]	10 y (%), 72.90%[a]	Univariate analysis (*P* value)	*P*	HR	95% CI
Stage				<0.001		NS	
I	0	100%	100%				
IIA	14 (29.8%)	86%	72.90%				
IIB	3 (6.4%)	82.30%	NA				
IIC	1 (2.1%)	90%	NA				
IIIA	2 (4.3%)	50%	NA				
IIIB	12 (25.5%)	80.90%	80.90%				
IIIC	15 (31.9%)	56%	NA				
N status				<0.001		NS	
N_0	18 (38.3%)	92%	80%				
N_1	14 (29.8%)	80.70%	71.70%				
N_2	15 (31.9%)	53.50%	NA				
T status				0.03		NS	
T_1	0	100%	100%				
T_2	0	100%	100%				
T_3	35 (74.5%)	80.20%	67.80%				
T_4	12 (26.4%)	75.90%	NA				
PNI (+)	8 (17%)	64.70%	NA	0.04		NS	
R_1 resection	2 (4.3%)	0%	0	<0.001	0.01	7.09	1.58–31.78
Lokoregional Recurrence (+)	6 (12.8%)	61.20%	NA	0.008		NS	
Distant metastasis (+)	27 (64.3%)	27.70%	NA	<0.001	<0.001	17.2	9.30–34.16

CI, confidence interval; HR, hazard ratio; NA, not available; NS, not significant; PNI, perineural invasion.

[a]82.10% and 72.90% are the overall survival rates of 5 years and 10 years, respectively.

reports these rates as being between 34% and 72.5%.[19,20] Performing *en bloc* resection of the affected organs along with the colon while avoiding dissecting through adhesions is essential for this unpleasant condition, commonly diagnosed preoperatively. Dissecting through tumor adhesions was found to be an independent prognostic factor.[19] There were LRs in 3 pT4 patients (17.6%) in our series, and presence of malignant invasion was found to significantly affect the development of LR in univariate analysis. Distant metastasis and peritoneal carcinomatosis were detected in 3 patients during follow-up, 2 of whom died of disease. Despite insignificant results on survival analyses, we recommend a close follow-up for these patients, especially for the first 4 years, because all LRs and distant metastases in this group occurred in the first 32 months.

Table 6 Latest conditions of 269 CC patients who underwent curative resections[a]

	Patient count, n (%)
DFS	212 (78.8)
Survival with disease	10 (3.7)
Mortality	47 (17.5)
Early mortality	5
Died of disease-related causes	28
Died of unrelated causes	14

[a]N = 269.

Surgical standardization in CRCs has been a topic that has received attention for years. In many studies, it has been attributed that prognostic factors are the surgeon and the surgery that has been carried out. One of the different surgical techniques mentioned is the "no-touch" technique, which has been described by Barnes[21] and has been implemented clinically by Turnbull[22] and Turnbull *et al*.[23] In their technique that we do not use, the authors primarily carry out LVI. The concept of the technique is that cancer cells are present in the portal venous system and that manipulation of the tumor can encourage their dissemination, leading to metastasis.[24–26] Isolation of the cancer by first dividing its feeding and draining vessels would prevent dissemination. Turnbull[22] and Turnbull *et al*[23] reported significantly better survival, especially in Dukes stage C patients. Wiggers and colleagues reported a randomized prospective study of Turnbull's technique compared with the standard procedure comprising mobilization of bowel before vessel ligation. They found a trend toward a reduction in the number of liver metastases in the

"no-touch" group. There was no difference in OS.[24] In a study where inferior mesenteric artery (IMA) had been tied high or low in 8666 cases (4281 high tie), Cirocchi *et al*[27] found no difference between groups regarding outcomes. Recently, centers like Cleveland Clinic have been using the "no-touch" technique and high ligation in their routine daily practice.[25]

The most important improvement in surgical technique occurred in 2009 and was described by Hohenberger *et al*.[28] This technique was called complete mesocolic excision and central vascular ligation, for which the principles were similar to those of total mesorectal excision (TME). This surgical technique is based on oncologic resection with dissection of the mesocolon along the embryologic tissue planes, resulting in a colon and mesocolon specimen lined by intact fascial coverage of the tumor and containing all blood vessels, lymphatic vessels, lymph nodes, and surrounding soft tissue.[29] Excision of specimens with intact mesocolon has been found to be associated with better survival rates and compared with excision of specimens with defective mesocolon.[28] In fact, the principle of operating in embryologic tissue planes for the resection of CC is not new, having been described in Leeds 106 years ago.[30] In particular, many Japanese surgeons would argue that they have been performing a similar procedure, known as D_3 dissection.[31] A recent systematic review of 21 studies of complete mesocolic excision involving 5246 patients found an operative mortality rate of 3.2% and a cumulative morbidity rate of 21.5%. The weighted mean local recurrence rate and the 5-year OS and DFS rates were 4.5%, 58.1%, and 77.4%, respectively.[32] These outcomes are notably worse than those in the study by Hohenberger *et al*.

