MULTIVISCERAL RESECTION FOR COLORECTAL CANCERS: AN ANALYSIS OF PROGNOSTIC FACTORS AND OUTCOMES

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ABSTRACT

Introduction: For colorectal cancer patients, long-term survival is achievable only after complete resection of the disease. However, the decision to embark on a multi-visceral resection must be made after weighing the risks against the potential benefits. **Methods:** We retrospectively analyzed the demographics, tumor parameters, perioperative results, oncological outcomes and survival details of 35 patients who underwent multivisceral resection for colorectal carcinoma between 1996 and 2013. 'Multivisceral resection' was defined as the resection of at least one other organ in addition to cancer affected the colon. **Results:** There were 19 males and 16 females who had a mean age of 52.7 ± 13.6 years. The most common primary site of the tumor was the rectum, followed by the sigmoid, the left, and the right colon. Most frequently resected additional organ was the pancreas followed by the uterus, small bowel, urinary bladder, ureter, vagina, spleen, duodenum, ovary, and liver. Postoperative histopathological examination confirmed tumor infiltration in the adjacent organs in 48.5%. The postoperative complication was developed in 21 (60%) patients. There was no surgery-related mortality. Ten patients had evidence of recurrence at last follow-up in June 2014. The 5-year survival rate was of 73.1% according to Kaplan-Meier survival analysis. **Conclusion:** Multivisceral resection for colorectal cancer is associated with a high morbidity rate, but the long-term survival is good.

KEYWORDS: Colorectal carcinoma, multivisceral resection, colorectal surgery

Introduction

The incidence of colorectal cancer in India is close to the lowest rates in the world being 4.3/100000 for males and 3.4/100000 for females [1]. It usually occurs in individuals older than 60 years of age. Until 50 years ago, colorectal cancer appearing to infil-

trate the surrounding tissue was considered to be unresectable. However, there is evidence that extensive surgical procedures aimed at complete resection of such tumors can be performed with an acceptable morbidity with enhanced long-term survival [2]. Multivisceral resection is defined as an en bloc resection of adherent organs and structures in addition to the standard operation. The rationale for multivisceral resection is that microscopic infiltration of the organs and adjacent structures cannot be assessed pre- or intra-operatively and such adhesions have a high risk of being malignant [3].

The dissection of the tumor and the adjacent structures can seed malignant cells on the peritoneal surface, resulting in local recurrence [4, 5]. Patients are undergoing such resection experience considerable postoperative morbidity because such resections are demanding for both patients and surgeons. Therefore, the associated risks of complications must be weighed against the potential benefits of survival [6]. However, 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 resections. In the present study, we have analyzed surgical factors for short-term and long-term outcomes after multivisceral resection for colorectal cancer.

Patients and Methods

A total of 674 patients with colorectal cancer were operated at our department from August 1996 to December 2013 out of which 35 (5.2%) patients underwent multivisceral resection. Patients with dysplasia, in situ cancer, non-adenocarcinoma tumor, synchronous metastases and recurrent tumor were excluded. Patients who underwent emergency procedure or removal of unattached organs such as the gallbladder for symptomatic gallstone disease, splenic resection for iatrogenic injury, and others were also excluded from the study. Patients were evaluated pre-operatively with colonoscopy, abdominal ultrasound, computed tomography scan and magnetic resonance imaging. Patients with full-thickness and lymph node positive lower 1/3 rd rectal cancer on pre-operative imaging underwent neoadjuvant 5-Flurouracil based chemo-radiotherapy with a total dose of 45 Gy and surgery was scheduled 4-6 weeks after completion of therapy.The stage of cancer was determined according to the classification of cancer disease stage of the 7 th American Joint Committee on Cancer [7]. Major complications were defined as those that required additional medical treatment or surgical intervention. Surgery-related mortality was defined as death within 30 days after the procedure. Follow-up evaluation included physical examination and measurement of liver function tests, carcinoembryonic antigen level, chest radiography, ultrasound of the liver and yearly colonoscopy. If there were abnormalities in the liver function tests or a rise in the level of carcinoembryonic antigen level, computed tomography scan of the abdomen and pelvis were performed. Adjuvant Oxaliplatin and 5-Flurouracil based chemotherapy were administered to patients with pTNM stages IIb, IIC, and III. We analyzed demographics, tumor localization, invaded organs, pathological infiltration of tumor, completeness of the resection, operation time, intraoperative blood loss, postoperative complications, surgery-related mortality, length of stay, pathological data (tumor differentiation, number of harvested lymph nodes, status of surgical margins, presence/absence of lymphovascular permeation and perineural invasion of the tumor), follow-up period, recurrence pattern, adjuvant therapy and survival.

