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A comparative study of short-term outcomes of Colorectal Cancer Surgery in the elderly population

--Manuscript Draft--

Full Title:	A comparative study of short-term outcomes of Colorectal Cancer Surgery in the elderly population
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Keywords:	colorectal cancer; postoperative complications; morbidity; mortality; elderly; surgery
Abstract:	Background: Colorectal Cancer (CRC) is a disease of the elderly, and with an ageing population, oncological surgical procedures for CRC in the elderly is expected to increase. However, the balance between surgical benefits and risks associated with age and comorbidities in elderly patients is obscure. Material and Methods: A retrospective database of consecutive patients who received CRC surgery was used to compare short-term surgical and oncological outcomes between patients aged ≥75 and <75 years old undergoing CRC resection. Results: There were 54 patients (63.5%) in the <75 group and 31 patients (36.5%) in the ≥75 group. Overall, there were no differences between the <75 and ≥75 groups in postoperative HDU/ITU stay, median hospital LOS or 30-day mortality rates. Patients ≥75 had a higher preoperative performance status (25.9% vs 71.0%, p<0.001), but no difference in ASA Grade and referral pattern, proportion of emergency operations, cancer staging, resection margins, achievement of curative resection or median lymph node yield. There was a significantly higher use of adjuvant chemotherapy in the <75 age group (48.1% vs 25.8%, p=0.043). Conclusion: With adequate patient selection, CRC resection in elderly patients is not associated with higher postoperative mortality or worse short-term oncological benefits.
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Re: Submission of Manuscript, "A comparative study of short-term outcomes of Colorectal Cancer Surgery in the elderly population"

19th December 2016

Clarence Yen

Flat E 60 Longridge Road

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Dear Editors of Acta Chirurgica Belgica,

I am a medical student currently in my final year of MBBS degree with Imperial College London, having graduated with a BSc in Surgery and Anaethesia. My research interest is mainly in colorectal surgery with Department of Surgery and Cancer, Chelsea and Westminster Hospital, Imperial College London NHS Trust, London, U.K. I am keen to submit my manuscript to ACTA for review.

The manuscript is titled: A comparative study of short-term outcomes of Colorectal Cancer Surgery in the elderly population. We performed a retrospective cohort study to compare the short-term surgical and oncological outcomes in patients aged ≥75 against <75 with colorectal. Our paper presents a single center experience of 54 patients <75 and 31 patient's ≥75.

Our main findings indicate that elderly patients (≥ 75) do not carry higher postoperative mortality or a worse short-term oncological benefit. This supports the use of more aggressive approaches to improve postoperative outcomes,

We hope you would consider a publication in ACTA and do not have a preference for any reviewers. Thank you for considering the manuscript for publication. Please do not hesitate to contact me at clarenceyenjj@gmail.com or 07563218622.

Sincerely,
Clarence Yen
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Final Year Medical Student, Imperial College London

A comparative study of short-term outcomes of Colorectal Cancer Surgery in the elderly population

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Abstract

Background: Colorectal Cancer (CRC) is a disease of the elderly, and with an ageing population, oncological surgical procedures for CRC in the elderly is expected to increase. However, the balance between surgical benefits and risks associated with age and comorbidities in elderly patients is obscure.

Material and Methods: A retrospective database of consecutive patients who received CRC surgery was used to compare short-term surgical and oncological outcomes between patients aged ≥75 and <75 years old undergoing CRC resection.

Results: There were 54 patients (63.5%) in the <75 group and 31 patients (36.5%) in the ≥75 group. Overall, there were no differences between the <75 and ≥75 groups in postoperative HDU/ITU stay, median hospital LOS or 30-day mortality rates. Patients ≥75 had a higher preoperative performance status (25.9% vs 71.0%, p<0.001), but no difference in ASA Grade and referral pattern, proportion of emergency operations, cancer staging, resection margins, achievement of curative resection or median lymph node yield. There was a significantly higher use of adjuvant chemotherapy in the <75 age group (48.1% vs 25.8%, p=0.043).