Our operative technique is a less aggressive one, and it is neither a complete mesocolic excision as described by Hohenberger *et al*[28] nor as radical as the D_3 lymphadenectomy suggested by Kanemitsu *et al*.[31] However, especially during lateral-to-medial mobilization, mesocolic dissection is carried out delicately following embryonic planes, similarly to these techniques. But the mentioned techniques mandate the dissection of all of the lymph nodes to the root of main vessels, resulting in a high number of dissected lymph nodes. In our technique, dissection throughout the large vessels has not been carried out, and there is no special attempt performed to excise all lymph nodes. Thus, it is believed that this technique, besides being easy to learn and apply, also has a low potential for intraoperative and postoperative morbidity. Average dissected lymph node count was 17.7 per patient in our series, and sufficient lymph node dissection rate was 78.8%, which is successful with respect to reported values in the literature. According to the recommendations of National Comprehensive Network, AJCC, and the American Collage of Pathologists, at least 12 nodes should be dissected for effective staging.[33] However, data from more than 100,000 patients (National Cancer Institute Registry) who underwent operation between 1988 and 2001 demonstrated that 12 or more lymph nodes were dissected in less than 50% of patients.[34] Besides positively affecting survival, sufficient lymph node dissection allows effective staging as well as excision of micrometastatic lymph nodes and more accurate selection of patients who are eligible for chemotherapy.[28,31,33,34] Insufficient lymph node dissection did not statistically alter survival results in our series. However, all patients (except patients with stage I disease) in this group received chemotherapy.

Postoperative mortality and morbidity rates were rather low, being 1.1% and 6.7%, respectively. Reported mortality rates were between 0% and 8.1%,[3,28] and morbidity rates were between 18% and 47.8%[28,33–35] in the literature. Exclusion of patients who underwent emergent operations and our low rate of multivisceral resections can be named among possible reasons for our relatively low morbidity rates. There was no mortality or need for reoperation due to surgical complications in the early postoperative period. No severe surgical complications, such as bleeding, anastomosis leakage, stercoral fistula, peritonitis, sepsis, and evisceration, were observed. However, because there is no routine radiologic leakage screening in our department, it is impressive to note that there was no clinically evident leakage. In addition to meticulous anastomosis technique, we believe use of drains may lower the risk of anastomosis leakage by preventing postoperative hematomas and abscesses with irrigation, especially in patients with total colectomy + ileorectal anastomosis and anterior resection. The LR rate was significantly higher among the patients with postoperative morbidities in our series. Similarly, there are some reports suggesting that septic complications increase recurrence rates and decrease OS.[36,37] Survival analyses were unaffected in our patients with morbidity.

Histologic characteristics of the tumor are among the most important but unchangeable prognostic factors. Many studies have proven that the stage of the disease (TNM) is a particularly significant prognostic factor affecting both recurrence and survival.[9,15,19,34,38,39] Similarly, stage of the disease (stage IIIC), T status (T4), and N status (N2) were found to significantly increase disease recurrence and decrease all survival rates in all univariate analyses of our study. In Cox regression analysis pT4 was found to significantly increase LR. Among histologic properties of the tumor, differentiation is particularly important and has been shown to be a negative prognostic factor (poorly differentiated, mucinous or signet ring cell types) by many studies.[40] Tumor histology (mucinous adenocarcinoma) significantly affected LR in univariate analysis; however, it did not change survival rates in our study. Another important histologic property of the tumor is the presence of PNI, LVI, or satellite nodules. Mentioned factors that negatively affect prognosis when present were also found to be effective in our study. Presence of PNI, LVI, or both was found to affect distant metastasis in univariate analysis. LVI alone and together with PNI significantly affected DFS. CSS was affected by the presence of LVI and satellite nodules, and OS was affected by the presence of PNI. It is important to emphasize that DFS significantly decreases and frequency of distant metastases increases when PNI and LVI synchronously present. Among 17 patients with synchronous PNI and LVI, 13 (76%) had stage III disease, 10 (58%) had N2 nodes, and 7 (41%) had distant metastasis. Coexistence of PNI and LVI was first discussed in 2013 by Huh *et al*[41] in the literature, and they showed a remarkable decrease in OS and DFS (univariate and multivariate analyses) with increased coexistence of PNI and LVI among patients with stage II or III CRC. This study—corresponding with our results—puts forward the coexistence of PNI and LVI as a strong predictor of poor prognosis.[41]

Because of extremely low postoperative mortality rates, most disease-related mortalities are attributed to disease recurrence. Average survival was 113.9 months in our series, which dropped to 56 months among patients with recurrence. Our 5- and 10-year survival rates were 78% to 75.8% for DFS, 82.6% to 72.9% for OS, and 87.5% to 82.9% for CSS, respectively. There was little difference in survival at 5 and 10 years, possibly because of a lower incidence of recurrence after 5 years. All types of survival rates were commonly correlated with stage, T status, N status, and R_0 resection in univariate analysis. When Cox regression was applied on significant results, the most effective prognostic factor was found to be distant metastasis, followed by R_0 resection for CSS and OS. The most important prognostic factor affecting DFS was N_2, which was again followed by R_0 resection. Briefly, the most effective prognostic factors on survival were found to be R_0 resection and histologic properties (stage IIIC, T_4, N_2, M_1) of the tumor.

Conclusions

The most important points of the treatment of CC are R_0 resection and adequate lymphadenectomy. This is also true for cancers with adjacent organ invasion or recurrent tumors. Long-term survival and even cure is only possible with these measures. No adjuvant therapy is capable of correcting the consequences of insufficient surgery. However, high-risk patients with stage II and all patients with stage III disease should receive chemotherapy. Close monitoring of patients in the first 5 years is mandatory. Close follow-up of patients, especially those with a high risk of recurrence, enables early diagnosis and radical surgical treatment of LR or distant metastases. Cancer treatment is a multidisciplinary process. Other dedicated disciplines besides the surgical team are also crucial in order to acquire successful results. Standardization of surgery and a dedicated team are prognostic factors.

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