Statistics

Continuous data were presented as mean and median with ranges. Percentages were used for discrete data. The Fisher's exact test and chi-square test were used for discrete data analysis. The unpaired t-test was used for continuous data analysis. The clinicopathological factors independently associated with morbidity were analyzed using logistic regression analysis and those independently associated with blood loss, and hospital stay were analyzed using multiple regression analysis. The survival rates were calculated using the Kaplan-Meier method and tested by the log-rank test. The factors associated with patient survival were analyzed using the Cox proportional hazard model. A p value of <0.05 was considered to be statistically significant. GraphPad, Prism (version 6.0) software was used for analysis.

Table 1 Clinicopathological characteristics.

Characteristics	Mutivisceral resection (n=35)
Median Age	52 (25-79)
Gender Male Female	19 (54.2) 16 (45.8)
ASA classification I II III	13 (37.1) 16 (45.8) 6 17.1)
Tumor location Rectum Sigmoid Left colon Transverse colon Right colon	14 (40) 10 (28.6) 4 (11.4) 3 (8.6) 4 (11.4)
Tumor depth pT1 pT2 pT3 pT4	1 (2.8) 4 (11.4) 13 (37.3) 17 (48.5)
Lymph node metastases Present Absent	16 (45.7) 19 (54.3)
Tumor grading Well-differentiated Moderately-differentiated Poorly-differentiated	6 (17.2) 22 (62.8) 7 (20)
Lymphovascular permeation Present Absent	10 (28.5) 25 (71.5)

Results

Clinico-pathological characteristics:

The median age of the patients was 52 (25-79) years. The most common presenting features were a pain (45.7%), weight loss (25.7%), rectal bleeding (25.7%), change in bowel habits (22.8%), loss of appetite (20%) and vaginal bleeding (2.8%). A palpable mass was found only in one patient (2.8%).

The rectum was the most common site for the primary tumor followed by the sigmoid, left, transverse and right colon (Table-1). The average tumor size was 6 (2-11) cm.

Histopathological examination confirmed tumor invasion in 17(48.5%) patients and inflammatory adhesions were present in the remaining 18 patients. The average number of harvested lymph nodes was 14 (3-49), and lymph node metastasis was present in 16 (45.7%) patients. There was no difference in lymph node metastasis in tumors with histologically confirmed infiltration (pT4) compared to tumors with inflammatory adhesions (clinical T4) with eight patients in each group. Regarding tumor grading, moderately differentiated adenocarcinoma was the most prevalent (62.8%). In the present study, eight patients with rectal tumor and one patient with anorectal tumor had received neoadjuvant chemoradiotherapy.

Multivisceral resection and blood loss:

Average operation time was 290 ± 92 min. Resection included an additional one organ in 15 (42.5%) patients, two bodies in 10 (28.5%) patients, three bodies in 6 (17.1%) patients, four organs in 3 (8.5%) patients and five organs in 1 (2.8%) patient. Removal of all cancerous tissue was confirmed histopathologically in all patients. The pancreas was the most frequently removed additional organ followed by the uterus, small bowel, urinary bladder, ureter, vagina, spleen, duodenum, ovary and liver (Table.2).

