

Influence and impact of cognitive trajectories on outcome in patients undergoing radical cystectomy: an observational study.

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Abstract

Objectives: To evaluate cognitive trajectories after radical cystectomy and their impact on surgical outcomes, including urinary continence.

Methods: Ninety patients received cognitive testing using the Mini Mental State Exam (MMSE) before open radical cystectomy as well as 3 days and 2 weeks after surgery. Based on MMSE changes ≥ 3 points between the three time points, five cognitive trajectories emerged (stable cognition, persistent or transient deterioration or persistent or transient improvement). Surgical outcomes were assessed 90 days, 6 months and 1 year postoperatively.

Results: Mean age was 67.9 ± 9.3 years (range 40 - 88 years). Sixty-six patients (73.3%) had stable cognition, nine patients (10.0%) persistent and seven patients (7.8%) transient deterioration, five patients (5.6%) persistent and three patients (3.3%) transient improvement. An impaired preoperative cognition was the only significant risk factor of short-term cognitive deterioration (OR adjusted for age and sex 9.4, 95%CI 1.6–56.5, $p=0.014$). Cognition showed no associations with 1-year mortality, 90-day complication rate, cancer progression or duration of in-hospital stay. Patients with transient or persistent cognitive deterioration had an increased risk for nighttime incontinence (OR adjusted for age and sex 5.1, 95%CI 1.1–22.4, $p=0.032$).

Conclusions: In this study, the majority of patients showed stable cognition after major abdominopelvic surgery. Cognitive deterioration occurred in a small subgroup of patients, and an impaired preoperative cognition was the only significant risk factor. Postoperative cognitive deterioration was associated with nighttime incontinence.

Introduction

There is good evidence that major cardiac and non-cardiac surgical procedures may affect cognitive function [1-5]. The incidence of postoperative cognitive dysfunction (POCD) varies greatly with reported rates of 4% to 41% after major surgery [5-7]. Most POCD cases recover within a few weeks following surgery and anesthesia [1-5]. However, POCD may persist being a risk factor for long-term cognitive deterioration [4,5]. There are currently ongoing controversies on the clinical relevance of POCD and its impact on surgical outcomes [8].

Adequate cognitive function is a prerequisite to learn to live with an orthotopic bladder substitute. It is therefore conceivable that POCD may affect functional outcome, but to the best of the authors' knowledge, no previous study investigated the impact of POCD on postoperative continence. We identified only one study specifically addressing cognitive function after radical cystectomy [9]. The study revealed that a lower Mini Mental State Exam (MMSE) score was a risk factor for postoperative delirium, which occurred in about one third of the patients. Considering the paucity of information, we evaluated pre- and postoperative cognitive function in a cohort of patients undergoing radical cystectomy and analyzed its impact on surgical outcomes.

Material and Methods

Study population

We recruited and followed-up our cohort from a larger patient sample included in a previously published randomized controlled trial between November 2009 and September 2012 (Clinicaltrials.gov (NCT01276665)), in which the primary outcome was the in-hospital postoperative complication rate [10]. Only native German speaking patients were included in the assessment of the cognitive function. All patients underwent open radical cystectomy with either an ileal conduit or an ileal orthotopic bladder substitute. We excluded patients with American Society of Anesthesiologists (ASA) physical status of IV or higher, with significant hepatic or renal dysfunction, with congestive heart failure (New York Heart Association functional class III or higher). All patients provided written informed consent and for use of their anonymized data for research purposes.

Ethical approval for the study (registration number 154/08, 09.07.2009) was provided by the Cantonal Ethics Committee (Kantonale Ethikkommission Bern, Postfach 56, 3010 Bern. Contact: Dr. sc. nat. Dorothy Pfiffner). The STROBE checklist for observational studies was used to guide the methods and to structure this manuscript. The authors confirm that all ongoing and related trials for this drug/intervention are registered.

Surgery and Anesthesia:

Surgery was standardized and performed as previously described in the presence of one senior urologist [11-13]. All patients received a thoracic epidural analgesia.

