Clinical Frailty Scale is a useful tool for predicting postoperative complications following elective colon cancer surgery in the age of 80 years and older: A prospective, multicentre observational study.

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What does this paper add to the literature? This study showed that aged patients have high morbidity rates after curative colon cancer surgery despite modern achievements in operative treatment. However, the fittest patients had acceptable and similar operative outcomes to younger

patients. Clinical Frailty Scale appears like a beneficial screening tool for predicting these adverse events.

Abstract

Background Identifying risks of postoperative complications may be challenging in older patients with heterogeneous physical and cognitive status. The aim of this multicentre, observational study was to identify variables that affect colon cancer surgery outcomes and, especially to find tools to quantify the risks related to surgery.

Methods Patients aged ≥80 years with electively operated stage I-III colon cancer were recruited. The prospectively collected data included comorbidities, onco-geriatric screening tool (G-8), Clinical Frailty Scale (CFS), Charlson Comorbidity Index (CCI), Mini Nutritional Assessment-Short Form (MNA-SF), operative and postoperative outcomes.

Results A total of 161 patients (mean 84.5 years, range 80-97, 60% female) were included. History of cerebral stroke (64% vs 37%, p=0.02), albumin level 31-34 g/L compared to ≥35 g/L (57% vs 32%, p=0.007), CFS 3-4 and 5-9 compared to CFS 1-2 (49% and 47% vs 16%, respectively) and ASA >3 (77% vs 28%, p=0.006) were related to higher risk of complications. In multivariate logistic regression analysis CFS ≥3 (OR 6.06, 95% CI 1.88-19.5, p=0.003) and albumin level 31-34 g/L (OR 3.88, 1.61-9.38, p=0.003) were significantly associated with postoperative complications. Severe complications were more common in patients with COPD (43% vs 13%, p=0.047), renal failure (25% vs 12%, p=0.021), albumin level 31-34 g/L (26% vs 8%, p=0.014) and CCI >6 (23% vs 10%, p=0.034).

Conclusion Surgery on physically and cognitively fit aged colon cancer patients with CFS 1-2 can lead to excellent operative outcomes, like those of younger patients. CFS could be a useful screening tool for predicting postoperative complications.

Introduction

Colorectal cancer is the second leading cause of cancer death and the fourth most diagnosed malignancy in the world (1). The risk of developing colorectal cancer increases with age. Thus, as the world population ages, the number of patients experiencing colorectal cancer rises (2). Colorectal cancer surgery in the aged is considered high risk for postoperative complications and compromised functional recovery (3). The incidence of adverse events with colon cancer surgery ranges from 20% to 76% (4,5,6,7). It is more significant with advancing age and frailty, identified as a greater vulnerability in physical and cognitive status (7,8).

Old people are a heterogeneous group of patients, so the risk of postoperative complications cannot be judged only by chronological age (9). Preoperative risk estimation of postoperative complications, recognition of frailty, and identification of patients at greater risk of unfavourable treatment consequences are essential for optimising aged patients for surgery and thereby improving postoperative outcomes (10,11).

Tools used in the preoperative comprehensive geriatric assessment of onco-geriatric surgical patients are often time-consuming and require special training and knowledge of gerontology (12). Clinical Frailty Scale (CFS) has been developed for rapid frailty screening without the need for specific geriatric expertise or functional testing (13). The only prospective study concerning CFS and postoperative complications in older patients after elective colorectal cancer surgery concluded that frail patients (CFS ≥4) had more severe postoperative complications, leading to higher mortality rates (14). Otherwise, prospective studies in elective colon cancer surgery with aged patients focusing on preoperative frailty and postoperative complications are lacking.

This prospective observational multicentre study aimed to identify characteristics of aged colon cancer patients that affect postoperative morbidity and mortality. Special interest was focused on screening tools like CFS and their relationship to postoperative outcomes in patients 80 years and over.

