

Original Article

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Post-operative recovery is not a limiting factor for adjuvant chemotherapy in patients undergoing surgery for colorectal cancer

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ABSTRACT

INTRODUCTION: Little is known about factors affecting the initiation of adjuvant chemotherapy (AC) after minimally invasive surgery. The aim of this study was to describe the ratio of patients undergoing uncomplicated colorectal cancer surgery in a standardised enhanced recovery after surgery setting receiving AC. Furthermore, the association between post-operative quality of recovery and initiation of AC was investigated.

METHODS: This was a prospective study. Post-operative recovery was measured with the Quality of Recovery-15 questionnaire preoperatively, post-operatively on day 1, at discharge and on post-operative day 30.

RESULTS: A total of 115 patients were included between October 2016 and May 2017. Among these, 20 patients were excluded. Hence, 95 patients were followed up as uncomplicated cases. The median length of stay was three days (interquartile range: 2-4). A total of 40 patients were referred for oncological evaluation, but nine patients did not proceed to receive AC. Among the 31 patients starting AC, 48% (n = 15) received AC < 4 weeks and 52% (n = 16) > 4 weeks. No significant difference was seen in post-operative quality of recovery, either when investigating the full cohort or subgroups of patients who initiated AC before and after four weeks.

CONCLUSIONS: Post-operative recovery may not be the factor limiting patients from receiving adjuvant chemotherapy either before or after post-operative week four.

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TRIAL REGISTRATION: The study was approved by the Data Protection Agency (reg. no. REG&;044&;2018).

Approximately 40% of colorectal cancer patients will be offered adjuvant chemotherapy (AC) after surgery for colorectal cancer to improve disease-free and overall survival [1, 2]. In this context, pre- and post-operative morbidity, recovery and risk of post-operative complication are essential for the patient to initiate AC early [3-5]. In patients undergoing laparoscopic liver resection in an enhanced recovery after surgery (ERAS) programme, an increased proportion of patients may receive AC owing to earlier post-operative recovery and shorter length of hospital stay [6].

Little is known about the proportion of patients undergoing uncomplicated ERAS colorectal cancer surgery who

actually receive early AC or about factors affecting initiation of chemotherapy. Additionally, the association between quality of recovery and initiation of AC has not been investigated previously [7].

We aimed to describe the ratio of patients receiving AC and undergoing uncomplicated colorectal cancer surgery in a standardised ERAS regime. Furthermore, the association between post-operative quality of recovery and initiation of AC was investigated.

METHODS

All patients undergoing elective colorectal cancer surgery at the Department of Surgery, Zealand University Hospital, Denmark, were included in a prospective study investigating outcomes in an ERAS setting, as described previously [8]. Patients receiving neoadjuvant therapy, patients with carcinomatosis and patients undergoing abdominoperineal resections or total colectomies were excluded. Only patients undergoing elective resections were planned to be included in the study.

This was a standardised ERAS protocol including standardised information by surgeon, anaesthesiologist, physiotherapist, dietitian, and nurse in the patient school, no bowel preparation, and oral carbohydrate two hours before surgery. Surgery was performed laparoscopically or robot-assisted with a standardised four-port technique with specimen extraction site in the right-sided cancers through a transverse incision in the upper abdomen or the left-sided/rectal resection through a Pfannenstiel incision. Anaesthesia was given as total intravenous anaesthesia or inhalational anaesthesia on the preference of the anaesthesiologist. No epidural was used, only port-site infiltration with local anaesthesia. Post-operative analgesia consisted of oral 1,000 mg of paracetamol four times daily and tramadol 50 mg or 5 mg morphine as rescue analgesia. Patients received oral nutrition 2-4 hours after surgery and were mobilised the same afternoon or evening. Bladder catheters were planned to be removed within 24 hours post-operatively in both colonic and rectal cancer patients [9, 10]. Standardised discharge criteria were used after daily evaluation of the patient's bowel function, pain control and adequate mobilisation and no evidence of post-operative complications [11, 12].