Anesthesia was induced with propofol, fentanyl, rocuronium and maintained with isoflurane.

Postoperative Patient Management

Postoperative epidural analgesia was achieved with a mixture composed of bupivacaine 0.1%, fentanyl 2µg/ml and epinephrine 2µg/ml using an ambulatory infusion pump. After surgery patients were admitted to the intermediate care unit. Intravenous paracetamol and metamizol (both 1g every 6h) were given postoperatively. The epidural catheter was removed on postoperative day (POD) 5.

Postoperative hydration was identical in both groups and consisted primarily of 1000ml of balanced Ringer's solution and 500ml of glucose 5% per 24 hours until resumption of normal food intake [10].

Postoperatively patients were allowed to drink clear fluids immediately. A peroral liquid diet was started on POD 1 and active mobilization was encouraged.

Measurements

General preoperative evaluation

We recorded patient history including comorbidities, prescribed drugs, and years of education. Based on comorbidity information, we calculated the Charlson comorbidity index (CCI) [14,15]. Physical examination included the measurement of weight, height and body mass index (BMI). Creatinine, hemoglobin and prealbumin were measured in all patients.

Cognitive testing and definition of cognitive trajectories

We used the MMSE for cognitive evaluation [16]. The MMSE was assessed by a study nurse specifically trained in cognitive tests. The MMSE was performed at three timepoints: preoperatively, on day 2 after surgery, and approximately 10 days after surgery. For the purpose of this analysis, we dichotomized the MMSE global score at a standard cut-off point according to current literature [17]. A global score ≥ 26 points was defined normal, and a score < 26 points was defined impaired. To determine relevant cognitive deterioration or improvement between two of the exams, we calculated the MMSE score difference and defined *a priori* that a decrease of ≥ 3 points indicates deterioration and an increase ≥ 3 points improvement. This cut-off was chosen based on clinical and statistical considerations [18-21].

We then defined five cognitive trajectories based on our definition of relevant change and the availability of three consecutive tests. First, cognitive function was considered stable, if both postoperative MMSE global scores were within a range of +2 and -2 points compared to the preoperative score. Second, we assumed persistent cognitive deterioration, if the last MMSE global score was ≥ 3 points lower than the preoperative score. Third, transient cognitive deterioration was considered present, if the first postoperative MMSE global score was ≥ 3 points lower than the preoperative score and returned within a range of +2 and -2 points compared to the preoperative score. Fourth, we assumed persistent cognitive improvement, if the last MMSE global score was ≥ 3 points higher than the preoperative score. Finally, transient cognitive improvement was considered present, if the first postoperative MMSE global score was ≥ 3 points higher than the preoperative score and returned within a range of +2 and -2 points compared to the preoperative score.

Surgical outcomes

Patients were routinely followed at 3, 6 and 12 months postoperatively to assess oncological and functional outcomes. To evaluate associations with cognitive function, the following surgical outcomes were analyzed: 1) one-year mortality; 2) 90-day postoperative complication rate, which was assessed according to the Clavien-Dindo classification [22]; 3) cancer progression; 4) duration of in-hospital stay in days; and, 5) daytime or nighttime incontinence. Continence was assessed using a standardized questionnaire [23]. Incontinence was defined as loss of more than a few drops of urine more than once a week and/or use of 1 or more pads per day or night [24].

Statistical analysis

We first descriptively analyzed baseline characteristics. We then descriptively analyzed MMSE global scores for the three time points and the frequency of the predefined cognitive trajectories. In nine patients (10.0%), one of the three MMSE was missing (in four patients the preoperative MMSE, in one patient the first postoperative MMSE, and in four patients the last postoperative MMSE); in one patient (1.1%), two MMSE were missing. Considering the low missing quote, we imputed the missing MMSEs using the median MMSE global score of 28 points [25]. Group differences were assessed by a Wilcoxon rank-sum test for continuous variables, and change differences by a paired Wilcoxon signed rank test. Third, we performed logistic regression models to identify risk factors of short-term or persistent cognitive deterioration. Short-term cognitive deterioration was defined as deterioration between preoperative and first postoperative evaluation, and persistent cognitive deterioration was defined based on the corresponding trajectory. Age, sex, BMI, CCI, laboratory measurements, years spent on education, and preoperative MMSE global score were selected as independent variables. All models were done univariably (i.e., containing only the independent

