Delirium in frail surgical oncology patients

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Contents

1

General Introduction

Introduction

Background

The world's population is ageing, and it is predicted that when this ageing reaches its peak in 2050, 27.6% of Europeans will be over 65 years of age [1]. As the population ages, the prevalence of illness and hospitalization increases. Before long, cancer will be the leading cause of death, and more than half of new solid tumours will occur in patients over 70 years of age [2] . Surgery is an essential part of the multimodal treatment of solid tumours, and frail elderly patients are especially at risk of developing postoperative complications [3-5].
After surgery, postoperative delirium is a common and serious complication with incidences varying from less than 10% up to 50% depending on the type of surgery [6-12]. Delirium is associated with increased morbidity and mortality, persistent functional and cognitive decline, longer hospital stays, higher rates of nursing home placement and increased health-care costs [11,13-16].

Pathophysiology of delirium

Delirium is characterized by an acute onset of disturbances in consciousness and cognition [17]. The symptoms fluctuate during the day. The pathophysiological pathway which leads to delirium is poorly understood. It is likely that each individual case of delirium is provoked by a unique set of factors resulting in a sufficient disruption of the neuronal networks in the brain, leading to a delirium. Thus, a single mechanism for delirium will probably not be discovered [18]. Cholinergic deficiency or a failure of cholinergic neurons is thought to be the final common pathway [19]. Two possible etiological factors are 1) direct brain insults (e.g. hypotension, hypoxia, hypercapnia, infarcts and brain haemorrhage) and 2) aberrant stress responses to stressors such as infection and surgery. It has been hypothesized that the interaction of the enhanced response of stress hormone (cortisol) and inflammation systems (cytokines and prostaglandins) in older patients with damaged neurons finally leads to delirium [20-22]. The described stress response, in combination with elevated inflammatory markers, is probably more distinct in patients undergoing major surgery compared to those undergoing minor surgery. This hypothesis is supported by previous studies in which it was shown that surgical procedures for superficial tumours (breast and skin) result in few and mostly local complications, even in patients over the age of 80. Consequently, postoperative delirium is more common following major surgery. [8,23,24]

Risk factors

Many risk factors for delirium have been identified in the past in different patient populations (internal medicine, hip fracture and (cardiac) surgery). Although there is a substantial heterogeneity in the findings, it is evident that the occurrence of delirium increases with age and cognitive dysfunctioning is considered as the strongest independent risk factor [6,23,25-27]. Additional predisposing risk factors (pre-existing factors that contribute to the patient's vulnerability to develop delirium) include: co morbidity, functional impairment, sensory impairment, medical illness, various biochemical abnormalities, malnutrition, male gender, mental disorder, previous delirium, psychotropic drug use and alcohol abuse. Percipitating factors (perioperative and postoperative factors related to the surgical procedure) such as blood loss, perioperative transfusion and duration of the procedure have also been associated with postoperative delirium [11,28,29].

Prevention of postoperative delirium

Due to the lack of a general risk profile for delirium across different patient populations and settings and the still poorly understood pathophysiological pathway leading to delirium, there is currently no uniformity in the preventive approach to postoperative delirium. Both pharmacological- and non-pharmacological-, mostly multicomponent, interventions are used. Until now, most delirium prevention studies of the elderly included orthopaedic patients (usually hip-fracture patients) or patients from an acute care unit.

Aims and outline

In this thesis we aim to get better inside in the prevention of postoperative delirium in a selected group of cancer patients. Main backbone are the results of the Liaison Intervention in Frail Elderly (LIFE) study. Within this observational multicentre prospective study we compared the effect of a multi component intervention on the incidence of postoperative delirium to standard care in frail elderly cancer patients treated with an elective surgical procedure for a solid tumour.

Several aspects need to be studied. In the first place a retrospective chart review is necessary to investigate which perioperative risk factors are predictive for postoperative delirium in elderly patients undergoing a surgical procedure for a solid tumour (**Chapter 2).**

The next step is an analysis of all the interventions which are effective in the prevention of delirium (**Chapter 3**).

Chapter 4a presents the results of the Liaison Intervention in Frail Elderly (LIFE) study. This is a multicenter, randomized, clinical trial. The aim of this trial was

to evaluate the effect of a geriatric liaison intervention in comparison with standard care on the incidence of postoperative delirium in frail elderly cancer patients treated with an elective surgical procedure for a solid tumour.

In **chapter 4b** long-term outcomes of a geriatric liaison intervention in comparison with standard care were described. In addition, factors influencing physical functioning 3 months after discharge in frail elderly patients who underwent surgery for a solid tumour were investigated.

Chapter 5 offers an overview of the problems we encountered when conducting a randomized controlled trial in a frail elderly population and their possible solutions.

Chapter 6 provides a summary of the main findings of this thesis and discusses the clinical and scientific implications of the results.

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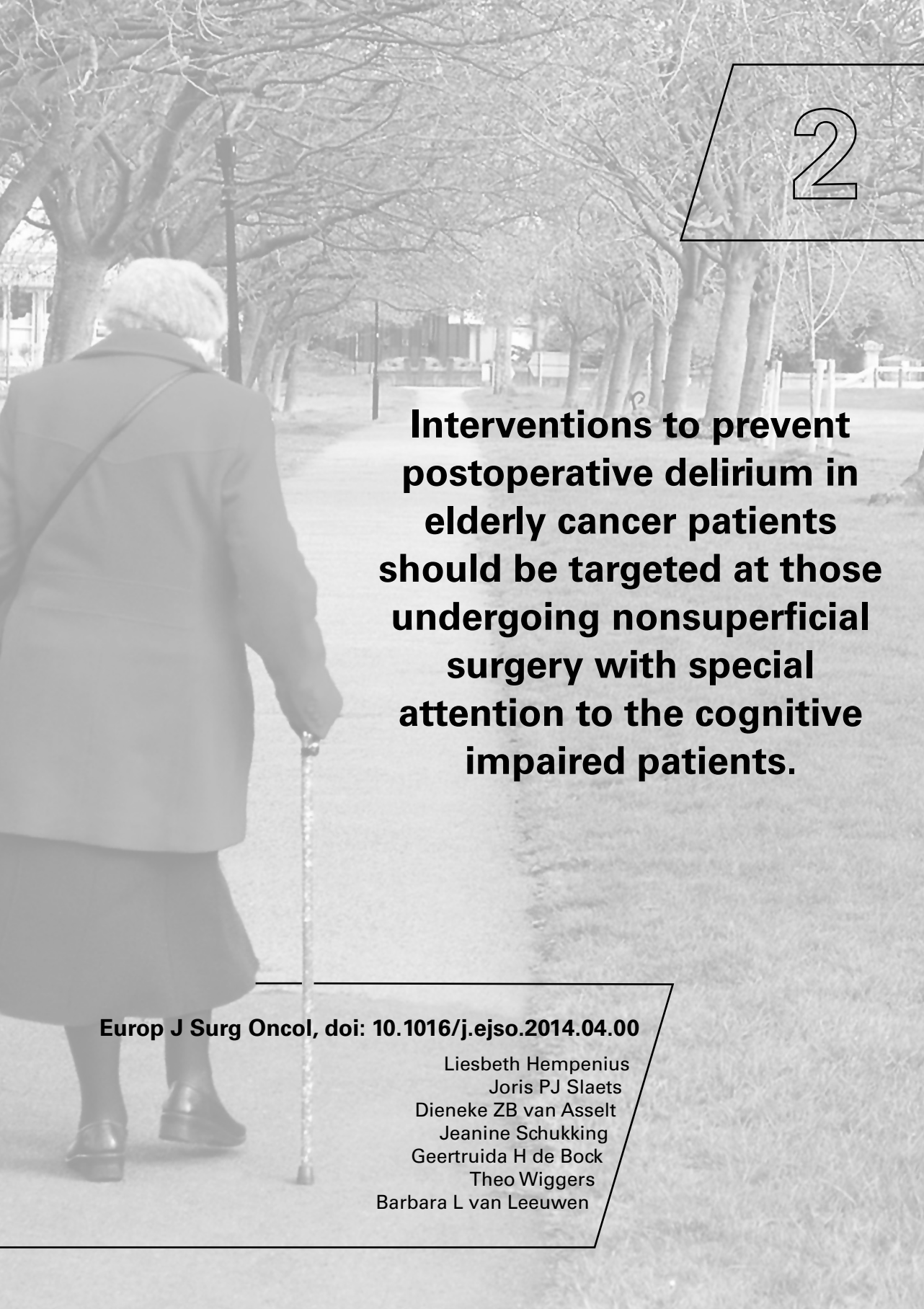

2

Interventions to prevent postoperative delirium in elderly cancer patients should be targeted at those undergoing nonsuperficial surgery with special attention to the cognitive impaired patients.

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Abstract

Aims: The aim of this study was to determine risk factors for postoperative delirium (POD) in elderly cancer patients.

Methods: This study was an observational multicentre retrospective study performed in the University Medical Center Groningen and Medical Center Leeuwarden, the Netherlands. Patients over 65 years of age undergoing elective surgery for a solid tumour were included. The main outcome was POD. Medical records were screened for POD using a standardized instrument. The risk factors considered were: age, gender, severity of the surgical procedure, co-morbidity, American Society of Anaesthesiologists (ASA) score and 15 items suggestive for frailty as measured with the Groningen Frailty Indicator (GFI). To examine an association between the risk factors and the development of POD, univariate and multivariate logistic regression analysis was performed to estimate odds ratios (ORs) and 95% confidence intervals (CIs).

Results: We reviewed 251 medical records. Forty-six patients developed POD (18.3%). Preoperative cognitive functioning (as measured by the item cognition of the GFI) (OR: 23.36; 95% CI: 5.33-102.36) and severity of the surgical procedure were identified as independent risk factors for POD; intermediate (OR: 15.44, 95% CI: 1.70-140.18) and major surgical procedures (OR: 45.01, 95%CI: 5.22-387.87) significantly increased the risk for POD as compared to minor surgery.

Conclusions: Preoperative cognitive functioning and the severity of the surgical procedure are independent risk factors for POD in elderly undergoing elective surgery for a solid tumour.

Introduction

Surgery is an essential part of the multimodality treatment of solid tumours. After surgery, postoperative delirium (POD) is a common and serious complication with incidences varying from less than 10% up to 50% depending on the type of surgery [1-7]. Delirium is associated with increased morbidity and mortality, persistent functional and cognitive decline, longer hospital stays, higher rates of nursing home placement and increased health-care costs [6,8-11]. Early identification of patients at risk for POD is the first step in possible prevention and optimization of care for this growing group of patients.

In the literature patient related risk factors for developing (postoperative) delirium are well described in orthopaedic-, general surgical-, thoracic surgical- and medical (elderly) populations. Although there is a substantial heterogeneity in the findings, it is evident that the occurrence of delirium increases with age and cognitive dysfunctioning is considered as the strongest independent risk factor. Additional risk factors concerning physical and mental functioning have been identified [1,12]. These factors include co-morbidity, functional impairment, sensory impairment, medical illness, various biochemical abnormalities, malnutrition, male gender, mental disorder, previous delirium, psychotropic drug use and alcohol abuse. Variables related to the surgical procedure such as blood loss [13], perioperative transfusion [6,14] and duration of the procedure [14] have also been associated with POD. However, to date no study has been performed on a specific elderly oncological surgical population investigating predictors of postoperative delirium.

The objective of this study was to investigate which perioperative risk factors were predictive for POD in elderly patients undergoing a surgical procedure for a solid tumour.

Patients and methods

Design

This study was a retrospective chart review performed in the University Medical Center Groningen and Medical Center Leeuwarden, the Netherlands.

This study was a side study from the Liaison Intervention in Frail Elderly study (LIFE, Trial ID NTR 823). The LIFE study is a multicenter randomized controlled trial that was conducted between April 2007 and June 2010 [15]. For this study, we recruited patients over 65 years of age undergoing surgery under general anaesthesia for a solid tumour at the outpatient's departments of general surgery, gynaecology, oral surgery and Ear, Nose and Throat medicine. We

excluded patients undergoing surgery under local anaesthesia and patients with a benign tumour. A total of 911 patients were screened for frailty with the GFI, 270 were classified as frail and 641 were classified as non-frail. Frail was defined as GFI score greater than three [16] (Appendix 1). One hundred-and-ninety frail patients participated in the intervention study in which they were randomized to standard treatment versus a geriatric liaison intervention. The primary outcome was the incidence of POD.

Patients included in the current analysis

In the here presented analysis, the eighty frail patients that did not participate in the intervention study were included and compared to a sample of non-frail patients (see figure 1). To compose the non-frail patients group for the current study, a sample of the screened non-frail patients (n = 641) was taken based on the proportion of non participating frail patients (n = 80) of the in total screened frail patients (n = 270): (80/ 270) * 641 = 189 (figure 1).

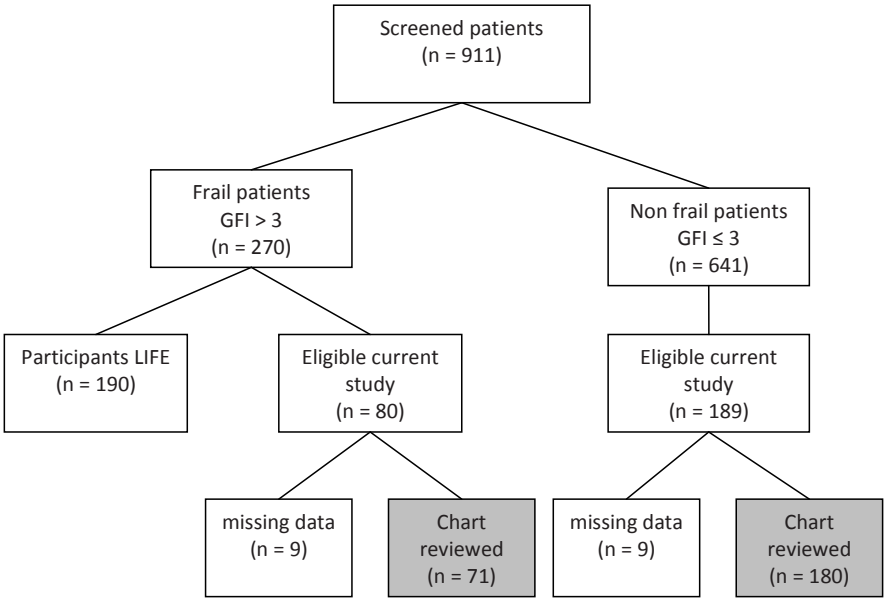

Figure 1: Flow chart of the study. participants current investigation.

Main outcome

Postoperative Delirium

The chart-based instrument developed by Inouye et al. was used to screen for POD in the medical records of the patients [17]. This is a validated instrument for groups of patients with a sensitivity of 74% and a specificity of 83% compared to the Confusion Assessment Method [18].

With this instrument the chart abstractor searched for key terms for identification of delirium, particularly any evidence of an acute change in mental status (e.g., delirium, mental status change, inattention, disorientation, hallucinations, agitation, inappropriate behavior, etc.). Delirium was coded as ''yes'' if any key terms or descriptors were present and evidence of acute onset or acute change in symptoms was present. Evidence of reversibility was not required for the chart diagnosis of delirium.

Risk factors

Age and gender

Age and gender of the participants were collected from their medical record.

Co-morbidity

Co-morbidity was quantified using the Charslon co-morbidity index (CCI) [19]. Each medical condition was assigned a weighted score.

American Society of Anaesthesiologists (ASA) score

ASA score as preoperatively determined by the treating anaesthesiologist was used.

Frailty

To measure frailty, patients were assessed preoperatively with the Groningen Frailty Indicator (GFI) [16,20,21] (Appendix 1). The GFI screens for the loss of functions and resources in 4 domains of functioning: physical (mobility functions, multiple health problems, physical fatigue, vision, hearing), cognitive (cognitive functioning), social (emotional isolation), and psychological (depressed mood and feelings of anxiety). A score of 0 is non-frail and 15 is the maximum score of frailty. The GFI is an internal consistent scale (Cronbach's Alpha 0.77) [21].

Severity of the surgical procedure

Surgical procedures were divided into three categories: minor, intermediate and major based on the duration of the operation and the localization of the tumour (intracavitary versus superficial) (Table 1).

Table 1. Classification of the type of surgery by duration of the procedure and tumour localization

Severity of the surgical procedure	Tumour localisation
Minor	breast and skin
Intermediate	vulva, cervix, endometrium, uterus, head/neck and retroperitoneum
Major	gastrointestinal, liver, pancreas, lung, ovary, oropharynx and larynx and intra-abdominal sarcoma

Analysis

The risk factors were dichotomized where needed. Age was categorized in ≤75 versus > 75 years and ASA score in ≤ 2 (healthy patient or mild systemic disease) versus > 2. The CCI was dichotomized in ≤ 3 and > 3 based on a median score of 3. All items of the GFI were analyzed separately.

IBM SPSS Statistics Version 20 was used for the statistical analysis. For the primary question the dependent variable was the occurrence of POD. To examine an association between the risk factors and the development of POD, univariate logistic regression analysis was used and Odds Ratios (ORs) with 95% Confidence Intervals (CI) were calculated. The variables with a p value <0.05 in the univariate analyses were entered into a backward stepwise multiple logistic regression model requiring a p value of less than 0.05 to remain.

Results

Participants

Characteristics of the patients are shown in Table 2. The mean age of the population under study was 74.2 ± 6.4 (65 – 92). Forty-six patients developed POD. Most patients underwent major surgery.

Table 2. Demographic characteristics

Characteristics	n = 251
Age (years)	
Mean ± SD (range)	74.2 ± 6.4 (65 – 92)
Women, n (%)	146 (58.2)
Co morbidities (CCI[a])	
mean ± SD (range)	4 ± 2.2 (0-10)
ASA score[b], n (%)	
1	15 (6)
2	153 (61)
3	76 (30.3)
4	5 (2)
missing	2 (0.8)
Frail[c], n (%)	71 (28.3)
Severity of the surgical procedure, n (%)	
Minor	77 (30.7)
Intermediate	54 (21.5)
Major	120 (47.8)
Delirium, n (%)	46 (18.3)

[a] Charlson co-morbidity index, a weighted index which measures the burden of co morbidities and predicts 1-year mortality (range 0-19 indicating respectively no co morbidities to considerable co morbidities.

[b] American Society of Anaesthesiologists score (assess the fitness of patients prior to surgery, 1= a normal healthy individual and 5 = a moribund patient who is not expected to survive without the operation).

[c] Patients with a Groningen Frailty indicator score >3 were regarded as frail.

Risk factors for postoperative delirium

Univariate analyses showed that male gender (OR: 2.31, 95% CI: 1.21-4.44), ASA score (OR: 2.21, 95% CI 1.14-4.29), intermediate (OR: 17.27, 95% CI: 2.14-139.49) and major surgery (OR: 31.29, 95% CI: 4.19-233.96) were associated with an increased risk of POD. Although the combined frailty score of the GFI was not associated with and increased POD risk, the score of three individual items of the GFI: grocery shopping (OR: 3.09, 95% CI: 1.39-6.87), cognition (OR: 12.57, 95% CI: 4.12-38.40) and rating of ones own physical fitness (OR: 2.23, 95% CI: 1.24-2.77), were associated with an increased risk for POD. POD was not significantly associated with age, comorbidities according to the Charlson co-morbidity index or other GFI items (table 3).