The Quality of Recovery 15 (QoR-15) questionnaire was used. The QoR-15 is validated to measure quality of recovery after surgery and anaesthesia. Scores were divided into four subgroups; poor (0-89), moderate (90-121), good (122-135) and excellent recovery (136-150) [13]. All patients received a QoR-15 questionnaire before surgery, the day after surgery, on the day of discharge and 30 days after surgery [7, 13, 14]. After the Department of Pathology had analysed the specimen, the patient had an outpatient visit on day 10-14 at the Department of Surgery, receiving the results for further admittance to oncological evaluation.

The time from surgery to pathology was defined as the number of days from the specimen was received at the Department of Pathology (always the day of surgery) until the written pathology report was made. Time from pathology to outpatient consultation at the Department of Surgery was calculated from the day that the pathology report was made to the patient was seen in the outpatient department. The time from pathology report to referral to the Department of Oncology was registered as was the time from initial evaluation at the Department of Oncology to start of oncological treatment.

All patients with a Union for International Cancer Control (UICC) high-risk stage II or UICC stage III or non-microradical resections were defined as having an indication for AC [15, 16]. For UICC stage II patients, the following parameters were considered high-risk factors: pT4 tumour, signet-ring cell carcinoma, anastomotic leakage or other acute intervention for ileus or perforation (self-expandable metal stents SEMS, diverting stoma or resection), < 12 lymph nodes harvested. The reason why AC was not received when indicated was registered. Finally, it was examined how many patients actually finished the planned AC.

Return to intended oncological treatment (RIOT) was defined as time from surgery to the first dose of AC was administered. Delay of initiation of AC was defined as initiation beyond four weeks post-operatively.

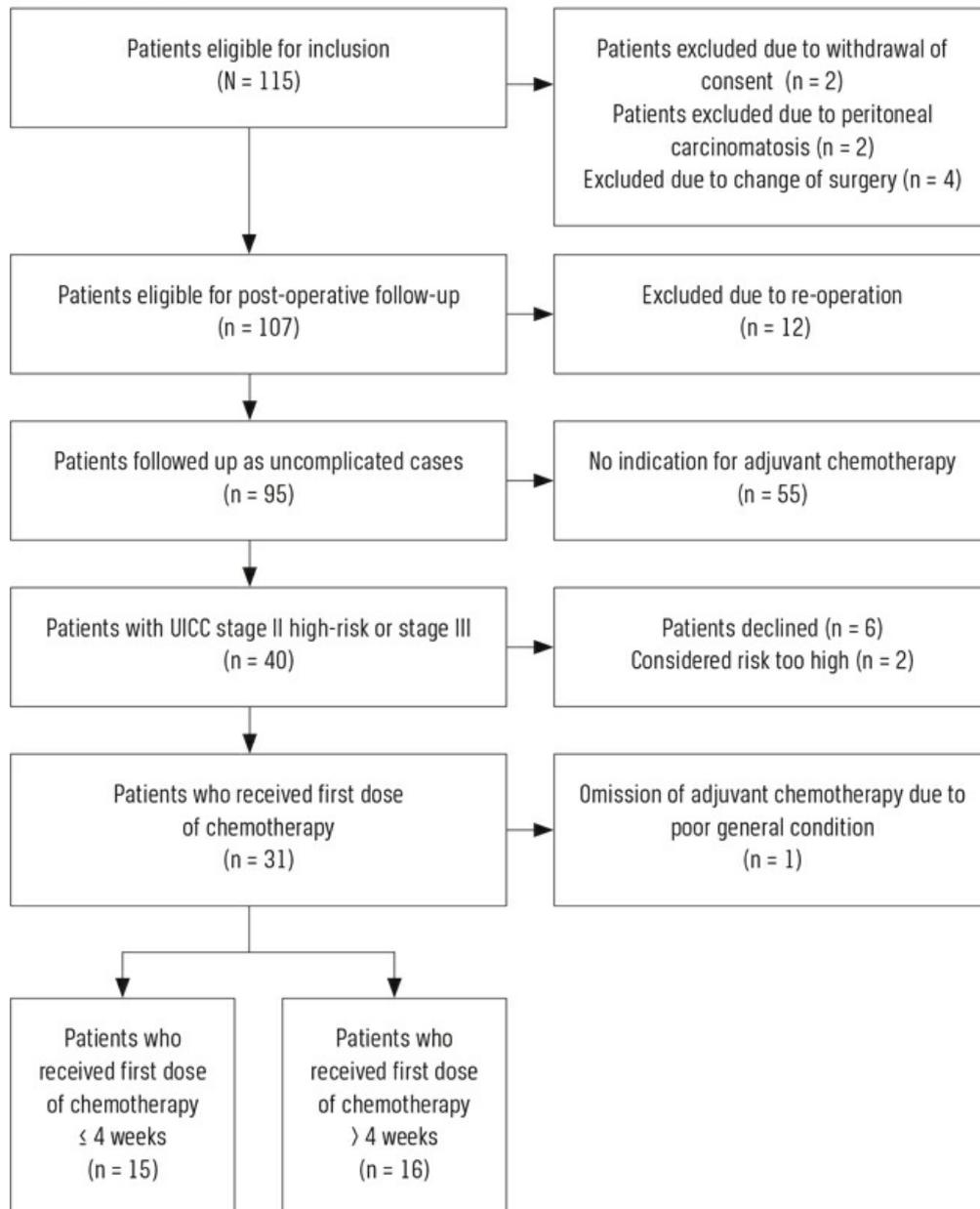
Statistical analysis was performed using R statistical software, R Foundation for Statistical Computing, Vienna, Austria. The Mann-Whitney U test or the Kruskal-Wallis test was used for continuous variables when appropriate. Categorical variables were tested using Fisher's exact test. A two-sided p-value < 0.05 was considered significant. No ethical approval was needed as all patients went through a standardised treatment regimen and follow-up at the Department of Surgery with the study-related data collection being a part of the standard treatment.