variable of interested), and multivariably after adjustment for age and sex. We also performed a longitudinal analysis using a random effects model to confirm the results from logistic regression. Fourth, we used logistic regression to evaluate associations between cognitive function and surgical outcomes. For each of the surgical outcomes, age, sex, CCI, preoperative MMSE global score, and persistent and/or transient cognitive deterioration were evaluated as independent variables. All models were done univariably and after adjustment for all other independent variables. We finally performed a sensitivity analysis without imputation of missing data. Results from logistic regression analysis are reported as odds ratios (ORs) with 95% confidence intervals (CIs). P values <0.05 were considered statistically significant. Data were analyzed with Stata 12.1 (StataCorp LP, College Station, TX, USA).

Results

Study population

The study population consisted of 90 patients (Figure 1). Table 1 shows their baseline characteristics. Mean age was 67.9 ± 9.3 years with a maximum range from 40 to 88 years. Most study participants (70.0%) were male. Fifty-four patients (60.0%), of which 16 were female (29.6%), received an orthotopic bladder substitute. Study participants had few comorbidities with 79 participants (87.8%) having a CCI of one or less. Fifty-five study participants (61.1%) had a preoperative ASA score of two, and 35 participants (38.9%) of three.

Development of cognitive function and cognitive trajectories

Table 2 summarizes the pre- and postoperative MMSE global scores. Between the preoperative and the first postoperative evaluation, the MMSE global score significantly decreased and the proportion of patients with impaired cognition significantly increased (Table 2). Between the first and second postoperative evaluation, cognitive function recovered slightly, but did not achieve preoperative status (Table 2). Median time from preoperative to first postoperative evaluation was 3 days (IQR 2 – 5 days) and to second postoperative evaluation 11 days (IQR 9 – 14 days).

According to the predefined cognitive trajectories, a majority of 66 patients (73.3%) had stable cognitive function. Nine patients (10.0%) had persistent cognitive deterioration, and seven patients (7.8%) had transient cognitive deterioration. Five patients (5.6%) had persistent cognitive improvement, and three patients (3.3%) had transient cognitive improvement. Figure 2 displays the marked individual changes in cognitive function of

patients with cognitive deterioration or improvement. Mean age of the sixteen patients with persistent or transient cognitive deterioration was 67.0 ± 10.2 years with a maximum range from 47 to 81 years, which was not significantly ($p = 0.676$) different from the mean age of 68.1 years in the subgroup of patients without cognitive deterioration.

Risk factors of cognitive deterioration

Overall, 10 patients (11.1%) had cognitive deterioration between baseline and first postoperative evaluation. Logistic regression showed that an impaired preoperative cognition was the only significant risk factor for short-term cognitive deterioration (univariable OR for MMSE global score <26 vs. ≥ 26 points 8.1, 95% CI 1.5 – 43.9, $p = 0.015$; multivariable OR adjusted for age and sex 9.4, 95% CI 1.6 – 56.5, $p = 0.014$). All other investigated baseline characteristics showed no significant association with short-term cognitive deterioration. Results from the random effects model confirmed these findings.

Nine patients (10.0%) had persistent deterioration between baseline and second postoperative evaluation. None of the investigated baseline characteristics was significantly associated with persistent cognitive deterioration in logistic regression analysis. There was a statistically non-significant trend that an impaired preoperative cognition increased the risk of persistent cognitive deterioration (univariable OR for MMSE global score <26 vs. ≥ 26 points 4.3, 95% CI 0.7 – 26.6, $p = 0.112$; multivariable OR adjusted for age and sex 4.4, 95% CI 0.7 – 26.9, $p = 0.113$).