Conclusion: With adequate patient selection, CRC resection in elderly patients is not associated with higher postoperative mortality or worse short-term oncological benefits.

Introduction

Colorectal Cancer (CRC) represents the third and second most common diagnosed cancer in males and in females, respectively, which amounts to almost 10% of new cancer diagnosis throughout the world (1,2). The rates and outcomes of CRC have been improving and is largely attributed to the introduction of screening programs leading to earlier detection and, therefore, more patients amenable to surgical intervention (3). Furthermore, CRC is predominately a disease of the elderly and with an ageing population with peak incidence in the 7th and 8th decade. Hence, it is natural to expect an increase of oncological colorectal surgeries within the elderly population (4,5).

One of the medical conundrums of the management of CRC is the clinical justification and tolerability of surgery in an elderly population. Elderly patients tend to carry lower health performance status and more severe and significant comorbidity, complicating not only the surgical outcomes, but the benefits of surgical management (6–9). In the past, this has resulted in older patients less likely to receive surgery for CRC (10,11). However, with an improvement in anaesthetic and surgical techniques, the authors postulate that with proper patient selection, surgery in the elderly would not be associated with worse short term surgical and oncological outcomes.

The aim of this retrospective study was to compare the clinical profile, short-term surgical and oncological outcomes of patients aged 75 years and above versus those that are younger than 75 years old undergoing CRC resection.

Methods

A retrospective study was conducted on 85 consecutive patients who received surgery for CRC at our center from October 2014 till July 2016. A database capturing the age of the patient at surgery, pattern of surgical referral, pre-operative Eastern Cooperative Oncology Group performance status (PS) and American Society of Anaesthesiologist (ASA) grade was built. PS status was dichotomized to 0 versus 1-2, and ASA grade to 0-2 versus 3-4 during analysis.

Mode of surgery was classified as laparoscopic/laparoscopic-assisted versus open surgery and a comparison of negative resection margins versus positive resection margins was made. Curative resection was defined as when there was no radiological evidence of metastasis with complete pathological tumour excision. The number of lymph node (LN) dissected was compared as a continuous variable and as a proportion of those who achieved at least 12 LNs (12).

The use of neoadjuvant and adjuvant therapies was recorded and stage of CRC was reconstructed using operative histological and radiological information. Total follow up duration was calculated from the date of surgery to either the date of death or date of last active follow up in clinic. For patients who passed away during the hospital stay, the date of death was taken as their date of discharge.

Statistical Analysis

Continuous data were analysed using descriptive statistical methods and presented as median and interquartile range (IQR). Test for normality using Shapiro-Wilk test before Mann-Whitney U-test and independent T-test were used for comparisons between non-parametric and parametric data respectively. Pearson chi-square test was used for analysis of proportions. All statistical analysis was performed using SPSS version 21.0 (IBM Inc., Chicago, IL, USA) and conducted at 95% confidence intervals, $p<0.05$. The study was performed in accordance to Good Clinical Practice standards and ethical guidelines published in the Declaration of Helsinki.

Results

Clinical characteristics (Table 1)

Eighty-five patients were included in the analysis, consisting of 54 patients (63.5%) in the <75 group and 31 patients (36.5%) in the ≥75 group. Overall, the study population had a median age of 69 years (58-79). The median age of the <75 group was 61 (53-68) and 81 (79-84) for the ≥75 group ($p<0.001$). The median follow-up duration was 225 (111 – 426) and 314 (126 – 404) days for age <75 and ≥75 respectively ($p=0.541$).

There were no significant difference in gender ($p=0.758$) and ASA grade ($p=0.062$) between the two groups. However, patients belonging to the ≥75 group were found to have a significantly higher PS with 22 patients (71.0%) scoring 1-2, whereas in the <75 group only 14 patients (25.9%) fell under the same category ($p<0.001$). There was no significant difference in the referral

patterns (i.e. whether the patients were referred from the emergency department, primary care, or inter-hospital referrals) between the two groups (p=0.578).