Table 3. Univariate analysis of risk factors for the development of postoperative delirium

	No delirium n = 205	Postoperative delirium n = 46	OR (95%CI)
Age, n (%)			
≤ 75 years	127 (83.6)	25 (16.4)	
>75 years	78(78.8)	21 (21.2)	1.37 (0.72-2.61)
Gender, n (%)			
Women	127 (87)	19 (13)	
Men	78 (74.3)	27 (25.7)	2.31 (1.21-4.44)[a]
Co morbidities (CCI)[b], n (%)			
≤ 3	112 (84.2)	21 (15.8)	
> 3	93 (78.8)	25 (21.2)	1.43 (0.75-2.72)
ASA score[c], n (%)			
≤ 2	145 (86.3)	23 (13.7)	
> 2	60 (74.1)	21 (25.9)	2.21 (1.14-4.29)[a]
Severity of the surgical procedure, n (%)			
Minor	76 (98.7)	1 (1.3)	
Intermediate	44 (81.5)	10 (18.5)	17.27 (2.14-139.49)[a]
Major	85 (70.8)	35 (29.2)	31.29 (4.19-233.96)[a]
Groningen Frailty Indicator			
Mobility (perform the following tasks without assistance)			
Grocery shopping			
Yes	184 (84.4)	34 (15.6)	
No	21 (63.6)	12 (36.4)	3.09 (1.39-6.87)[a]
Walk outside			
Yes	196 (82)	43 (18)	
No	9 (75)	3 (25)	1.52 (0.40-5.85)
Getting (un)dressed			
Yes	194 (82.2)	42 (17.8)	
No	11 (73.3)	4 (26.7)	1.68 (0.51-5.53)
Visiting restroom			
Yes	202 (82.4)	43 (17.6)	
No	3 (50)	3 (50)	4.70 (0.92-24.07)
Vision			
Impaired vision			
No	194 (81.5)	44 (18.5)	
Yes	11 (84.6)	2 (15.4)	0.80 (0.17-3.75)
Hearing			
Impaired hearing			
No	171 (82.2)	37 (17.8)	
Yes	34 (79.1)	9 (20.9)	1.22 (0.54-2.77)
Nutrition			
Unintentional weight loss			
No	172 (82.3)	37 (17.7)	
Yes	33 (78.6)	9 (21.4)	1.27 (0.56-2.87)
Co-morbidity			
≥ 4 different types of medication			
No	103 (84.4)	19 (15.6)	
Yes	102 (79.1)	27 (20.9)	1.44 (0.75-2.74)

Table 3. Continued

	No delirium n = 205	Postoperative delirium n = 46	OR (95%CI)
Groningen Frailty Indicator			
Cognition			
Any complaints on memory (or diagnosed with dementia)			
No/ sometimes	200 (85.1)	35 (14.9)	
Yes	5 (31.2)	11 (68.8)	12.57 (4.12-38.40)[a]
Psychosocial			
Experience of emptiness			
No	181 (81.2)	42 (18.8)	
Yes/ sometimes	24 (85.7)	4 (14.3)	0.72 (0.24-2.18)
Missing other people around			
No	159 (81.1)	37 (18.9)	
Yes/ sometimes	46 (83.6)	9 (16.4)	0.84 (0.38-1.87)
Feel left alone			
No	190 (81.5)	43 (18.5)	
Yes/ sometimes	15 (83.3)	3 (16.7)	0.88 (0.25-3.19)
Feel down or depressed			
No	150 (82)	33 (18)	
Yes/ sometimes	55 (80.9)	13 (19.1)	1.07 (0.53-2.19)
Feel nervous or anxious			
No	128 (81)	30 (19)	
Yes/ sometimes	77 (82.8)	16 (17.2)	0.89 (0.45-1.73)
Physical fitness			
Rating own physical fitness (0 = very bad, 10 = very good)	159 (85.5)	27 (14.5)	
7-10	46 (70.8)	19 (29.2)	2.23 (1.24-2.77)[a]
0-6			

[a] Significant difference.[b] Charlson co-morbidity index, a weighted index which measures the burden of co morbidities and predicts 1-year mortality (range 0-19 indicating respectively no co morbidities to considerable co morbidities. [c] American Society of Anaesthesiologists score (assess the fitness of patients prior to surgery, 1= a normal healthy individual and 5 = a moribund patient who is not expected to survive without the operation).

Multivariate logistic regression analyses with the factors significantly associated with POD in univariate analyses identified the item cognition of the GFI (OR: 23.36; 95% CI: 5.33-102.36) and severity of the surgical procedure as independent risk factors for POD (table 3). Both intermediate (OR: 15.44, 95% CI: 1.70-140.18) and major surgery (OR: 45.01, 95%CI: 5.22-387.87) significantly increased the risk for POD compared to minor surgery (Table 4).

Table 4. Multivariate analysis of preoperative risk factors for POD

	Odds Ratio	95% CI
Cognition[a]	23.36	5.33-102.36 [b]
Severity of the surgical procedure		
Minor	1	
Intermediate	15.44	1.70-140.18[b]
Major	45.01	5.22-387.87[b]

[a] Any complaints on memory (or diagnosed with dementia).
[b] Significant difference.

Discussion

In this study POD was found in 64 of the 251 elderly undergoing elective surgery for a solid tumour. Our results suggest that in this population the severity of the surgical procedure is a more important predictor of delirium than other predisposing factors, with the exception of reported cognitive dysfunctioning. From previous studies it is known that surgical procedures for superficial tumours (breast and skin) result in few and mostly local complications, even in patients over the age of 80 [3,22,23]. Also POD is more common following major surgery [3,24,25]. The pathophysiological pathway which leads to delirium is poorly understood. Cholinergic deficiency or a failure of cholinergic neurons is thought to be the final common pathway [26]. Two possible etiological factors are 1) direct brain insults (e.g. hypotension, hypoxia, hypercapnia, infarcts, and brain haemorrhage) and 2) aberrant stress responses to stressors such as infection and surgery. It has been hypothesized that the interaction of the enhanced response of stress hormone (cortisol) and inflammation systems (cytokines and prostaglandins) in older patients with damaged neurons finally leads to delirium [27-29]. The described stress response, in combination with elevated inflammatory markers, is probably more distinct in patients undergoing major surgery.

As mentioned in the introduction, findings according to risk factors for delirium are heterogeneous. Many risk factors have been identified in the past in different patient populations (internal medicine, hip fracture and (cardiac) surgery). From previous studies, cognitive functioning was known as the strongest independent risk factor for delirium [1,12,24,30,31]. Other risk factors vary in the literature and it seems difficult to establish a general risk profile for delirium across different patient populations and settings. In the present study, cognitive dysfunctioning as identified with the GFI and severity of surgical procedure appeared to be independent risk factors for POD in elderly undergoing elective surgery for a solid tumour. All other risk factors (age, gender, co-morbidity, ASA score and items of the GFI in the domains of

physical-, social- and psychological functioning) lost significance in multivariate analysis.

Although most variables were collected prospectively, it was not always possible to retrieve a delirium diagnosis according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (* DSM IV) criteria. By using a chart-based instrument, it is possible that over reporting of POD occurred as patients with minor (prodromal) symptoms were diagnosed with POD. On the other hand it is known that documentation of delirium in the medical chart is poor [32], although we used a validated screening instrument. As part of the population of this study was composed of patients that refused participation in an intervention trial this may have led to a selection bias. Patients are possibly frailer than in a general population; although this is not apparent form the results. Nor is the POD incidence much higher than expected.

In conclusion, this retrospective study shows that cognitive functioning and the severity of the surgical procedure correlate with the incidence of POD in elderly patients undergoing surgery for a solid tumour. For clinical practice this implies that vulnerable elderly can undergo minor surgery with nearly no increased risk of delirium. Interventions to prevent POD should be focused on elderly undergoing intermediate or major surgery with special attention to those with impaired cognitive functioning (table 5).

Table 5. Crosstab of the identified risk factors

	Cognition (Any complaints of memory or diagnosed with dementia)		
	No/ sometimes	Yes	Total, n (%)
Severity of the surgical procedure			
Minor (n=77)			
No delirium, n (%)	74 (96.1)	2 (2.6)	76 (98.7)
Postoperative delirium, n (%)	0 (0)	1 (1.3)	1 (1.3)
Intermediate (n=54)			
No delirium, n (%)	42 (77.8)	2 (3.7)	44 (81.5)
Postoperative delirium, n (%)	5 (9.3)	5 (9.3)	10 (18.5)
Major (n=120)			
No delirium, n (%)	84 (70)	1 (0.8)	85 (70.8)
Postoperative delirium, n (%)	30 (25)	5 (4.2)	35 (29.2)

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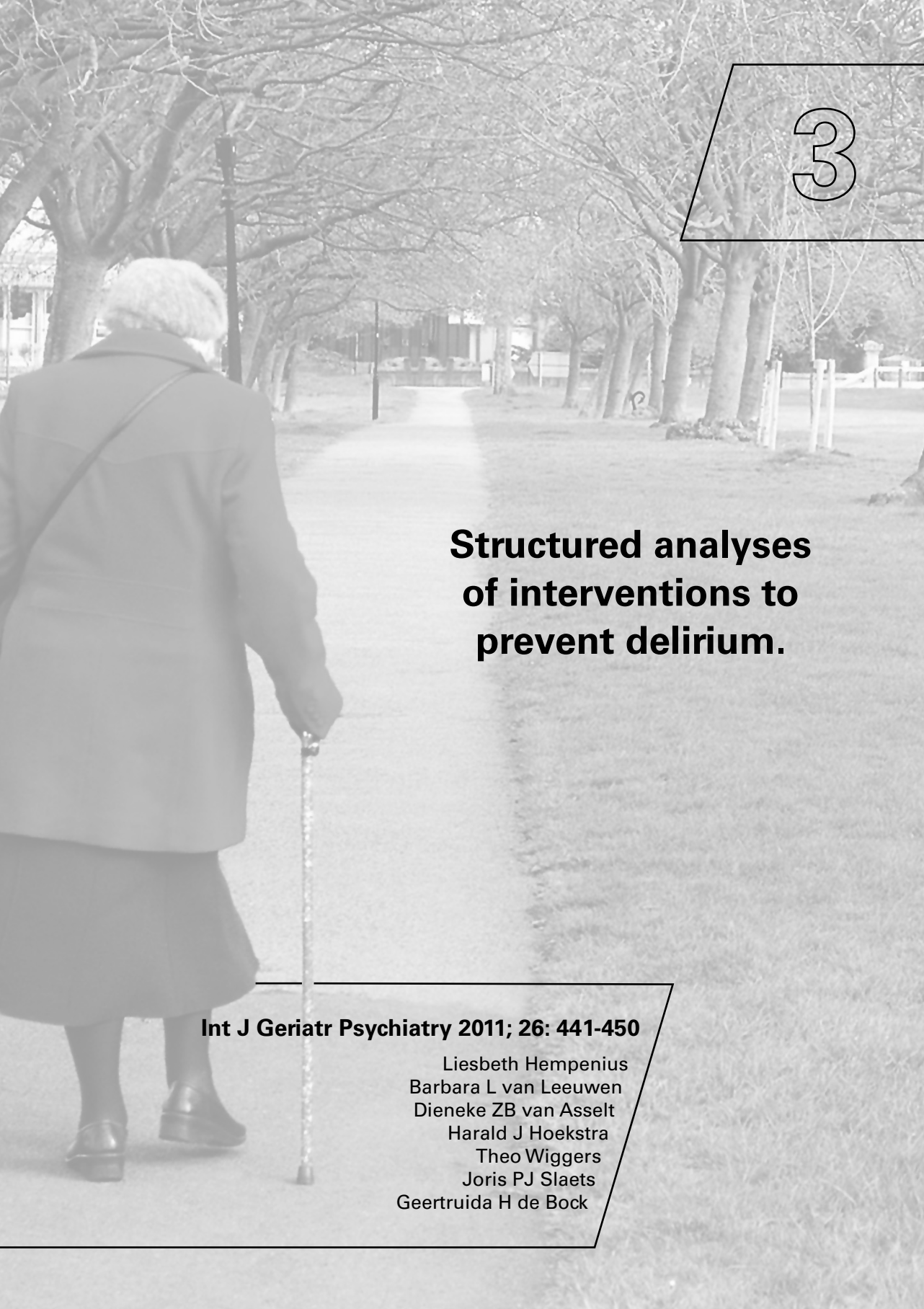
APPENDIX 1

Groningen Frailty Indicator

CIRCLE THE APPROPRIATE ANSWER AND ADD SCORES

	Yes	No	
Mobility Can the patient perform the following tasks without assistance from another person (walking aids such as a cane or wheelchair are allowed)			
1. Grocery shopping	**0**	**1**	
2. Walk outside house (around house or to neighbours)	**0**	**1**	
3. Getting (un)dressed	**0**	**1**	
4. Visiting restroom	**0**	**1**	
Vision 5. Does the patient encounter problems in daily life because of impaired vision?	**1**	**0**	
Hearing 6. Does the patient encounter problems in daily life because of impaired hearing?	**1**	**0**	
Nutrition 7. Has the patient unintentionally lost a lot of weight in the past 6 months (6kg in 6 months or 3 kg in a month)	**1**	**0**	
Co-morbidity 8. Does the patient use 4 ore more different types of medication?	**1**	**0**	
	Yes	No	Sometimes
Cognition 9. Does the patient have any complaints on his/her memory (or diagnosed with dementia)	**1**	**0**	**0**
Psychosocial 10. Does the patient ever experience emptiness around him?	**1**	**0**	**1**
11. Does the patient ever miss the presence of other people around him?	**1**	**0**	**1**
12. Does the patient ever feel left alone?	**1**	**0**	**1**
13. Has the patient been feeling down or depressed lately?	**1**	**0**	**1**
14. Has the patient felt nervous or anxious lately?	**1**	**0**	**1**
Physical fitness 15. How would the patient rate his/her own physical fitness? (0-10, 0 is very bad, 10 is very good) 0-6=1 7-10= 0	**1**	**0**	
TOTAL SCORE GFI			



3

Structured analyses of interventions to prevent delirium.

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Abstract

Background: Delirium is one of the most serious complications in hospitalized elderly, with incidences ranging from 3-56%. The objective of this meta-analysis was two-fold, first to investigate if interventions to prevent delirium are effective and second to explore which factors increase the effectiveness of these interventions.

Methods: An electronic search was carried out on articles published between January 1979 and July 2009. Abstracts were reviewed, data were extracted and methodologic quality was assessed by two independent reviewers. Effect sizes of the interventions were expressed as ORs (Odds Ratios) and 95%CIs (Confidence Intervals). A random effect model was used to provide pooled ORs. To explore which factors increase the effectiveness of the interventions, ORs were stratified for several factors.

Results: 16 relevant studies were found. Overall the included studies showed a positive result of any intervention to prevent delirium (pooled OR 0.64; 95%CI 0.46-0.88). The largest effect was seen in studies on populations with an incidence of delirium above 30% in the control group (pooled OR 0.34; 95%CI 0.16-0.71 versus 0.76; 95%CI 0.60-0.97).

Conclusions: Interventions to prevent delirium are effective. Interventions seem to be more effective when the incidence of delirium in the population under study is above 30%. To maximize the options for a cost-effective strategy of delirium prevention it might be useful to offer an intervention to a selected population.

Introduction

Delirium is one of the most serious complications in hospitalized elderly. It is associated with increased morbidity and mortality, persistent functional and cognitive decline, longer hospital stay, higher rates of nursing home placement and increased health care costs [1-5]. Mortality rates vary from 4-20% in patients who develop delirium during hospital stay [5;6].
Delirium is characterized by an alteration of consciousness with reduced ability to focus, sustain and shift attention (DSM-IV) [7]. The reported incidence of delirium varies widely between and within the populations under investigation. Incidences range from 5.1% to 52.2% after noncardiac surgery [8] from 3% to 47% after cardiac surgery [9] and from 14% to 56% in elderly hospitalized medical patients [10]. Many studies have examined the risk factors for delirium (e.g. [6;11;12]). In two systematic literature reviews [8;13] it was shown that dementia/ cognitive impairment, medical illness and advanced age were most strongly associated with postoperative delirium. Other identified risk factors included sensory impairment, functional impairment, medications/ greater co-morbidity, preoperative psychotropic drug use, psychopathological symptoms, institutional residence, abnormal blood urea nitrogen/ creatinine ratio, abnormal sodium or potassium level and alcohol abuse.
Several interventions to prevent delirium have been developed. Some studies focus on pharmacological interventions only, others contain (a combination of) non pharmacological interventions. An intervention aimed at multiple risk factors is also called a multicomponent intervention. When studying the effectiveness of interventions to prevent delirium, results are not conclusive. The purpose of this meta-analysis is first to investigate the effectiveness of interventions studies to prevent delirium and second to explore the influence of various factors on the effectiveness of intervention studies to prevent delirium.

Methods

Search strategy

An electronic search was carried out using PubMed, the Cochrane Register of Controlled Trials and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases between January 1979 and July 2009. The following keywords were used: “delirium” or “acute confusion” and “prevention and control” or “primary prevention” or “intervention”. Only original research published in English concerning adult inpatients (i.e. age > 18) was considered. Studies with a terminal ill or sedated population were

excluded. In addition, the reference list of relevant articles was searched for supplemental articles.
Articles meeting the following criteria were selected:

- evaluation of a controlled intervention for prevention of delirium,
- exclusion of patients with delirium at baseline,
- inclusion of an operational definition for delirium consistent with the Diagnostic and Statistical Manual of Mental disorders (DSM)-criteria. Studies using the Confusion Assessment Method (CAM) [14] to diagnose delirium were also included because the CAM instrument consists of nine operationalized criteria from the DSM-III-R.

Selection of studies

The literature search in PubMed yielded 60 studies, of which 10 fulfilled the inclusion criteria. The Cochrane database yielded 11 new articles of which 1 fulfilled the inclusion criteria and the CINAHL database yielded 7 new articles of which 1 fulfilled the inclusion criteria.
The remaining studies were not included in this review for the following reasons:

1) Study population including delirious patients at baseline, terminal ill or sedated patients (n = 8).
2) Intervention not targeted at the prevention of delirium or not executed in the hospital (n = 51).
3) Not using the DSM definition of delirium (n = 6).

In the study of Schindler et al. (1989) a research old age psychiatrist established delirium after a single assessment. It was assumed that in this study this psychiatrist used the DSM criteria to establish the diagnosis. Sampson et al. (2007) used the Delirium Symptom Interview (DSI) [15] to diagnose delirium, which has proven to be valid and reliable instrument in hospitalized elderly.
Besides these 12 selected studies, 4 additional studies, that fulfilled the inclusion criteria, were extracted from reference lists. Therefore, in total 16 articles were analyzed.

Data extraction and assessment of methodologic quality

The following study characteristic were assessed: population, selection of patients at high risk for the development of delirium based on patient-related factors, number of participants, age range and mean age of the population, intervention, incidence of delirium in control and intervention group and p-value describing the effectiveness of the intervention. Methodologic quality of included studies was evaluated based on their study design using the criteria proposed by the Cochrane Collaboration [16].

Abstract selection, data extraction and assessment of methodological quality were done by LH and BL independently. Points of disagreement were discussed to reach consensus. Some studies had heterogeneous populations, for example Caplan et al. (2007) included patients with a fracture, patients who had collapsed as well as patients with an infection [17]. For such heterogeneous populations we assumed that that both the intervention and control groups were equally divergent and equally treated.

Analysis

To compare the effect of interventions the odds ratio (OR) between odds of incidence of delirium in the control group and intervention group of the individual studies was calculated for every study separately. In addition, the 95% confidence intervals (CIs) were calculated. Because of small study sizes, a meta-analysis was carried out to estimate the effect of several factors expected the influence the effectiveness of the interventions as accurate as possible under the assumption of homogeneity. Therefore the Mantel-Haenszel method (random effect model) in Review Manager Version 5.0[18] was used to provide a pooled OR across studies with 95%CI. 95%CIs of the subgroups were compared to judge the influence of the covariate. If there was a substantial overlap between the confidence intervals, it was assumed that the impact of the covariate did not differ for the subgroups under study. Effect estimates were stratified for the following potential covariates: incidence of delirium in the control group (low incidence *versus* high incidence), type of intervention (pharmacological *versus* one-component *versus* multicomponent), type of treatment (surgical *versus* non-surgical) and selection of patients based on patient related risk factors for delirium (no selection *versus* selection). It was assumed that the incidence of delirium in the control group reflected the expected incidence of delirium in the population under study in a non research situation. When the incidence was high in the control group, it was expected that a high risk population was included. Because there is no consensus on what constitutes a high prevalence of delirium, the median percentage was used as cut off point (30%).

To detect a possible publication bias a funnel plot was created.

Results

Study characteristics

The descriptive characteristics of the 16 included articles are provided in Table 1. Twelve studies contained a surgical population. Ten randomized controlled trials were included. Three studies included only patients with an increased risk for delirium. The age of the participants was 40 years or above. In nine of the studies a pharmacological intervention was tested. The number of included patients per study ranged from 21 to 852. The incidence of delirium varied between 0 and 44% in the control group and 0 and 50% in the intervention group.

Validity of studies

Tables 2 and 3 show the methodological quality of the studies. Pharmacological interventions are overall of a better methodological quality than non-pharmacological interventions.

Meta-analysis results

Overall the selected studies showed a positive result of interventions to prevent delirium (pooled OR 0.64; 95%CI 0.46-0.88) (figure 1). The effect of the interventions to prevent delirium varied widely among studies, with ORs ranging from 0.10 (95%CI: 0.01-0.89 and 0.00-2.07, respectively) to 6.03 (95%CI: 0.27-136).

