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Original Research Article

Delirium, Frailty, and Fast-Track Surgery in Oncogeriatrics: Is There a Link?

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Keywords

Delirium · Functional impairment · Geriatrics · Neuroinflammatory aspects of dementia and delirium

Abstract

Background/Aims: Postoperative delirium (POD) is more frequent in elderly patients undergoing major cancer surgery. The interplay between individual clinical vulnerability and a series of perioperative factors seems to play a relevant role. Surgery is the first-line treatment option for cancer, and fast-track surgery (FTS) has been documented to decrease postoperative complications. The study sought to assess, after comprehensive geriatric assessment (CGA) and frailty stratification (Rockwood 40 items index), which perioperative parameters were predictive of POD development in elderly patients undergoing FTS for colorectal cancer. ***Methods:*** A total of 107 consecutive subjects admitted for elective colorectal FTS were enrolled. All patients underwent CGA, frailly stratification, Timed up & go (TUG) test, 4AT test for delirium screening, anesthesiologists physical status classification, and Dindo-Clavien classification. ***Results:*** The incidence of POD was 12.3%. Patients' prevalent clinical phenotype was pre-frail. The multivariate analysis indicated physical performance (TUG in seconds) as the most significant predictor of POD for each second of increase. ***Conclusions:*** Only few procedure-specific studies have examined the impact of FTS for colorectal cancer on POD. This is the first study to investigate the risk factors for POD, in a vulnerable octogenarian oncogeriatric population submitted to FTS surgery and frailty stratification.

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Introduction

Postoperative delirium is a common clinical condition in elderly patients undergoing surgery, ranging from 28 to 50% [1, 2]. The interplay between patient's clinical vulnerability and a series of perioperative variables is considered a major determinant [3–6]. Due to the aging population, colorectal cancer has been continuously increasing, and surgery is the first-line effective treatment option, shifting to less invasive interventions because of better post-operative technical results [7].

The concept of fast-track surgery (FTS) has been developed and documented to be successful by decreasing postoperative complication rate, length of stay, comorbidity, and convalescence [8]. This new model of care is based on a combination of unimodal evidence-based care interventions; it optimizes nutrition, decreased use of tubes, drains, and catheters, mechanical bowel preparations, early mobilization, and multimodal nonopioid analgesia, compared to traditional surgery.

Most of the evidence on postoperative delirium (POD) derives from cardiac and orthogeriatric settings; so far, its association with oncogeriatrics and, in particular, solid cancer resections has received less attention [9–11]. Recently, it has been found that colon rectal surgery was associated with higher postoperative delirium and poorer clinical outcomes, including length of hospital stay and mortality [12]. Similarly, age, past history of delirium, and the operative approach were risk factors for POD after colorectal cancer surgery [7]. In particular, the laparoscopic procedure was significantly associated with lower POD incidence [7]. Remarkably, a cornerstone randomized clinical trial [13] compared FTS with traditional perioperative protocols and their impact on a set of postoperative complications in oncogeriatric patients undergoing colorectal surgery. The major findings indicated that FTS reduced the length of stay and postoperative complications, including delirium. So far, opportunities for earlier interventions in patients with cancer who are increasingly susceptible to delirium by virtue of surgical elective interventions are warranted.

The objective of this study was to investigate which preoperative, intraoperative, or postoperative parameters were predictive of POD development in elderly patients undergoing elective FTS for colorectal cancer and frailty assessment.

Material and Methods

This was a cross-sectional study performed in the oncological gastrointestinal surgery ward of Ospedale Policlinico San Martino, Genoa, Italy.

Patient Selection

Between January and December 2016, 107 consecutive patients admitted for elective colorectal FTS [8] were enrolled after obtaining their written informed consent. The study was approved by the Local Ethical Committee and met the guidelines of the local Governmental Agency.

Patients were included if they were >70 years old, had a first diagnosis of colorectal cancer (according to the 5th edition of the TNM staging system) and were scheduled for elective FTS according to the FTS protocol illustrated in Table 1.

Patients were excluded if they were younger than 70 years, had a previous history of delirium, had a scheduled intervention for cancer relapse or palliative intervention, had previous neo-adjuvant radiotherapy or chemotherapy treatment, or had any clinical instability needing acute surgery.