Patients and methods

Study design

A multicentre, prospective observational cohort study of patients aged 80 years or older with stage I-III colon cancer was designed to analyse the impact of surgery on functional ability, complications, and mortality along with the predictors of these outcomes. Nine Finnish hospitals participated in the study. The total catchment area was 3.88 million people, representing 70.4% of Finland's population. Treatment of colon cancer in Finland is performed by public health care. Patients were treated at precise hospitals based on their place of residence, so the study provided a nationwide spectrum of operative management of colon cancer in the aged.

This study followed the STROBE guidelines (15) (Appendix 1). The Ethics Committee of Tampere University Hospital and the institutional review boards at each study site approved the study protocol (reference approval number R19028). The study was registered in ClinicalTrials.gov (NCT03904121) in April 2019.

Participants

Recruitment was initiated in April 2019 and, for this study, continued until July 2020. All patients aged 80 years or over with recently diagnosed stage I-III colon cancer referred to surgical units for consideration of operative treatment were eligible to participate in the study. Patients were informed of the study and gave written informed consent. If the patient was cognitively impaired, the consent was provided by a legally authorised representative or family member. Patients with metastatic disease, emergency operations, or an expected life expectancy of less than six months were excluded. Patients who consented to the study but were treated nonoperatively, had metastatic or benign disease at surgery were excluded from the present analysis.

Data collection

Data was collected prospectively in the electronic case record forms using RedCap (Research Electronic Data Capture) database (16). The primary investigator, who was the managing

surgeon at each study site, was responsible for data collection. The primary investigator or research nurses of each study site were charged to ensure that the patient questionnaires (Appendix 1) were completed. Operative data and postoperative outcomes were gathered prospectively during hospital stay and at follow-up visits. Patient questionnaires were collected before and one month after surgery at outpatient clinics, and surgical follow-ups conducted either by telephone call or by mail.

The collected clinical data included patient physical and functional characteristics, G-8 (17), CFS (13), comorbidities, nutritional status and characteristics of surgical treatment (Appendix 2). Postoperative complications were defined and determined using the Clavien-Dindo classification (CD) graded from grade 0 to V (18). Classes III-V complications were considered severe. Tumours were staged according to the Union for International Cancer Control (UICC) TNM classification (19). The number of positive and total number of lymph nodes was recorded in every case. The lymph node ratio (LN) ratio (20) was calculated by defining the proportion of metastatic lymph nodes from the total number of LNs examined.

Definition of variables

Age was analysed in three groups of 80-84 years, 85-89 years, and ≥90 years. Body mass index (BMI) was categorised into three groups: <24 kg/m^2, 24-29 kg/m^2 and ≥30 kg/m^2 (21).

G-8 ranged from 0 to 17. Geriatric evaluation is recommended for patients whose score was ≤14 (17). For analyses, patients were divided into three groups: <12, 12-14 and >14 for the clinical facility.

CFS was subdivided and analysed in three groups: very fit or fit (1-2), independent but not regularly active in daily life or vulnerable (3-4) and frail with severe limitations in daily activities (5-9) (13).

American Society of Anaesthesiologists risk score ASA (22), and age-adjusted Charlson Comorbidity Index CCI (23) were used as measures of anaesthesiologist, comorbidity burden and mortality risk. Based on ASA, the patients were analysed in three groups: 2, 3 and 4 (the lowest score was 2, as all patients were 80 years or older). CCI scores ranged from 4–15 (solid tumour was ignored, all patients received four points for their age). Patients were analysed in two groups: ≤6 and >6.

Mini Nutritional Assessment–Short Form (MNA-SF) classifies nutritional status as normal (scores >11), risk of malnutrition (8-11) or malnourished (<8) (24).

Patients with haemoglobin ≤120 g/L (cut-off selected for clinical utility) were considered to have anaemia. Albumin was analysed in three groups: ≤30, 31-34 and >34 g/L for clinical relevance. Renal function was categorised in three groups based on estimated glomerular filtration rate (GFR), calculated using CKD-EPI equation (25): normal to mildly decreased (≥60 mL/min), mildly to moderately decreased (45-60 mL/min) or moderately to severely decreased (<45 mL/min) renal function.

The LN ratio was analysed in three groups: <10% (LN ratio 1), 10-25% (LN ratio 2) and >25% (LN ratio 3).