When stratifying the individual studies by factors expected to influence the effectiveness of the studies, 95%CI became broader and estimates less accurate through less observation per stratum. When comparing CIs of subgroups per covariate, for most covariates there was a large overlap of confidence intervals, indicating little influence of the several levels of the covariate on the effectiveness of interventions. The results in Table 4 show that there was no difference in effectiveness between pharmacological interventions *versus* multicomponent interventions *versus* one component interventions (OR 0.58; CI 0.39 – 0.87 *versus* OR 0.59; CI 0.38 – 0.92 *versus* OR 1.05; CI 0.09-11.57) (Table 4). In non-surgical patients the interventions were as effective as in surgical patients (OR 0.59; CI 0.40 – 0.89 *versus* OR 0.65; CI 0.41 - 0.1.04) (table 3). Overall only three studies pre-operatively selected patients with an increased risk for delirium based on patient-related risk factors (17;19;20). There was no difference in effectiveness when comparing these studies with studies not using selection based on patient-related factors (OR 0.66; CI 0.38 – 1.14 versus OR 0.62; CI 0.41 -0.95) (table 3). The two studies with the largest populations [19;20] selected patients at high risk for delirium

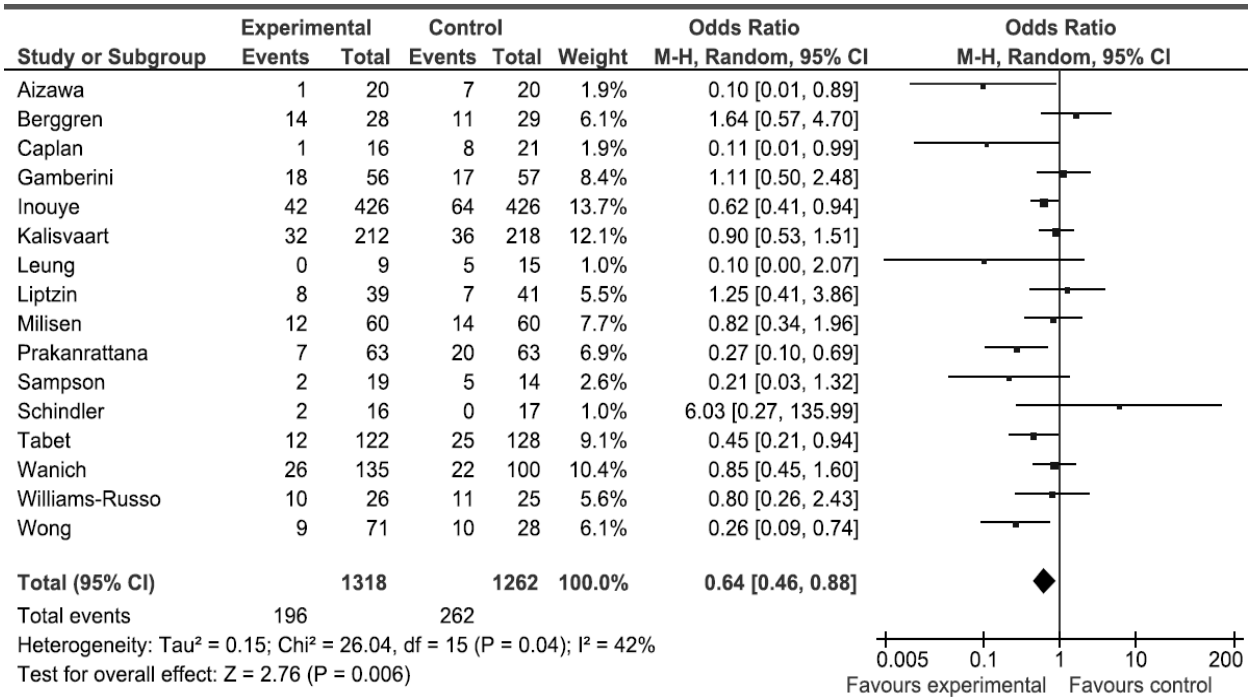

Figure 1. Forest plot of individual and pooled ods ratio analysis of the selected intervention studies to prevent delirium. A square represents the OR for a given study with the size of a square being proportional to the weighting of that study in the meta-analysis. A horizontal line indicates the OR's 95% confidence interval (CI). The diamond ate the bottom represents the pooled OR. The width of the diamond represents the 95% CI for the pooled OR.

based on patient-related factors but showed an incidence rate of delirium below 30% in the control group, namely 15% and 16.5% respectively.
For studies with an incidence of delirium > 30% in the control group versus an incidence of delirium ≤ 30% the overlap of confidence intervals is minimal, indicating that interventions in the studies with a high incidence of delirium were more effective (OR 0.34; CI 0.16-0.71 *versus* OR: 0.76; CI 0.60-0.97, respectively) (Table 3). Among the studies with an incidence of delirium above 30% in the control group, 7 out of 8 studies showed a positive effect of the intervention.
The funnel plot of the included studies has a symmetric shape which shows that an increased study size is not related to an increased treatment effect and makes publication bias unlikely (see Figure 2).

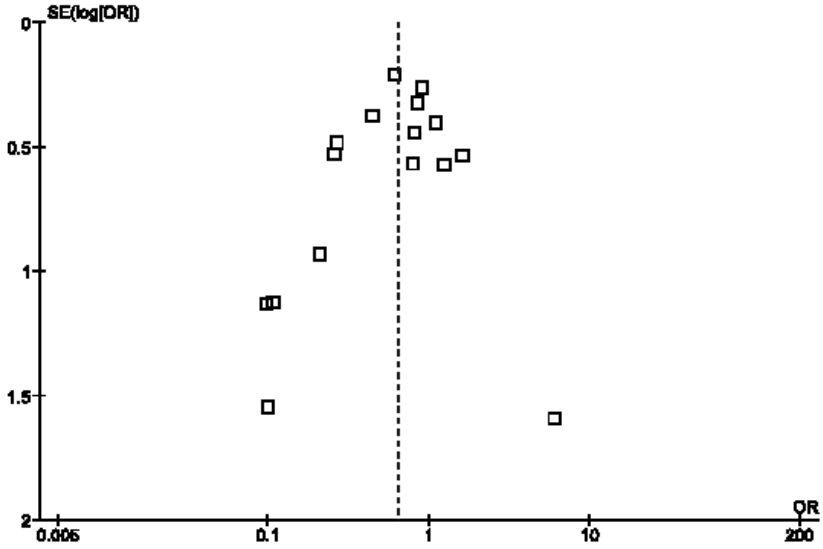

Figure 2. Funnelplot of selected studies

Table 1. Characteristics of 16 included studies

Study	Population	Selection	Age range and mean age	Intervention	Definition delirium	Incidence of delirium % (n)		p-value
						Control	Intervention	
Aizawa *et al.* (2002) [32] RCT	Surgery gastric or colon cancer	No	R: 71-86 MC: 76.2 MI: 75.9	Pharmacological: Diazepam injection and continuous infusion of flunitrazepam and pethidine for the first 3 nights postoperative	DSM-IV	35 (7/20)	5 (1/20)	p = 0.023
Berggren *et al.* (1987) [33] RCT	Surgery femoral neck fracture	No	R: 65-92 MC: 77 MI: 78	Pharmacological: Epidural vs. halothane anaesthesia	DSM-III	38 (11/29)	50 (14/28)	Ns
Caplan and Harper (2007) [18] Before-after	Patients admitted to the geriatric wards	Yes	R: >70 MC: 83.8 MI: 85.6	Non-Pharmacological: Multicomponent volunteer-mediated prevention programme vs. care as usual	CAM	38.1 (8/21)	6.3 (1/16)	p = 0.032
Gamberini *et al.* (2009) [34] RCT	Elective cardiac surgery with cardiopulmonary bypass	No	R: ≥ 65 MC: 74.4 MI: 74.1	Pharmacological: rivastigmine vs. placebo	CAM	30 (17/57)	32 (18/56)	p = 0.8
Inouye *et al.* (1999) [20] NRCT	General-medicine service patients	Yes	R: ≥ 70 MC: 79.8 MI: 79.6	Non-pharmacological: Multicomponent intervention. Interdisciplinary team, intervention aimed at six risk factors	CAM	15 (64/426)	9.9 (42/426)	p = 0.02
Kalisvaart *et al.* 2005 [21] RCT	Hip-surgery (elective and acute)	Yes	R: ≥ 70 MC: 79.6 MI: 78.1	Pharmacological: Haloperidol vs. placebo All patients: proactive geriatric consultation.	DSM-IV and CAM	16.5 (36/218)	15.1 (32/212)	ns

Table 1. Continued (I)

Study	Population	Selection	Age range and mean age	Intervention	Definition delirium	Incidence of delirium % (n)		p-value
						Control	Intervention	
Leung *et al.* (2006) [35] Pilot RCT	Spine surgery under general anesthesia	No	R: ≥ 45 MC: 61.4 MI: 57.2	Pharmacological: Gabapentin pre- and post-surgery vs. placebo	CAM	42 (5/12)	0 (0/9)	p = 0.045
Liptzin *et al.* (2005) [36] RCT	Elective total hip or knee arthroplasty	No	R: 51-90 MC: 67.6 MI: 66.8	Pharmacological: Donepezil vs. placebo	DSM-IV	17.1 (7/41)	20.5 (8/39)	ns
Milisen *et al.* (2001) [37] Before-after	Traumatic hip fracture surgery	No	Median control= 80 Median intervention= 82	Non-pharmacological: (1) Education of nursing staff (2) systematic cognitive screening (3) geriatric consultative services (4) scheduled pain protocol.	CAM	23.3 (14/60)	20 (12/60)	p = 0.82
Prakanrattana and Prapaitrakool (2007) [38] RCT	Cardiac surgery with cardiopulmonary bypass	No	R: >40 MC: 60.7 MI: 61.3	Pharmacological: Risperidone vs. placebo	CAM	31.7 (20/63)	11.1 (7/63)	p = 0.009
Sampson *et al.* (2006) [39] RCT (pilot phase 2a study)	Elective total hip replacement surgery	No	R: 52-86 MC: 65.1 MI: 69.7	Pharmacological: Donepezil vs. placebo	DSI	35.7 (5/14)	9.5 (2/19)	P = 0.08

Table 1. Continued (II)

Study	Population	Selection	Age range and mean age	Intervention	Definition delirium	Incidence of delirium % (n)		p-value
						Control	Intervention	
Schindler *et al.* (1989)[40] RCT	Coronary artery bypass graft surgery	No	R: 40-79 MC: 60.6 MI: 57.6	Non-pharmacological: Structured psychiatric interview prior to surgery and daily supportive psychotherapy throughout hospitalization.	DSM-III	0 (0/17)	12.5 (2/16)	ns
Tabet *et al.* (2005) [41] NRCT	Acute assessment ward patients	No	R: >70 MC: 79.3 MI: 81.4	Non-pharmacological: Staff education vs. care as usual	Single assessment by a research old age psychiatrist (point prevalence)	19.5 (25/128)	9.8 (12/122)	p = 0.034
Wanich *et al.* (1992) [42] NRCT	General medicine patients	No	R: ≥ 70 Mean total: 77	Non-pharmacological: Nursing interventions	DSM-III	22 (22/100)	19 (26/135)	p = 0.61
Williams-Russo *et al.* (1992) [43] RCT	Bilateral knee replacement surgery	No	R: 48-84 Mean total: 68	Pharmacological: Post-operative analgesia using epidural versus intravenous infusions	DSM III	44 (11/25)	38 (10/26)	p = 0.69
Wong *et al.* (2005) [44] Before-after	Osteoporotic hip fracture	No	R: 50-96 MC: 81.3 MI: 82.3	Non-pharmacological: Introduction of a series of strategies by a geriatric registrar and staff education	CAM	35.7 (10/28)	12.7 (9/71)	p = 0.012

Abbreviations: R=range, MC=mean control group, MI=mean intervention group DSM= CAM = Confusion Assessment Method, CGA = Comprehensive Geriatric Assessment, SPMSQ = Short Portable Mental Status Quotient, DSI = Delirium Symptom Interview, NEECHAM = Neelon/ Champagne, CBRS= Confusion Behaviour Rating Scale, ns = not significant

Table 2. Methodologic quality of (N)RCTs

Study	Randomization	Patient Blinding	Clinician Blinding	Outcome Assessor Blinding	Similar groups at baseline	Complete follow-up	Intention-to-treat analysis	Equally treated groups
Aizawa *et al.* (2002) RCT	+	-	-	+	+	- (2/42)	-	+
Berggren *et al.* (1987) RCT	+	-	-	+	-	+	+	+
Gamberini *et al.* (2009) RCT	+	-	+	+	+	- (12/120)	-	+
Inouye *et al.* (1999) NRCT	-	-	+	+	+	+	+	+
Kalisvaart *et al.* (2005) RCT	+	+	+	+	+	- (35/430)	+	+
Leung *et al.* (2006) pilot RCT	+	+	+	+	+	+	-	+
Liptzin *et al.* (2005) RCT	+	+	+	+	+	- (22/80)	-	+
Prakanrattana and Prapaitrakool (2007) RCT	+	+	+	-	+	+	-	+
Sampson *et al.* (2006) RCT (pilot phase 2a study)	+	+	+	+	+	- (17/50)	-	+
Schindler *et al.* (1989) RCT	+	-	-	-	+	+	-	+
Tabet *et al.* (2005) NRCT	-	+	-	-	-	- (14/250)	-	+
Wanich *et al.* (1992) NRCT	-	-	-	-	-	+	-	+
Williams-Russo *et al.* (1992) RCT	+	-	-	+	-	- (3/51)	-	+

Table 3. Methodologic quality of before-after studies

Study	Clear definition of groups	Selection bias	Clear outcome measurement	Blind-rated outcomes	Appropriate follow-up period	Selective loss to follow-up	Were possible confounding factors identified?	Did authors adjust for the effects of confounding factors?
Caplan and Harper (2007) before-after	+	-	+	-	+	- (1/37)	+	±
Milisen *et al.* (2001) before-after	+	+	+	?	+	- (0/120)	+	+
Wong *et al.* (2005) before-after	+	-	+	-	+	- (0/99)	+	-

Table 4. Comparison of stratified ORs for six covariates

Covariates	Number of studies	Participants	Odds Ratio (M-H, random, 95%CI)
Incidence delirium control group			
> 30%	8	462	0.34 (0.16-0.71)
≤ 30%	8	2113	0.76 (0.60-0.97)
Type of intervention			
Pharmacological	9	951	0.67 (0.39-1.14)
Multicomponent	5	1343	0.58 (0.38-0.92)
One-component	2	283	1.05 (0.09-11.57)
Type of patients			
Surgical	12	1203	0.65 (0.41-1.04)
Non-surgical	4	1374	0.59 (0.40-0.89)
Selection of patients*			
Selection	3	1319	0.66 (0.38 – 1.14)
No selection	13	1258	0.62 (0.41 – 0.95)

*Selection of patients based on patient related risk factors for delirium.

Discussion

The aim of this meta-analysis was two-fold. First to investigate if interventions to prevent delirium are effective and second to explore the influence of several factors on the effectiveness of these interventions. Overall the included studies showed a positive result of any intervention to prevent delirium (pooled OR 0.64; 95%CI 0.46-0.88). Interventions to prevent delirium were more effective when the incidence of delirium in the population under study was high (> 30%) (pooled OR 0.34; 95%CI 0.16-0.71 *versus* 0.76; 95%CI 0.60-0.97). This result was not significant, but there was only a slight overlap between the CIs.

The question arises how to select a population with an increased risk for delirium. One important factor to predict an increased risk to develop delirium in hospitalized elderly is patient-related factors. Identified patient-related risk factors include dementia/ cognitive impairment, medical illness, advanced age, sensory impairment, functional impairment, medications/ greater co-morbidity, preoperative psychotropic drug use, psychopathological symptoms, institutional residence, abnormal blood urea nitrogen/ creatinine ratio, abnormal sodium or potassium level and alcohol abuse [13,14]. Most strong evidence exists for an association between delirium and cognitive impairment/ dementia, psychotropic drug use, advanced age and medical illness. Other important factors are the rapidity of onset of the disease, severity of the disease and the load of its treatment [21].

Patient selection based on the presence of patient related risk factors for delirium seems the most obvious way to go. Two studies selected their

population based on patient related factors (visual impairment, cognitive impairment and dehydration) and severity of the disease (APACHE score) according to the predictive model of Inouye [22]. In these studies there was a lower rate of delirium in the control group than one would expect in a high risk population (respectively 15 and 16.5%). In one study the low rate was suggested to have resulted from a contamination effect in the usual care group, which underestimates the effect of the intervention, although significant [19]. Further there were 67 patients in this study who agreed for enrolment but could not be matched. These unmatched patients were significantly older and at higher risk for the development of delirium in this study. In the other study the patients at low risk of developing delirium, and thus not included, were also followed [20]. Only 4.1% of them developed postoperative delirium in comparison with 16.5% in the high risk control group. Both studies concerned non-surgical patients. Probably the low incidences of delirium are partly due to the exclusion of patients with such cognitive impairments making them unable to participate in interviews in both studies. It can be concluded that in spite of a relatively low incidence of delirium in the selected population, the selection seems successful.

The used predictive model [22] in the above mentioned studies is one way to select patients at high risk for delirium. Worldwide, there are different broader focused initiatives targeted at optimizing selection of elderly patients. For example in a collaboration between geriatricians and oncological surgeons, a Comprehensive Geriatric Assessment (CGA) to select elderly at high risk for morbidity and mortality was created and an integrated intervention plan in order to improve outcome was developed [23]. A CGA is a multidisciplinary comprehensive evaluation of an older individual's functional status, comorbid medical conditions, cognition, psychological state, social support, nutritional status, and a review of the patient's medications. A CGA is time consuming and may not benefit patients with intact physiology and psychosocial conditions [24]. As an alternative, simple questionnaires can be used as screening tools for selection, for example the Vulnerable Elders Survey (VES-13) [25] or the Groningen Frailty Indicator (GFI) [26;27]. The VES-13 identifies older people at increased risk for functional decline and death. It is a 13-item function-based scoring system that concerns age, self-rated health, limitation in physical function, and functional disabilities. The GFI is a 15-item screening instrument used to determine a person's level of frailty. The GFI screens for the loss of functions and resources in 4 domains of functioning: physical (mobility functions, multiple health problems, physical fatigue, vision, hearing), cognitive (cognitive functioning), social (emotional isolation), and psychological (depressed mood and feelings of anxiety).

It warrants further investigation if selection of patients based on heightened risk for adverse events in hospital in general, instead of selection solely based on risk factors for delirium is also appropriate to select high risk cases regarding delirium. In fact these broader selection criteria correspond more closely to the holistic geriatric view.
After selection of patients, the most effective intervention has to be chosen. The interventions to prevent delirium generally show a positive result. Earlier reviews reported effectiveness of a combination of non-pharmacological interventions [28-31].
Our analyses showed no difference in effectiveness between studies when stratifying for type of intervention, type of treatment and selection of patients based on patient related factors. Although we expected multicomponent interventions to be more effective than one-component interventions to prevent a multi-factorial syndrome such as delirium, this was not supported in our analyses.
Methodological quality of studies investigating pharmacological interventions was better than of studies on non-pharmacological interventions. This may be attributed to the fact that most non-pharmacological interventions are multicomponent. It is challenging to carry out a multi-component intervention in a methodological correct way with respect to randomization, blinding and contamination. Blinding is impossible for some interventions, for example a daily visit of a research nurse. Separating control and intervention patients especially when multiple caregivers are involved in the intervention can be difficult. Contamination occurs because caregivers are inclined to apply knowledge obtained from implementing the intervention, to the control group.
Although stringent inclusion criteria for this meta-analysis were used, heterogeneity across selected studies with respect to the study population, interventions and methodological quality could not be prevented. This is inherent to the subject under study and to a meta-analysis. Delirium is a multi-factorial syndrome existing in various patient groups and as a result of that, different interventions to prevent delirium have been developed.

Currently we are conducting a multicenter prospective randomized clinical trial in The Netherlands in which the effectiveness of a multicomponent intervention in a selected population of elderly surgical patients is studied. The study is entitled the Liaison Intervention in Frail Elderly (LIFE) study (NL15136.042.06). The objective of this study is to show that a geriatric liaison intervention in frail elderly patients undergoing a surgical procedure for a solid tumour will decrease the occurrence of delirium and consequent morbidity and mortality, without an increase in costs. The multicomponent intervention is

targeted at factors that emerge from the screening and make the patient vulnerable at admission. In addition the intervention is targeted at risk factors for delirium related to hospitalization and operation, for example: pain, intake, sleep, infection, medication and defecation.

Conclusion

Interventions to prevent delirium are effective. Interventions seem to be more effective when the incidence of delirium in the population under study is above 30%. To maximize the options for a cost-effective strategy of delirium prevention it might be useful to offer an intervention to a selected population at heightened risk for delirium. Worldwide there are different initiatives to create strong selection tools, but there is no uniformity yet.

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4A

Outcomes of a geriatric liaison intervention to prevent the development of postoperative delirium in frail elderly cancer patients: Report on a multicentre, randomized, controlled trial.

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Abstract

Background: Delirium is a serious and common postoperative complication, especially in frail elderly patients. The aim of this study was to evaluate the effect of a geriatric liaison intervention in comparison with standard care on the incidence of postoperative delirium in frail elderly cancer patients treated with an elective surgical procedure for a solid tumour.

Methods: Patients over 65 years of age who were undergoing elective surgery for a solid tumour were recruited to a multicentre, prospective, randomized, controlled trial. The patients were randomized to standard treatment versus a geriatric liaison intervention. The intervention consisted of a preoperative geriatric consultation, an individual treatment plan targeted at risk factors for delirium, daily visits by a geriatric nurse during the hospital stay and advice on managing any problems encountered. The primary outcome was the incidence of postoperative delirium. The secondary outcome measures were the severity of delirium, length of hospital stay, complications, mortality, care dependency, quality of life, return to an independent preoperative living situation and additional care at home.

Results: In total, the data of 260 patients were analysed. Delirium occurred in 31 patients (11.9%), and there was no significant difference between the incidence of delirium in the intervention group and the usual-care group (9.4% vs. 14.3%, OR: 0.63, 95% CI: 0.29-1.35).