The mean blood loss was 428 ml with only one patient having a blood loss of more than 1000 ml. At a cutoff volume of 500 ml, tumor size (p=0.034), the number of resected organs (p=0.002) and operation time (p=0.038) were significantly associated with a higher blood loss. However, operation time (95% confidence interval: 0.22 to 1.88; p=0.014) and some resected organs (95% confidence interval: 7.38 to 144.22; p=0.031) were independently associated with higher blood loss on multivariate analysis.

Postoperative complications:

Postoperative complications were developed in 21 (60%) patients. The most common complication was prolonged ileus (20%) (Table.3). Two patients required re-exploration for acute adhesive obstruction as they did not improve with conservative management and another three required reoperations for anastomotic leaks. The mean postoperative hospital stay was 10 (5-33) days. Tumor invasion (p=0.032), the number of resected organs (p=0.035), blood loss (p=0.050) and age (p=0.081) were significantly associated with morbidity by univariate analysis. However, multivariate analysis revealed that only the number of resected organs (odds ratio: 2.472; 95% confidence interval: 1.00 to 6.10; p=0.049) was an independent factor for morbidity.

There was no surgery-related mortality among these patients.

Follow up and Recurrence:

Two patients were lost during follow-up immediately after surgery and were therefore excluded from analysis. The follow-up period ranged from 7 to 167 months (mean=51 months; median=22 months). The status of patients at the end of the study was: 21 (63.6%) alive without cancer, 6 (18%) died with recurrence, 2 (6%) died due to causes not related to cancer and 4 (12%) alive with evidence of recurrence. Twenty-five patients with lymph node progressive disease and/or particular thickness disease had received adjuvant chemotherapy.

10 (28.5%) patients had evidence of recurrence with the frequency of 6 patients (17%) had a local recurrence, one patient (2.85%) had distant metastasis and three patients (8.57%) had local as well as distant metastasis.

Survival:

The 5-year survival rate was 73.1% (Fig.1) and the median survival time was 24 months. Univariate analysis of the clinicopathological factors showed that tumor invasion (p=0.002), lymph node metastasis (p=0.020), lymphovascular permeation (p=0.053) and blood loss were significantly associated with overall survival (Table.4). Only lymph node metastasis (odds ratio: 5.369; 95% confidence interval: 1.07 to 26.80; p=0.030) and blood loss (odds ratio - 1.032; 95% confidence interval - 1.01 to 2.56; p=0.038) were independently associated with overall survival in multivariate analysis. 5-year cancer-related survival rate was 72.2% (Fig.1). Univariate analysis revealed that tumor size (p=0.020), tumor invasion (p=0.017), lymph node metastasis (p=0.0005) and lymphovascular permeation (p=0.0001) were significantly associated with cancer-related survival. Only tumor size (odds ratio: 0.462; 95% confidence interval: 0.23 to 0.90; p=0.023), tumor infiltration (odds ratio - 5.22; 95% confidence interval - 3.36 to 8.07; p=0.004) and lymph node metastasis (odds ratio - 4.36; 95% confidence interval - 3.06 to 6.23; p=0.005) were independently associated with cancer-related survival on multivariate analysis.

Discussion

Complete removal of the tumor has a strong prognostic impact on the survival of colorectal cancer patients [8]. Tumor invasion into adjacent organs accounts for 5 to 16%, but only 50 to 85% of these patients have true pathological tumor invasion [9]. The rate of pathological tumor invasion to adjacent organs or structures in our patients (48.5%) was comparable with previous reports.

The SEER Registry data revealed that females had a higher risk of undergoing multivisceral resection than males [10]. It might be due to barrier effect of internal female genitalia against tumor invasion to the urinary bladder that is a common location for tumor invasion in males, and this leads to higher rate of multivisceral resection of genital organs in female patients [3].