Trial registration: The study was approved by the Data Protection Agency (reg. no. REG&044&2018).

RESULTS

A total of 115 patients were included between October 2016 and May 2017. Among these, two were excluded due to withdrawal of consent, two due to peritoneal carcinomatosis and four due to change of the surgical procedure (three patients had an abdominal perineal resection and one patient had a subtotal colectomy). Hence, a total of 107 patients were eligible for post-operative follow-up. Among these, 12 patients (11%) were excluded due to re-operation during their hospital stay (eight due to anastomotic leakage, two due to post-operative bleeding, one due to suspicion of mechanical bowel obstruction, and one due to wound dehiscence). Consequently, 95 patients were followed up as uncomplicated cases, as summarised in the patient flow chart in **Figure 1**.

Patient demographic data and perioperative data are shown in **Table 1**. In total, 40 patients (42%) had UICC stage II with high-risk features or UICC stage III disease. All patients underwent minimally invasive surgery with a 4% (n = 4) conversion rate, and 19% (n = 18) of the patients had a stoma. The median length of stay was three days (interquartile range (IQR): 2-4 days). Among the 40 patients referred to oncological consultation, nine patients did not initiate adjuvant chemotherapy, of whom six declined to proceed to combination AC and two patients were deemed unsuitable to receive AC due to various reasons. Lastly, one patient who was referred to oncological consultation did not initiate AC due to a poor general condition as evaluated by the oncologist.

FIGURE 1 / Summary of inclusion.

UICC = Union for International Cancer Control.

TABLE 1 / Demographics of patients.