Conclusions: Within this study, a geriatric liaison intervention based on frailty for the prevention of postoperative delirium in frail elderly cancer patients undergoing elective surgery for a solid tumour has not proven to be effective.

Introduction

The world's population is ageing, and it is predicted that when this ageing reaches its peak in 2050, 27.6% of Europeans will be over 65 years of age [1]. As the population ages, the prevalence of illness and hospitalization increases. Before long, cancer will be the leading cause of death, and more than half of new solid tumours will occur in patients over 70 years of age [2]. Surgery is an essential part of the multimodal treatment of solid tumours, and frail elderly patients are especially at risk of developing postoperative complications [3] - [5]. Postoperative delirium is a common and serious complication in hospitalized elderly people. Its incidence varies from less than 10% to 50% after orthopaedic [6], abdominal [7]-[11] and cardiac surgery [12]. Delirium is associated with persistent functional and cognitive decline, increased morbidity and mortality, longer hospital stays, higher rates of nursing home placement and increased health-care costs [13-17]. Mortality rates vary from 4% to 20% in patients who develop delirium during their hospital stay [7], [18]. It is therefore important to optimize the care for this growing group of patients.
The current treatment to prevent delirium consists of pharmacological and non-pharmacological, mostly multicomponent, interventions. Both have proven effective [19], [20], but until now most delirium prevention studies of the elderly included orthopaedic patients (usually hip-fracture patients) or patients from an acute care unit. The aim of this multicentre, randomized, clinical trial was to evaluate the effect of a geriatric liaison intervention in comparison with the effect of standard care on the incidence of postoperative delirium in frail elderly cancer patients treated with an elective surgical procedure for a solid tumour.

Methods

The protocol for this trial and supporting CONSORT checklist are available as supporting information; see Checklist S1 and Protocol S1.

Ethics statement

The study was approved by the Medical Ethical Committee of the University Medical Center Groningen, trial ID NTR 823.

Study design

The study, entitled Liaison Intervention in Frail Elderly (LIFE), was a multicentre, randomized clinical trial. The participating centres were the University Medical Center Groningen (serving a population of three million people), the Medical

Center Leeuwarden (a large teaching hospital) and Diaconessenhuis Leiden (a community hospital). All participating centres are located in the Netherlands.

Participants

From June 2007 to June 2010 all consecutive patients over 65 years of age undergoing elective surgery for a solid tumour were assessed with the Groningen Frailty Indicator (GFI) [21] at the outpatient departments of general surgery, gynaecology, ear, nose and throat medicine and maxillofacial surgery at the participating centres. The GFI is a short 15-item screening instrument used to determine an individual's level of frailty. It screens for the loss of function and resources in four domains of functioning: physical (mobility functions, multiple health problems, physical fatigue, vision and hearing), cognitive (cognitive functioning), social (emotional isolation) and psychological (depressed mood and feelings of anxiety). It is an internally consistent scale (Cronbach's Alpha 0.77) [22]. Patients with a GFI score greater than 3 were regarded as frail [21], [22] and recruited to this study. The GFI has not been specifically validated in a cancer population before. After informed consent, the participants were randomly allocated to either the control group or the geriatric liaison intervention group. The randomization was stratified by tumour type. A distinction was made between tumours in the chest or abdomen and tumours elsewhere. The research nurses used an interactive voice response telephone service provided by the University Medical Center Groningen for the randomization.

If it was obvious that patients would be unable to complete the study protocol and follow-up schedule before inclusion, they were excluded from participation (e.g. for logistical reasons or if any extra hospital visits would be too burdensome). Patients unable to fill in the questionnaires used in this study were also excluded.

Intervention

The multicomponent intervention focused on best supportive care and the prevention of delirium. Patients in the intervention group were assessed preoperatively by a geriatric team and monitored during their hospital stay. As the three participating centres are heterogeneous and this could cause variance in how the intervention was conducted, checklists were used to standardize the intervention as much as possible.

The geriatric team was supervised by a geriatrician, and helped devise the individual care plan. The preoperative comprehensive geriatric assessment by a geriatrician consisted of a medical history, physical examination and follow-up examinations on indication. In order to standardize this consultation a checklist

was composed based on expert opinion. This checklist contained items concerning medication, co-morbidities, loss of vision and hearing, nutrition, mobility, depression, incontinence and cognitive, social and instrumental functioning (instrumental Activities of Daily Life ([i]ADL)). An individual treatment plan was drawn up paying specific attention to patient-related risk factors for delirium, namely, cognitive impairment, visual impairment, hearing impairment, malnutrition and impaired mobility. Preventive pharmacological measures were an optional but non-imperative part of the intervention protocol.
During their hospital stay, the patients in the intervention group were assessed daily by a geriatric nurse. A daily checklist was used to ensure the uniformity of the geriatric intervention in the participating centres [23] (Appendix 1). This checklist consisted of nine items: orientation, mobility, anxiety, senses, pain, sleep, intake, defecation and infection. If a problem concerning one of these was encountered, the geriatric nurse or geriatrician contacted the treatment team to discuss the proposed intervention and establish a treatment plan, checking daily to determine whether the advice had been followed.

Standard care
Patients in the usual-care group received standard care, which means that additional geriatric care was only provided at the request of the treating physician.

Surgical procedure
Surgical procedures were divided into three categories: minor, intermediate and major according to the duration of the operation and the localization of the tumour (intracavitary versus superficial) (Table 1).

Table 1. Classification of the type of surgery by duration of the procedure and tumour localization

Surgery load	Tumour localization
Minor	Breast and skin
Intermediate	Vulva, cervix, endometrium, uterus, head/neck and retroperitoneum
Major	Gastrointestinal, liver, pancreas, lung, ovary, oropharynx, larynx and intra-abdominal sarcoma

Outcomes

The primary outcome was the incidence of delirium up to 10 days postoperatively.

Secondary outcome variables were the severity of delirium, length of hospital stay, complications, mortality, care dependency, quality of life, return to an independent preoperative living situation and additional care at home.

Assessments

The data were collected at admission, during hospital stay and at discharge, using a paper-based standardized form and then entered into Oracle Clinical© Remote Data Capture program by trained research nurses. After entry, the data were checked by an independent individual. The research nurse helped the patients fill in the questionnaires during an interview. See Table 2 for an overview of the assessments.

The baseline assessment was completed by the research nurses at least 24 hours before surgery and was taken prior to randomization. The baseline assessment included the collection of demographic data; assessment of the quality of life, measured by a Short Form-36 (SF-36) score [24]; care dependency, measured by the Care Dependency Scale (CDS) [25]; and cognitive functioning, measured by the Mini-Mental State Examination (MMSE) [26]

The Delirium Observation Scale (DOS) was used in both groups to screen for delirium. The DOS [27] was recorded three times a day (up to 10 days postoperatively) during the hospital stay by the nurses on the wards to monitor early warning signs of delirium. All nurses on the participating wards were trained by the research nurse to score the DOS. In the case of a mean DOS score ≥ 3 (possible delirium) a geriatrician or psychiatrist examined the patient to confirm the diagnosis according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM IV). The severity of delirium as measured by the highest value of the Delirium Rating Scale – Revised – 98 (DRS-R-98) [28].

The research and ward nurses were not blinded to the group the patients had been assigned to. The doctor diagnosing a possible delirium was, however, masked to the study group.

Table 2. Overview of assessments used in the LIFE study

Time point	Outcome	Scale/measurement used
Selection	Frailty	Groningen Frailty Indicator (GFI)
Baseline	-Demographic data	Age, sex, comorbidities, living situation, supportive care, type of surgery
	-Quality of Life	Short Form – 36 (SF-36)
	-Care dependency	Care Dependency Scale (CDS)
	-Cognitive functioning	Mini-Mental State Examination (MMSE)
1st to 10th postoperative day	-Sign of delirium	Delirium Observation Scale (DOS) three times a day
	-Delirium	Confirm diagnosis by geriatrician or psychiatrist according to DSM IV criteria
	-Delirium severity	Delirium Rating Scale – Revised – 98 (DRS-R-98)
	-Postoperative complications	
At discharge	-Quality of Life	Short Form – 36 (SF-36)
	-Care Dependency	Care Dependency Scale (CDS)
	-Living situation	
	-Supportive care	

Statistical Analysis

To achieve a power of 80% with an α of 5% (one-sided), a β of 95% and an expected drop-out rate of 10%, it was calculated that a total of at least 294 patients would need to be included in this study. The reported incidence of postoperative delirium varies widely from less than 10% to 50%. Based on these data and the fact that this study included a high-risk population, a delirium incidence of 30% was expected in the study population. An absolute reduction of 15% was expected in the intervention group based on Inouye's results (1999) [29].

Differences in baseline characteristics between the groups were examined using a Fisher exact test for nominal variables and a two-sample Smirnov test for ordinal or continuous variables.

For the primary analysis of the effectiveness of the intervention, delirium was considered a binary outcome (present or absent), according to its earliest occurrence, and only one episode of delirium per patient was counted. Univariate binary logistic regression analysis was used and Odds Ratios (ORs) with a 95% Confidence Interval (CI) were calculated to examine the effectiveness of the intervention strategy on the primary and secondary outcomes.

All of the statistical tests were one-sided, with $\alpha = 0.05$ as the criterion of statistical significance. Furthermore, the analyses were carried out using IBM SPSS Statistics Version 20.

Results

1468 patients were screened from June 2007 to June 2010 (Figure 1). Of these patients, 470 were found to be frail and 998 non-frail. One hundred and seventy-three frail patients were excluded from the analysis: 57 patients failed to meet the inclusion criteria, 86 refused to participate, 13 were excluded for logistical reasons and 17 patients for reasons unknown. Thirty-seven patients (12.5%) were lost to follow-up: 23 patients were inoperable or were operated on under local anaesthesia, four were lost for logistical reasons, six withdrew informed consent, two died before surgery, one had a benign tumour and one had severe cognitive impairment that was incompatible with the study design. The complete case analysis included 260 patients.

Baseline measurements

Table 3 shows the characteristics of the patients at the time of inclusion. There were no significant differences between the groups at baseline.

Outcomes

The results of the logistic regression analyses for delirium and the secondary outcomes are shown in Tables 4 and 5 (quality of life). Each outcome is discussed separately below.

Incidence of delirium

In total, 260 patients were analysed for the primary outcome measure. Delirium was found to have occurred in 31 of these patients (11.9%). There was no significant difference between the incidence of delirium in the intervention group and in the usual-care group (9.4% vs. 14.3%, OR: 0.63, 95% CI: 0.29-1.35). The relative risk of delirium in the intervention group versus the usual-care group was 0.66. The severity of delirium as measured by the highest value of the DRS-R-98 did not differ significantly between the intervention group and the usual-care group (9 [5-30] vs. 15 [5-29], $p = 0.11$).

The delirium incidence rates varied per category of surgical procedure with 1.5% (1/65), 14.6% (7/48) and 15.6% (23/ 147) in the minor, intermediate and major groups respectively (see Table 1 for classification of interventions). The delirium incidence differed most between the groups of patients undergoing an

intermediate intervention (21.4% in the control group and 5% in the intervention group, OR: 0.14, 95%CI: 0.02-1.75).

Postoperative complications
There was no significant difference between the groups in the number and type of complications that occurred (Table 6). Cardiovascular complications (31.5% in the intervention group and 27.8% in the control group) and pulmonary complications (24.4% in the intervention group and 20.3% in the control group) were the most common. Wound infection, electrolyte disturbance, urinary retention and ileus/gastroparesis also occurred frequently (around 10%).
In the intervention group, 42 patients (33.1%) had more than one postoperative complication versus 38 patients (28.6%) in the control group (OR: 1.24, 95% CI: 0.73-2.10).

Mortality
Two patients died before the operation. Fourteen patients died during the hospital stay. There was no significant difference between the intervention group and the usual-care group (7.9% versus 3.0%, OR: 2.76, 95% CI: 0.84-9.03).

Length of hospital stay
The median length of the hospital stay was eight days in both groups, ranging from one to 135 days in the intervention group and from one to 44 days in the usual-care group. The percentage of patients who stayed in hospital longer than eight days did not differ between the groups (49.6% versus 42.9%, OR: 1.28 [0.77-2.12]). Of the 260 patients analysed for the primary outcome measure, 76 (29.2%) stayed in the intensive-care unit postoperatively, 39 (30.7%) in the intervention group and 37 (27.8%) in the usual-care group. Of these 76 patients, the median stay was one day for both groups, ranging from one to nine days in the intervention group and from one to 22 days in the usual-care group ($p = 0.35$).

Return to preoperative living situation and care
In the intervention group, 67.3% (76 out of 113) returned to an independent preoperative living situation on discharge versus 79.1% in the usual-care group (87 out of 110). This was a significant difference (OR: 1.84, 95% CI: 1.01-3.37).

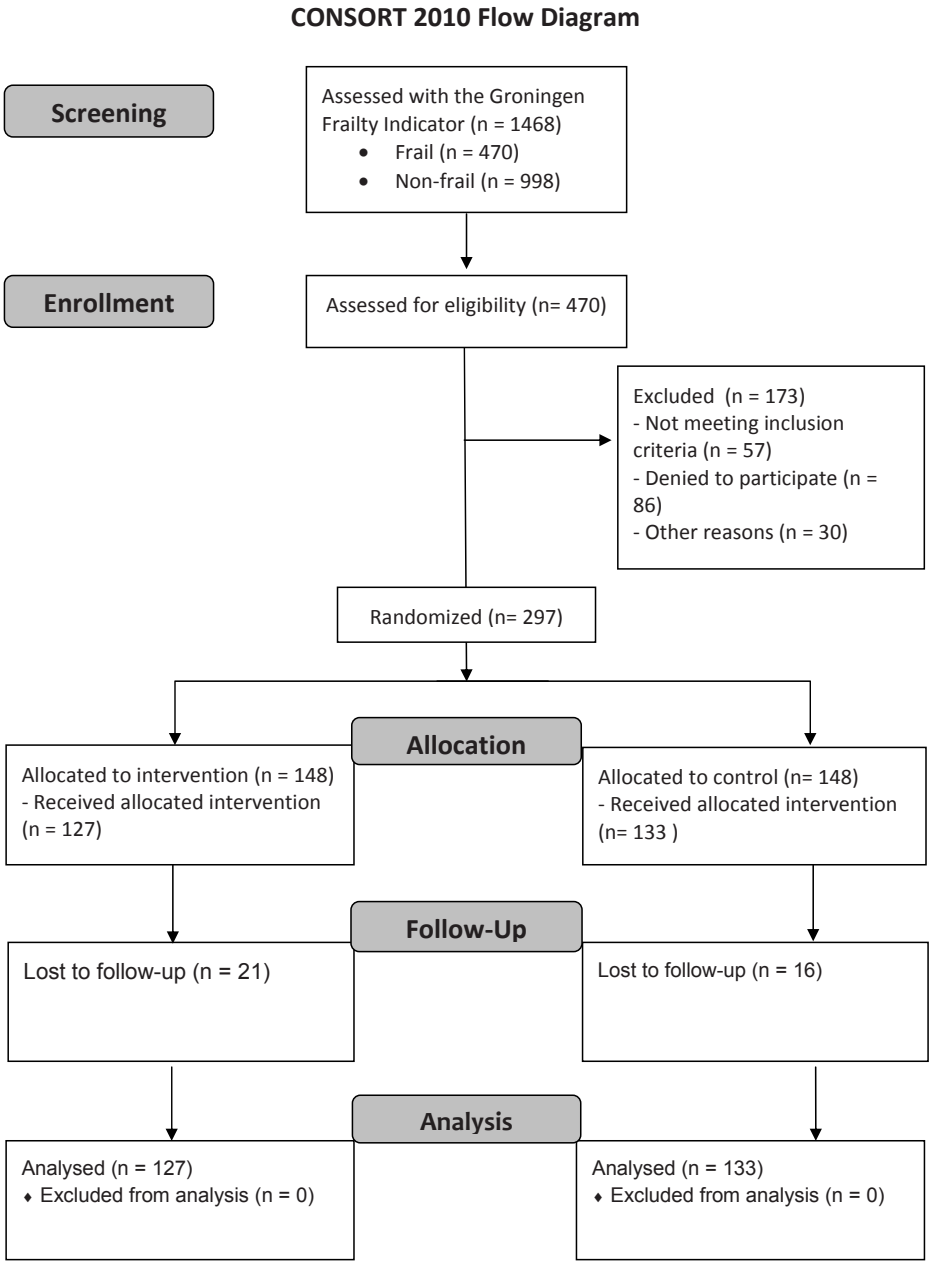
CONSORT 2010 Flow Diagram
Screening
Assessed with the Groningen Frailty Indicator (n = 1468)
Frail (n = 470)
Non-frail (n = 998)
Enrollment
Assessed for eligibility (n= 470)
Excluded (n = 173)
- Not meeting inclusion criteria (n = 57)
- Denied to participate (n = 86)
- Other reasons (n = 30)
Randomized (n= 297)
Allocation
Allocated to intervention (n = 148)
- Received allocated intervention (n = 127)
Allocated to control (n= 148)
- Received allocated intervention (n= 133)
Follow-Up
Lost to follow-up (n = 21)
Lost to follow-up (n = 16)
Analysis
Analysed (n = 127)
♦ Excluded from analysis (n = 0)
Analysed (n = 133)
♦ Excluded from analysis (n = 0)

Table 3. Baseline characteristics of the patients at inclusion according to study group

Characteristic	Intervention group (n = 148)	Usual-care group (n = 149)	P-value
Age (years), mean (SD)	77.45 (6.72)	77.63 (7.69)	0.64†
Female, n (%)	92 (62.2%)	98 (65.8%)	0.55‡
Type of surgery∫, n (%)			0.47‡
minor	40 (27.0)	37 (24.8)	
intermediate	28 (18.9)	37 (24.8)	
major	80 (54.1)	75 (50.3)	
Comorbidities*, n (%)			0.49‡
≤ 2	57 (39.6)	59 (40.4)	
>2	87 (60.4)	87 (59.6)	
missing	4	3	
Living situation, n (%)			0.06‡
independent	125 (87.4)	116 (80.0)	
alone	59 (41.3)	55 (37.9)	
with others	66 (46.1)	61 (42.1)	
dependent	18 (12.6)	29 (20.0)	
protected housing	1 (0.7)	4 (2.8)	
home for the elderly	14 (9.8)	22 (15.2)	
nursing home	3 (2.1)	3 (2.1)	
missing	5	4	
Supportive care, n (%)			
Domestic help			0.45‡
No	65 (45.8)	64 (44.4)	
Yes	77 (54.2)	80 (55.6)	
Care assistance			0.42‡
No	96 (67.6)	100 (69.4)	
Yes	46 (32.4)	44 (30.6)	
Informal care			0.41‡
No	75 (52.8)	73 (50.7)	
Yes	67 (47.2)	71 (49.3)	
Missing	6	5	
Care Dependency Score, mean (SD)	72.29 (8.92)	73.53 (9.08)	0.28†
Missing	6	5	
Mini Mental State Examination, mean (SD)	26.68 (2.97)	26.33 (3.91)	0.49†
Missing	30	37	

Table 3. Continued

Characteristic	Intervention group (n = 148)	Usual-care group (n = 149)	P-value
Short Form-36, mean (SD)			
Physical Function	46.01 (30.56)	50.03 (30.51)	0.47†
Social Function	67.96 (29.49)	68.36 (27.17)	0.99†
Role Physical	45.08 (34.06)	45.65 (32.55)	0.99†
Role Emotional	62.26 (31.99)	65.46 (30.98)	0.98†
Mental Health	56.99 (18.28)	58.12 (17.15)	1.00†
Vitality	48.91 (20.03)	51.28 (18.55)	0.99†
Bodily Pain	67.86 (29.81)	70.62 (27.07)	0.84†
General Health	45.98 (20.16)	48.05 (18.65)	0.17†
Health Change	30.63 (24.98)	31.55 (25.86)	0.98†
Missing	6, 1 incomplete	4	

†Kolmogorov-Smirnov test, ‡ Fisher's exact test, ʃSurgery load: Major = gastrointestinal, liver, pancreas, lung, ovary, oropharynx, larynx and intra-abdominal sarcoma. Intermediate = vulva, cervix, endometrium, uterus, head/neck and retroperitoneum. Minor = breast and skin. *Comorbidities = diabetes, COPD, hypertension, myocardial infarction, other cardiovascular disorders, neurological disorders, cerebrovascular disorders, hearing and vision problems, memory problems in daily life, psychiatric disorders or musculoskeletal disorders.

Care dependency

On discharge most patients were more care dependent than before the operation. There was no significant difference between the groups (74.1% versus 75.6%, OR: 0.93, 95% CI: 0.52-1.65).

Quality of life

There was no significant difference between the groups in most aspects of the SF-36 scale, although patients in the intervention group did report significantly less bodily pain at discharge than at admission compared with the usual-care group (OR: 0.49, 95% CI: 0.29-0.82).