The incidence of complications after a multivisceral resection is ranging from 11 to 54%, with an average of approximately 36% [5, 6, 9, 11]. Gebhardt et al. reported the lowest rate (11.4%) in an analysis of 173 patients treated with a multivisceral resection [5]. Nakafusa et al. investigated 53 patients treated with a multivisceral resection and reported morbidity rate of 49.1% [11]. In our study, the morbidity rate was 60%. Tumors requiring multivisceral resection are larger in size and deeper in wall invasion; although these are not independent risk factors but the combination of them might influence morbidity [11]. These factors and multivisceral resection itself influence the operation time and blood loss. The higher morbidity rate might be related to the increased number of anastomosis and width of dissection. We found that an increased number of resected organs was an independent risk factor for morbidity (p=0.022). The average

operation time was 290 min that was comparable with the previous study groups [6]. Although operation time was not an independent risk factor of complications in our study (p=0.732), it has been shown to increase the risk of infectious complications [12]. It might be the reason for the overall increase in morbidity rate among a present group of patients. Gebhardt et al. reported a mortality rate of 3.6% in 173 patients [5]. We did not have any surgery-related mortality among 35 patients.

Croner et al. reported a local recurrence rate of 6.5% in 162 patients treated with a multivisceral resection and found that lymph node metastasis and the dissemination of cancer cells during surgery might be the major factors responsible [13]. In our series, we found several pathological characteristics that were related to a better prognosis for colorectal cancer, such as inflammatory adhesions, non-metastatic lymph nodes, low-grade tumors, the absence of perineural infiltration and lymphovascular permeation. Patients with positive lymph nodes who were treated with a multivisceral resection had a 5-year cancer-related survival of 45% in our study. Lymph node metastasis, pathological tumor infiltration, and tumor size are the independent prognostic factors for locoregional recurrence in multivariate analysis of clinicopathological factors of the present study. Lymph node status is an established prognostic factor for cancer-related survival in colorectal cancer [14]. It is a crucial point in improving the surgical approach because the increased locoregional recurrence rate in patients with lymph node metastasis might be due to inadequate dissection of the potentially affected lymph nodes (p>0.05). Therefore, adjuvant chemotherapy is recommended after multivisceral resection in the presence of lymph node metastasis, residual tumor, poor histological grade or intraoperative tumor cell dissemination.

In our study age did not influence survival. Therefore, older patients should not be excluded from potentially curative surgery. Increased number of involved organs did not have any effect on survival (p=0.132), proving that multiple organ involvements should not be a contraindication for surgery. Previous data presented 5-year survival rates as low as 30 to 38% [15]. Nakafusa et al. reported that the 5-year survival rate for patients treated with a multivisceral resection was 76.6% [11].

The 5-year survival in our patients was 73.1%, which might have been achieved because of exclusion of emergency operations and stage IV diseases. Lehnert et al. demonstrated that lower long-term survival of patients treated with a multivisceral resection was related to early postoperative deaths (mortality-7.5%) [6]. Therefore, reducing surgery-related mortality is one strategy for improving long-term outcome. They also revealed that the 5-year survival rate for patients with a stage IV tumor treated with a multivisceral resection was very low (12%) compared with that of patients with a stage II–III tumor (56%). Because of the poor prognosis, further elucidation is needed to clarify when multivisceral resection for stage IV colorectal cancer is indicated. In our study, lymph node metastasis and intra-operative blood loss were the independent risk factors of survival. Lymph node metastasis is the most significant survival related prognostic factor for colorectal cancer [16]. For intra-operative blood loss, the reported results are controversial, and patient selection, a proportional relation between intra-operative blood loss and amount of blood transfusion are thought to affect the survival results [17, 18, 19]. Although it is not clear, immunomodulation by transfusion is a possible mechanism of worsening the prognosis [20]. The combination of higher intra-operative blood loss, perioperative blood transfusion and subsequent development of postoperative infectious complications has been reported to be associated with a poor prognosis [12].

Conclusion

Although multivisceral resection for colorectal tumor is safe irrespective of age and older patients should not be excluded from potentially curative surgery, this procedure is associated with higher morbidity rate. Therefore, patients' selection should be done precisely. An effort towards reducing the need for blood transfusion may improve survival. The increased locoregional recurrence in the presence of lymph node metastasis might be associated with inadequate dissection of the potentially affected lymph nodes which indicates the importance of having experienced, well-trained surgeons.

Authors' Statements

Competing Interests
The authors declare no conflict of interest.

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