	Full cohort (N = 95)	Patients who received adjuvant chemotherapy		p-value
		after 4 wks (n = 16)	before 4 wks (n = 15)	
Male gender, n (%)	53 (55.79)	11 (68.8)	9 (60)	0.72 ^a
Age, median (IQR)	70 (65-74)	69.5 (62.25-77.00)	70 (62.50-73.00)	0.692 ^b
BMI, median (IQR)	-	25.1 (22.7-28.2)	27.2 (23.2-28.7)	0.649 ^b
<i>Smoker, n (%)</i>				
Never	-	9 (56.2)	5 (33.3)	0.285 ^a
Former	-	6 (37.5)	6 (40)	1 ^a
Current	-	1 (6.2)	4 (26.7)	0.172 ^a
<i>Alcohol consumption, n (%)</i>				
< 14 U/wk	-	3 (18.8)	2 (13.3)	1 ^a
> 21 U/wk	-	0	6 (40)	0.007 ^a
<i>ASA scale, n (%)</i>				1 ^a
1	32 (34)	-	-	
2	49 (51)	-	-	-
3	14 (15)	-	-	-
<i>WHO performance score, n (%)</i>				0.484 ^a
0	86 (91)	-	-	-
1	8 (8)	-	-	-
2	1 (1)	-	-	-
Adjuvant chemotherapy indication, n (%)	40 (42)	-	-	-
<i>Tumour localisation, n (%)</i>				0.865 ^a
Rectum	21 (23)	-	-	-
Colon	74 (77)	-	-	-
<i>Type of operation, n (%)</i>				0.867 ^a
<i>Technique, n (%)</i>				
Laparoscopic	71 (74)	-	-	-
Robotic-assisted	24 (26)	-	-	-
Open	0	0	0	-
Converted	4 (4)	1 (6.2)	0	1 ^a
Anastomosis, n (%)	86 (91)	12 (75.0)	14 (93.3)	0.333 ^a
Stoma, n (%)	18 (19)	5 (31.2)	3 (20)	0.685 ^a
LOS, days, median (IQR)	3 (2-4)	3.5 (2.00-5.00)	3.00 (2.00-4.00)	0.394 ^b
<i>Quality of recovery score, median (IQR)^c</i>				
Preoperative	-	138 (135.75-143.00)	140 (135.00-145.00)	0.62 ^b
At post-operative day 1	-	115 (100.00-124.25)	106.5 (85.00-123.25)	0.49 ^b
At discharge	-	130 (117.25-139.25)	118.0 (115.0-137.0)	0.356 ^b
At post-operative day 30	-	144 (137.5-148.5)	137 (129.50-145.0)	0.059 ^b

ASA = American Society of Anesthesiologists physical status; LOS = length of stay; IQR = interquartile range.

a) exact test, b) Kruskal-Wallis Rank sum, c) Scale 0-150 (poor-excellent).

Parameters regarding the course of the patient treatment can be seen in **Table 2**. A total of 15 patients (48%) received the first dose of chemotherapy within post-operative week four. At five weeks, 26 of the patients had their first AC treatment, and the remaining patients (n = 5) had their AC within seven weeks (Table 2). In all, 21 (68%) patients completed their AC as planned; among these, 13 (42%) received treatment within four weeks. We found seven days (IQR: 4-8 days) of waiting from referral to the Department of Oncology to first consultation was found. Delay from first consultation to first dose of chemotherapy was four days (IQR: 2.5-6 days).

TABLE 2 / Surgery and initiation of adjuvant chemotherapy.

	From surgery to first dose of adjuvant chemotherapy		Patients, n (% (accumulated)) (N = 31)
	time between phases, days, median (IQR)	post-operative time until initiation of chemotherapy, days	
<i>Phase interval until day 1 of chemotherapy</i>			
From surgery to pTMN	14 (13-14)	14	-
From pTMN to oncological visitation	2 (1-3)	16	-
From visitation to 1st appointment in Department of Oncology	7 (4-8)	23	-
From 1st appointment to day 1 of chemotherapy	4 (2.5-6)	27	-
<i>Chemotherapy initiation</i>			
< 3 wks	-	-	2 (6.5 (7))
< 4 wks	-	-	13 (41.9 (49))
< 5 wks	-	-	11 (35.5 (84))
< 6 wks	-	-	4 (12.9 (97))
≥ 6 wks	-	-	1 (3.2 (100))