Table 4. Logistic regression analyses (intervention group versus control group)

Outcome	Intervention group n = 127	Control group n = 133	OR (95% CI)
Primary outcome			
Delirium, n (%)			
Yes	12 (9.4)	19 (14.3)	0.63 (0.29-1.35)
No	115 (90.6)	114 (85.7)	
Severity of delirium, median (range)	*9 (3-30)*	*15 (5-29)*	*p = 0.23*
Secondary outcomes			
Complications, n (%)			
> 1	42 (33.1)	38 (28.6)	1.24 (0.73-2.10)
≤ 1	85 (66.9)	95 (71.4)	

Table 4. Continued

Outcome	Intervention group n = 127	Control group n = 133	OR (95% CI)
Secondary outcomes			
Mortality, n (%)			
Yes	10 (7.9)	4 (3.0)	2.76 (0.84-9.03)
No	117 (92.1)	129 (97.0)	
Length of hospital stay (days), n (%)			
Above median	63 (49.6)	57 (42.9)	1.28 (0.77-2.12)
Below median	57 (44.9)	66 (49.6)	
Care dependency*, n (%)			
Increased	86 (74.1)	96 (75.6)	0.93 (0.52-1.65)
Same/ decreased	30 (25.9)	31 (24.4)	
Return to independent preoperative living situation, n (%)			
No	37 (32.7)	23 (20.9)	1.84 (1.01-3.37)
Yes	76 (67.3)	87 (79.1)	
Supportive care, n (%)			
Domestic help†			
Increased	21 (18.4)	33 (26.6)	0.62 (0.34-1.16)
Same/ decreased	93 (81.6)	99 (73.4)	
Care assistance‡			
Increased	65 (57.5)	75 (60)	0.90 (0.54-1.51)
Same/ decreased	48 (42.5)	50 (40)	
Informal care∫			
Increased	41 (36.3)	37 (30.3)	1.31 (0.76-2.25)
Same/ decreased	72 (63.7)	85 (69.7)	

* No Care Dependency Score was available for 3 patients † No data were available about domestic help for 8 patients ‡ No data were available about care assistance for 8 patients ∫ No data were available about informal care for 11 patients

Table 5. Efficacy of intervention on quality of life

Short Form-36 Admission-discharge scores per domain*	Intervention Group N = 117	Usual-Care Group N = 129	OR (95% CI)
Physical Function, n (%)			
Same/ better	26 (22.8)	29 (23.2)	1.02 (0.56-1.87)
Worse	88 (77.2)	96 (76.8)	
Social Function, n (%)			
Same/ better	51 (44.7)	57 (45.6)	1.04 (0.62-1.72)
Worse	63 (55.3)	68 (54.4)	
Role Physical, n (%)			
Same/ better	41 (36.0)	48 (30.4)	1.11 (0.66-1.88)
Worse	73 (64.0)	77 (61.6)	
Role Emotional, n (%)			
Same/ better	55 (48.2)	74 (59.2)	1.56 (0.93-2.60)
Worse	59 (51.8)	51 (40.8)	
Mental Health, n (%)			
Same/ better	71 (62.3)	71 (56.8)	0.80 (0.47-1.34)
Worse	43 (37.7)	54 (43.2)	

Table 5. Continued

Short Form-36 Admission-discharge scores per domain*	Intervention Group N = 117	Usual-Care Group N = 129	OR (95% CI)
Vitality, n (%)			
Same/ better	43 (37.7)	49 (39.2)	1.07 (0.63-1.79)
Worse	71 (62.3)	76 (60.8)	
Bodily Pain, n (%)			
Same/ better	57 (50)	41 (32.8)	0.49 (0.29-0.82)
Worse	57 (50)	84 (67.2)	
General Health, n (%)			
Same/ better	67 (58.8)	68 (54.4)	0.84 (0.50-1.40)
Worse	47 (41.2)	57 (45.6)	
Health Change, n (%)			
Same/ better	74 (64.9)	96 (72.0)	1.39 (0.80-2.41)
Worse	40 (35.1)	35 (28.0)	

* No Short Form-36 score was available for seven patients, while 14 patients died during hospital stay

Table 6. Number of patients with complications according to study group

Postoperative complication	Intervention group n = 127	Control group n = 133	p-value (1-sided)
Pulmonary complication, n (%)	31 (24.4)	27 (20.3)	0.22
Neurological complication, n (%)	8 (6.3)	8 (6.0)	0.46
Cardiovascular complication, n (%)	40 (31.5)	37 (27.8)	0.26
Thromboembolic complication, n (%)	1 (0.8)	0 (0)	0.15
Bleeding, n (%)	11 (8.7)	6 (4.5)	0.09
Wound infection, n (%)	13 (10.2)	12 (9.0)	0.37
Wound dehiscence, n (%)	4 (3.1)	4 (3.0)	0.47
Urinary tract infection, n (%)	8 (6.3)	7 (5.3)	0.36
Anastomotic leakage, n (%)	5 (3.9)	2 (1.5)	0.11
Pressure ulcer, n (%)	5 (3.9)	7 (5.3)	0.31
Renal failure, n (%)	5 (3.9)	2 (1.5)	0.11
Electrolyte disturbance, n (%)	15 (11.8)	12 (9.0)	0.23
Fall, n (%)	4 (3.1)	2 (1.5)	0.19
Urinary retention, n (%)	15 (11.8)	12 (9.0)	0.23
Ileus/gastroparesis, n (%)	9 (7.1)	14 (10.5)	0.16

Discussion

This randomized controlled trial could not provide evidence that a geriatric liaison intervention decreases postoperative delirium in frail elderly patients undergoing surgery for a solid tumour. Nor did the study find an effect of the intervention on the severity of delirium.

Furthermore, there was no significant difference between the groups in the number and type of complications, mortality, care dependency, length of hospital stay and length of ICU stay. The quality of life differed only in the area of bodily pain on the SF-36 in favour of the intervention group. More patients

in the usual-care group returned to an independent preoperative living situation than in the intervention group.
Other non-pharmacological multicomponent intervention studies aimed at decreasing delirium in hospitalized elderly have shown varying results. Most studies have investigated the incidence of postoperative delirium in elderly hip-fracture patients, and some of these have found a significant reduction in delirium incidence [30], [31], severity [30], [32] and duration [32], while others have shown no effect on either delirium incidence or socioeconomic outcome parameters [31], [32]. The same applies to studies in geriatric and general medicine populations. The studies of Inouye (1999) and Caplan (2007) have both shown a significant reduction in delirium incidence; the effect of an intervention on the severity and duration of delirium remains controversial, however [29], [33]. The latter study indicated cost effectiveness, and showed a significant positive effect on ADL and MMSE scores even though no significant effect was shown on readmissions, discharge to residential care and length of hospital stay.
In summary, our negative results correspond with previous studies, and there are several possible reasons for our outcomes.

Primary outcome measure
This study was aimed at improving postoperative outcomes in frail elderly cancer patients. Postoperative delirium was chosen as the primary outcome measure given its association with increased morbidity and mortality, persistent functional and cognitive decline, longer hospital stay, higher rates of nursing home placement and increased health care costs [13]-[17]. Moreover, delirium is a short-term outcome, reducing the likelihood of bias.
Most previous delirium prevention studies included orthopaedic patients (usually hip-fracture patients) or patients from an acute care unit. There is broad experience of different models of shared orthopaedic and geriatric care for elderly hip-fracture patients. The positive effect of a daily geriatric consultative service has been described, but there is a trend towards integrated care as the most effective model [34]. In such care, a geriatrician is added to the orthopaedic team to oversee the management of the patient from admission until discharge. A positive effect has been seen here on mortality, length of hospital stay and mean time to surgery. The effect on medical complication rates is not clear, however, because a wide range of definitions of complications is used in the included studies. The benefits of a consultative service on request and an orthopaedic consultative service on the geriatric ward are less clear. Up to now, evidence for any benefits of consultation-based management of delirium in any setting is lacking. This

implies that the intervention model chosen in this study has failed, but that it may be effective when applied in an integrated care model.

The present study is unique in terms of the selected population. Delirium incidence rates in this study were unexpectedly low in both the intervention group and the usual-care group. In the population studied the relative incidence decreased by 34% (14.3% vs. 9.4%) with an overall incidence rate of 11.9%. Although this is an impressive overall reduction, the study was underpowered due to the low overall incidence of delirium. The power calculation was based on delirium incidence rates in orthopaedic, abdominal and cardiac surgery patients. To our knowledge, data on delirium incidence rates in the geriatric oncological surgical patients have not previously been reported.

There may be several explanations for this low incidence rate. First, it implies a high standard of care for frail elderly patients in the participating hospitals. Each hospital already had specialized geriatric care available before the start of this trial. Although standard consultation for frail elderly patients was not part of the routine treatment, there was already some awareness in the medical and nursing staff of the risks involved in treating frail elderly patients.

Patients with severe cognitive impairment were unable to comply with the study protocol and were excluded; however, this group is at the highest risk of the development of delirium. In addition, the study not only included patients undergoing major surgery, but also patients undergoing minor and intermediate surgical procedures. It is well known that surgical procedures for breast cancer and dermal tumours result in few and mostly local complications, even in patients over the age of 80 [35], [36]. For example, Ansaloni et al. found a delirium incidence rate of 1.6% for salpingovariectomy, quadrantectomy, mastectomy, axillary lymph node dissection and thyroidectomy versus 33.3% for gastric resection and gastrointestinal perforation closure [11]. The results of the present study show that this also applies to frail patients. A probable explanation for this difference is that a stress response in combination with elevated inflammatory markers provoked by surgery or infectious states plays an important role in the pathogenesis of postoperative delirium [37], [38]. One can imagine that this response is more distinct in patients undergoing major surgery. Another explanation might be that patient characteristics differed per tumour type with respect to, for example, sex, nutritional status and quality of life. These characteristics may have influenced the delirium risk.

In this study, patients were selected with the GFI, which was originally developed to screen for level of frailty [22]. Frail persons have decreased ability to compensate for disruptions in homeostasis due to a loss of reserves. Frailty is associated with an increased risk of falls, hospitalization, institutionalization,

disability and death in community-dwelling older adults [39]-[41], as well as with an increased risk of post-operative complications (including delirium), length of hospitalization and inability to be discharged home in hospitalized patients [3]-[5]. The GFI distinguishes itself from most other frailty measurement instruments in that it includes not only physical but also cognitive, psychological and social items. Based on literature suggesting that frailty and delirium may be different clinical expression of a shared vulnerability to stress, we expected that patients considered frail by the GFI would be at higher risk of postoperative delirium [42]. Given the low delirium incidence rate in this study, the GFI was probably not an accurate selection method. For future delirium prevention studies, we would recommend to select patients at high risk of postoperative delirium based on earlier identified risk factors [6], [18], [43]-[45].

Finally, the nature of the geriatric intervention was broadly defined in a pre-operative and post-operative checklist. The geriatric checklist was recorded and adhered to per patient, but analysing these extensive data proved to be very complicated. For example, at the beginning of the study we tried to record drugs usage for all participants, but this proved to be unfeasible due to the voluminous data. In retrospect, we could have focused on deliriogenic drugs only. These are important limitations of the study and a focus for future multicomponent delirium prevention studies.

Contamination

As mentioned before, the ward and research nurses were not blinded to the group to which a patient was randomized. This could lead to contamination, that is, additional interventions in the standard care group. In the case of contamination, one would expect a decrease in the difference in the incidence rate of delirium between the groups as the study progressed. As the lines in Figure 2 are not convergent, this argues against contamination.

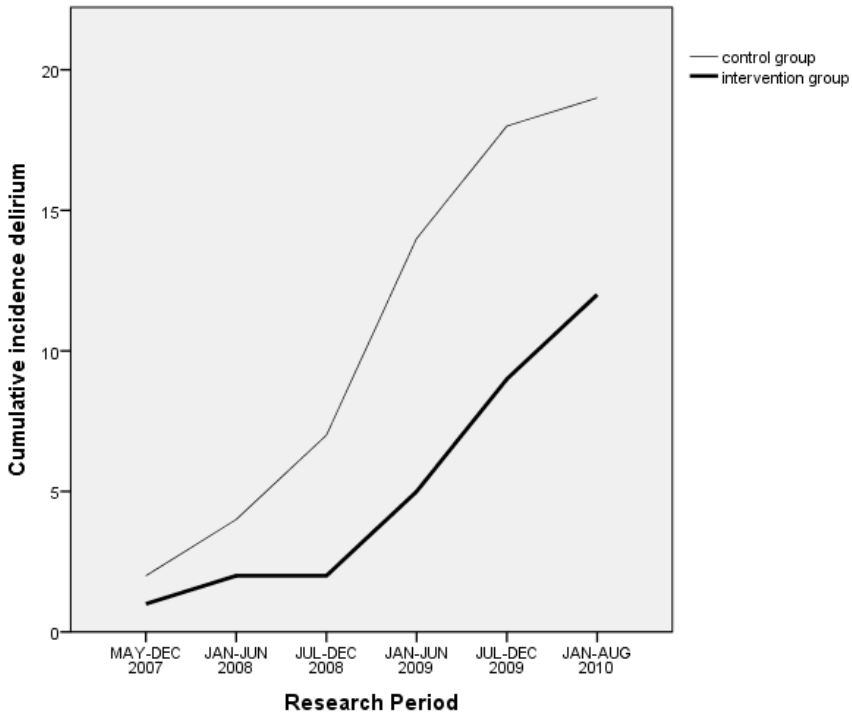

Figure 2. Cumulative delirium incidence in the control group and research period.

Secondary outcomes

There was no difference between the groups in terms of postoperative complications, mortality, care dependency post-discharge and length of hospital stay. More patients in the usual-care group returned to the preoperative living situation. Patients in the intervention group who lived independently preoperatively were more often (temporarily) discharged to a nursing home than such patients in the control group. A possible reason was that geriatric care may lead to rehabilitation in a nursing home after discharge. The effect of the intervention on the quality of life was only seen in the domain of bodily pain of the SF-36. The clinical importance of this outcome is unclear.

Selection and inclusion of frail elderly

In a separate paper, we presented an overview of problems we encountered while conducting this study [45]. The first problem is that the selection of patients is extremely important in this research population. Patients who are too frail or too fit should be excluded to optimize internal validity (the need to focus the study group to maximize the chances of detecting any impact of the intervention). However, eligibility criteria should not be too strict with respect

to external validity (the ability to generalize to a larger population). For example, patients unable to understand questionnaires were excluded, although patients with decreased cognitive abilities are at high risk of developing delirium. Furthermore, patients undergoing surgery for a superficial tumour (skin, breast) were included in the study, although they are at low risk of developing postoperative delirium. Both criteria may have lowered the delirium incidence rate in our study and reduced the likelihood of showing the intervention to be effective.

However, the main problem was that the actual inclusion rate fell short of expectations. This was due to: 1) Limited physical and cognitive reserve of frail elderly patients, making participation and extra visits to the hospital a burden for them; 2) Difficulty in understanding written information and information given over the phone; and 3) Insufficient awareness of the study by health-care professionals. To increase inclusion rates, follow-up measurements were taken during a home visit. To overcome barriers to understanding written information and information given over the phone, patients were informed face to face and questionnaires were completed in an interview format. To increase awareness, posters, pencil and sweets with the logo of the study were distributed, and the study protocol was repeatedly explained to new staff. Moreover, checks were made as to whether possible eligible patients coming to the hospital were indeed screened for participation. These measures increased inclusion rates but also caused an increased time investment and consequently extra staffing costs.

Finally, the drop-out rate (12.5%) was higher than the expected 10%, which is a widely used drop-out rate in research with adults. This should be considered in future research in this population.

Further analyses are needed to determine the cost-effectiveness and long-term effect of the intervention on related postoperative outcomes such as mortality, quality of life, care dependency and living situation.

Conclusion

Within this study, geriatric liaison intervention for the prevention of postoperative delirium in frail patients in a general oncological surgical population has not proven to be effective. Certain limitations to the study design, such as patient selection, may have played a role. Future intensive collaboration between surgeons and geriatricians may be warranted to improve postoperative outcomes in frail elderly cancer patients.

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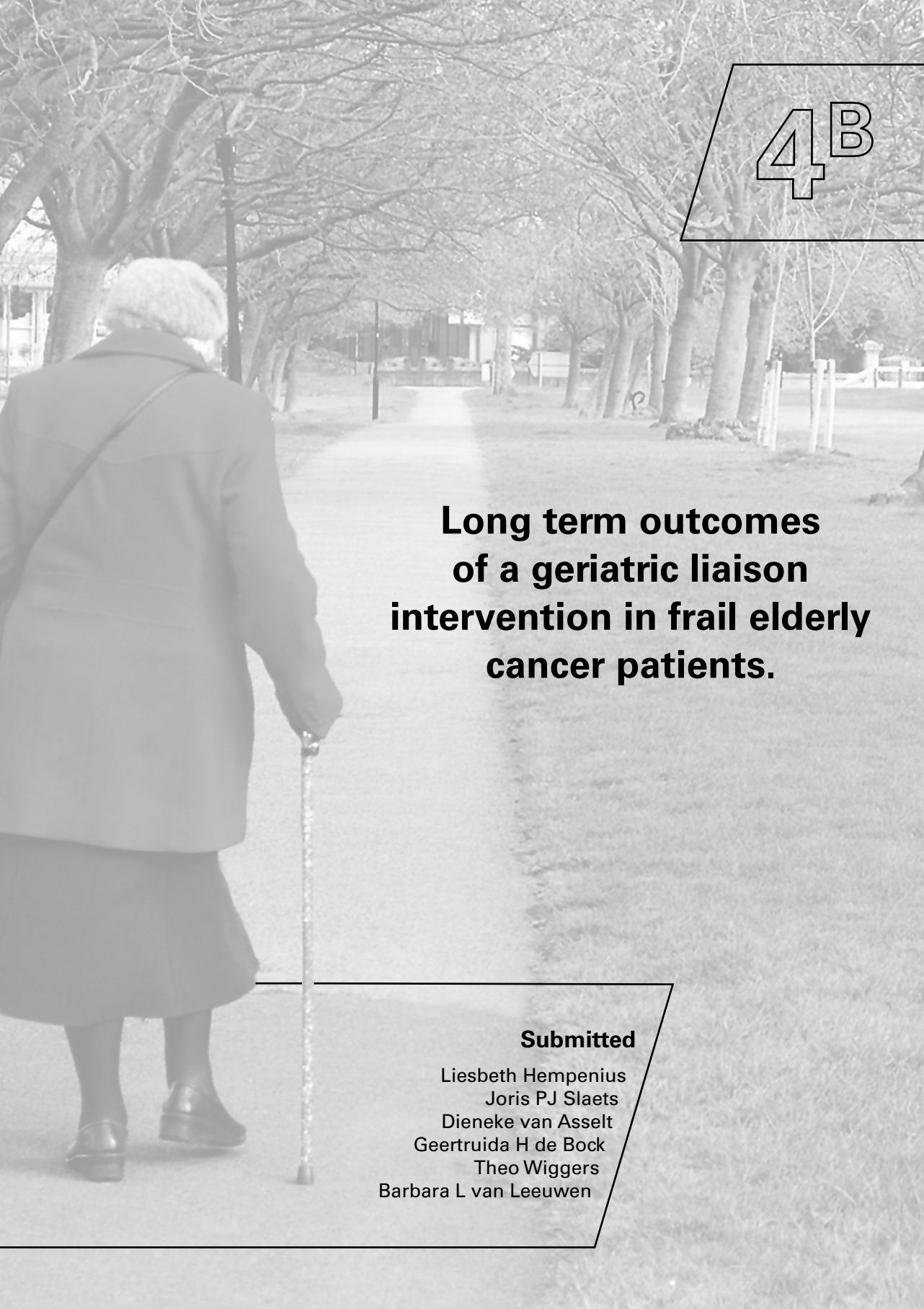

4B

Long term outcomes of a geriatric liaison intervention in frail elderly cancer patients.

Submitted

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Abstract

Background: The aim of this study was to evaluate the long term effects after discharge of a hospital-based geriatric liaison intervention to prevent postoperative delirium in frail elderly cancer patients treated with an elective surgical procedure for a solid tumour. In addition, the effect of a postoperative delirium on long term outcomes was examined.

Methods: A three month follow-up was performed in participants of the Liaison Intervention in Frail Elderly study, a multicentre, prospective, randomized, controlled trial. Patients were randomized to standard treatment or a geriatric liaison intervention. The intervention consisted of a preoperative geriatric consultation, an individual treatment plan targeted at risk factors for delirium and daily visits by a geriatric nurse during the hospital stay. The long term outcomes included: mortality, rehospitalisation, ADL functioning, return to the independent pre-operative living situation, use of supportive care, cognitive functioning and health related quality of life.

Results: Data of 260 patients (intervention n=127, Control n=133) were analysed. There were no differences between the intervention group and usual-care group for any of the outcomes three months after discharge. Postoperative delirium increased the risk of decline in ADL functioning (OR: 2.65, 95% CI: 1.02-6.88) resulting in increased use of supportive assistance (OR: 2.45, 95% CI: 1.02-5.87) and decreased chance to return to the independent preoperative living situation (OR: 0.18, 95% CI: 0.07-0.49).