Table 1. Fast-track colorectal surgery protocol

Preoperative assessment
Anesthesiology assessment
Comprehensive geriatric assessment
Cardiologist visit if needed
Diabetologist visit if needed
Pulmonologist visit if needed
Nutritionist visit for tailored nutritional intervention along with standard oral hypercaloric supplementation (2 days, 600 kcal/day) if needed
Physiotherapist assessment for pre-and postoperative rehabilitative plan and training if needed
Intraoperative assessment
Peridural catheter or peripheral venous access for pain control
General anesthesia with propofol and remifentanil by target control technique
Total intravenous liquid infusion (saline solution 0.9% 6 mL/kg/h + 500 mL hydroxyethylamide 130/0.4)
Mechanical or physical devices to maintain normothermia if needed
Ondansetron 4 mg 30 min before intubation
Hemotransfusion if blood pressure <20% estimated basal value
Droperidol 0.625 mg after surgery
Urinary catheter placement/drainage placement/peripheral venous access placement
Nasogastric tube placement and removal after surgery
Colorectal surgery, laparoscopic
Surgical technique
Laparotomy
Laparoscopy
Mean duration of surgery (155 ± 55 min)
Laparotomy
Laparoscopy
Postoperative assessment – first day
Analgesic control: Peridural catheter or by peripheral venous access with acetaminophen 1 g i.v. × 4/day and tramadol 100 mg i.v. if needed (pain control: numeric rating scale [NRS] <4/10)
Trunk control and patient seated for at least 2 h a day
Respiratory rehabilitation for 10 min a day
Early oral liquid assumption (maximum 1 L a day) if possible
Oral nutritional supplementation (protein and caloric supplementation 300 kcal/day per single supplement) if possible or parenteral i.v. nutrition (1,000 mL/day, 700 kcal/day) for 5 consecutive days after surgery
Bowel evacuation daily and peristalsis assessment
Postoperative assessment – day 2 to day 5
Analgesic control: acetaminophen 1 g × 4/day and tramadol 100 mg/day if needed (pain control: NRS <4/10)
From day 3 to day 5 after surgery: pain control: peridural catheter withdrawal and oral analgesic therapy: paracetamol 300 mg and oxycodone 5 mg 3 tablets a day OR paracetamol 300 mg and oxycodone 10 mg 3 tablets a day (pain control: NRS <4/10); if needed, ketorolac 30 mg i.m. (maximum 90 mg in 24 h)
Trunk control and patient seated for 6–8 h a day
Walking rehabilitation from 3 to 5 times a day
Respiratory rehabilitation for 10 min 4 times a day
Early oral liquid assumption (maximum 1 L a day) if possible
Oral nutritional supplementation (protein and caloric supplementation) if possible or parenteral i.v. nutrition (1,000 mL/day, 700 kcal/day) for 5 consecutive days after surgery
Bowel evacuation daily, peristalsis assessment, and normal bowel movement
Parenteral nutrition withdrawal and oral normal feeding (3 meals a day) with oral nutritional supplementation (2 a day, if needed)
Withdrawal surgical drainage
Withdrawal urinary catheter

Table 2. Factors precipitating POD in elective fast-track surgery oncogeriatric patients: standardized clinical parameters according to fast-track protocol

Nutrition Standardized clinical protocol for nutrition: oral supplementation (300 kcal/day for 1 supplement day and/or i.v. parenteral nutrition (1,000 mL i.v./day for 5 days; 700 kcal/day)
Devices Standardized device use (peripheral venous access, urinary catheter, and abdominal drainage)
Bowel movement Standardized clinical protocol for constipation (osmotic agents for 7 days) with daily report of patient bowel evacuation and movement
Pain Standardized clinical protocol for pain (i.v. paracetamol 1 g a day for 48 h) and additional narcotics given above standards record
Physical constraints Standardized application of bedrail constraints for 72 h Plasmatic determination of hemoglobin, creatinine, sodium, potassium, C-reactive protein, after 48/72 h from surgery Incident postoperative drug administration record Postoperative blood transfusion record

Factors Predisposing to Delirium, Comprehensive Geriatric Assessment and Frailty Status

Patients' clinical characteristics were assessed at hospital admission and included sociodemographic and comprehensive geriatric assessment (CGA) [14]. The latter included: cognitive status (Mini-Mental State Examination [MMSE] and Shulman I Clock Drawing Test) [15, 16]; functional status (Barthel Index and Instrumental Activities of Daily Living) [17, 18]; comorbidity (Cumulative Illness Rate Scale for Geriatrics) [19]; depression (Geriatric Depression Scale) [20]; malnutrition (Mini-Nutritional Assessment) [21]; risk of falls (Tinetti Scale) [22]; and pain (Numeric Rate Scale). A CGA score of >3 defined patients as frail and a score of 2 <CGA >3 defined patients as pre-frail.