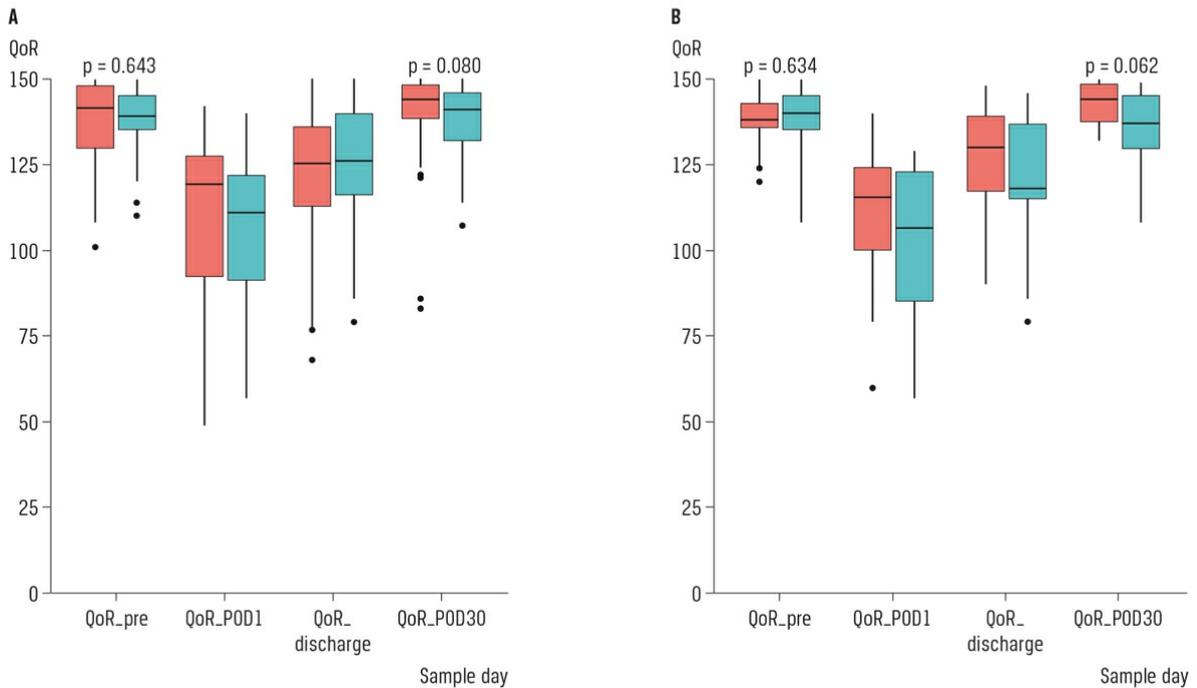
IQR = interquartile range; pTMN = pathological tumour site, lymph node involvement and metastatic spread.

Table 1 shows an analysis of demographics of the patients who received AC before and after four weeks, showing no significant differences between the subgroups.

When investigating the difference between the preoperative values of QoR of all patients with no indication for adjuvant chemotherapy and patients with UICC high-risk stage II and stage III disease; there was no significant difference between the two groups, $p = 0.643$; 95% confidence interval (CI): -3.00-5.00. Likewise, no significant difference was observed in the QoR score at post-operative day 30 between the two groups, $p = 0.08$; 95% CI: -0.0000148-6.99. Results are shown in **Figure 2A**.

FIGURE 2 / Development of post-operative quality of recovery (QoR) scores measured by the Quality of Recovery-15 questionnaire. The values are medians (interquartile range).

- A.** ■ patients with no indication for adjuvant chemotherapy.
 ■ patients with Union for International Cancer Control stage II high-risk or stage III disease.
- B.** ■ patients who received first dose of adjuvant chemotherapy after four weeks.
 ■ patients who received first dose of adjuvant chemotherapy before four weeks.