Associations of cognitive function with postoperative surgical outcomes

Fourteen patients (15.6%) died within one year after the surgical intervention. Of all investigated preoperative patient characteristics, only increasing age was significantly associated with death at one year (univariable OR per year increase 1.1, 95% CI 1.0 – 1.2, $p = 0.010$; multivariable OR adjusted for sex, CCI and MMSE global score 1.1, 95% CI 1.0 – 1.2, $p = 0.012$). Similarly, only increasing age showed some association with short-term surgical complications after 90 days (univariable OR per year increase 1.1, 95% CI 1.0 – 1.1, $p = 0.044$; multivariable OR adjusted for sex, CCI and MMSE global score 1.0, 95% CI 1.0 – 1.1, $p = 0.090$). Impaired preoperative cognition, transient cognitive deterioration and/or persistent cognitive deterioration showed no association with these two outcomes as well as with other relevant outcomes such as cancer progression or duration of in-hospital stay.

In a subgroup of patients with orthotopic bladder substitutes ($n=54$), information on postoperative incontinence was available for 53 patients. Of these, 7 patients (13.2%) had daytime incontinence and 16 patients (30.2%) had nighttime incontinence. There was no association between cognitive status and daytime incontinence. Patients with cognitive deterioration between the preoperative evaluation and the first postoperative evaluation (univariable OR 8.0, 95% CI 1.3 – 46.9, $p = 0.022$; multivariable OR adjusted for age and sex 8.0, 95% CI 1.3 – 48.5, $p = 0.024$) as well as patients with transient or persistent cognitive deterioration (univariable OR 5.0, 95% CI 1.2 – 21.1, $p = 0.031$; multivariable OR adjusted for age and sex 5.1, 95% CI 1.1 – 22.4, $p = 0.032$) had a markedly increased risk for nighttime incontinence.

Sensitivity analyses

The sensitivity analyses without imputation of missing data confirmed the results of the main analyses.

Comment

This cohort study revealed several interesting findings. Overall, cognitive function was fairly well preserved after major abdominopelvic surgery and nearly three-quarters of the patients showed a stable cognitive trajectory. Considerable individual variations in cognitive trajectories were observed. A relevant cognitive deterioration, either transient or persistent, was detected in approximately every sixth patient after the surgical procedure. Impaired preoperative cognition was identified as the most important risk factor for postoperative deterioration. Neither preoperative cognitive function nor cognitive trajectory were risk factors for postoperative mortality or complications. However, transient or persistent cognitive deterioration was associated with an approximately five-fold increased risk of nighttime incontinence.

The 17.8% POCD incidence rate found in our study is in the range reported in previous studies as well as the observation that preexisting impaired cognitive function is one of the strongest risk factors for POCD [5-7]. Furthermore our study confirms previous reports that POCD may also occur in adult patients at younger ages [1-5]. In our study, a 47-year as well as a 54-year old patient suffered from transient POCD. Age itself appears to be less important.

We also found that a transient or persistent cognitive deterioration markedly increases the risk of nighttime incontinence. One explanation could be that due to the cognitive deficit the resting tonus responsible for maintaining continence is decreased and possibly due to a concomitant neurosensory deficit the guarding reflex is impaired.

Another explanation could be that due to the cognitive impairment adherence to instructions, such as extending voiding intervals to achieve an adequate bladder substitute despite incontinence is inadequate as well as getting up at night to void. As a result bladder capacity is lower which could explain nighttime incontinence despite setting the alarm clock at 4-hourly intervals.

Some limitations need to be mentioned. First, findings of this study originate from a single center. Therefore, confirmation in an independent sample is of importance to document generalizability of our findings. Second, we used the MMSE for the evaluation of cognition. Though the MMSE tests a variety of important cognitive domains, it does not cover all cognitive domains. In particular, executive and visuo-spatial orientation are, to some extent, underrepresented in the MMSE. Findings might therefore be somewhat different, if other instruments are used. Third, our study sample was relatively small. It was not large enough to confirm the proven association between POCD and mortality [5]. We therefore believe that our negative finding was due to type 2 error. Fourth, our follow-up duration was too short to investigate cognitive deterioration persisting for several weeks to months.