All patients underwent frailty index assessment based on the Rockwood 40-item index [23]: a score of ≤0.09 defined patients as fit; a total score of ≥0.25 as frail and a score between 0.08 and 0.25 as pre-frail. All patients underwent ECOG Performance Status (ECOG PS) [24] oncological assessment, anesthesiologists physical status [25], and the Timed up & go test (TUG) [26] to assess physical performance.

Delirium was diagnosed by an experienced geriatrician using DSM-V criteria at baseline [27]. This same geriatrician was in charge of patients postoperatively as part of a multidisciplinary assessment of elderly surgical patients in our hospital.

Moreover, delirium was also assessed by a second independent geriatrician, using a rapid assessment test for delirium (4AT) [28] after 48 h from surgery. 4AT is a recently developed and validated screening tool for the assessment of delirium in geriatric patients. Patients who scored ≥4/12 on the 4AT test were also assessed with the Delirium Motor Subtype scale [29] for the evaluation of delirium psychomotor subtype.

The postoperative complications rate was recorded according to Dindo-Clavien classification [30] along with non-surgical-related adverse events. Postoperative blood transfusions were also registered. The perioperative mortality (after 7 days) and 1 month mortality rates were calculated regardless of whether the death occurred in hospital or after discharge. The number of drugs taken by the patients was also collected.

Table 3. Patients' clinical characteristics based on Comprehensive Geriatric Assessment (CGA) and Rockwood Frailty Index (40-item FI)

Assessment tool	Mean ± SD[a]
MMSE	27.13±0.35
CIRS	4.39±0.19
CDT	2.57±0.15
4AT test	3.47±0.23
Tinetti	24.29±0.57
MNA	23.32±0.32
Barthel index	97.68±0.65
IADL	7.19±0.16
GDS	3.62±0.32
Gijon scale	8.71±0.26
NRS	0.60±0.18
TUG	10.84±0.59
CGA	3.48±0.23
Rockwood FI (40 items)	0.23±0.01
ASA	2.28±0.07
Dindo-Clavien	1.07±0.12
SF36	0.73±0.05
Karnofsky	89.38±1.19
ECOG PS	0.37±0.06
Mean drugs	4.82±0.29

SD, standard deviation. For other abbreviations, see Table 4.
[a] 97 patients: no missing data.

Factors Precipitating Delirium: Postoperative Clinical Assessment

The optimization of factors precipitating POD, on the basis of the FTS protocol, is illustrated in Table 2.

Statistics

Results were reported as mean ± standard deviation. Factors predisposing to and precipitating delirium (POD) were analyzed prospectively, comparing the delirious group with the nondelirious group of patients, based on the 4AT score (cut-off ≥4). The parametric T test was used to compare delirious and nondelirious patients on quantitative measures. All significant measures at univariate analysis were selected with a stepwise approach to be included into the multivariable model, adjusted for age and gender. A p value of 0.10 was used as threshold for inclusion into the model and $p < 0.05$ was considered statistically significant. Graph Pad v.5.0b and Stata (v.14; StataCorp) were used for the computation.

Results

Patients' clinical characteristics are illustrated in Table 3. The mean age was 80.26 ± 0.65 years (female 73 and male 34 years). Patients had surgery for colon carcinoma in 71% (n = 72) of cases and rectum carcinoma in 29% (n = 35) of cases.

Seventy percent (n = 77) of patients underwent laparoscopic surgery, while 30% (n = 30) underwent laparotomy. The patients diagnosed with colon or rectal cancer were classified as stage I (20.86%), stage II A (43.69%), stage II b (6.50%), stage III A (4.34%), stage III B (17.01%), and stage III C (7.60%) following the TNM V classification.

The incidence of POD after elective FTS was 12.3%. Delirium subtypes, according to DSMM, were classified as: hyperactive delirium 75%; hypoactive delirium 20%; mixed type 5%.

