

**A REVIEW OF THE 2-YEAR RECURRENCE RATES IN
LAPAROSCOPICALLY RESECTED COLORECTAL MALIGNANCIES
IN HOSPITAL UNIVERSITI SAINS MALAYSIA**

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ABSTRAK

Pengenalan

Pembedahan dianggap sebagai modaliti rawatan utama dalam kebanyakan kes kanser kolorektal dan pencapaian pembedahan yang selamat dari segi onkologi telah terbukti dapat dilakukan secara pendekatan laparoscopi. Keraguan dalam mengamalkan kaedah ini mungkin disebabkan oleh lengkung graf pembelajaran yang curam dan kebimbangan keselamatan dari segi onkologi. Salah satu kajian yang biasa dilakukan untuk hasil onkologi adalah kadar kes kanser kolorektal berulang yang berlaku paling kerap dalam tempoh 2 tahun pertama selepas pembedahan. Untuk kemajuan ke arah pembedahan secara laparoscopi sebagai rutin, kajian ini bertujuan untuk membandingkan kadar kes ulangan 2 tahun bagi kes-kes kanser kolorektal yang di bedah secara laparoscopi dengan ulasan antarabangsa dan untuk menggambarkan faktor klinikopatologi yang boleh menyumbang kepada risiko berulang.

Methodologi

Ini adalah kajian pemerhatian retrospektif terhadap pesakit-pesakit yang telah disahkan menghidap kanser kolorektal dan telah menjalani pembedahan kolekomi laparoskopik secara elektif di HUSM dari Januari 2007 hingga Disember 2014. Semua pesakit yang mendapat rawatan susulan untuk minimum 24 bulan dan mempunyai rekod klinikal di HUSM dimasukkan dalam kajian ini manakala pesakit yang mempunyai pathologi lain pada masa yang sama dikeluarkandari pada kajian ini. Data kliniko-pathologi dan butiran rawatan susulan selama 2 tahun selepas pembedahan dikaji. Data dikumpulkan dalam proforma berstruktur dan analisis survival dilakukan menggunakan "Cox regression formula". Hasil pengumpulan data dan analisis kemudiannya dibandingkan dengan hasil kajian yang dilakukan di peringkat antarabangsa.

Keputusan

Dari tempoh Januari 2007 sehingga Disember 2014, sejumlah 53 pesakit menjalani pembedahan kolektomi laparoskopik secara elektif bagi rawatan kanser kolorektal. Sejumlah 13 pesakit dikecualikan, analisis dilakukan ke atas 40 pesakit. Umur purata ketika pembedahan ialah 61.5 tahun. 55% daripada pesakit adalah lelaki dan 45% adalah wanita dan 90% daripada pesakit adalah Melayu manakala 10% lagi adalah Cina. Kebanyakan kes adalah kanser pada usus kiri (95%), 42.5% daripada mereka adalah kes kanser anorektal atau rektal sahaja. Terdapat 4 pesakit (10%) dengan penyakit pada tahap I, 14 pesakit (35%) pada tahap II, 12 pesakit (30%) pada tahap III dan 10 pesakit (25%) pada tahap IV. Daripada 40 pesakit tersebut, terdapat 5 kes berulang dalam masa 2 tahun selepas pembedahan menjadikan kadar berulang sebanyak 12.5%. Masa purata untuk penyakit berulang adalah 21.2 bulan dengan pengulangan terawal terjadi pada 15 bulan selepas pembedahan. Berdasarkan formula “simple cox regression”, mereka yang mempunyai serum “carcinoembryonic Antigen” (CEA) yang lebih tinggi selepas pembedahan mempunyai risiko yang lebih untuk mendapat karsinoma kolorektal yang berulang (HR=1.05, 95% CI: 1.00, 1.10, nilai P =0.04). Faktor-faktor lain seperti pesakit yang mempunyai satu atau lebih komorbiditi, tahap T, N atau M akhir, tahap kumpulan akhir, limfovaskular atau perineural invasi dan terdapat terapi tambahan sebelum ataupun selepas pembedahan secara statistiknya, tidak signifikan (nilai P \geq 0.05) dalam menambah risiko untuk ulangan dalam masa 2 tahun.