Surgical Intervention and oncological outcomes (Tables 2 and 3)

Although more patients in the <75 group (n=17, 31.5%) received emergency surgery compared to the ≥75 group (n=4, 12.9%), this was statistically insignificant (p=0.056). All acute presentations were due to symptomatic bowel obstructions, except for 6 (23.5%) patients in the <75 group who presented with bowel perforation. There was no significant difference in the surgical approach (laparoscopic or open, p=0.983), resection margins (p=0.404), or proportion of curative resections (p=0.615) between the <75 group and the ≥75 group.

Median LN yield was similar in both groups (p=0.735), with similar proportion of patients from the <75 group (n=51, 94.4%) and the ≥75 group (n=29, 93.5%) achieving at least 12 LN sampled. There was no significant difference between the two groups in T stage (p=0.958), N stage (p=0.685), and M stage (p=0.385). In addition, there was no significant difference between the two groups in Duke's staging (p=0.715). While there was no significant difference between the two groups in the usage of neoadjuvant therapy (p=0.599), the <75 group had a higher proportion of patients (n=26, 48.1%) who went on to received further adjuvant therapy compared to the ≥75 group (n=8, 25.8%), p=0.043.

Mortality and Hospital stay (Table 4)

More patients in the ≥75 group required admission postoperatively to HDU/ITU (n=28, 90.3%) compared to the <75 group (n=40, 74.1%), although this was not statistically significant (p=0.071). Of those who needed postoperative admission to HDU/ITU, there was no significant difference in median duration of stay (p=0.951). The median LOS was longer the <75 group (13.0 days, IQR 7.0-19.3), compared to the <75 group (8.5 days, IQR 6.0-21.5), but this was statistically insignificant (p=0.392).

There was no significant difference in 30-day mortality between the two groups (p=0.269), with 1 death (1.9%) in the <75 group and 2 deaths (6.5%) in the ≥75 group. Similarly, there was no significant difference in 90-day mortality between the two groups (p=0.565), with 2 death (3.7%) in the <75 group and 2 deaths (6.5%) in the ≥75 group.

Discussion

With increased understanding, patient selection and improvements in the delivery of surgical and anesthetic care, postoperative outcomes and mortality will inevitably improve for elderly patients undergoing surgery for CRC.

This study has identified a slight difference of short-term postoperative outcomes between the two groups of patients, with 90.3% of ≥75 group and 74.1% of <75 group needing postoperative HDU/ITU stay and a longer median total hospital LOS in the ≥75group (13.0 days versus 8.5 days). While the numerical difference is large, both data is insignificant at p=0.071 and p=0.392

respectively. This finding contradicts previous literature, whereby age has inevitably been identified as a risk factor for longer LOS and in needing higher postoperative care (13–15). However, caution must be exercised in the analysis of this data as the small study sample size could be limiting the analysis. Other short-term postoperative outcomes measures also similar, for those who needed admission to HDU/ITU, the median LOS in HDU/ITU were similar, p=0.951. Similarly, there were no differences in both the 30-day and 90-day postoperative mortality, p=0.269 and p=0.565 respectively, which was not observed before in previous literature (14,16–18).

One of the other reasons that may explain this finding might be the similar ASA grade and referral patterns between the two cohorts of patients observed in this study. In fact, a higher but insignificant proportion of patients in the <75 group received emergency operation from symptoms of bowel obstruction or perforation (31.5% versus 12.9%, p=0.056). This finding is inconsistent with established consensus that the elderly population tends to present with symptoms requiring emergency surgical intervention (16,19). However, this may be a reflection of local demographics as seen in another UK-based and Swedish based study (17,20). On the flipside, one may argue that the indifferent postoperative outcomes between the two cohorts may be due to the unusually high proportion of younger patients in our population presenting with emergency surgery. Emergency surgery has been shown to be associated with an increase morbidity and mortality and may serve as a possible confounder to this study's results (20,21). Furthermore, because many surgeons hold this view, there might be an inherent selection bias in the elderly population of this study

as surgeons may refrain from operating on elderly patients with bowel obstruction/perforation.