Outcomes

The primary outcome measures were postoperative morbidity and mortality 30 days after primary treatment. The complications were graded with CD classification (18). Outcome measures were assessed during the hospital stay and at one-month clinical follow-up visits. Multiple complications occurring in the same patient were independently rated, and the highest CD grade experienced was used in the analyses.

Sample size

The sample size calculation for postoperative complications was based on earlier studies (4,5,6,7) showing 21% incidence of complications in fit patients and 48% in frail patients. To identify 2-fold differences in complication rates with α value of 0.05 and 80% power, it was calculated that 96 patients needed to be recruited and analysed.

Statistical analysis

Percentages were used to describe demographic data and the occurrence of outcomes. The median and range were calculated for age, preoperative laboratory values, body mass index (BMI), operation time and perioperative blood loss. Associations between the categorical variables were tested with the Chi-Square-test or the Fisher's exact test, when appropriate. Uni- and multivariate analysis of the factors influencing morbidity and mortality were carried out using logistic regression. Results are shown as odds ratios (OR) with 95% confidence interval (95% CI). All variables that were statistically significant ($p<0.005$) in the univariate model were included in the multivariate model. Statistical analyses were performed by using SPSS version 26.

Results

Patients and clinical characteristics

Of the 241 eligible patients, 180 (75%) patients consented to participate. Eleven patients were treated non-operatively because of their age or personal refusal, declined functional status or risk of anaesthesia due to severe comorbidities. Most of the non-operatively treated patients were considered frail (CFS ≥5; 90%) and to have increased risk of postoperative complications and recovery (G-8 ≤14; 100%, ASA ≥3; 100%, CCI >6; 70%). Eight patients were excluded because of metastatic or benign findings at operation or in the pathological sample. Figure 1 shows patient flowchart.

Altogether 161 patients were included in the study. The median age was 84.5 years (range 80-97 years and 60% were female. Most patients had an ASA III classification (67%), and CCI score ≤6 (62%). Almost all patients scored ≤14 (92%) in G-8, and 77% were considered vulnerable or frail (CFS ≥3). Most of the patients (91%) were at risk of malnutrition or malnourished (MNA-SF<12). Table 1 shows patients` baseline characteristics.

TNM-stages were as follows: stage I 29 patients (18%), stage II 86 patients (54%) and stage III 45 patients (28%). Lymph node ratio was as follows: 84% ratio 1, 10% ratio 2 and 6% ratio 3. Postoperative adjuvant therapy was given to 27% (12/45) of stage III patients.

Most of the operative procedures were performed for right-sided colon cancer (65%). An intended laparoscopic resection was performed in 122 patients (76%), and 15 cases (9.3%) were converted to open surgery due to anatomical or technical reasons. Median operation time was 129 min (range 54-433 min) and blood loss 50 ml (range 0-2390 ml). The median length of stay in the operating hospital was five days (range 2-36 days). Ninety patients (56%) were discharged home and the rest of the patients to other hospitals or primary healthcare centre wards.

Morbidity and mortality

Overall postoperative morbidity was 41% (66/161) with 24% (39/161) of patients having surgical complications. The most common surgical complications were ileus (12%), anastomotic leakage (5%), superficial surgical site infections (3.6%) and wound dehiscence (2.5%). Four patients had iatrogenic bowel perforations, and one patient had postoperative colon necrosis. Sixteen patients (10%) were reoperated. The reasons for reoperations were anastomotic leakage (8/16), iatrogenic bowel perforation after the primary operation (4/16), wound dehiscence (2/16), colon necrosis after right hemicolectomy (1/16) and unclear abdominal infection (1/16). The most common non-surgical complications were cardiovascular 6% (9/161) and pulmonary 8% (12/161). One patient had a massive cerebral stroke, causing permanent disability. Nine patients had both surgical and non-surgical complications. According to the CD classification, 15% (24/161) of patients had severe complications. Table 2 shows postoperative complications and figure 2 incidence of complications compared to CFS.