Conclusions: A hospital-based geriatric liaison intervention for the prevention of postoperative delirium in frail elderly cancer patients undergoing elective surgery for a solid tumour did not improve outcomes 3 months after discharge from hospital. The negative effect of a postoperative delirium on late outcome was confirmed.

Introduction

Hospitalized elderly are at increased risk for functional decline resulting in adverse health outcomes such as mortality, prolonged hospital stay, nursing home placement and increased dependency at home. It is estimated that approximately 35% of patients aged 75 and older develop a new disability after hospitalization or suffer functional decline [1-3].
To limit functional decline after hospital stay, the prevention of delirium is of great importance. Delirium is a common and serious complication in hospitalized elderly people. It is associated with persistent functional and cognitive decline, increased morbidity and mortality, longer hospital stays, higher rates of nursing home placement and increased health-care costs [4-7]. Mortality rates vary from 4% to 20% in patients who develop delirium during their hospital stay [8,9].
We performed a randomized controlled trial to evaluate the effect of a multicomponent intervention compared to standard care, on the incidence of postoperative delirium in frail elderly cancer patients undergoing surgery for a solid tumour [10]. The intervention was targeted at risk factors for postoperative delirium: cognitive impairment, visual impairment, hearing impairment, malnutrition, pain, sleep disturbance, defecation problems, infection and impaired mobility. Delirium was chosen as the primary outcome measure because it could be determined within the intervention period during hospital stay. The intervention has not shown to be effective for preventing postoperative delirium [10]. Three months after discharge, a follow-up was performed. The follow-up measurements were focused on postoperative functional outcomes such as ADL functioning, return to the independent pre-operative living situation, use of supportive care, cognitive functioning and health related quality of life, next to mortality and rehospitalisation. Most previous studies on adverse outcomes after cancer surgery in the elderly were targeted at outcomes such as postoperative complications, mortality, length of hospital stay and readmissions [11-14], while ADL functioning and quality of life (QOL) are at least as important outcomes of surgical treatment for the elderly.
In this manuscript, the long term results, three months after discharge, and the effect of postoperative delirium on long term outcomes are described.

Methods

Ethics statement

The study was approved by the Medical Ethical Committee of the University Medical Center Groningen, trial ID NTR 823. Written informed consent was obtained from the participants.

Study design

The study, entitled Liaison Intervention in Frail Elderly (LIFE), was a multicentre, randomized clinical trial [10]. The participating centres were the University Medical Center Groningen (serving a population of three million people), the Medical Center Leeuwarden (a large teaching hospital) and Diaconessenhuis Leiden (a community hospital). All participating centres are located in the Netherlands.

Participants

From June 2007 to June 2010 all consecutive patients over 65 years of age undergoing elective surgery for a solid tumour were assessed with the Groningen Frailty Indicator (GFI) [15-17] at the outpatient departments of general surgery, gynaecology, ear, nose and throat medicine and maxillofacial surgery at the participating centres. The GFI is an internally consistent 15-item screening instrument used to determine an individual's level of frailty [15,17]. Patients with a GFI score greater than 3 were regarded as frail and recruited to the LIFE study. The participants were randomly allocated to either the control group or the geriatric liaison intervention group. The randomization was stratified by tumour type. A distinction was made between tumours in the chest or abdomen and tumours elsewhere. The research nurses used an interactive voice response telephone service provided by the University Medical Center Groningen for the randomization.

Patients were excluded if the research nurse or the responsible physician estimated they were unable to complete the study protocol and follow-up schedule before inclusion (e.g. for logistical reasons or if any extra hospital visits would be too burdensome). Patients unable to fill in the questionnaires used in this study were also excluded.

Intervention

The multicomponent intervention focused on best supportive care and the prevention of delirium. Patients in the intervention group were assessed preoperatively by a geriatric team and monitored during their hospital stay. As the three participating centres are heterogeneous and this could cause variance in how the intervention was conducted, checklists were used to standardize the intervention as much as possible.

The geriatric team was supervised by a geriatrician, and helped devise the individual care plan. The preoperative comprehensive geriatric assessment by a geriatrician consisted of a medical history, physical examination and follow-up examinations on indication resulting in an individual treatment plan, with specific attention to patient-related risk factors for delirium.

During their hospital stay, the patients in the intervention group were assessed daily by a geriatric nurse. If a problem was encountered, the geriatric nurse or geriatrician contacted the treatment team to discuss the proposed intervention and establish a treatment plan, checking daily to determine whether the advice had been followed.
For a detailed description of the intervention we refer to [10].

Standard care
Patients in the usual-care group received standard care, meaning that additional geriatric care was only provided at the request of the treating physician.

Surgical procedure
Surgical procedures were divided into three categories: minor, intermediate and major according to the duration of the operation and the localization of the tumour (intracavitary versus superficial (Table 1).

Table 1. Classification of the type of surgery by duration of the procedure and tumour localization

Surgery load	Tumour localization
Minor	Breast and skin
Intermediate	Vulva, cervix, endometrium, uterus, head/neck and retroperitoneum
Major	Gastrointestinal, liver, pancreas, lung, ovary, oropharynx, larynx and intra-abdominal sarcoma

Outcomes
The long term outcomes were mortality, rehospitalisation, ADL functioning, return to the independent pre-operative living situation, supportive care, cognitive functioning and health related quality of life.

Assessments
The baseline assessment was completed by the research nurses at least 24 hours before surgery and was performed prior to randomization. Follow-up data were collected by the research nurses 3 months following hospital discharge during a telephone interview or a home visit.
At baseline, demographic data were collected. Both the baseline assessment and the follow-up assessment included the measurement of the health related quality of life by the Physical Component Summary measure (PCS) and the Mental Component Summary measure (MCS) of the Short Form-36 (SF-36) score [18-20]; basic ADL functioning by the Care Dependency Scale (CDS) [21] and cognitive functioning by the Mini-Mental State Examination (MMSE) [22].

Data regarding the living situation and supportive care (domestic help, care assistance and informal care) were also collected.
To screen for delirium during hospital stay, the Delirium Observation Scale (DOS) was used in both groups [23]. The DOS was recorded three times a day, up to 10 days postoperatively. In the case of a mean DOS score ≥ 3 (possible delirium) a geriatrician or psychiatrist examined the patient to confirm the diagnosis according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM IV).
A paper-based standardized form was used to collect data. Data were entered into Oracle Clinical© Remote Data Capture program by trained research nurses. After entry, the data were checked by an independent individual.
The research nurses were not blinded to the group the patients had been assigned to.

Statistical Analysis
IBM SPSS Statistics Version 20 was used for the statistical analysis. Differences in baseline characteristics between the groups were examined using a Fisher exact test for nominal variables and a two-sample Smirnov test for ordinal or continuous variables.
Univariate binary logistic regression analysis was used and Odds Ratios (ORs) with a 95% Confidence Interval (CI) were calculated to examine the effectiveness of the intervention strategy on the long term outcomes at 3 months follow up. The effect of postoperative delirium on the outcomes at 3 months follow up was also calculated using univariate binary logistic regression analysis.

Results

The CONSORT diagram showing the flow of participants through each stage of the LIFE study was presented in a previous article [10]. Of the 260 patients who were followed during hospital stay, 33 were lost to follow-up at the time of the 3-month assessment: 14 died during hospital stay, 12 died before follow-up assessment, seven withdrew informed consent post discharge. Therefore the final sample size for this study was 227 (106 intervention group and 121 usual-care group). There were no significant differences between the groups at discharge (Table 2).

Table 2. Characteristics of the patients at discharge according to study group

Characteristic	Intervention group (n = 127)	Usual-care group (n = 133)	P-value
Age (years), mean (SD)	77.37 (6.88)	77.42 (7.71)	0.49†
Female, n (%)	76 (59.8)	85 (63.9)	0.53‡
Type of surgery∫, n (%)			0.54‡
Minor	32 (25.2)	33 (24.8)	
Intermediate	20 (15.7)	28 (21.1)	
Major	75 (59.1)	72 (54.1)	
Comorbidities*, n (%)			0.47‡
≤ 2	51 (40.2)	55 (41.4)	
>2	76 (59.8)	78 (58.6)	
Living situation, n (%)			0.10‡
independent	113 (89.0)	110 (82.7)	
alone	55 (43.3)	53 (39.8)	
with others	58 (45.7)	57 (42.9)	
dependent	14 (11.0)	23 (17.3)	
protected housing	0 (0.0)	4 (3.0)	
home for the elderly	11 (8.7)	16 (12.0)	
nursing home	3 (2.4)	3 (2.3)	
Supportive care, n (%)			
Domestic help			0.46‡
No	60 (47.2)	61 (46.2)	
Yes	67 (52.8)	71 (53.8)	
Missing	0	1	
Care assistance			0.40‡
No	87 (69.0)	94 (71.2)	
Yes	39 (31.0)	38 (28.8)	
Missing	1	1	
Informal care			0.49‡
No	68 (54.0)	70 (53.0)	
Yes	58 (46)	62 (47.0)	
Missing	1	1	
Care Dependency Score, mean (SD)	72.49 (8.52)	74.23 (6.97)	0.27†
Mini Mental State Examination, mean (SD)	26.97 (2.47)	26.51 (3.74)	0.97†
Missing	19	31	
Short Form-36, mean (SD)			
Physical component summary measure	48.36 (9.07)	49.32 (7.02)	0.17†
Mental component summary measure	44.69 (8.79)	44.38 (8.42)	0.98†

†Kolmogorov-Smirnov test, ‡ Fisher's exact test, ∫Surgery load: Major = gastrointestinal, liver, pancreas, lung, ovary, oropharynx, larynx and intra-abdominal sarcoma. Intermediate = vulva, cervix, endometrium, uterus, head/neck and retroperitoneum. Minor = breast and skin. *Comorbidities = diabetes, COPD, hypertension, myocardial infarction, other cardiovascular disorders, neurological disorders, cerebrovascular disorders, hearing and vision problems, memory problems in daily life, psychiatric disorders or musculoskeletal disorders.

Long term outcomes

The results of the logistic regression analyses for the outcome variables are shown in Table 3. There were no significant differences between the intervention and usual-care group for any of the outcomes.

Table 3. Logistic regression analyses for long term outcomes (intervention group versus control group)

Outcome	Intervention group n = 127	Control group n = 133	OR (95% CI)
Mortality, n (%)			
Yes	17 (13.4)	9 (6.8)	2.13 (0.91-4.97)
during hospital stay	*10*	*4*	
after discharge	*7*	*5*	
No	110 (86.6)	124 (93.2)	
Hospital readmission, n (%)			
Yes	24 (22.9)	22 (18.3)	1.32 (0.69-2.53)
No	81 (77.1)	98 (81.7)	
Missing values	1	1	
ADL functioning, n (%)			
Decreased	64 (60.4)	68 (56.2)	1.19 (0.70-2.02)
Same/ increased	42 (39.6)	53 (43.8)	
Return to independent preoperative living situation, n (%)			
No	15 (16.5)	9 (8.9)	2.02 (0.84-4.87)
Yes	76 (83.5)	92 (91.1)	
Use of supportive care, n (%)			
Domestic help			
Increased	33 (32.4)	38 (32.2)	1.01 (0.57-1.78)
Same/ decreased	69 (67.6)	80 (67.8)	
Care assistance			
Increased	42 (41.2)	39 (33.3)	1.40 (0.81-2.43)
Same/ decreased	60 (58.8)	78 (66.7)	
Informal care			
Increased	39 (38.2)	37 (31.6)	1.34 (0.57-1.78)
Same/ decreased	63 (61.8)	80 (68.4)	
Missing cases	4	4	
Cognitive functioning, n (%)			
MMSE score decreased ≥ 2 points	15 (23.1)	9 (14.1)	1.83 (0.74-4.56)
MMSE score same/ increased	50 (76.9)	55 (85.9)	
Missing cases	41	57	
Health related quality of life, n (%)			
SF-36 Physical component summary measure			
Decreased	63 (60)	80 (66.7)	1.33 (0.77-2.30)
Same/ increased	42 (40)	40 (33.3)	
SF-36 Mental component summary measure			
Decreased	51 (48.6)	53 (44.2)	0.84 (0.50-1.42)
Same/ increased	54 (51.4)	67 (55.8)	
Missing cases	1	1	

Influence of postoperative delirium on long term outcomes

In total, 227 patients were analysed for the long term outcomes of delirium. A postoperative delirium occurred in 26 of these patients (11.5%). Delirium increased the risk of a decline in ADL functioning (OR: 2.65, 95% CI: 1.02-6.88) resulting in an increased need for care assistance (OR: 2.45, 95% CI: 1.02-5.87) and a decreased chance to return to the independent preoperative living situation (OR: 0.18 (0.07-0.49). These results are presented in Table 4.

Table 4. Logistic regression analyses for 3-month outcomes (postoperative delirium versus no delirium)

Outcome	Postoperative delirium n = 26	No postoperative delirium n = 201	OR (95% CI)
Mortality, n (%)			
Yes	5 (19.2)	21 (10.4)	1.90 (0.66-5.48)
during hospital stay	*4 (15.4)*	*10 (5.0)*	
after discharge	*1 (3.8)*	*11(5.5)*	
No	21 (80.8)	180 (89.6)	
Hospital admission after discharge, n (%)			
Yes	3 (12)	43 (21.5)	0.50 (0.14-1.74)
No	22 (88)	157 (78.5)	
Missing values	1		
ADL functioning, n (%)			
decreased	20 (76.9)	112 (55.7)	2.65 (1.02-6.88)*
Same/ increased	6 (23.1)	89 (44.3)	
Return to independent preoperative living situation, n (%)			
No	8 (38.1)	17 (9.9)	0.18 (0.07-0.49)*
Yes	13 (61.9)	155 (90.1)	
Use of supportive care, n (%)			
Domestic help			
Increased	6 (26.1)	65 (33.0)	0.72 (0.27-1.90)
Same/ decreased	17 (73.9)	132 (67)	
Care assistance			
Increased	13 (56.5)	68 (34.7)	2.45 (1.02-5.87)*
Same/ decreased	10 (43.5)	128 (65.3)	
Informal care			
Increased	8 (34.8)	68 (34.7)	1.00 (0.41-2.49)
Same/ decreased	15 (65.2)	128 (65.3)	
Missing cases	3	3	
Cognitive functioning, n (%)			
MMSE score decreased ≥ 2 points	3 (23.1)	21 (18.1)	1.36 (0.34-5.36)
MMSE score same/ increased	10 (76.9)	95 (81.9)	
Missing cases	3	85	

Table 4. Continued

Outcome	Postoperative delirium n = 26	No postoperative delirium n = 201	OR (95% CI)
Health related quality of life, n (%)			
SF-36 Physical component summary measure			
Decreased	20 (80)	123 (61.5)	2.26 (0.96-5.36)
Same/ increased	5 (20)	77 (38.5)	
SF-36 Mental component summary measure			
Decreased	16 (64)	88 (44)	2.50 (090-6.95)
Same/ increased	9 (36)	112 (56)	
Missing cases	1	1	

Discussion

Three months after discharge from hospital no benefit could be detected from a geriatric liaison intervention targeted at risk factors for postoperative delirium in frail elderly patients undergoing surgery for a solid tumour. Because postoperative delirium is a known risk factor for functional decline after hospital stay [4-7], we, a priori, hypothesized that prevention of postoperative delirium would result in decreased risk for adverse outcomes after hospitalisation. However, the multicomponent intervention appeared not to be effective in preventing delirium in the population under study, it meets the criteria for good geriatric care for hospitalized frail elderly patients [24]. Therefore, the intervention could have been effective in preventing negative long term results as shown in other studies [25,26].

The long term results may be influenced by a wash-out effect due to interventions performed after discharge and outside the study protocol. Probably, continuation of in hospital interventions after discharge might overcome this, although, little is known about the effect of prolonged interventions in elderly patients who were hospitalized. One study showed a significantly decreased mortality in older cancer patients after a 4 weeks lasting intervention post discharge [27].

Several reasons for the low delirium incidence rate in the LIFE study were described [10]. In short, not only patients at high risk for the development of postoperative delirium were selected for this study, and there was probably a high standard of care for frail elderly patients in the participating hospitals before the start of the study. The introduction of the Delirium Observation Scale (DOS) [28] on the wards to screen for delirium may have ensured

increased alertness among medical staff for the prevention of postoperative delirium, in both the intervention and control group.

For the frail elderly surgical oncology patients participating in the LIFE study, postoperative delirium was a risk factor for functional decline after discharge. Delirium was associated with an increased risk of a postoperative decline in ADL functioning resulting in increased care assistance and a decreased chance to return to the independent preoperative living situation. This confirms that a postoperative delirium is a sign of increased (brain) vulnerability associated with poorer prognosis [29]. Therefore, targeting preventive interventions at those elderly at risk for (postoperative) delirium remains a major concern in minimizing functional decline after hospitalization.In an other multicomponent intervention study aimed at decreasing delirium in elderly hospitalized on a general medicine ward, the effect of the intervention on outcomes 6 months after hospital discharge was examined [30,31]. There were no differences between the intervention and control groups for any of the ten outcomes, except that incontinence was less common in the intervention group. Following a subgroup analysis, the authors suggested that only selected patients at high risk for a particular adverse outcome may benefit from a targeted intervention. Up to 50% of elderly patients suffer functional decline after hospitalization resulting in a decline in health-related quality of life and loss of independence in (I)ADL functioning [1,32]. In our study, also a considerable part of patients suffered a postoperative decline in ADL functioning (60.4% in the intervention group versus 56.2% in the control group) and health related QOL (physical component: 60% in the intervention group versus 66.7% in the control group; mental component: 48.6% in the intervention group versus 44.2% in the control group) (Table 2). In the end, we assign greater value to these long term outcome measures than, for example, to developing a postoperative delirium, because maintaining autonomy is crucial for life satisfaction in the elderly patient. In conclusion, the lower than expected delirium incidence rate and the high standard of basic care may have influenced the long term results. The association between postoperative delirium and functional decline after hospitalization was confirmed in the population under study. Therefore prevention of postoperative delirium seems one of the ways to limit functional decline after surgery in this patient group.

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Inclusion of frail elderly patients in clinical trials: solutions to the problems

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Abstract

With aging of the population, the interest in clinical trials concerning frail elderly patients has increased. Evidence-based practice for the elderly patient is difficult because elderly patients, especially the frail, are often excluded from clinical trials. To facilitate the participation of frail elderly patients in clinical trials, investigators should be more aware of possible barriers when setting up research. While conducting a trial entitled 'A randomized controlled trial of geriatric liaison intervention in frail surgical oncology patients' (LIFE) the main problem was low inclusion rates. This was due to: 1) limited physical and cognitive reserve of frail elderly making participation and extra visits to the hospital a burden for patients; 2) difficulty with understanding written information and information given by telephone; and 3) insufficient awareness of the study by health care professionals. To increase inclusion rates, follow-up measurements were taken at a home visit. To overcome barriers tot understanding written information and information given over the phone, patients were informed face to face and questionnaires were filled in an interview format. To increase awareness, posters, pencil and sweets with the logo of the study were distributed and the study protocol was repeatedly explained to new staff. Moreover it was checked if possible eligible patients coming to the hospital were indeed screened for participation. The mentioned measures, increased inclusion rates but also caused an increased time investment and consequently extra financial resources for staff costs.

Introduction

The world's population is aging, with the prediction being that in 2050, when the greying of the population reaches a peak, 27.6% of Europe's population will be over 65 years of age [1]. In the past, elderly patients were often withheld treatment because of their age. Today, with an increasing elderly population and growing treatment options, physicians are responsible for choosing the optimal treatment for the elderly patient. However, evidence-based practice is difficult because elderly patients, especially the frail, are often excluded from clinical trials [2-4]. The perceived extra burden to frail patients for participating in a clinical trial and the doubt regarding whether the elderly patient might benefit from the trial hamper their inclusion [3];[5-8]. To facilitate the participation of frail elderly patients in clinical trials, investigators should be more aware of possible barriers when setting up research. This paper offers an overview of the problems encountered when conducting a randomized controlled trial in a frail elderly population and their solutions.

The trial

This article is based on practical experience gained while conducting a trial entitled 'A randomized controlled trial of geriatric liaison intervention in frail surgical oncology patients' (LIFE). The objective of LIFE was to show that a geriatric liaison intervention in frail elderly patients undergoing a surgical procedure for a solid tumour would decrease the occurrence of delirium and consequent morbidity and mortality, without an increase in costs. Three centers participated in this study: center A, a university medical center; center B, a large teaching hospital; and center C, an inner-city hospital.