QoR_discharge = QoR at discharge; QoR_POD1 = QoR at post-operatively day 1; QoR_POD30 = QoR on post-operatively day 30; QoR_pre = preoperative QoR.

A subgroup analysis was made on patients who received the first dose of AC < 4 weeks compared with patients receiving treatment > 4 weeks. No significant difference was demonstrated preoperatively in QoR between patients who received treatment < 4 weeks and > 4 weeks, $p = 0.634$; 95% CI: -7.99-3.00. In addition, when investigating QoR on post-operative day 30, no statistical difference was observed between the two groups, $p = 0.062$; 95% CI -0.00004.616-13.99. Results are shown in Figure 2B.

DISCUSSION

This study demonstrated that AC is received by 80% of patients undergoing laparoscopic resection for colorectal cancer in an ERAS programme with either UICC stage II high-risk cancer or stage III disease. Among these patients, half initiated AC after post-operative week four. No significant difference was seen in quality of recovery when investigating either the full cohort or subgroups of patients who initiated treatment before and after four weeks. To our knowledge, no other studies have investigated post-operative recovery following colorectal cancer surgery in an ERAS setting and its possible association with initiation of AC.

Though consensus on the timing and timeframe of AC is not complete, it should be initiated as soon as the patient is fully recovered [17-20]. A systematic review and meta-analysis [17] investigated the association between time to adjuvant chemotherapy and survival in UICC stage II - III colorectal cancer patients. The study showed that increased time to initiation of AC was negatively associated with overall survival and disease-free survival. More specifically, every four-week delay triggered a 14% decrease in overall survival [17].

However, aiming to initiate adjuvant chemotherapy within four weeks post-operatively, 53% of the patients in our study received the first dose of adjuvant chemotherapy after four weeks post-operatively, which may negatively impact long-term survival outcomes. Even so, the clinical impact of this delay is questionable as a Danish population-based study investigating delay to chemotherapy in UICC stage III cancer patients [18] showed that only a delay exceeding eight weeks after surgery was associated with a survival reduction.

Post-operative recovery measured with the QoR-15 questionnaire on POD30 among patients with an indication for adjuvant chemotherapy scored a median value of 141 out of 150 maximum points compared with a median value of 144 for patients with no indication for AC. As defined previously, 141 points equals excellent recovery [13]. No significant difference was observed between patients who received the first dose of AC within four weeks post-operatively and patients who initiated treatment after four weeks. Hence, post-operative recovery measured with QoR-15 did not seem to be a limiting factor when considering initiation of AC. The tool we used for assessing recovery has not been developed in a selected group of patients without complications. This may be a limitation to our study as we excluded these patients.

Unfortunately, we were unable to establish the exact reason for delayed initiation of adjuvant chemotherapy (> 4 weeks post-operatively) in 52% of the well-recovered patients with no post-operative complications. Time to RIOT is affected by both patient-related factors and course-related logistic factors. There is no significant difference in patient-related characteristics between patients who failed to RIOT and patients who succeeded to RIOT. Post-operative recovery measured using the QoR-15 questionnaire did not differ significantly between the two groups. This indicates that the delay may be due to other factors. These may be multiple, but logistic delay may be the primary reason, as seen in Table 2. It seems reasonable to expect that this logistical delay might be reduced by revision of simple interdisciplinary protocols.

This study has several limitations. Firstly, it was a single-centre study with a small sample size, hence limiting further analysis on factors affecting time of initiation of chemotherapy. Furthermore, the small sample size increases the risk of type II error and may lead to insignificance. The external validity of the study is somewhat limited due to institutional local and regional differences. Another limitation is that the included patients were not interviewed about whether they viewed themselves as ready to receive AC earlier than they did. Additionally, we did not investigate post-operative quality of care at the outpatient consultation. This would have contributed to a more stratified analysis. A major strength of this study was that all patients underwent follow-up.

In conclusion, our study has shown that post-operative recovery may not be an important limiting factor for patients receiving adjuvant chemotherapy either before or after post-operative week four measured by the QoR-15 questionnaire.

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LITERATURE

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