Another important aspect of surgery for CRC is the successful oncological outcomes. This study showed no differences in short-term oncological outcomes as measured by LN yield, achievement of resection margin and curative resections. Previous authors found no difference in complete resection margins between patients aged 80 and above versus those below 80, 77.4% versus 77.9% respectively (9,22). Likewise, this study observed similar, albeit higher, rates at 92.6% in <75 age group and 87.1% in the ≥75 age group, p=4.04. However, unlike kotake et al, no difference was found in LN yield between the two groups of patients (22).

Performance status is another important consideration in assessing the suitability of various cancer treatment and are often higher in the elderly population (23). This study found that 71.0% of ≥75 group patients had a PS score of 1-2 while only 25.9% of <75 group patients in that category, p<0.001. While this did not translate into a clinically significant longer hospital stay or HDU/ITU burden, it may be imbibed in the decision making in the risk-benefit analysis of adjuvant therapy. Hence, lower PS score, and the virtue of being more elderly, may partly explain the lower use of adjuvant therapies in ≥75 group patients, which may affect longer term oncological outcomes (8,22,24,25). Overall, there were no difference of tumour staging in the elderly cohort, a finding which seems to be equivocal in current literature (15–18,22,25)

Cost effectiveness of CRC surgery in the elderly patients has been a rising topic for discussion. Govaert et al recently showed that hospital cost of CRC surgery is actually lower in patients aged ≥85, with the major driver of lower cost related to ward and ICU cost (26). The authors postulated that another explanation for the lower hospital cost might be a less aggressive approach in managing complications for CRC surgery in the elderly as seen in previous studies (27). This study found that the patients with ≥75 group do not present with more advanced cancer and carry similar short-term surgical oncological outcomes. Therefore the results of the study support the view that surgery is worthwhile in the elderly population (25). This is further supported by evidence that long-term cancer-related survival is similar for both groups if elderly colorectal patients survive their first year (25,28). With these results in mind, age should not be a contraindication in CRC surgery; but instead, clinicians should acknowledge that elderly patients, with their co-morbidities, are a higher risk group who might require ITU/HDU admission postoperatively. It is arguable that, although HDU/ITU cost are higher, providing them with more aggressive treatment might translate to an overall shorter hospital stay and better longer-term oncological outcomes. Therefore, the way forward might be to maximize preoperative fitness by providing a more holistic surgical care by the involvement of a multidisciplinary team - anaesthetists, intensivist, surgeon and geriatrician (24,26). This should be used in conjunction with less invasive laparoscopic techniques and the enhanced recovery programme after surgery postoperative pathway to decrease post-operative complications and hospital LOS (24,29–31).

The limitation of this study was made apprised of, and as mentioned, the small sample size being a major limitation. One of the inconsistencies of cancer research performed in the elderly population lies in the definition of "elderly". Past research has used arbitrary definitions varying from age 70 to 80 (13–16,18,27), and this study has adopted an arbitrary cut-off of 75 years old. While having patients from a single tertiary center can standardise patient selection, it however provides only a very small cohort of patients and therefore limit generalisation of results. Furthermore, this study did not take into account specific co-morbidities but adopted a more global approach in measuring ASA and PS as surrogate markers.

With adequate patient selection, we can conclude that surgical resection of CRC in elderly patients (≥ 75) is not associated with higher postoperative mortality or worse short-term oncological benefits. Surgical benefit on longer-term oncological outcomes of in patients aged ≥75 requires further evaluation, but a more aggressive approach to improve postoperative outcomes might be necessary and beneficial.