Patients over 65 years of age undergoing surgery for a solid tumour were assessed with the Groningen Frailty Indicator (GFI) [9] at the outpatient departments of general surgery. The GFI is a short 15-item screening instrument used to determine an individual's level of frailty. It screens for the loss of functions and resources in four domains of functioning: physical (mobility functions, multiple health problems, physical fatigue, vision, and hearing), cognitive (cognitive functioning), social (emotional isolation), and psychological (depressed mood and feelings of anxiety). Patients with a GFI score greater than 3 are regarded as frail [9;10] and were recruited for this study. Patients with any psychological, familial, sociological or geographical circumstances potentially hampering compliance with the study protocol and follow-up schedule were excluded from participation. Patients unable to fill in

the questionnaires were also excluded. From June 2007 to December 2009, 238 patients were included and randomized.
The intervention consisted of a preoperative consultation with a geriatrician and an individual treatment plan targeted at several risk factors for delirium, daily visits by a geriatric nurse during the hospital stay and advice on managing any problem encountered on the basis of a nine-item checklist.
The primary outcome was the occurrence of delirium up to 10 days postoperatively. In both groups the Delirium Observation Scale (DOS) [11] was used to screen for delirium. In the case of a mean DOS score ≥ 3 (possible delirium) a geriatrician or psychiatrist examined the patient to confirm the diagnosis according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM IV) criteria.
Data were collected at admission, during the hospital stay and three months after discharge. Patients were asked to complete several questionnaires which was estimated to take 30 minutes at admission (collection of demographic data, assessment of the quality of life, measured by a Short Form-36 (SF-36) score [12] and care dependency, measured by the Care Dependency Scale (CDS) [13], 15 minutes daily during hospital stay (a nine-item checklist concerning orientation, mobility, anxiety, senses, pain, sleep, intake, defecation and infection completed by a research nurse), 15 minutes at discharge (SF-36 and CDS) and 15-30 minutes for 3 months postoperatively (SF-36, living situation).
Funding was obtained from the Netherlands Organisation for Health Research and Development, trial number 945-07-516. The study was approved by the Medical Ethical Committee of the University Medical Center Groningen (UMCG).

The main problem: inclusion

In the surgical ward of university center A, a minimum of 180 patients aged 65 years and over are treated for a solid tumour each year. In a prospective study, 85 consecutive admissions for oncological surgery in UMCG were assessed with the GFI, 30% of these patients had a score greater than 3. Based on this pilot study, it was expected that one-third of these patients would be frail. With an expected inclusion rate of 90%, it was calculated that around four patients from center A could be included per month. After similar calculations this number amounted to four patients per month from center B and two from center C. Financial support was available for a total of 30 months: from April 2007 to October 2009. During the course of the study it became clear that the actual inclusion rate fell short of expectations (see Figures 1 and 2).

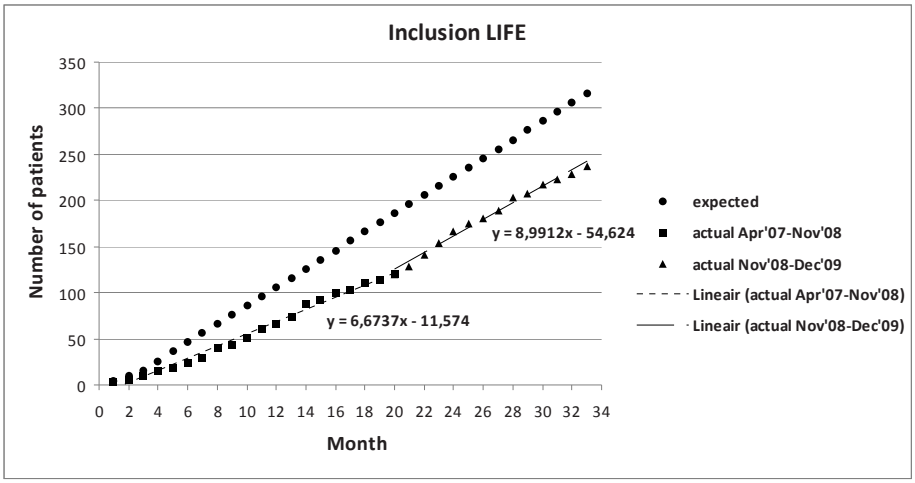


Figure 1. Expected versus actual inclusion in the LIFE study. Trend lines and formula added for the actual inclusion rates from April 2007–November 2008 and from November 2008–December 2009

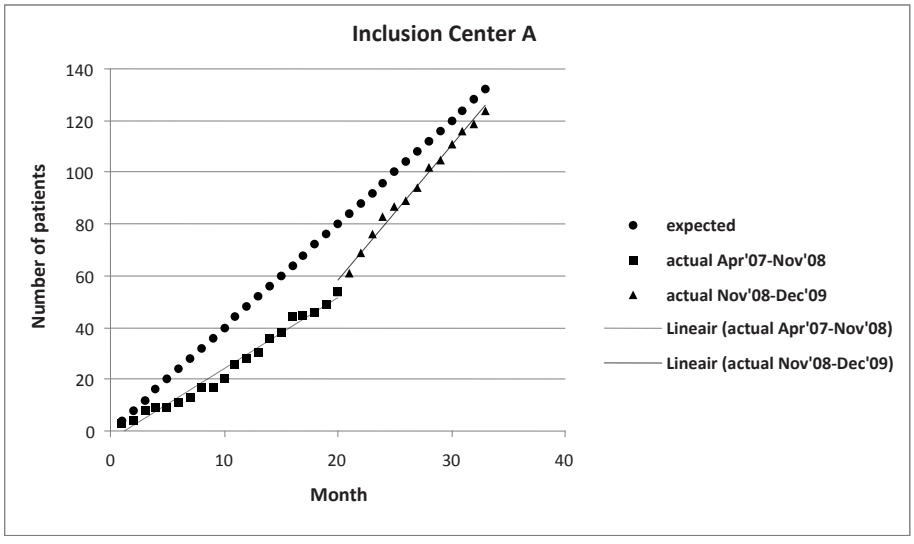
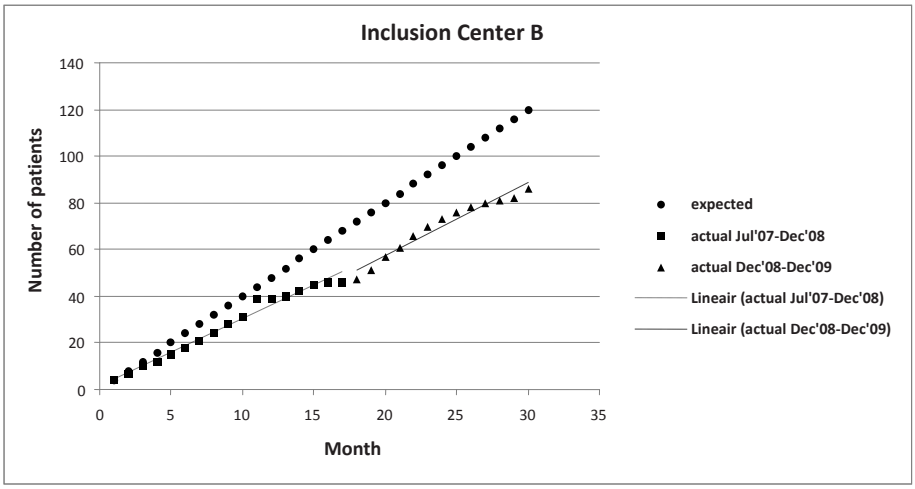


Figure 2 (part I). Inclusion per center. Trend lines and formulae added for the actual inclusion rates for the first and second parts of the study



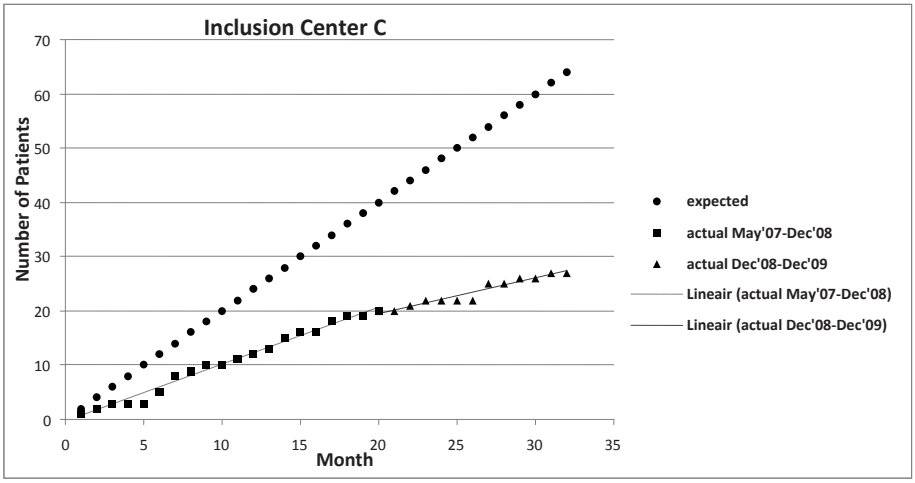


Figure 2 (part II). Inclusion per center. Trend lines and formulae added for the actual inclusion rates for the first and second parts of the study

Reasons for low inclusion rate and possible solutions

High incidence of refusal to participate

From June 2007 to December 2009, 1256 patients were screened and 359 (28.6%) were found to be frail. Thirty-eight patients failed to meet the inclusion criteria (10.6%). Of the remaining 321 eligible patients, 238 (74.1%) were randomized. This was much less than the expected inclusion rate of 90%. The

most important reasons for not entering the study were refusal to participate (n = 54; 16.8%) and logistics (planning and transportation) (n = 12; 3.7%).

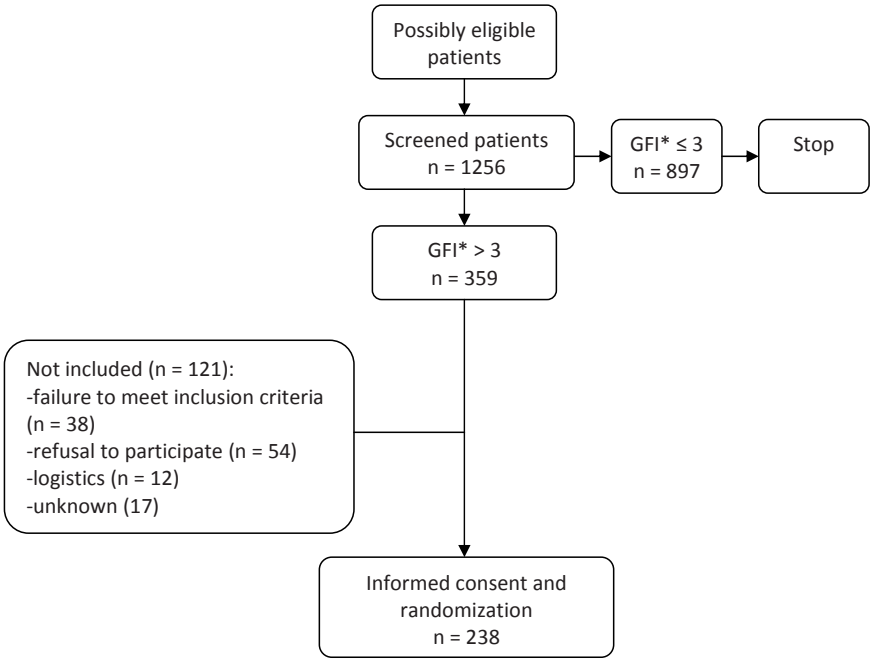


Figure 3. Flow chart of inclusion rates. *GFI = Groningen Frailty Indicator, a screening instrument used to determine an individual's level of frailty. Patients with a score greater than 3 were regarded as frail and were recruited for this study.

It appeared that patients refused to participate primarily because they felt overburdened by their physical condition, stress, and concerns about the future after the cancer diagnosis. Additional visits and travel to the hospital also discouraged them from participation. This latter problem was solved by home visits and flexible scheduling, for example, appointments related to the study were combined with a scheduled appointment at the hospital to prevent unnecessary travel. In addition, many elderly reported that they did not want to be a burden to their relatives by asking to be accompanied. In general, family members had a major influence on the decision to participate. The approval or rejection of relatives largely determined the decision of a frail older person to participate in the trial. For this reason, relatives were involved in the informed consent process which took place when the research nurse visited eligible patients and their accompanying relatives at the outpatient clinics. The

research nurse was able to give them information in a face to face meeting and gave them the opportunity to ask questions.

Communication problems

In center A the inclusion rates were lower than expected because of problems in the initial communication process. A research nurse was appointed who had vast research experience but no specific experience in the care for and communication with the elderly patient. Potential eligible patients were informed about the study by nurses on the outpatient clinics. Often only written information was given. Afterwards patients were contacted by telephone by the research nurse for participation. When a patient decided to participate, informed consent had to be returned by post, this was an additional barrier.

While in this population it is important to take extra time when communicating, as communicative capacity is often restricted because of a higher incidence of sensory loss (hearing and visual problems), speech problems such as aphasia and dysarthria and cognitive decline. In our experience it is by far more preferable to communicate with patients face to face as they seem to understand information given in this way much better than by telephone. Jansen (2009) studied communication between the older cancer patient and clinician [14] and found that patients are better able to recall information when: 1) only the most important information is discussed with the elderly patient and the duration of a consultation is limited; 2) a companion is present during the consultation – a patient who prefers to be accompanied should be stimulated to bring someone with them; 3) empathy is expressed when a patient shows emotion. These recommendations should be taken into account when communicating with older people.

After persistent disappointing inclusion rates, it was decided that a nurse with ample experience in caring for and communicating with elderly patients should be appointed. Her efforts increased the inclusion rate substantially from December 2008 (see Figure 3). She was informed when there was an eligible patient on the outpatient clinic and then visited the patient immediately on the outpatient clinic to give them face to face information. Then questions of the patient and relatives could be answered and informed consent could be signed if the patient decided to participate.

Relocation of frail patients

Unexpectedly, frail patients were often operated on in the university hospital near center C. Because the participation of center C was not cost-effective,

funding was partly withdrawn and the inclusion of patients from this center ended prematurely.

Staff insufficiently aware of the study

In all centers it became apparent that 10–20% of eligible patients were not screened. To increase general awareness of the study, posters, pencils and sweet jars with the logo of the study were distributed to the outpatient clinics and wards. During the following months every patient that visited the outpatient clinic and was possibly eligible for LIFE was marked in the patient list by the research nurses. Afterwards it was checked if these patients were indeed screened. Also, weekly reports of screening results were presented to the nursing staff involved. In addition, because all surgical patients were discussed in multidisciplinary meetings before treatment, patient lists of these meetings were checked weekly to detect unscreened patients.

In center B, the study started months later than planned. While the start of the study was agreed to by all medical staff, the nurses were poorly informed. The success of this study depended largely on the commitment of nurses in the outpatient clinics and the wards.

Again it became clear that supplying adequate information and instructions to the health care professionals involved benefited the progress of the study. For both doctors and nurses, clinical research often means that there are additional tasks to do alongside their daily care activities. Our experience indicates that the research tasks usually are low in priority, especially when the provision of information is poor. It is preferable to plan time for research tasks in the usual schedule. It is also desirable to repeatedly explain the study protocol and continue to remind existing staff and instruct new staff in this regard. We realize that this problem is not specific to research in a frail elderly population, but is important for clinical research in general.

An additional measure taken to increase the inclusion rate was the involvement of the departments of gynaecology; ear, nose and throat medicine; and maxillofacial surgery in centers A and B. This required further investment of time and resources to inform and educate staff.

Due to the above-mentioned measures, the inclusion rates increased in centers A and B. The trend in the inclusion rate for the second part of the study shows an increased slope in comparison with the first part (Figure 3). In center C the inclusion rate decreased during the second part of the study (Figure 3). One reason was that the geriatrician responsible for the study moved to another hospital. Additionally, the distance between center C and center A (the work

location of the primary investigator) made intensive supervision difficult. These factors may have influenced the low inclusion rate in center C.
After 30 months the estimated number of patients had not yet been recruited, resulting in a prolonged inclusion phase of 8 months and the redistribution of financial resources. Due to the disappointing results in center C, the inclusion phase and financial support were not prolonged there.

Other problems and solutions

Although the inclusion of frail elderly patients in this trial proved to be the biggest problem, we encountered several other issues influencing the success of this study.

Sample size calculation: estimating incidences was difficult due to the heterogeneity of the population
To achieve a power of 80% with an α of 5% (one-sided), a β of 95% and an expected drop-out rate of 10%, a total inclusion of 294 patients was calculated for this study. The reported incidence of delirium varies widely between and within the populations under investigation. Incidences vary from less than 10% up to 50% after orthopaedic [15], abdominal[15-16] and cardiac surgery [17]. Based on these data the incidence of delirium in our population was assumed to be 30%. Because we studied a high risk population, we thought that an incidence of 30% was a conservative estimate. We expected to find an absolute reduction of 15%. Based on the results of Inouye (1999), we felt that aiming for a total reduction of 15 % (and thus a final incidence of 15 %) would be feasible [18]. Inouye et al. found a final incidence of 10%.
The preliminary results of the LIFE study showed a lower overall incidence of delirium than expected. A great variance in outcome measures is inherent to the elderly population due to heterogeneity with respect to physical, mental and social functioning. We recommend using cautious estimates of incidence when calculating sample size in this population to maintain power.

Time management
All parts of the trial (recruitment, intervention, measurements and analysis) took more time than anticipated and, consequently, more financial resources than calculated. We had calculated an overall mean time investment of 2 h per patient but the actual time investment per patient amounted to be more than 6 h. Since patients in this population have difficulty interpreting self-administered questionnaires, the questions were administered in an interview form. Studies have shown that frail older adults have difficulty with self-

administered questionnaires. For example, the Short Form-36 (SF-36) [12] has proven to be reliable and valid in a frail elderly population only when used in an interview setting [19-20].
The interview setting used made it difficult to strictly adhere to the content of the questionnaires due to the addition of personal comments and questions leading the patients to disclose tangential information. This contributed to the questionnaires taking more time than anticipated. In addition, in the course of the study some questionnaires were added to the protocol, namely the Mini-Mental State Examination (MMSE) [21] to measure preoperative cognitive functioning and 3 months after, the Geriatric Depression Scale (GDS) [22] to measure preoperative depression, and the Mini Nutritional Assessment – Short Form (MNA-SF) [23] to measure preoperative malnutrition.
The additional visit to the hospital for the follow-up measurement at three months was a stressful experience for many patients. It was necessary to adapt the research protocol to allow visits to the home for this measurement, taking into account the patients' physical and cognitive abilities. The travel time needed increased the time investment per patient considerably.

Other potential pitfalls

Beyond the problems we encountered while conducting the LIFE study there are other potential pitfalls. We want to emphasize the importance of the selection of patients. Patients who are too frail or too fit should be excluded to optimize internal validity (the need to focus the study group to maximize the chances of detecting an impact of the intervention if it exists). However, eligibility criteria should not be too strict with respect to external validity (the ability to generalize to a larger population) [5]. For example, in the LIFE study patients unable to understand questionnaires were excluded, although patients with decreased cognitive abilities are at high risk to develop delirium. Furthermore patients undergoing surgery for a superficial tumour (skin, breast) were included in the study, although they are at low risk to develop postoperative delirium. Both criteria may have lowered the delirium incidence rate in our study and reduced the change to show effectiveness of the intervention.
Moreover, problems with judging decision-making capacity due to cognitive problems may be a barrier to the inclusion of frail elderly people in clinical trials. The gold standard for making a judgement about capacity is an evaluation of the criteria for decision-making capacity in a semi-structured interview [16]. We did not use this in our study, but it seems a useful tool for inclusion of elderly patients with cognitive impairment in clinical trials.

Conclusion

Executing a clinical trial in frail elderly patients requires an adjusted approach. When designing a protocol and scheduling measurements, the limited physical (mobility problems, sensory losses and reduced exercise capacity) and mental abilities (cognitive impairments) of frail elderly should be taken into account. Members of the research team should have an affinity with the elderly and be aware of the fact that extra time and financial resources are needed when conducting research in a frail elderly population.

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6

General discussion

Chapter 6

Introduction

The results of the Liaison Intervention in Frail Elderly (LIFE) study are central in this thesis. Within this multicentre prospective study the effect of a geriatric liaison intervention on the incidence of postoperative delirium was compared to standard care in frail elderly cancer patients treated with an elective surgical procedure for a solid tumour. Cognitive dysfunction and severity of the surgical procedure were identified as independent risk factors for postoperative delirium in these frail elderly cancer patients (chapter 2). In a meta-analysis, both pharmacological- and non-pharmacological interventions were found to be effective in the prevention of delirium (chapter 3). To date, a non-pharmacological multicomponent approach targeted at risk factors for delirium is widely accepted as the most effective strategy. However, within the LIFE study the effect of a such an intervention on the incidence rate of postoperative delirium in frail elderly cancer patients with a solid tumour has not proven to be effective (chapter 4a). Also, three months after discharge from hospital no benefit could be detected from this intervention. The association between postoperative delirium and functional decline after hospitalization was confirmed in the population under study (chapter 4b). Both short- and long term results were influenced by an unexpectedly low delirium incidence rate and the high standard of basic care in the participating hospitals. Based on the problems encountered while executing the LIFE study, the conclusion was that executing a clinical trial in frail elderly patients requires an adjusted protocol taking into account the physical and cognitive limitations of this patient group. These adjustments ask for extra time investment to perform assessments and interventions and as a consequence extra financial resources are needed (chapter 5). In this final chapter all findings are discussed in a broader perspective with recommendations for future research and clinical practice.