Readmission within 30 days of discharge occurred for 13 patients (8.1%). Nine had surgical, and four had non-surgical reasons for readmission. One patient needed reoperation because of new anastomotic leakage after primary relaparotomy with re-resection. The third operation was finished with protective stoma formation.

The overall 30-day mortality rate was 1.9% (3/161), but 8.3% (2/24) for those with CD grade III-IV complications. One patient died on the 23rd postoperative day after prolonged ileus and two reoperations due to wound dehiscence. One patient died on the 25th postoperative day, after relaparotomy for anastomotic leakage and peritonitis. The third patient died on the 18th postoperative day from complications of ischemic heart disease.

Predictors of postoperative complications

Postoperative complications were significantly more common in patients with a history of cerebral stroke (64% vs 37%, p=0.02), albumin level 31-34 g/L (57% vs 32% in patients with albumin ≥35 g/L, p=0.007), CFS 3-4 and 5-9 (49% and 47% vs 16% in CFS 1-2, respectively) and ASA >3 (77% vs 28%, p=0.006). In patients with CFS 5-9, non-surgical complications were more common than surgical complications (34% vs 25%), whereas in patients with CFS 1-2, both complication types were equally common (8% vs 11%). Age, BMI, preoperative hospital admissions,

polypharmacy, comorbidity burden, G-8, nutritional status, anaemia, type of operation, duration of operation or operative blood loss were not associated with increased rates of complications. In multivariate logistic regression analysis CFS ≥3 (OR=6.06, 95% CI 1.88-19.5, p=0.003) and albumin level 31-34 g/L (OR=3.88, 1.61-9.38, p=0.003) were significantly associated with postoperative complications. AUC for all complications was 0.747, (95% CI 0.67-0.83). Table 3 shows predictors of postoperative complications.

Severe complications (CD III-V) were significantly more frequent in patients with chronic obstructive pulmonary disease COPD (43% vs 13%, p=0.047), renal failure (25% vs 12%, p=0.021), albumin level 31-34 g/L (26% vs 8% in patients with albumin >34 g/L, p=0.014) and CCI-score >6 (23% vs 10%, p=0.034). Patients with CFS 3-4 and 5-9 seemed to have more severe complications (OR 3.40, 0.73-15.9, p=0.121 and OR 4.63, 0.93-23.0, p=0.061) compared to patients with CFS 1-2, but the differences were not statistically significant. In multivariate logistic regression analysis, albumin level 31-34 g/L (OR 4.39, 1.31-14.7, p=0.017) was the only significant variable causing postoperative complications. AUC for severe complications was 0.756, (95% CI 0.65-0.86). Table 4 shows predictors of severe postoperative complications. Figure 3 shows distributions of all and severe postoperative complications, according to CFS.

Discussion

This prospective study demonstrated that CFS (13) predicts early postoperative complications following elective curatively aimed colon cancer surgery in aged patients. Patients, who are vulnerable or frail with CFS scores ≥3 or have severe comorbidities, had significantly more complications than fit patients with CFS scores 1-2, whereas age did not affect postoperative outcomes. On the contrary, fit patients managed exceptionally well and showed a very low complication rate and mortality. Altogether these results emphasise the importance of patient assessment irrespective of chronological age (26).

The study sample represented only colon cancer patients as they have homogenous treatment strategies compared to rectum cancer patients. Our study showed higher frequency of right-sided colon cancers and female patients, which is in line with previously reported studies of aged patients (6,27). Colon cancer surgery is performed in Finland by surgeons specialised exclusively in colon operations following uniform, standardised protocols for colon cancer treatment (28). The study sample is nationally representative providing realistic and novel information on postoperative outcomes of aged patients.

Our study showed high morbidity rates in the early postoperative period. Almost 41% of the patients developed postoperative complications, and 15% had severe complications. These figures are comparable to other studies of colon cancer surgery in the aged (5,6,7). Complications were overrepresented in patients who were well-managing but inactive or mildly frail (CFS 3-4) and frail (CFS 5-9) compared to fit patients (CFS 1-2) with complication rates of 49% and 47% vs 16%. This indicates that fit aged patients can manage invasive surgical treatments like their younger counterparts (4). On the other hand, particularly vulnerable patients might benefit from preoperative medical optimisation and comprehensive geriatric assessment (29).