There are clinical and research implications. Our study suggests implementing cognitive testing should be implemented before and after radical cystectomy. Preoperative cognitive impairment should prompt delirium prevention measures. Though we did not systematically assess postoperative delirium, there is good evidence that postoperative cognitive deterioration is due to delirium in most patients [10]. Postoperative cognitive trajectory should also be assessed in all patients not to miss POCD. In patients with

POCD, measures ensuring postoperative compliance (e.g., drug adherence) should be implemented, because these patients are at risk of not following doctors' recommendations [27-29]. In patients with cognitive dysfunction the indication for an orthotopic bladder substitution needs to be made with care. Despite the fact that in all of our patients we take their mental status into account the cognitive impairment in these patients was not recognized based on standard clinical evaluation. Research activities in surgical disciplines should include evaluation of cognitive function, whenever reasonable. Ideally, evaluation is extended by instruments for other important geriatric domains (e.g., mobility) [27-29].

Conclusions:

In conclusion, nearly three-quarters of patients undergoing radical cystectomy have a stable cognitive trajectory. In 17.8% of the patients a relevant cognitive deterioration occurs after the surgical procedure and an impaired preoperative cognition is the most important risk factor for this deterioration. Postoperative cognitive deterioration was associated with nighttime incontinence in patients with orthotopic bladder substitutes. Based on these observations cognitive evaluation before and after radical cystectomy should be performed and preoperative decision making and postoperative management adapted to optimize outcome.

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Figure Legends:

Figure 1. Flow chart

Figure 2. Individual cognitive trajectories of patients with cognitive deterioration or improvement. For visualization reasons, the figure does not display patients with stable cognitive function.

Table 1. Baseline characteristics.

Characteristic	Study participants (N = 90)
Age, years, mean \pm SD	67.9 \pm 9.3
Male sex, n (%)	63 (70.0)
Body mass index, kg/m ² , mean \pm SD	24.5 \pm 4.2
Comorbidities	
Hypertension, n (%)	51 (56.7)
Diabetes mellitus, n (%)	6 (6.7)
Coronary artery disease, n (%)	22 (24.4)
COPD, n (%)	21 (23.3)
Charlson comorbidity index	
- 0, n (%)	43 (47.8)
- 1, n (%)	36 (40.0)
- 2 or more, n (%)	11 (12.2)
Laboratory measurements	
Creatinine, μ mol/l, mean \pm SD	82.7 \pm 25.0
Hemoglobin, g/l, mean \pm SD	131 \pm 17
Prealbumin, mg/dl, mean \pm SD	22.4 \pm 5.3
Education	
Years of education, years, mean \pm SD	10.4 \pm 2.7
Type of urinary diversion	
Ileal conduit, n (%)	36 (40)
Orthotopic bladder substitution, n (%)	54 (60)
Oncological characteristics	
pT0-2b, n (%)	55 (61)
pT3a-pT4, n (%)	35 (39)
pN negative, n (%)	64 (71)
pN positive, n (%)	36 (29)
90 day postoperative complication rate	
No complication, n (%)	36 (40)
Minor (Clavien Dindo 1-2), n (%)	44 (49)
Major (Clavien Dindo 3a-5), n (%)	10 (11)

Abbreviations: COPD, chronic obstructive pulmonary disease; SD, standard deviation.

Table 2. Pre- and postoperative Mini Mental State Exam (MMSE) global scores.