Table 4. Comparisons between predisposing factors, precipitating factors in delirious patients and nondelirious patients

Clinical parameters	Delirious (n = 12)[a]	Nondelirious (n = 85)[a]	p value[b]
Age, years	80.02±0.45	80.05±0.34	0.5
4AT score	8.61±0.71	2.68±0.07	<0.0001
ASA score	2.28±0.43	2.98±0.23	0.5
MMSE score	24.31±1.14	27.56±0.34	<0.02
CIRS	5.46±0.44	4.22±0.20	0.12
CDT	3.36±0.38	2.45±0.16	0.09
MNA	22.38±0.89	23.47±0.16	0.46
Barthel index	93.08±2.56	98.39±5.71	<0.02
IADL	6.00±0.63	7.37±0.15	0.03
GDS	3.84±1.03	3.58±0.33	0.95
Gijon scale	10.08±0.81	8.50±0.26	0.33
Tinetti score	19.69±1.94	25.02±0.55	<0.01
NRS	1.07±0.47	0.53±0.19	<0.04
TUG score	18.15±2.55	9.63±0.42	<0.02
CGA score	5.69±2.05	3.14±0.24	<0.005
RI	0.29±0.04	0.22±0.01	0.15
Dindo-Clavien score	1.07±0.34	1.07±1.19	0.58
SF36 score	0.90±0.26	0.70±0.04	0.43
Karnofsky score	82.31±4.55	90.48±1.16	0.25
ECOG PS	0.69±0.23	0.32±0.06	0.42
Hemoglobin, g/dL	10.72±0.44	10.90±0.16	0.79
Sodium, MEq/L	140.30±0.67	140.7±0.33	0.49
Potassium, MEq/L	4.07±4.59	4.06±0.05	0.07
Creatinine, mg/dL	1.35±0.13	1.16±0.04	0.17
Mean drugs	4.35±1.23	4.01±0.11	0.33

MMMSE, Mini-Mental State Examination – cognitive status; CDT, Clock drawing test Shulman 1 – visuospatial impairment; 4AT, rapid assessment test for delirium – screening test for delirium; CIRCS, Cumulative Illness Rate Scale for Geriatrics – multimorbidity; MNA, Mini-Nutritional Assessment – nutritional status; Barthel Index, functional status; IADL, Instrumental Activities of Daily Living – functional status; GDS, Geriatric Depression Scale – depression; Gijon scale – social frailty; Tinetti Scale – risk of falls; NRS, Numeric Rate Scale – pain; CGA, comprehensive geriatric assessment; RI, Rockwood 40-Item Index – frailty; Dindo-Clavien score – postsurgical complications; ECOG Performance Status (ECOG score) – physical performance in oncology; Karnofsky score, physical performance in oncology; ASA, anesthesiologists' physical status; SF-36, 36-item Short Form Survey – quality of life; TUG, Timed up & go. [a] No missing data. [b] Parametric t test.

The rate of postsurgical complications based on Dindo-Clavien assessment was 26% (grade 2: 11%; grade 3: 3%; grade 4: 4%; and grade 5: 3%). The rate of non-surgery-related adverse events was 3% (urinary infection and upper respiratory disease), while 0.04% (5/107) of patients needed postoperative blood transfusion. The mean length of in-hospital stay was 8.8 ± 1.24 days. No perioperative mortality (7 days after surgery) was recorded, while the 30-day mortality rate was 4.95%. Ninety percent of patients were discharged home, 5% of patients were admitted to intermediate care unit, while 5% of patients entered nursing homes for extensive physical rehabilitation.

Patients who developed postoperative delirium showed different clinical variables compared to nondelirious patients (Table 4). Namely, delirious patients were those more cognitively impaired, with decreased physical performance, increased functional decline, and reduced postural stability; these same patients showed a more significant impairment on the CGA.

Furthermore, the multivariate analysis indicated that physical performance (TUG in seconds) was the most significant predictor of POD with an OR of 1.18 (95% CI: 1.05–1.31; p = 0.005) for each second of increase. Cognitive status (MMSE score) showed a trend in predicting POD (OR = 0.85; 95% CI: 0.71–1.01; p = 0.068).

Patients submitted to laparoscopic procedure showed a lower trend in experiencing delirium, although the difference was not significantly different, compared to patients submitted to laparotomy (p = ns).

Discussion

FTS procedures in highly vulnerable oncogeriatric populations have not yet answered how effective they are in predicting the main clinical outcomes. To the best of our knowledge, this is the first study to investigate the risk factors for POD in a vulnerable octogenarian oncogeriatric population submitted to FTS surgery and frailty stratification.

In our study, the incidence of POD was 12.3%, which is higher compared to the other procedure-specific studies. So far, few studies have examined the impact of FTS for colorectal cancer on POD. Namely, Krenk et al. [31] have shown no cases of POD after fast-track knee replacement surgery, compared to the usual incidence of 4–10%.

Moreover, the fast-track setup in colonic oncogeriatric surgery was correlated with a shorter length of hospital stay and reduced incidence of POD (2.8%) [32]. Recently, a subanalysis of the randomized clinical trial of Jia et al. [13] on patients over 80 years has indicated the protective role of FTS on postoperative complications, including delirium, in both elderly and oldest old patients [33]. In relation to these other studies, the heterogeneity associated with elderly populations and delirium assessment methodology may account for the wide range of these reported series. In particular, the findings of Kurbegovic et al. [32] were retrospective in nature, and there was no systematic geriatric assessment of patients' clinical vulnerability. Similarly, the study of Jia et al. [13], despite the lower incidence of POD (3.4%) in patients submitted to FTS, did not include focused geriatric assessment of frailty.

Our relatively higher incidence of POD may be explained by the pre-frail phenotype of patients, which accounts for increased clinical vulnerability and decreased brain resilience.

It is noteworthy that the physical performance (TUG) was the best predictor of POD incidence, suggesting that the initial trajectory of frailty may be mostly linked to walking speed and physical ability [34]. Above-average physical performance probably reflects decreased resilience that characterizes these pre-frail categories of patients and predicts their decreased homeostasis and brain resilience in the presence of surgical stressors. These last features reflect the loss of structural and functional integrity and have been recently added to the concept of frailty [35]. In compliance with that, the current findings confirm frailty continuum as a key determinant predictor of POD [34] in surgical oncogeriatric patients as well.

Interestingly, the postoperative complication rate was 26%, lower than the rates reported in the other procedure-specific studies [13, 32, 33]. The present findings confirmed the effectiveness of FTS in accelerating patient recovery and home discharge, even in vulnerable oncogeriatric patients.

The main limitations of this study were that it was carried out at a single institution and was relatively small in size. Delirium assessment was carried out at a single assessment point; thus, it did not include delirium duration, severity, or any change in clinical subtype as would be the case in longitudinal assessment. However, the single point assessment was established on the basis of the reference study by Jia et al. [13]. In compliance with that, the higher incidence of POD occurred at day 1 after FTS surgery, reflecting higher stressors such as anes-

thetics, type of surgery, inflammatory response, and pain. Conversely, POD incidence during the course of hospital stay could be related to surgical and nonsurgical complications.

Notwithstanding these limitations and even if exploratory in nature, the study originally investigated the risk factors associated with POD, in major oncogeriatric colon surgery, after combining a clinical approach (FTS and CGA). Furthermore, the strength of the study lies in the accurate oncogeriatric assessment of "real world" patients' clinical vulnerability (pre-frail patients). Given the extent of the problem in the elderly vulnerable population undergoing cancer surgery, POD is a research top priority.

Future directions justify investigation of the development of FTS procedures integrated with effective frailty instruments to minimize harm after oncological surgery. Understanding the decreased inflammatory response after FTS in vulnerable oncogeriatric populations and their distinguished clinical trajectories of frailty may be of additional help in counteracting the devastating effect of this postoperative geriatric syndrome.

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Disclosure Statement

No conflict of interest to disclose.

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Author Contributions

Dr. Monacelli is responsible for study design and conception, drafting the manuscript, and critically revising the manuscript. Dr. Prefumo and Dr. Giannotti did data collection and the analysis and interpretation of data. Dr. Scabini and Dr. Romairone did data acquisition and performed the analysis and interpretation of data. Dr. Signori, Prof. Nencioni, and Prof Odetti revised the literature, did manuscript interpretation and critically revised the manuscript. All authors have read the paper, have agreed to be listed as authors and gave the final approval of the manuscript.

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