Kesimpulan

Kadar kes berulang bagi kes-kes kanser kolorektal yang dibedah secara laparoskopik di HUSM adalah setaraf dengan kadar pada peringkat antarabangsa. Nilai serum CEA semasa rawatan susulan pertama yang lebih tinggi, mencadangkan kemungkinan risiko lebih tinggi

untuk berulang. Oleh itu, ia mampu menjadi satu indikator awal untuk kes berulang. Walaupun faktor-faktor lain seperti tahap penyakit, status nodal dan bilangan nodus limpa yang dikeluarkan mungkin mempunyai kaitan, tetapi tiada yang signifikan dari segi statistik. Sejalan dengan kemajuan tren ke arah pembedahan invasif minima, usaha yang berterusan dari segi audit dan kajian diperlukan bagi menambahbaik mutu hasil pembedahan.

ABSTRACT

Introduction

Surgical resection is considered the primary treatment modality in most cases of colorectal carcinoma and achievement of an oncologically-sound resection has been shown to be possible by laparoscopic approach. The hesitation in adopting this method may be because of the steep learning curve and concerns of oncologic safety. A commonly studied measure of oncologic outcome is the recurrence rate which, in colorectal cancer occurs most commonly within the first 2 years post resection. This study aims to compare the 2-year recurrence rates of colorectal cancer cases resected laparoscopically to that reported internationally and to describe clinicopathologic factors that may contribute to the risk of recurrence.

Methods

This is a retrospective observational study of the patients diagnosed with colorectal cancer who underwent elective laparoscopic colectomy in HUSM from January 2007 to December 2014. All such patients who had a minimum 24-month follow-up and traceable records were included in the study whilst those with concurrent pathologies were excluded. Patients' clinicopathological data and follow-up details for 2 years post-surgery was studied. Data was collected in a structured proforma and the survival analysis of which was done using Cox regression formula. The results of data collection and analysis were then compared to results of studies conducted internationally.

Results

From the period of January 2007 to December 2014, a total of 53 patients underwent elective laparoscopic colectomy for colorectal cancer. A total of thirteen patients were excluded thus, data analysis was performed for 40 patients. The mean age at surgery was 61.5 years. 55% of patients were male whilst 45% were female and 90% of the patients were Malay whilst the remaining 10% were Chinese. Majority of the cases were left sided cancers (95%), 42.5% of whom were cases of anorectal or rectal cancers. There were 4 (10%) patients with Stage I disease, 14 (35%) patients with Stage II disease, 12 (30%) patients with Stage III disease and 10 (25%) patients with Stage IV disease. Five patients had recurrence within 2 years post-surgery resulting in a recurrence rate of 12.5% which was within the range of recurrence rates of 3 to 15.6% reported internationally. The mean time to disease recurrence was 21.2 months with the earliest recurrence occurring at 15 months post-surgery. Based on the simple cox regression formula, those with higher post-operative serum CEA have a higher risk of recurrence of colorectal carcinoma (HR=1.05, 95%CI: 1.00, 1.10, P value=0.04). Other factors such as presence of one or more comorbidities, final T, N or M stage, final group stage, tumour margin clearance, presence of lymphovascular or perineural invasion and presence of neoadjuvant or adjuvant therapy were not significant (P value>0.05) in an increased risk of recurrence within 2 years post-surgery.

Conclusion

The recurrence rate for laparoscopically resected colorectal cancers done in HUSM is comparable to international standards. A higher post-operative serum CEA suggests a higher risk for recurrence and thus, may be used as an early indicator for recurrence. Although other factors such as disease stage, nodal status and lymph node harvest appeared to have a

possible association, none were statistically significant. 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.

A. Introduction

A. INTRODUCTION

i. Literature review

Surgical resection is considered the primary treatment modality in most cases of colorectal carcinoma and curative results can be achieved with appropriate adjuvant therapy. Keeping in mind the need for an oncologically-sound resection, the surgeon's goals would include complete excision of the primary tumour, its major vascular pedicle and lymphatic drainage basin of the affected colonic segment. (Wasserberg, 2010) Resection can be done either by the contemporary laparoscopic or the conventional open approach.

In the past decades, laparoscopic colectomy for resection of colorectal malignancies has been gaining its popularity though at a slow pace. There have been concerns regarding the oncologic outcomes of laparoscopically-resected colorectal malignancies as previously highlighted in a report of the forth port-site recurrence post laparoscopic colectomy by Cirrocco *et al.* The latter had even concluded that “abdominal wall cancer recurrence is enhanced by the laparoscopic approach to colorectal cancer” and shunned the method, suggesting that it only be performed in controlled, clinical studies. (Cirrocco, Schwartzman and Golub, 1994)

Thus, laparoscopic colectomy for malignancy remained infrequently performed until a number of large, prospective, randomized controlled studies such as the Barcelona, MRC-CLASSIC, COLOR and COST trials compared open to laparoscopic approach and addressed the major concern of oncologic safety.

The Barcelona trial involved 219 randomly selected patients who fit the inclusion criteria of a single tumour at least 15cm from the anal verge and studied their cancer-related survival over a 5-year period. They found that laparoscopic resection was superior in stage III colon cancer. The parameters that showed superior outcome in the laparoscopic colectomy group

were morbidity, hospital stay, tumour recurrence and cancer-related survival. (Lacy *et al.*, 2002)

A 48-institution-strong multicentre randomized control study performed by the COST study group recruited a sizeable sample of 1735 patients with the primary study objective of “time to tumour recurrence”. What they found was that the recurrent rates in laparoscopic-assisted colectomy and open colectomy were comparable and thus, an acceptable alternative to open surgery.(The Clinical Outcomes of Surgical Therapy Study Group, 2004) Based on this data, it was also discovered that laparoscopic colectomy done for curable colon was not inferior to open surgery with recurrence rates that were similar between both groups. Other oncologic outcomes such as disease-free 5-year survival and overall 5-year survival were also found to be similar between the open and laparoscopic groups.(Fleshman *et al.*, 2007)

Consolidating all the above trials in a meta-analysis was a refreshing effort by the Transatlantic Laparoscopically Assisted vs Open Colectomy Trials Study Group who aimed to enhance the surgeon’s ability to choose between laparoscopic or open techniques. They concluded that laparoscopic colectomy was oncologically safe. (Bonjer *et al.*, 2007)

Evidently, as noted by the COLOR study group in 2005, a higher volume of cases has been shown to have a positive impact on the short term results of laparoscopic colectomy for colorectal carcinoma.(Veldkamp *et al.*, 2005) A self-audit done by the Royal Brisbane Hospital in Australia showed that amongst the 181 patients who underwent laparoscopic resection for colorectal cancer in their hospital, the procedure produces acceptable intermediate to long-term oncologic outcomes and a low long-term complication rate in selected patients.(Lumley *et al.*, 2002) For centers about to embark on or new to the laparoscopic colectomy as the primary choice of resection, it may be reassuring to know that

in a small-volume setting this technique is safe when performed by the general surgeon with advanced laparoscopic skills. (Gandy & Berney, 2014)

Perhaps owing to the steep learning curve and advanced skills required, not many surgeons choose to perform laparoscopic resection in Malaysia. This is reflected in the Malaysian local census which found that only about 16% of colorectal carcinoma cases underwent laparoscopic resection. To date, there is no existing local data on the oncologic outcomes of laparoscopically resected colorectal cancers. With the knowledge that majority of cases recur within the first 2 years of resection,(Scholefield *et al.*, 2002) it seems logical to look into the recurrence rates within this period when evaluating our progress at the early stage of our learning curve. Thus, this study aims to provide better knowledge of the short to midterm oncologic outcome of laparoscopic colectomy in HUSM and describe the factors that may contribute to higher risk for recurrence.

ii. Rationale for study

In Hospital Universiti Sains Malaysia (HUSM), one of the major teaching hospitals in Malaysia, laparoscopic surgeries have been in place since the mid-1990s but laparoscopic colectomy for colorectal carcinoma has been used as the choice technique only recently.

Currently, there is no existing data on our progress in terms of the oncologic outcome of the cases of laparoscopically resected colorectal cancers. Possibly, more information at hand may serve as an encouragement to choose the laparoscopic approach to resection of colorectal carcinomas. And, perhaps, it can help us to identify any short-comings in our perioperative management and post-operative follow-up.

This study aims to:

- To determine the proportion cases of with recurrence within 2 years post-surgery amongst those who had undergone laparoscopic resection of colorectal carcinomas in HUSM.
- To describe factors that may contribute to the risk of recurrence, specifically:
 - Patient factors (age and gender, co-morbid diseases)
 - Disease factors (pre- and post-operative staging, tumour site and serum Carcinoembryonic Antigen (CEA) levels)
 - Histopathologic factors (TNM stage, histologic type and differentiation of the tumour, involvement of resection margin)
 - Presence of neoadjuvant or adjuvant therapy
 - Time lapse between surgery and commencement of neoadjuvant and/or adjuvant therapy

B. STUDY PROTOCOL

B. STUDY PROTOCOL

i. Document submitted for ethical approval

Chairperson

Jawatankuasa Etika Penyelidikan (Manusia) USM

Health Campus

Universiti Sains Malaysia

16150 Kubang Kerian, Kelantan

Dear Sir/ Madam,

RE: Revised Study Protocol for Protocol Title: A Review of the 2-Year Recurrence Rates in Laparoscopically Resected Colorectal Malignancies in Hospital Universiti Sains Malaysia, JEPeM Code: USM/JEPeM/17010059

Herewith is the revised study protocol as per the recommendations of the ethical committee board for your perusal. The modifications have been underlined and bolded as per instructions and the following is the list of modifications made:

- 1) Objectives: Rephrased general objective to “To determine” and specific objective to “To describe” on page 4 of this document.
- 2) Additional information regarding recurrence rates in pre-existing literature with citation on pages 2 and 6 of this document.
- 3) Modifications and correction of methodology particularly the sampling design, inclusion and exclusion criteria, statistical and data analysis plan on pages 7, 8 and 9 of this document.
- 4) Removal of “Name” section in Data collection form on page 13 of this document.

Your consideration to accept the ethics application for this study protocol is much appreciated.

Thank you for your time.

Regards,

Dr Khairun Nisa' Binti Mohamed

Department of Surgery

School of Medical Sciences

Health Campus,

Universiti Sains Malaysia

A review of the 2-year recurrence rates in laparoscopically resected colorectal malignancies in Hospital Universiti Sains Malaysia.

Semakan kadar kes berulang kanser kolorektal yang telah dibedah secara “laparoscopic” dalam jangkamasa 2 tahun di Hospital Universiti Sains Malaysia.

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Introduction

Colorectal cancer is any malignant growth that develops within any part of the large bowel (from caecum to the anorectal junction). It is one of the commonest cancers globally; and in Malaysia, it is the second commonest with an incidence rate of 21.3 per 100,000 populations.⁽¹⁾ Locally, majority of colorectal cancer cases are diagnosed at stage III or IV and they account for 63.5% of newly diagnosed cases.⁽²⁾

Surgical resection is considered the primary treatment modality in most cases and curative results can be achieved with appropriate adjuvant therapy. Keeping in mind the need for an oncologically-sound resection, the surgeon's goals would include complete excision of the primary tumour, its major vascular pedicle and lymphatic drainage basin of the affected colonic segment. Resection can be done either by the "contemporary" laparoscopic or the "conventional" open approach.

Post primary curative resection, colorectal cancer has a reported incidence of recurrence between 10-30% with the highest rate of recurrence for stage 3 disease.^(3,4,5,6) Majority of cases, about 80%, develop recurrence within the first 2 years post resection which emphasizes the need for more frequent follow-up during this period.^(6,7)

Based on the latest available Malaysian NCR data, 70.8% of colorectal cancer cases between 2008 and 2013 were treated by surgical resection whilst 88.4% of patients diagnosed with stage III colorectal cancer were treated surgically. Of these patients who underwent surgery, about 16% underwent laparoscopic colectomy.

It has become common knowledge that laparoscopic surgeries have produced better outcomes such as reduced post-operative pain, faster return of bowel function and subsequently, reduced hospital stays and faster return to work. This has made the laparoscopic approach more favorable compared to open.⁽⁸⁾

Here in Hospital Universiti Sains Malaysia (HUSM), one of the major teaching hospitals in Malaysia, laparoscopic surgeries have been in place since the mid-1990s but laparoscopic colectomy for colorectal carcinoma has been used as the choice technique only recently.

Being a technically-demanding procedure, the laparoscopic approach for resection of colorectal malignancies poses a steep learning curve for the novice surgical team.⁽⁹⁾

Consequently, in this process of gaining new skills, the short and long-term outcomes may be greatly influenced.

Currently, there is no existing data on our progress in terms of the oncologic outcome of the cases of laparoscopically resected colorectal cancers. Possibly, more information at hand may serve as an encouragement to choose the laparoscopic approach to resection of colorectal carcinomas. And, perhaps, it can help us to identify any short-comings in our perioperative management and post-operative follow-up.

Objectives

Primary objective

To determine the proportion cases of with recurrence within 2 years post-surgery amongst those who had undergone laparoscopic resection of colorectal carcinomas in HUSM.

Secondary objectives

To **describe** factors that may contribute to the risk of recurrence, specifically:

- Patient factors (age and gender, co-morbid diseases)
- Disease factors (pre- and post-operative staging, tumour site and serum Carcinoembryonic Antigen (CEA) levels)
- Histopathologic factors (TNM stage, histologic type and differentiation of the tumour, involvement of resection margin)
- Presence of neoadjuvant or adjuvant therapy
- Time lapse between surgery and commencement of neoadjuvant and/or adjuvant therapy

Research Questions

What is the 2-year recurrence rate of colorectal carcinoma in laparoscopically resected colorectal carcinoma done in HUSM?

What are the factors that may contribute towards recurrence (particularly in terms of patient demographics, intraoperative findings and histopathological findings, duration of which adjuvant therapy is given)?

Research Hypothesis

H₀: The recurrence rate of laparoscopically resected CRC done in HUSM is comparable to international standards.

H_A: The recurrence rate of laparoscopically resected CRC done in HUSM is not comparable international standards.

Literature review

As acknowledged earlier, surgical resection is considered the primary treatment modality in most cases and curative results can be achieved with appropriate adjuvant therapy. Keeping in mind the need for an oncologically-sound resection, the surgeon's goals would include complete excision of the primary tumour, its major vascular pedicle and lymphatic drainage basin of the affected colonic segment.⁽⁸⁾ Resection can be done either by the "contemporary" laparoscopic or the "conventional" open approach.

In the past decades, laparoscopic colectomy for resection of colorectal malignancies has been gaining its popularity though at a slow pace. There have been concerns regarding the oncologic outcomes of laparoscopically-resected colorectal malignancies as previously highlighted in a report of the forth port-site recurrence post laparoscopic colectomy by Cirrocco *et al.*⁽¹⁰⁾ The latter had even concluded that "abdominal wall cancer recurrence is enhanced by the laparoscopic approach to colorectal cancer" and shunned the method, suggesting that it only be performed in controlled, clinical studies.

Thus, the 'dark age' of laparoscopic colectomy for malignancy ensued until a number of large, prospective, randomized controlled studies such as the Barcelona, MRC-CLASSIC, COLOR and COST trials compared open to laparoscopic approach and addressed the major concern of oncologic safety.

The Barcelona trial involved 208 randomly selected patients who fit the inclusion criteria of a single tumour at least 15cm from the anal verge and studied their cancer-related survival over a 5-year period. They found that laparoscopic resection was superior in stage III colon cancer.⁽¹¹⁾

A 48-institution-strong multicentric randomized control study performed by the COST study group recruited a massive sample of 1735 patients with the primary study objective of "time to tumour recurrence". What they found was that the recurrent rates in laparoscopic-assisted colectomy and open colectomy were comparable and thus, an acceptable alternative to open surgery.⁽¹²⁾ Based on this data, it was also studied that laparoscopic colectomy was not inferior to open surgery.⁽¹³⁾

Consolidating all the above trials in a meta-analysis was a refreshing effort by Transatlantic Laparoscopically Assisted vs Open Colectomy Trials Study Group who aimed to "enhance"

the surgeon's power to choose between laparoscopic or open techniques. They concluded that laparoscopic colectomy was oncologically safe.⁽¹⁴⁾

Evidently, as noted by the COLOR study group in 2005, a higher volume of cases has been shown to have a positive impact on the short-term results of laparoscopic colectomy for colorectal carcinoma.⁽¹⁵⁾ A self-audit done by the Royal Brisbane Hospital in Australia showed that amongst the 181 patients who underwent laparoscopic resection for colorectal cancer in their hospital, the procedure produces acceptable intermediate to long-term oncologic outcomes and a low long-term complication rate in selected patients.⁽¹⁶⁾

Perhaps owing to the steep learning curve and advanced skills required, not many surgeons choose or are able to perform laparoscopic resection in Malaysia. This is reflected in Malaysian local census which found that only about 16% of colorectal carcinoma cases underwent laparoscopic resection. To date, there is no existing local data on the oncologic outcomes of laparoscopically resected colorectal cancers. Keeping in mind that majority of cases recur within the first 2 years of resection, it seems logical to look into the recurrence rates within this period when evaluating our progress at the early stage of our learning curve. Thus, this study aims to provide better knowledge of the oncologic outcome of laparoscopic colectomy in HUSM and describe the factors that may contribute to higher risk for recurrence.

Methodology

Study design

This is a retrospective observational study of the patients diagnosed with colorectal cancer who underwent laparoscopic colectomy in HUSM from January 2007 to January 2014.

Sampling

Reference population: Colorectal cancer patients in Kelantan

Source population: Colorectal cancer patients who underwent laparoscopic colectomy from January 2007 to January 2014 in HUSM.

Sampling frame: Patients listed in the Operation Theatre Census books as having undergone laparoscopic colectomy for colorectal cancer in HUSM from January 2007 to January 2014. Only the data from patients who meet the inclusion and exclusion criteria will be used for this study.

Inclusion Criteria

- 1 Traceable records
- 2 Underwent elective laparoscopic colectomy between 2007 to 2014 and had a post-operative follow-up period of at least 2 years.
- 3 Diagnosed with colorectal cancer

Exclusion Criteria

- 1 Missed follow-up
- 2 Presence of different concurrent pathology

Sampling method: No sampling method applied

Sample size determination

The sample size determination for this study was obtained using Power and Sample Size Calculation (PS) Software. The significant level was set at (α) 0.05 and the power study ($1 - \beta$) was 80%. The sample size estimation will be based on survival analysis. The ratio of control to cases (m) and medium survival time on control (m1) was obtained from experts. The accrual time (A) for this study will be seven years (84 months) and there will be about 24 months (F) additional follow up after the recruitment. The detectable hazard ratio of the control relative to experimental group (R) is determined by researcher and expert opinion. Additional 10% sample size (n) required for considering estimated 10% missing data or loss to follow up.

Summarize information for sample size calculation using Power and Sample Size (PS) software;

- (α) : Significant level = 0.05
- ($1 - \beta$) : Power = 0.8
- (R) : Hazard ratio (relative risk) of the control treatment relative to experimental treatment was determine by clinical expert = 3
- (m1) : Medium retention time on control treatment was obtained from literature = 33 months
- (m) : Ratio of control to experimental patients = 1
- (A) : The accrual time during which subject were recruited = 84 months
- (F) : Additional follow-up after end of recruitment = 24 months
- (n) : Sample size determination by PS Software (Considering estimated 10% for missing data/loss to follow up (additional 10% was added))

Based on result of sample size calculation from Power and Sample Size Calculation (PS) Software, the required sample size will be 60 subject after adding 10% possible missing data or loss to follow up.

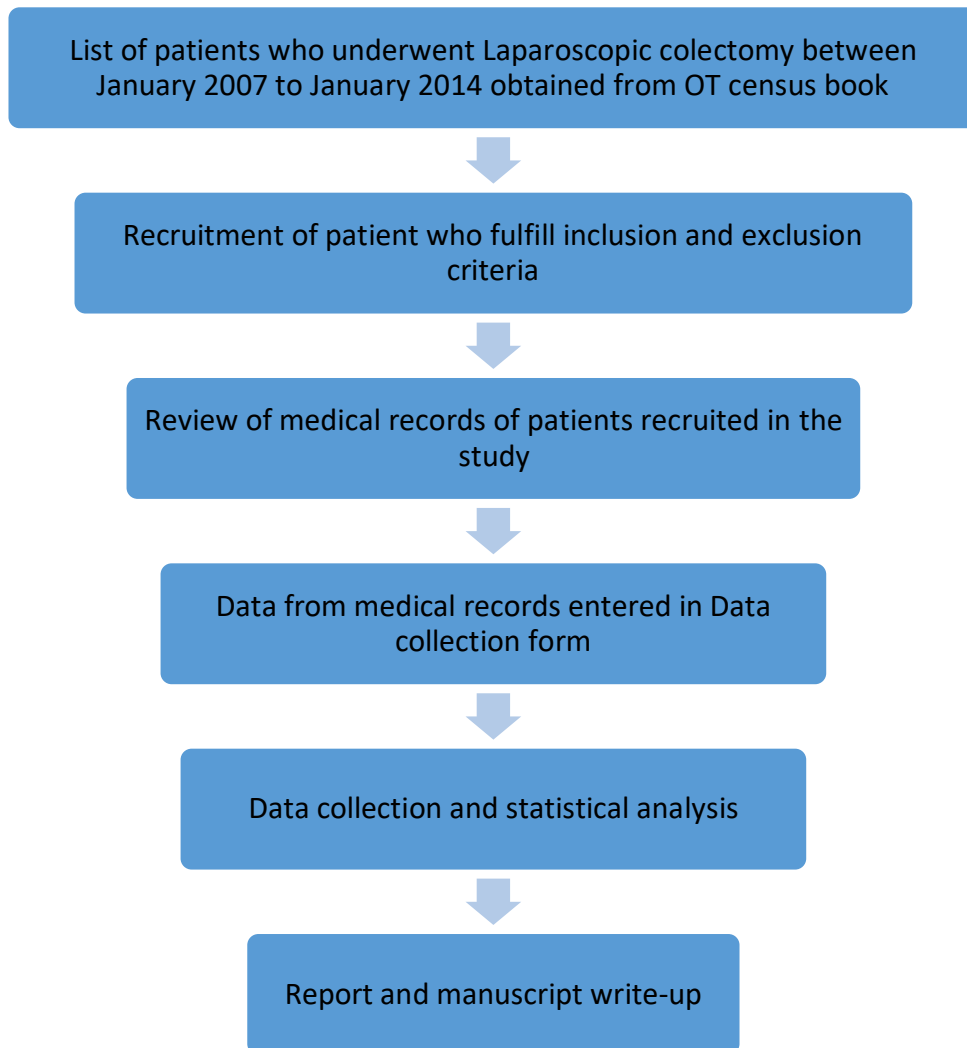
Data collection

Data collection will be recorded in a data collection form (Appendix 1). The following information will be recorded: patients' demographics, Serum CEA before surgery, pre and post-operative diagnosis and stage, histopathological report of resected specimen, time interval between surgery and commencement of adjuvant therapy and presence with evidence of recurrence.

Intended statistical analysis

Data collected will be keyed into SPSS version 23. Determination of recurrence rate, Kaplan-Meier analysis will be used and possible risk factors for recurrence will be analysed by cox regression analysis.

Study Flow Chart



Gantt Chart

Research Activity	2016				2017												
	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	
Dissertation topic discussion at department and Ethics approval	■	■	■	■	■												
Subjects recruitment and Data collection						■	■										
Data analysis and interpretation							■	■									
Presentation and submission of reports									■	■							
Report writing											■	■	■				
Submission of dissertation papers														■	■		

Data Collection Form

Patient's Demographics					
Age	At diagnosis		At Surgery		
Gender	Male		Female		
Race	Malay	Chinese	Indian	Others	
Co morbidities	Diabetes	Hypertension	Ischaemic heart disease	End-stage renal failure	
Disease-Related					
Pre-operative	Diagnosis		Stage		
Post-operative	Diagnosis		Stage		
Site of tumour			Presence of synchronous tumour		
Serum CEA	Pre-operative		Post-operative		
Histopathological Features					
TNM Stage	T	N	M	Final TNM stage:	
Histologic Type	Adenocarcinoma		Others	Not specified	
Tumour differentiation	Well	Moderate	Poor	Not specified	
Number of lymph nodes					
Lymphovascular invasion	Yes		No		
Perineural invasion	Yes		No		
Tumour margin	Proximal: involved/ not involved		Distal: Involved/ not involved		Circumferential (rectum/anorectum): involved/ not involved

Treatment given					
Neoadjuvant therapy given	Yes			No	
Type of surgery performed (laparoscopically)	Anterior resection	Right hemicolectomy	Left hemicolectomy	Abdominoperineal resection	Others (please specify):
Adjuvant therapy given	Yes: Chemotherapy/ Radiotherapy/ Both			No:	
Time interval between completion of neoadjuvant therapy and surgery					
Time interval between surgery and commencement of adjuvant therapy					
Follow-up details (during first 2 years only)					
Post-operative follow-up interval (in months)					
Disease recurrence	Yes			No	
	Site of recurrence:				
Post-operative mortality within 2 years	Yes			No	
	Disease-related morbidity:				
	Yes				
	No				
	Unknown				

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ii. Ethics Board Approval

5th June 2017

517-3072654
Dr. Khairun Nisa' Mohamed
Department of Surgery
School of Medical Sciences
Universiti Sains Malaysia
16150 Kubang Kerian, Kelantan.

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JEPeM Code : USM/JEPeM/17010059

Protocol Title : A Review of the 2 Year Recurrence Rates in Laparoscopically Resected Colorectal Malignancies in Hospital Universiti Sains Malaysia.

Dear Dr.,

We wish to inform you that your study protocol has been reviewed and is hereby granted approval for implementation by the Jawatankuasa Etika Penyelidikan Manusia Universiti Sains Malaysia (JEPeM-USM). Your study has been assigned study protocol code **USM/JEPeM/17010059**, which should be used for all communication to the JEPeM-USM related to this study. This ethical clearance is valid from 5th June 2017 until 4th June 2018.

Study Site: Hospital Universiti Sains Malaysia.

The following researchers also involve in this study:

1. Dr. Mohd Nizam Md Hashim
2. Assoc. Prof. Dr. Zaidi Zakaria

The following documents have been approved for use in the study.

1. Research Proposal

In addition to the abovementioned documents, the following technical document was included in the review on which this approval was based:

1. Data Collection Form

Attached document is the list of members of JEPeM-USM present during the full board meeting reviewing your protocol.

While the study is in progress, we request you to submit to us the following documents:

1. Application for renewal of ethical approval 60 days before the expiration date of this approval through submission of **JEPeM-USM FORM 3(B) 2015: Continuing Review Application Form**. Subsequently this need to be done yearly as long as the research goes on.
2. Any changes in the protocol, especially those that may adversely affect the safety of the participants during the conduct of the trial including changes in personnel, must be submitted or reported using **JEPeM-USM FORM 3(A) 2015: Study Protocol Amendment Submission Form**.
3. Revisions in the informed consent form using the **JEPeM-USM FORM 3(A) 2015: Study Protocol Amendment Submission Form**.
4. Reports of adverse events including from other study sites (national, international) using the **JEPeM-USM FORM 3(G) 2014: Adverse Events Report**.
5. Notice of early termination of the study and reasons for such using **JEPeM-USM FORM 3(E) 2015**.

6. Any event which may have ethical significance.
7. Any information which is needed by the JEPeM-USM to do ongoing review.
8. Notice of time of completion of the study using **JEPeM-USM FORM 3(C) 2014: Final Report Form.**

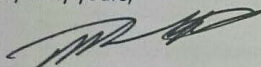
Please note that forms may be downloaded from the JEPeM-USM website: www.jepem.kk.usm.my

Jawatankuasa Etika Penyelidikan (Manusia), JEPeM-USM is in compliance with the Declaration of Helsinki, International Conference on Harmonization (ICH) Guidelines, Good Clinical Practice (GCP) Standards, Council for International Organizations of Medical Sciences (CIOMS) Guidelines, World Health Organization (WHO) Standards and Operational Guidance for Ethics Review of Health-Related Research and Surveying and Evaluating Ethical Review Practices, EC/IRB Standard Operating Procedures (SOPs), and Local Regulations and Standards in Ethical Review.

Thank you.

"ENSURING A SUSTAINABLE TOMORROW"

Very truly yours,



PROF. DR. HANS AMIN VAN ROSTENBERGHE

Chairperson

Jawatankuasa Etika Penyelidikan (Manusia) JEPeM
Universiti Sains Malaysia

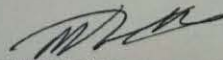
Date of meeting : 23rd March 2017
 Venue : Meeting Room, Division of Research & Innovation,
 USM Kampus Kesihatan.
 Time : 9.00 a.m – 3.00 p.m
 Meeting No : 356

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Members of Committee of the Jawatankuasa Etika Penyelidikan (Manusia), JEPeM Universiti Sains Malaysia who reviewed the protocol/documents are as follows:

Member (Title and Name)	Occupation (Designation)	Male/ Female (M/F)	Tick (✓) if present when above items, were reviewed
Chairperson : Professor Dr. Hans Amin Van Rostenberghe	Chairperson of Jawatankuasa Etika Penyelidikan (Manusia), JEPeM USM	M	✓ (Chairperson)
Secretary: Mr. Mohd Bazlan Hafidz Mukrim	Science Officer	M	✓
Members :			
1. Professor Dr. Lee Yeong Yeh	Lecturer, School of Medical Sciences	M	✓
2. Associate Professor Dr. Mohtar Ibrahim	Lecturer, School of Medical Sciences	M	✓
3. Professor Dr. Nik Hazlina Nik Hussain	Lecturer, School of Medical Sciences	F	✓
4. Associate Professor Dr. Nor Azwany Yaacob	Lecturer, School of Medical Sciences	F	✓
5. Mrs. Norleha Mohd Noor	Executive Secretary, School of Dental Sciences	F	✓
6. Associate Professor Oleksandr Krasilshchikov	Lecturer, School of Health Sciences	M	✓
7. Associate Professor Siti Hawa Ali	Lecturer, School of Health Sciences	F	✓
8. Mrs. Zawiah Abu Bakar	Community Representative	F	✓
9. Professor Dr. Zeehaida Mohamed	Lecturer, School of Medical Sciences	F	✓

Jawatankuasa Etika Penyelidikan (Manusia), JEPeM-USM is in compliance with the Declaration of Helsinki, International Conference on Harmonization (ICH) Guidelines, Good Clinical Practice (GCP) Standards, Council for International Organizations of Medical Sciences (CIOMS) Guidelines, World Health Organization (WHO) Standards and Operational Guidance for Ethics Review of Health-Related Research and Surveying and Evaluating Ethical Review Practices, EC/IRB Standard Operating Procedures (SOPs), and Local Regulations and Standards in Ethical Review.


PROFESSOR DR. HANS AMIN VAN ROSTENBERGHE
 Chairperson
 Jawatankuasa Etika Penyelidikan (Manusia), JEPeM
 Universiti Sains Malaysia