Previous studies verified that aged patients with severe complications have a disproportionately high risk of 30-day and 1-year mortality (3,6). In this study, the 30-day mortality rate was 1.9% and 8.3% in patients with severe complications, showing a remarkable decline from mortality rates previously reported in Finland and Netherlands (6,30). The enhanced recovery after surgery (ERAS) protocol and mini-invasive surgery were well-established in the recruiting hospitals (31,32). Thus, the significant improvement in mortality rates indicates improved preoperative risk assessment and optimisation, counselling and awareness of frailty together with nationwide standardisation and advancements in modern multidisciplinary treatment.

Nutritional prehabilitation was implemented at some of the study hospitals (33) but is not standard nationwide and may not cover all patients. This might explain excess complications in patients with mildly reduced albumin level (31-34 g/L) than patients with clearly abnormal albumin, suggesting probable malnutrition. On the other hand, BMI had no effect, and thus it should not be used alone for evaluation of nutritional state.

Frailty is identified as a significant predictor of postoperative complications leading to greater health care utilisation and higher mortality (8,14). Our study focused on the growing population of colon cancer patients aged 80 years or over with even more significant heterogeneity in physical and cognitive status. Notably, most patients lived at home before surgery, but only 56% returned directly to home after operative treatment emphasising the major impact of surgery on functional recovery. Our findings demonstrated that patients with pre-existing frailty and morbidity express an excess number of complications, corroborated by a recently published meta-analysis (34).

CFS proved to be a beneficial tool for assessing preoperative daily physical and cognitive activities and independence. At present, only few surgical units have readily available geriatric services for comprehensive assessment, so easily implemented frailty screening tools are helpful for surgeons. We grouped patients in three categories (CFS 1-2, 3-4 and 5-9), as we wanted to demonstrate the importance of identifying patients with possible vulnerable physical status. CFS ≥3 was the only screening parameter, which significantly showed association with adverse outcomes. Patients with CFS 3-4 can be challenging for a surgeon to identify, as they can manage well independently and live with mild frailty.

Although an observational study cannot answer the question if the surgery is beneficial or not, performing a randomised trial in this patient group is not realistic. Instead, it is clinically more relevant to study outcomes in an observational setting with less selection bias and more relevance to real-life settings. The strengths of this study included the fact that it examined a representative, nationwide cohort, treated at several secondary and tertiary care hospitals instead of single-centre analysis with uniform and standardised protocols during perioperative period (ERAS protocol).

There are some limitations to this study. It was acknowledged that the tests used (G-8, CFS and MNA-SF) represented screening tests, and geriatric evaluation would be needed for precise diagnosis of frailty and other geriatric syndromes. Although we did not do cognitive testing, CFS gives some insight into cognition, and it can be anticipated that patients with CFS 1-2 had no or only mild cognitive impairment. The sample size was not quite sufficient for the analysis of

predictors of severe complications. More extensive patient data is needed to confirm the possible prognostic trends such as with CFS, ASA, MNA-SF and GFR. Moreover, a longer follow-up would be necessary to evaluate the complete impact of invasive cancer treatment (3,35). Future studies from this multicentre data will focus on long-term results with outcomes and especially functional recovery.

In conclusion, this study showed that aged patients have high morbidity rates after curative colon cancer surgery. However, the fittest patients had excellent operative outcomes, like younger counterparts. Surgeons should not abstain from curative surgery based only on age or comorbidities. Conversely, modern treatment decision-making should complement preoperative risk assessment with the considered use of CFS and counselling jointly with patients and their family.

Acknowledgements

The authors warmly thank M.D Kirk Langley Fremantle Hospital, WA Australia, for his help in editing the English language.

Funding information

Competitive State Research Financing of the Expert Responsibility area of Tampere University Hospital partly supported this study financially. Cancer Foundation Finland obtained external funding by awarding a grant, but they did not have any role in designing the study, collection, analysis, interpretation of the data or writing the manuscript.

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