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Table

Patient Characteristic		Age <75 N=54	Age ≥75 N= 31	P-value
Age of Operation				
	Mean (S.D)	58.8 (±12.1)	82.1 (±6.1)	**0.000**
Follow up Duration				
	Median (IQR) Days	225 (111 – 426)	314 (126 – 404)	0.541
Gender				
	Male	26 (48.1%)	16 (51.6%)	0.758
	Female	28 (51.9%)	15 (48.4%)	
ASA Grade#				
	0-2	34 (68.0%)	13 (46.4%)	0.062
	3-4	16 (32.0%)	15 (53.6%)	
Performance Status				
	0	40 (74.1%)	9 (29.0%)	**0.000**
	1-2	14 (25.9%)	22 (71.0%)	
Referral Pattern				
	Emergency Departme nt	20 (37.0%)	12 (38.7%)	0.578
	Primary Care	29 (52.7%)	18 (58.1%)	
	Inter-hospital Referrals	5 (9.3%)	1 (3.2%)	

Table 1: Clinical characteristics of patients included.
#Data unavailable for 5 Group 1 and 2 group 2 patients

Patient Characteristic		Age <75 N=54	Age ≥75 N= 31	P-value
Operation Urgency				
	Elective	37 (68.5%)	27 (87.1%)	0.056
	Emergency	17 (31.5%)	4 (12.9%)	
Operation Approach				
	Laparoscopic	26 (48.1%)	15 (48.4%)	0.983
	Open	28 (51.9%)	16 (51.6%)	
Resection Margin				
	Negative (R0)	50 (92.6%)	27 (87.1%)	0.404
	Micro/Macro (R1/2)	4 (7.4%)	4 (12.9%)	
Curative Resection		41 (75.9%)	25 (80.6%)	0.615
Lymph Node Yield				
	Median (IQR)	23.5 (21.0 – 33.5)	25.0 (18.8 – 35)	0.735
	<12	3 (5.6%)	2 (6.5%)	0.866
	≥12	51 (94.4%)	29 (93.5%)	

Table 2: Information on operative intervention and pathological outcomes.

Patient Characteristic		Age <75 N=54	Age ≥75 N= 31	P-value
Tumour (T)				
	1	2 (3.7%)	1 (3.2%)	0.958
	2	6 (11.1%)	4 (12.9%)	
	3	22 (40.7%)	14 (45.2%)	
	4	24 (44.4%)	12 (38.7%)	
Nodes (N)				
	0	23 (42.6%)	15 (48.4%)	0.685
	1	16 (29.6%)	10 (32.3%)	
	2	15 (27.8%)	6 (19.4%)	
Metastasis (M)				
	Absence	43 (79.6%)	27 (87.1%)	0.385
	Present	11 (20.4%)	4 (12.9%)	
Duke's Staging				
	A	6 (11.1%)	4 (12.9%)	0.715
	B	14 (25.9%)	11 (35.5%)	
	C	23 (42.6%)	12 (38.7%)	
	D	11 (20.4%)	4 (12.9%)	
Use of Neo-adjuvant therapies		5 (9.3%)	4 (12.9%)	0.599
Use of Adjuvant therapies		26 (48.1%)	8 (25.8%)	**0.043**

Table 3: Tumour staging and use of adjuvant and neoadjuvant therapies.

Patient Characteristic	Age <75 N=54	Age ≥75 N= 31	P-value
HDU/ITU Stay	40 (74.1%)	28 (90.3%)	0.071
Length of HDU/ITU Stay [#] (Median and IQR)	1.0 (1.0-3.0)	1.0 (1.0-3.0)	0.951
Total Duration of Hospital Stay	8.5 (6.0-21.5)	13.0 (7.0-19.3)	0.392
30-Day Mortality	1 (1.9%)	2 (6.5%)	0.269
90- Day Mortality	2 (3.7%)	2 (6.5%)	0.565

Table 4: Mortality, postoperative stay in ITU/HDU, and total postoperative hospital stay.