	Preoperative	Postoperative		Postoperative		
		follow-up 1		follow-up 2		
			<i>p value^a</i>		<i>p value^a</i>	<i>p value</i>
MMSE global score, mean ± SD	27.8±1.8	27.3±2.9	0.032	27.4±3.0	0.417	0.151
Cognition						
- normal (MMSE global score ≥26 points), n (%)	83 (92.2)	74 (82.2)	0.023	77 (85.6)	0.070	0.607
- impaired (MMSE global score <26 points), n (%)	7 (7.8)	16 (17.8)		13 (14.4)		

Abbreviations: MMSE, Mini Mental State Exam; SD, standard deviation.

^a p value as compared to preoperative evaluation.

Figure 1. Flow chart

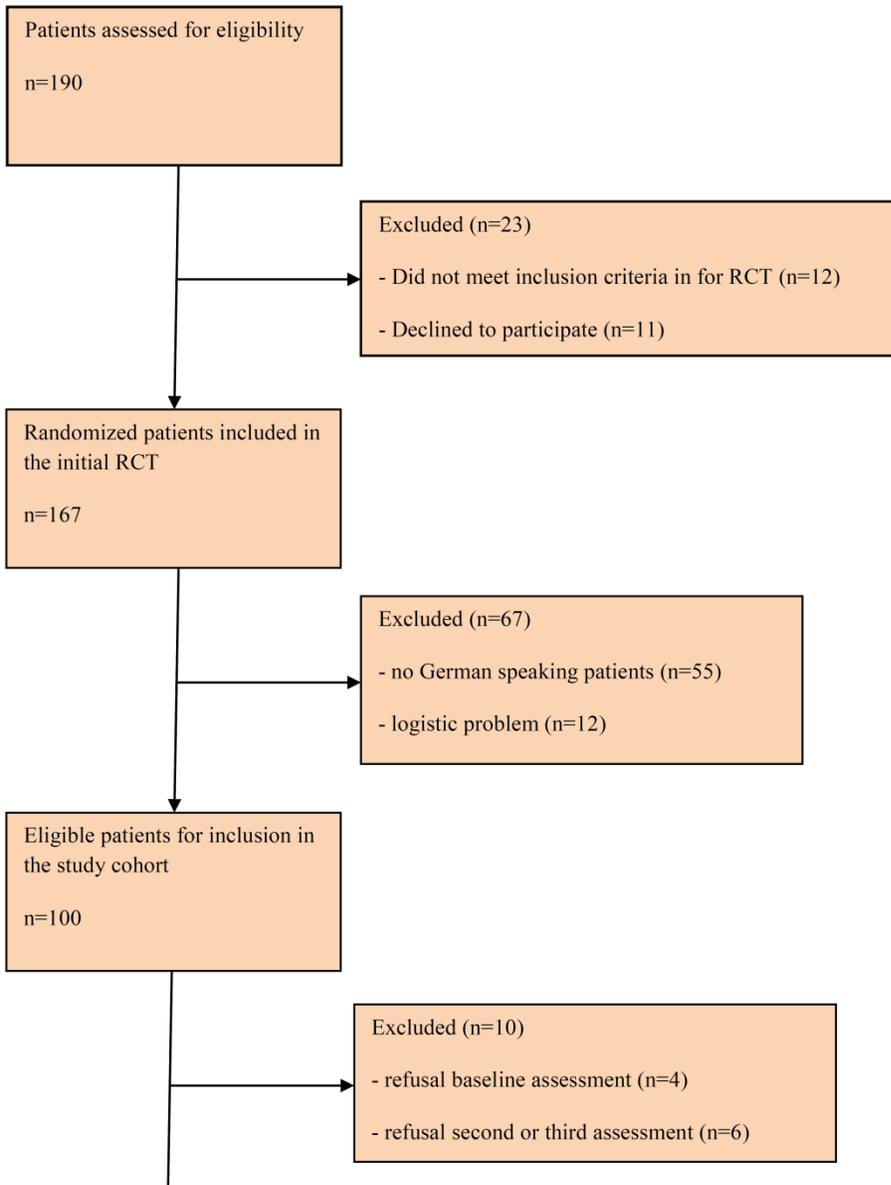


Figure 2:

