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ORIGINAL ARTICLE

Recurrence rate and prognostic factors in laparoscopically resected colorectal malignancies

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Background: There are limited data on the 2-year recurrence rate and prognostic factors for recurrence in laparoscopically resected colorectal malignancies. The aim of this study was to determine the 2-year recurrence rate and prognostic factors for recurrence of colorectal carcinoma in patients who underwent elective laparoscopic colectomy.

Methods: Data from patients with colorectal carcinoma who had undergone elective laparoscopic colectomy in HPUSM were retrospectively reviewed. All patients who had a follow-up of at least 24 months and traceable records were included in the study, whereas patients with concurrent pathologies were excluded. Patients' clinicopathologic data and follow-up data for 2 years after surgery were examined. Cox proportional hazard regression was used to determine the possible prognostic factors for colorectal cancer recurrence.

Results: Of 40 patients, five patients had recurrence within 2 years after surgery, representing a recurrence rate of 12.5%. The average time to recurrence was 21.2 months, with the earliest recurrence occurring on the 15th day after surgery. Postoperative serum level of carcinoembryonic antigen (CEA) was the prognostic factor for colorectal cancer recurrence [hazard ratio (HR): 1.05, 95% CI: 1.00, 1.10, p = 0.04].

Conclusion: The results of our study showed that the 2-year recurrence rate in this study setting was 12.5%. The significant prognostic factor for recurrence of colorectal cancer in patients who underwent elective laparoscopic colectomy was postoperative CEA levels.

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Colorectal carcinoma is any malignant growth that develops in any part of the colon (from the appendix to the anorectal junction). It is one of the most common cancers worldwide and the second most common in Malaysia with an incidence rate of 21.3 per 100,000 population.[1] Locally, the majority of colorectal cancers are diagnosed at stage III or IV and account for 63.5% of newly diagnosed cases.[2]

Surgical resection is considered the primary treatment modality in most cases, and curative outcomes can be achieved with appropriate adjuvant therapy. With regard to oncologically meaningful resection, the surgeon aims for complete removal of the primary tumour, its main vascular pedicle, and the lymphatic drainage basin of the affected colonic segment.[3] Resection can be performed through either the "modern" laparoscopic or the "conventional" open approach.

After primary curative resection, the incidence of colorectal cancer recurrence ranges from 10% to 30%, with the highest recurrence rate reported for stage III.[4-7] In the majority of cases, approximately 80%, recurrence occurs within the first two years after resection, underscoring the need for more frequent follow-up during this period.[7,8]

Based on the latest data from the Malaysian National Cancer Registry, 70.8% of colorectal cancer cases were treated by surgical resection between 2008 and 2013, while 88.4% of patients diagnosed with stage III colorectal cancer were treated surgically.[1] Of these patients who underwent surgical resection, approximately 16% underwent laparoscopic colectomy.[1] Laparoscopic procedures have yielded better outcomes, such as less postoperative pain, faster return of bowel function, and subsequently shorter hospital stays and faster return to work. These advantages make the laparoscopic approach more favourable compared to open surgery.[9] Here at Hospital Pakar Universiti Sains Malaysia (HPUSM), one of Malaysia's largest teaching hospitals, laparoscopic surgery has been performed since the mid-1990s, but laparoscopic colectomy for colorectal cancer has only recently become the method of choice. Because laparoscopic resection of colorectal malignancies is a technically challenging procedure, the learning curve for the inexperienced surgical team is steep.[10] Consequently, short- and long-term outcomes can be greatly affected in this process of acquiring new skills.

Currently, there are no data on our progress regarding the oncologic outcome of laparoscopically resected colorectal cancer. It is possible that more available information may help enforce the laparoscopic approach to resection of colorectal carcinomas. Perhaps they can help us identify any shortcomings in our perioperative management and postoperative follow-up. We felt it necessary to report our findings on the recurrence rate and prognostic factors in laparoscopically resected colorectal malignancies. This study examined the data of patients with colorectal carcinoma who underwent laparoscopic colectomy at HPUSM in Malaysia from January 2007 to December 2014. This study also investigated the 2-year recurrence rate and possible prognostic factors for colorectal cancer recurrence in patients who underwent elective laparoscopic colectomy.

METHODS

Participants

This is a retrospective observational cohort study of patients diagnosed with colorectal cancer who underwent elective laparoscopic colectomy at Hospital Pakar Universiti Sains Malaysia (HPUSM), Malaysia from January 2007 to December 2014. During the study period, 53 patients with colorectal carcinoma underwent elective laparoscopic colectomy sampled from the HPUSM hospital surgical records. Forty patients met the eligibility criteria. Inclusion criteria for this study included patients diagnosed with colorectal cancer who underwent elective laparoscopic colectomy during the study period and had a postoperative follow-up of at least 2 years. Patients who missed follow-up or had concurrent pathology were excluded. Ethical approval was granted by the Ethics Committee of Universiti Sains Malaysia (USM) in Kelantan, Malaysia (reference number: USM/JEPeM/17010059).

Data collection

Secondary data were collected as part of this study. The list of patients who underwent elective laparoscopic colectomy for colorectal cancer at HPUSM Hospital during the eight years from

January 1, 2007 to December 31, 2014 was obtained from the operating room census books. Patient case notes and the hospital's patient information database were reviewed in detail to obtain clinical data and other information needed for the study. All required information was entered into the data collection form to avoid bias. Variables required for the study included patient demographics, serum carcinoembryonic antigen (CEA) level before and after surgery, preoperative and postoperative diagnosis and cancer staging, histopathology report of the resected specimen, time interval between surgery and initiation of adjuvant therapy, and presence of evidence of recurrence and mortality.

Data analysis

Descriptive statistics (frequency and percentage for categorical variables; mean and standard deviation for numerical variables; median and IQR for skewed variables), Kaplan-Meier analysis, and proportional Cox hazard regression were used as methods of analysis. Kaplan-Meier analysis was used to determine the median survival of patients diagnosed with colorectal cancer who underwent elective laparoscopic colectomy. Cox proportional hazards regression was used to identify potential prognostic factors for colorectal cancer recurrence. Statistical analysis was performed using SPSS/Win software (version 22, SPSS, Inc., Chicago, IL, USA). The significance threshold was set at 0.05.

RESULTS

Patient demographic and clinical characteristics

Of the 53 patients who underwent elective laparoscopic colectomy for colorectal cancer, 40 patients met the inclusion and exclusion criteria and were enrolled in the study. Thirteen patients were excluded because follow-up was not possible after 1 year (n = 9) and data were incomplete or missing (n = 4). Table 1 shows the characteristics of patients with colorectal carcinoma who underwent elective laparoscopic colectomy. The mean age of patients was 61.3 years. Approximately 55% of patients had co-morbidities, including combinations of diabetes, hypertension, and ischaemic heart disease, while 45% had no co-morbidities. The pre-operative stage was predominantly Stage II and III.

Table 1 *Characteristics of patients with colorectal cancer who underwent elective laparoscopic colectomy (n = 40)*

Variables		
Age (years), mean (SD)	at diagnosis	61.3 (10.90)
	at surgery	61.5 (10.89)
Gender, n (%)	Male	22 (55.0)
	Female	18 (45.0)
Race, n (%)	Malay	36 (90.0%)
	Chinese	4 (10.0%)
Co-morbidities, n (%)	Diabetes	4 (10.0%)
	Hypertension	7 (17.5%)
	Ischaemic heart disease	2 (5.0%)
	Diabetes and hypertension	8 (20.0%)
	Diabetes and ischaemic heart disease	1 (2.5)
	None	18 (45.0)
Preoperative clinical staging, n (%)	Stage I	5 (12.5)
	Stage II	12 (30.0)
	Stage III	13 (32.5)
	Stage IV	9 (22.5)
	Unstaged	1 (2.5)
Postoperative clinical staging, n (%)	Stage I	4 (10.0)
	Stage II	14 (35.0)
	Stage III	12 (30.0)
	Stage IV	10 (25.0)
Site of tumour, n (%)	Caecum	1 (2.5)
	Ascending colon	0 (0.0)
	Transverse colon	1 (2.5)
	Descending colon	1 (2.5)
	Sigmoid colon	6 (15.0)
	Rectosigmoid colon	13 (32.5)
	Rectum	16 (40.0)
	Anorectum	2 (5.0)
Presence of synchronous tumour, n (%)	2 (5.0)	
Pre-operative serum CEA, median (IQR)*	9.0 (34.1)	
Post-operative serum CEA, median (IQR)**	2.9 (3.2)	

SD, standard deviation; IQR, interquartile range; CEA, carcinoembryonic antigen
*Serum carcinoembryonic antigen (CEA) levels were taken for 39 patients.
**Serum CEA levels were taken for 37 patients. Two of these patients succumbed 1 month post-operatively; one due to complication of ventilator-acquired pneumonia as a sequela of anastomotic leak and another due to respiratory failure secondary to lung metastases. The remaining patient had progressive disease and succumbed to disease progression of liver and lung metastases, at 6 months post-surgery.

A total of 10 cases underwent laparoscopic surgery from 2007 to 2011, and a total of 30 cases underwent laparoscopic surgery from 2012 to 2014 (Supplementary Table 1). The histopathologic characteristics of patients with colorectal carcinoma who underwent elective laparoscopic colectomy are described in Supplementary Table 2. Adjuvant treatment of patients with colorectal carcinoma who underwent elective laparoscopic colectomy is described in Supplementary Table 3.

Five patients experienced disease recurrence within 2 years after surgery, and the 2-year recurrence rate was 12.5%. The median time to disease recurrence was 21.2 months (SD 3.70) (Supplementary Table 4). When plotted on the Kaplan-Meir diagram (Figure 1), no median recurrence time could be determined. The earliest case of recurrence occurred 15 months after surgery. This patient was at stage III.

Prognostic factors for recurrence of colorectal cancer in patients who underwent elective laparoscopic colectomy

Table 2 shows simple Cox regression analyzes on the potential prognostic factors for colorectal cancer recurrence in patients who underwent elective laparoscopic colectomy. Postoperative CEA level was a significant prognostic factor for colorectal cancer recurrence. Patients with a higher postoperative CEA score were at higher risk for recurrence of

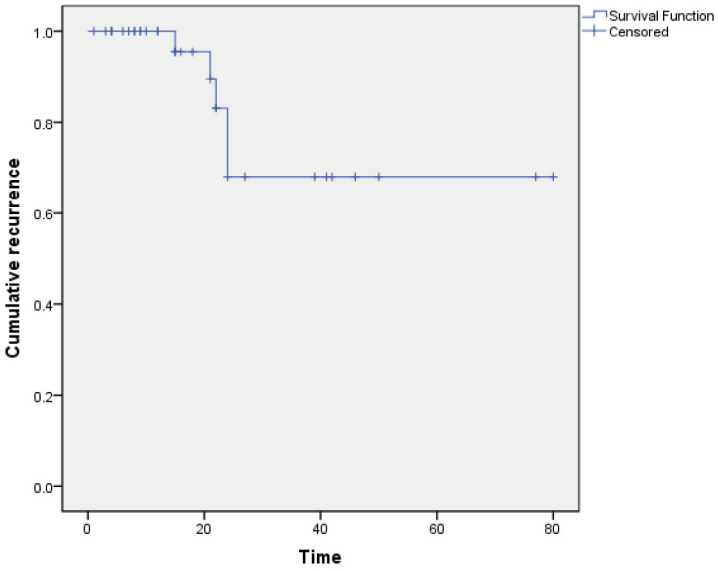

Figure 1 *Kaplan Meier Curve for cumulative recurrence of laparoscopic resected colorectal carcinomas*

Table 2 *Prognostic factors for recurrence of colorectal cancer in patients who underwent elective laparoscopic colectomy from simple Cox regression analyses (n = 40). [a]Crude Hazard ratio (95% confidence interval)*

Variables	Regression coefficient (b)	Crude HR (95% CI)[a]	Wald stats (df)	p value
Gender				
Male	0.00	1.00		
Female	0.77	2.17 (0.36–3.06)	0.72 (1)	0.398
Age at diagnosis	0.04	0.96 (0.84–1.10)	0.32 (1)	0.570
Co-morbidities				
None	0.00	1.00		
1	0.41	1.51 (0.21–10.78)	0.17 (1)	0.681
2	0.19	1.21 (0.11–13.39)	0.03 (1)	0.875
CEA				
Pre-operative	0.01	1.00 (0.99–1.02)	0.16 (1)	0.692
Post-operative	0.05	1.05 (1.00–1.10)	4.24 (1)	0.040
Final T stage				
T1	0.00	1.00		
T2	-0.71	0.49 (0.03–8.01)	0.25 (1)	0.618
T3	-0.63	0.53 (0.05–5.97)	0.26 (1)	0.611
T4	-0.79	0.45 (0.03-7.30)	0.31 (1)	0.576
Final N stage				
N0	0.00	1.00		
N1	2.30	9.94 (0.89–111.32)	3.47 (1)	0.062
N2	1.54	4.68 (0.42–51.65)	1.59 (1)	0.208
Final M stage				
M0	0.00	1.00		
M1	0.59	1.80 (0.30–10.76)	0.41 (1)	0.521
Lymph node harvested	-0.07	0.93 (0.80–1.09)	0.76 (1)	0.383
Lymphovascular invasion				
No	0.00	1.00		
Yes	1.14	3.14 (0.44–22.48)	1.30 (1)	0.255
Not mentioned	1.59	4.88 (0.44–54.40)	1.66 (1)	0.197
Perineural invasion				
No	0.00	1.00		
Yes	0.93	2.52 (0.35–18.08)	0.85 (1)	0.357
Not mentioned	0.10	1.10 (0.10–12.18)	0.01 (1)	0.938
Adjuvant therapy				
None	0.00	1.00		
Chemotherapy	10.37	0.69 (0.08–6.72)	0.04 (1)	0.947
Chemo-radiotherapy	11.29	0.46 (0.03–8.12)	0.05 (1)	0.942

laparoscopically resected colorectal cancer [hazard ratio (HR): 1.05, 95% CI: 1.00, 1.10, p = 0.04]. Gender, age at diagnosis, presence of one or more concomitant diseases, preoperative CEA level, final T, N, or M stage, number of lymph nodes harvested, presence of lymphovascular or perineural invasion, and presence of adjuvant therapy were not significant prognostic factors for colorectal cancer recurrence.

DISCUSSION

The present study investigated the 2-year recurrence rate and the possible prognostic factors for recurrence of colorectal carcinoma in patients who underwent elective laparoscopic colectomy. In our study, the local 2-year recurrence rate was 6.0%. The results were not significantly different from those of the Norfolk Surgical Group study in Virginia, which examined the oncologic treatment outcomes of laparoscopic colectomy.[11] Between June 1992 and September 1993, 39 laparoscopic-assisted colectomies were performed in patients with colorectal carcinoma. In this study, the 2-year recurrence rate was 9%.[11] In the review of long-term outcomes of laparoscopic-assisted colectomy for colorectal carcinoma performed in Japan between January 1993 and September 1999, the recurrence rate after a median follow-up of 58 months was 12.1% in patients with stage II or III.[12]

We examined several possible prognostic factors that might influence the recurrence of colorectal cancer in patients who underwent elective laparoscopic colectomy, including sex, age at diagnosis, presence of one or more concomitant diseases, CEA level, end-stage T, N, or M, number of lymph nodes harvested, presence of lymphatic or perineural invasion, and presence of adjuvant therapy.

Our study showed that postoperative CEA level is a significant prognostic factor for colorectal cancer recurrence. Patients with a higher serum CEA level 3 months after surgery have a higher risk of recurrence. In this study, preoperative CEA level was not a significant prognostic factor for colorectal cancer recurrence. Serum CEA is a useful marker and tool for preoperative prognosis and postoperative follow-up. Because of its relatively low sensitivity and specificity, it is less useful for diagnosis in asymptomatic patients.[13] In the past, a higher preoperative serum CEA level has been shown to be significantly associated with disease recurrence and to have a negative impact on survival as an independent prognostic factor when the level is ≥ 5 ng/mL.[14,15] In our study, univariate analysis identified postoperative CEA as a significant prognostic factor for colorectal cancer recurrence and survival. While further multivariate studies may be needed to confirm its independent role, these findings suggest that postoperative CEA remains a critical reference for monitoring. In the era of precision and personalized medicine, this serum biomarker may guide decisions regarding adjuvant chemotherapy or targeted therapy, depending on patient response.

Other factors studied, such as sex, age at diagnosis, presence of one or more comorbidities, end-stage T, N, or M, number of lymph nodes harvested, presence of lymphatic or perineural invasion, and presence of adjuvant therapy, were not significant prognostic factors for colorectal cancer recurrence.

Diabetes mellitus has been reported to be not only a factor that may increase the risk of colorectal cancer occurrence, but also poorer disease-free survival and higher all-cause mortality.[16] However, those underwent laparoscopic colorectal resection had better and earlier recovery of the immune level such as lower C-reactive protein, lymphocyte, neutrophil and natural killer cell that enhance the recovery peri-operatively.[28] Interestingly, the elderly patients who underwent this approach shown better physical and quality of life changes hence improved recovery peri-operatively.[30] In our study, we found that two of the five patients with recurrence were diabetic, while only four of the 12 patients had a poor postoperative outcome either in terms of morbidity or recurrence. This leaves seven diabetic patients who did not experience recurrence or mortality within the 24-month follow-up period of this study.

Patients at an advanced stage have a higher risk of recurrence, ranging from 11 to 61% in stage II patients and from 32 to 88% in stage III patients.[7] Locoregional recurrence was also more likely in rectal cancer than in colon cancer, possibly because it is more difficult to achieve a wide margin near the pelvis while preserving important structures.[17] In addition, recurrence occurred ranging in 14.8% at 2 years follow up and 2-year survival rate

was noted to be 87.7% among the study.[29] In our study, we found that most cases of recurrence occurred preoperatively at either stage III or IV, and four of the five patients had rectal cancer. In local context, by knowing these factors, we can learn, improve and identify modifiable prognostic factors such as comorbidities, lifestyles and stage at diagnosis that can be improve and give better peri-operatively hence give better prognosis and survival of this cohort colorectal malignancies. Awareness, early screening and educational initiatives will be much driven by these findings especially improvement in advanced minimally invasive approach and current peri-operatively approach.

Under the microscope, there are several factors that may indicate a worse prognosis or a higher risk of recurrence. This seemingly exhaustive list includes a lower nodal take [18], the histologic type of tumor, and patterns of lymphatic, vascular, or perineural invasion. The factors of particular interest to us were nodal sampling because, according to some authors, it reflects the oncologic quality of surgery and has an impact on oncologic outcome.[18-22] In our study, among patients with recurrent disease, only two patients had at least 12 lymph nodes sampled.

The increased risk of an unfavorable outcome in the presence of perineural invasion and lymphatic invasion is well known but still underappreciated, as pointed out by Schneider and Langner [23] in a review of prognostic stratification of colorectal cancer patients. In our study, the presence or absence of perineural invasion was not reported in 11 patients, whereas the status of lymphatic invasion was not reported in two patients. Of our patients who had recurrence, only two had both lymphovascular and perineural invasion, whereas one patient had neither.

Postoperative adjuvant therapy for colorectal cancer has been shown to improve outcomes, although opinions differ on the optimal time to start adjuvant therapy in different studies [15,24-27]. A meta-analysis found that adjuvant therapy started after 8 weeks was associated with worse overall outcome but not with lower recurrence-free survival.[24] Unfortunately, up to 70% of our patients, including all who developed recurrence, received adjuvant therapy, with a median time to initiation of therapy of 16.5 weeks (SD 14.88). Of the patients with recurrent disease, those with stage II and III underwent chemoradiotherapy, whereas those with stage IV received chemotherapy only. The duration of initiation of adjuvant therapy varied widely among these patients, ranging from 4 to 20 weeks. Possible reasons for such a delay in the start of adjuvant therapy include a gap in available oncology services and patient utilization, as well as reluctance or apprehension of patients and/or their family members to undergo adjuvant therapy.

Recent technology of minimally invasive approach for these colorectal malignancies such as robotic assisted surgery, usage of indocyanine green, synchronous resection of metastasis, usage of artificial intelligence and others had improved the surgical and oncological outcomes for patients.[31-35]

Some limitations were noted in this study. This study has the usual limitations of a retrospective study. Four patients were no longer in follow-up after one year, and records for nine patients were either lost or could

SUMMARY BOX

What is known about the subject

- One of the commonly studied endpoints of oncologic treatment outcome is the recurrence rate which, in colorectal cancer occurs most commonly within the first 2 years post resection.
- It is possible that more available information may help enforce the laparoscopic approach to resection of colorectal carcinomas. Perhaps they can help us identify any shortcomings in our perioperative management and postoperative follow-up.

New findings

- The recurrence rate of 12.5% for laparoscopically resected colorectal cancers done in Hospital Pakar Universiti Sains Malaysia (HPUSM) is comparable to recurrence rates reported in studies done internationally.
- A higher CEA level taken during the first follow-up clinic visit suggests a higher risk for recurrence and thus, may be used as an early indicator for recurrence.

not be located. The oncologic treatment outcome of colectomy for colorectal cancer is often measured by recurrence rates and 5-year disease-free survival. However, because laparoscopic colectomy is still in its infancy in our setting, we chose to study it for a minimum of 2 years. We advocate a prospective study with a larger number of patients to examine the results of long-term follow-up. This will provide us with an evidence-based outcome and help us in the management of colorectal carcinoma in patients who have undergone elective laparoscopic colectomy. In addition, future research directions that can be recommend such as improve quality of life, optimize of comorbidities, develop awareness and screening of this colorectal malignancies. In addition, study on tumor biology profiling besides depend on CEA that neither specific nor sensitive testing.

CONCLUSION

In conclusion, we found the recurrence rate of 12.5% for laparoscopically resected colorectal cancers done in HPUSM is comparable to recurrence rates reported in studies done internationally. This suggests that laparoscopic colectomy for colorectal cancers can be safe in the early stages of implementation under guidance of surgeons trained in the colorectal subspecialty. A higher CEA level taken during the first follow-up clinic visit suggests a higher risk for recurrence and thus, may be used as an early indicator for recurrence. As we catch on with the rising trend of minimally invasive surgery, continued effort towards self-audit and research is warranted to improve our surgical outcomes.

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