Risk factors for postoperative delirium

In our research population of elderly undergoing elective surgery for a solid tumour, cognitive dysfunction and severity of surgical procedure were independent risk factors for postoperative delirium (Chapter 2). As mentioned in the introduction, many risk factors for (postoperative) delirium have been identified in the past. In both surgical- and nonsurgical populations, impaired cognitive functioning has proven to be a strong independent risk factor for delirium [1-5]. Cognitive dysfunction is a marker for a damaged brain (due to vascular or Alzheimer pathology) which renders it vulnerable to stressors.

In surgical populations, perioperative factors related to the surgical procedure itself seem to have a bigger impact. Surgical procedures for superficial tumours, like breast and skin, result in few and when then mostly local complications, even in patients over the age of 80 [6-8]. Consequently, postoperative delirium is more common after major surgery [5,6,9]. These data lend support to the hypothesis that an interaction between stress hormones and the inflammatory systems (cytokines and prostaglandins), in older persons with a damaged cerebrum leads to delirium [10-13]. The stress and inflammatory responses are probably more pronounced in patients undergoing major surgery.
In other words: when undergoing a minor surgical procedure, even a cognitive impaired elderly patient is at minimal risk for developing postoperative delirium. Conversely, even robust elderly patients, without cognitive impairment, may develop postoperative delirium after a major surgical procedure. For clinical practice this implies that vulnerable elderly can undergo minor surgery with nearly no increased risk of delirium. Following this train of thought, we recommend investigating preventive strategies for postoperative delirium only in elderly patients undergoing intermediate and major surgery with special attention to those with impaired cognitive functioning.

Selection of patients at risk for postoperative delirium

The results of the meta-analysis on delirium prevention suggested that prevention strategies are more successful when applied to populations with a delirium incidence rate above 30% (chapter 3). To maximize the probability of the intervention to be a cost-effective strategy of delirium prevention, we choose to offer the intervention to a selected population.
In the LIFE study, frail patients were selected because it was expected that they would be at higher risk developing postoperative delirium. Frail persons have decreased ability to compensate for disruptions in homeostasis due to a loss of reserves. We therefore hypothesized that frailty would be associated with increased risk for the development of postoperative delirium [14]. Both delirium and frailty have a complex pathophysiology and both are associated with multiple adverse outcomes [15].
Although there is no consensus on the definition for frailty, one commonly used description is: a physiologic state of increased vulnerability to stressors that results from decreased physiologic reserves, and even dysregulation of multiple physiological systems [16]. Frailty is associated with an increased risk of postoperative complications including delirium[1,17-19].
In order to optimize selection and treatment of hospitalized elderly patients at risk of adverse events in hospital, various attempts have been undertaken to

operationalize the frailty concept. For example the Fried Frailty Index requires the presence of three or more of five components: unintentional weight loss, self-reported exhaustion, low energy expenditure, slow gait speed, and weak grip strength. Based on the scores, people are divided into three categories: robust (none of the criteria), pre-frail (one or two criteria) and frail (three or more criteria) [16].

Another commonly used screening method involves standardised, short questionnaires such as the Vulnerable Elders Survey (VES-13) [20] or the Groningen Frailty Indicator (GFI) [21,22].

[23]Despite the selection of frail patients, delirium incidence rates in the LIFE study were unexpectedly low in both the intervention and the usual-care group. In the population studied, the relative incidence decreased by 34% (14.3% vs. 9.4%) with an overall incidence rate of 11.9% (Chapter 4). Although this is an impressive overall reduction, there was no significant difference between the two groups (OR: 0.63; 95% CI: 0.29-1.35).

Probably, the GFI was not an appropriate method for patient selection for our research. The GFI reflects the holistic geriatric view in that it includes not only physical and cognitive items but also psychological and social items. It is debatable in what way and to what extent psychological and social problems can contribute to an increased risk for postoperative delirium. In addition, the GFI only distinguishes between frail and non-frail, without categorizing the degree of frailty.

Other factors that probably contributed to the low delirium incidence rate in our study are the exclusion of patients with severe cognitive impairment and the inclusion of patients undergoing superficial surgery.

In recent decades, delirium prediction models have been developed in patients undergoing cardiac surgery [24], noncardiac surgery [5] and orthopaedic surgery[4]. Although the individual models proved to be effective in predicting delirium risk within a particular patient population, none of them has proven to be generalizable to other patient categories. All models correspond in that they contain a factor for older age (or are tested in an elderly population), decreased cognitive functioning, high risk surgery (or are tested in a population undergoing high risk surgery) and abnormal biochemistry. Additional risk factors differ per model e.g. prior stroke/ TIA, poor functional status, alcohol abuse, visual impairment, symptoms of depression and severe illness. This shows once again, that a heterogeneous set of risk factors determines whether a patient develops postoperative delirium. In our point of view, it is therefore not feasible to select high-risk patients for postoperative delirium on an individual basis. At group level, e.g. for research purposes, usage of delirium prediction model can be valuable.

Preventive strategies for postoperative delirium

Due to the lack of a general risk profile for delirium across different patient populations and settings and the still poorly understood pathophysiological pathway leading to delirium, there is currently no uniformity in the preventive approach to postoperative delirium. Both pharmacological- and non-pharmacological-, mostly multicomponent, interventions are used. In a meta-analysis, both types of interventions to prevent delirium were found be effective (chapter 3). To date, the non-pharmacological multicomponent approach targeted at risk factors for delirium is widely accepted as the most effective strategy [25]. Positive effects of these multicomponent interventions have mainly been demonstrated in patients on medical and geriatric wards [26-29] and in hip fracture patients [30,31]. In patients on medical and geriatric wards the multicomponent interventions resulted in a reduction of delirium incidence rate to ≤ 10% compared to around 35% in patients after surgical repair of hip fracture.

Within the LIFE study the effect of a multicomponent intervention on the incidence rate of postoperative delirium was studied in frail elderly cancer patients who underwent surgery for a solid tumour. In this study, a multicomponent intervention was implemented by a geriatric consultation team giving advices to doctors and nurses on the surgical wards to optimize the care for these patients. Our intervention has not proven to be effective in the prevention of postoperative delirium (chapter 4). Also, three months after discharge from hospital no benefit could be detected from the intervention. Postoperative delirium increased the risk of decline in ADL functioning (OR: 2.65, 95% CI: 1.02-6.88) resulting in increased use of supportive assistance (OR: 2.45, 95% CI: 1.02-5.87) and decreased chance to return to the independent preoperative living situation (OR: 0.18, 95% CI: 0.07-0.49) (chapter 5). This confirms that a postoperative delirium is a sign of increased (brain) vulnerability associated with poorer prognosis [25]. Therefore, targeting preventive interventions at those elderly at risk for (postoperative) delirium remains a major concern in minimizing functional decline after hospitalization.

The unexpectedly low delirium incidence rates found in this study (14.3% in the intervention group versus 9.4% in the control group) may have been of crucial importance since this resulted in an underpowered study. The incidence rates probably indicate a high standard of care for frail elderly patients in the participating hospitals. Furthermore, the in- and exclusion criteria of the study probably played a role (as discussed in the previous “selection of patients” section). Finally, the introduction of the Delirium Observation Scale (DOS)[32] on the wards to screen for delirium may have ensured increased alertness

among medical staff for the prevention of postoperative delirium in both the intervention and control group. All nurses on the participating wards were trained by a research nurse to score the DOS. Although there is no literature known to us from previous studies that indicated a decrease in the incidence of delirium after entering a screening method.
The multicomponent delirium prevention intervention applied in the LIFE study was consultation-based. The main disadvantage of care by a consultation team is that its success is linked to adherence to the recommendations given. In other settings it was shown that treatment by a consultation team was not effective. For example, a Comprehensive Geriatric Assessment (CGA) in older people admitted to the hospital with acute medical disorders is solely effective when the patient is admitted to a geriatric ward. Then a CGA significantly increases the likelihood of being alive, living at home after discharge and lowers the risk on functional decline at discharge [33-35]. These positive effects have not been shown (or only to a limited extent) when a CGA was carried out by a geriatric consultation team on a general ward [34,36]. Also in the field of orthopedic surgery, where there is wealth of experience with different models of shared orthopaedic and geriatric care for elderly hip-fracture patients, there is a trend towards integrated care as the most effective model [37,38]. In this model, the orthopaedic surgeon and the geriatrician manage the patient together from admission until discharge. The patient is admitted to an orthopaedic ward where a geriatrician is integrated into the treatment team. We postulate that integrated care will also contribute to the effectiveness of a multicomponent intervention to prevent postoperative delirium in frail elderly cancer patients.
In conclusion: optimizing basic care targeted at predisposing risk factors for postoperative delirium (e.g. cognitive impairment, sensory losses, malnutrition and impaired mobility) seems to be the focal point in the prevention of postoperative delirium. The prevention of postoperative delirium will also contribute to limiting functional decline after surgery.

Participation of frail elderly (cancer) patients in clinical trials

In chapter 5 the problems encountered while conducting the LIFE study were described. The main problem was that the inclusion rate fell short of expectations. This was due to: 1) Limited physical and cognitive reserve of frail elderly patients, making participation and extra visits to the hospital burdensome; 2) Difficulties in understanding written information and oral information provided over the phone; and 3) Insufficient awareness of the study by health-care professionals.

In order to decrease the burden of the study protocol, the follow-up measurements were performed at home. To overcome difficulties in understanding written information and information given over the phone, patients were informed face to face and questionnaires were completed in an interview format. To increase awareness, posters, pencils and sweets with the logo of the study were distributed, and the study protocol was explained repeatedly to the staff. Moreover, checks were made as to whether patients coming to the hospital were in fact screened for eligibility. All these measures did increase inclusion rates but also caused an increased time investment and consequently extra (staffing) costs.

Executing a clinical trial in frail elderly patients requires an adjusted approach. When designing a protocol and scheduling measurements, the limited physical (mobility problems, sensory losses and reduced exercise capacity) and mental abilities (cognitive impairments) of frail elderly have to be taken into account. Members of the research team should have an affinity with elderly and be aware of the fact that extra time and financial resources are needed. Sponsors should provide extra funds for this kind of research.

Adequate supportive care for hospitalized frail elderly is a time consuming task, although certain principles are easily applicable (e.g. nutritional assistance, ensure use of spectacles or hearing aids and mobilization). To reduce costs, volunteers and proxies could play a role in the care process. In the USA broad experience has been gained with the volunteer-based hospital elder life program (HELP) to prevent delirium in older hospitalized patients. HELP has shown to be effective in internal medicine and surgical populations in the USA [39] and in a population undergoing major abdominal surgery in Taiwan [40]. Currently the effectiveness of HELP is investigated in the Dutch care system [41].

Future perspectives

Given the current available data on the effectiveness of multicomponent interventions to prevent delirium in different patient populations and the multifactorial etiology of delirium, a multicomponent prevention strategy is the method to decrease the incidence of postoperative delirium in elderly cancer patients. It is not deemed likely that the content of the intervention was responsible for the lack of effectiveness in the LIFE study. Rather, changes in the implementation process could increase the effectiveness. We would recommend changes in this process on several points. First, selection of patients based on frailty as measured with the GFI proved not to provide a population at increased risk for postoperative delirium. In frail elderly cancer

patients, as well as in other patient populations, impaired cognitive functioning appears to be an important risk factor for postoperative delirium. Further, the severity of the surgical procedure determines the risk for postoperative delirium. Therefore interventions to prevent postoperative delirium should be targeted on elderly with impaired cognitive function undergoing intermediate or major surgery. By recording the delirium incidence rate, the quality of care can be monitored easily and, when necessary, adjustments can be achieved.
Second, the use of a geriatric consultation service is probably not the most effective way of care delivery. Therefore, intensive collaboration between surgeons and geriatricians based on co-management is advisable. Given the growing number of elderly patients, it is imperative that surgeons and nurses on surgical wards become proficient in the care for frail elderly patients. Geriatricians could train surgical staff in these skills. In the transition phase, it is advisable that a geriatrician is a member of the treatment team and oncological surgeons and geriatricians should manage the patients together on a surgical ward. It would be preferable if a suitable care environment for frail elderly people is provided (e.g. presence of a living room, enough space to mobilize with walkers and wheelchairs, orientation points) and that extra staff is available for the time-consuming care for this population. When a high standard of care is achieved and patients are solely admitted to surgical wards where staff is skilled in the care for frail elderly, selection of high risk patients prior to admission may no longer be necessary. Hospitals organizing the care for frail elderly cancer patients this way, should be able to decrease the postoperative delirium incidence rate to 10-15%. To ensure the quality of care, delirium incidence rate should be monitored. When the incidence rate turns out to be higher than the target, the care process has to be optimized.
The recommendations, summarized in a flow chart (figure 2), can serve as a guideline for perioperative management of elderly undergoing surgery.

Although the LIFE study is a methodological sound study, some parts should be improved for future studies. Despite the fact that contamination did not seem to influence the results, it is an important source of bias in complex intervention studies designed to improve the care of frail elderly even when a RCT design is used [27,42,43]. In our view, this can only be avoided if patients in the control and usual care group are treated on separate wards, preferably in different hospitals (cluster randomized design). Cluster randomization may reduce the risk that the intervention under study is unintentionally mixed up with care as usual, the intervention of the control group [44].

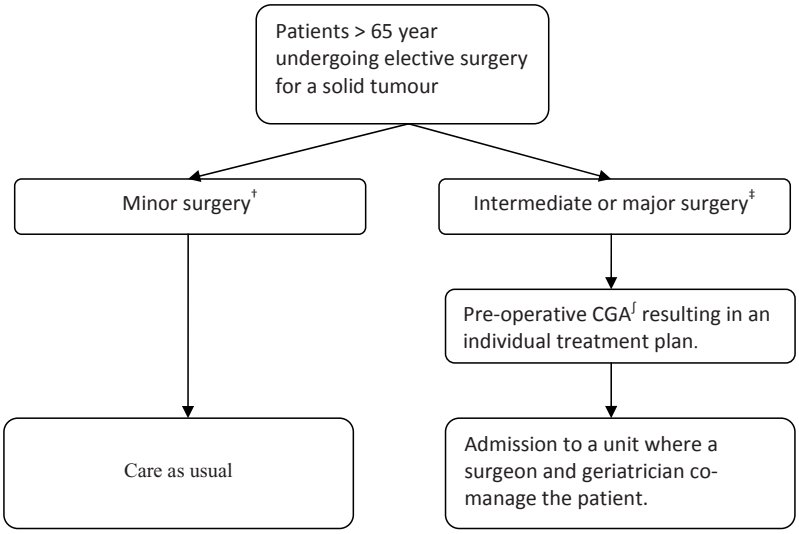

Figure 2. Flow chart for perioperative management of elderly undergoing sugery for a solid tumour.
†Minor surgery = breast and skin, ‡Intermediate surgery = vulva, cervix, endometrium, uterus, head/neck and retroperitoneum and major surgery = gastrointestinal, liver, pancreas, lung, ovary, oropharynx, larynx and intra-abdominal sarcoma.
∫CGA = comprehensive geriatric assessment targeted at risk factors for postoperative delirium (especially decreased cognitive functioning)

A unique example of a cluster randomized design is a stepped wedge cluster design. In this design, different clusters (hospitals) cross over from control group to intervention group at predefined time points in a random order.
The clusters cross over in one direction only – from control to intervention [44,45].
In this study, we choose for incidence of postoperative delirium as primary outcome. But in this heterogeneous population, with multiple chronic conditions, universal health outcomes that are relevant across diseases (e.g., function, survival, active life expectancy and health related quality of life) are probably more suitable to evaluate treatment effects [46].
In conclusion, additional investigation is necessary to establish the value of a multicomponent intervention to prevent postoperative delirium in elderly cancer patients. For future research we recommend to apply a multicomponent intervention targeted at risk factors for postoperative delirium to frail elderly cancer patients undergoing intermediate or major surgery. Patients should be admitted on a surgical ward where surgeons and geriatricians manage the patients together. The preferred study design is

cluster randomized and the primary outcome measures should be more oriented at physical and cognitive functioning after hospitalization.

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Summary

Postoperative delirium is a common complication in elderly patients. It is associated with poor outcomes following surgery. Most delirium prevention studies of the elderly have included orthopaedic patients (usually hip-fracture patients) or patients from an acute care unit. In this thesis we aimed to get better insight in the prevention of postoperative delirium in frail elder surgical oncology patients. This population was chosen because cancer is a disease of the elderly with over 50% of solid tumours and 80% of cancer deaths occurring in patients over 65 years of age.

Chapter 2 investigates which risk factors are predictive for postoperative delirium in patients over 65 years of age undergoing elective surgery for a solid tumour.
In an observational multicentre retrospective study, medical records of 251 patients were screened for postoperative delirium using a standardized instrument. Forty-six patients developed postoperative delirium (18.3%). Preoperative cognitive functioning (OR: 23.36; 95% CI: 5.33-102.36) and severity of the surgical procedure were identified as independent risk factors for postoperative delirium; intermediate (OR: 15.44, 95% CI: 1.70-140.18) and major surgical procedures (OR: 45.01, 95%CI: 5.22-387.87) significantly increased the risk for postoperative delirium as compared to minor surgery. This study suggest that, in clinical practice interventions to prevent postoperative delirium should be focused on elderly undergoing intermediate or major surgery with special attention to those with impaired cognitive functioning

Due to the lack of a general risk profile for delirium across different patient populations and settings, and the still poorly understood pathophysiological pathway leading to delirium, there is currently no uniformity in the preventive approach to postoperative delirium. Both pharmacological- and non-pharmacological-, mostly multicomponent, interventions are used.
Chapter 3 describes the result of a meta-analysis aimed to investigate if (non-) pharmacological interventions to prevent delirium were effective and to explore which factors increased the effectiveness of these interventions. Sixteen relevant studies were included. In nine of the studies a pharmacological intervention was tested. Overall, the included studies showed a positive result of any intervention to prevent delirium (pooled OR 0.64; 95% CI 0.46-0.88). The largest effect was seen in studies on populations with an incidence of delirium above 30% in the control group (pooled OR 0.34; 95%CI 0.16-0.71 versus 0.76; 95%CI 0.60-0.97). Interventions seemed to be more effective when the incidence of delirium in the population under study was above 30%. To

maximize the options for a cost-effective strategy of delirium prevention, it might be useful to offer an intervention to a selected population.

Chapter 4 presents the results of the Liaison Intervention in Frail Elderly (LIFE) study. This is a multicenter, randomized, clinical trial. The aim of this trial was to evaluate the effect of a geriatric liaison intervention in comparison with standard care on the incidence of postoperative delirium in frail elderly cancer patients treated with an elective surgical procedure for a solid tumour. The intervention consisted of a preoperative geriatric consultation, an individual treatment plan targeted at risk factors for delirium, daily visits by a geriatric nurse during the hospital stay and advice on managing any problems encountered. In total, the data of 260 patients were analysed. Delirium occurred in 31 patients (11.9%), and there was no significant difference between the incidence of delirium in the intervention group and the usual-care group (9.4% vs. 14.3%, OR: 0.63, 95% CI: 0.29-1.35). Certain limitations to the study design, such as patient selection, may have played a role.

Chapter 5 describes long term outcomes of the LIFE study. In addition, the effect of postoperative delirium on post discharge outcomes was examined. A three month follow-up was performed in patients who participated in the LIFE study. The long term outcomes included: mortality, rehospitalisation, ADL functioning, return to the independent pre-operative living situation, supportive care, cognitive functioning and health related quality of life. There were no differences between the intervention group and usual-care group for any of the outcomes. Postoperative delirium increased the risk of a decline in ADL functioning (OR: 2.65, 95% CI: 1.02-6.88) resulting in increased care assistance (OR: 2.45, 95% CI: 1.02-5.87) and decreased chance to return to the independent preoperative living situation (OR: 0.18, 95% CI 0.07-0.49). The lower than expected delirium incidence rate will have been of major influence on the long term results. Adjusting the criteria for patient selection could possibly increase the effectiveness of the intervention (see chapter 2).
The association between postoperative delirium and functional decline after hospitalization was confirmed in the population under study. Therefore, prevention of postoperative delirium seems one of the ways to limit functional decline after surgery in this patient group.

With aging of the population, the interest in clinical trials concerning frail elderly patients increases. Evidence-based practice for the elderly patient is difficult because elderly patients, especially the frail, are often excluded from clinical trials. To facilitate the participation of frail elderly patients in clinical

trials, investigators should be more aware of possible barriers when setting up research.

Chapter 6 offers an overview of the problems we encountered while conducting the LIFE study and their possible solutions. The main problem was lagging inclusion rates. This was due to i.e.: 1) Limited physical and mental abilities of frail elderly making participation and extra visits to the hospital a burden for patients. To increase inclusion rates, follow-up measurements were taken at a home visit. 2) Difficulty with understanding written information and information given by telephone. To overcome this, patients were informed face to face and questionnaires were filled in an interview form. 3) Insufficient awareness of the study by health care professionals. To increase awareness, posters, pencil and sweet jars with the logo of the study were distributed and the study protocol was repeatedly explained to (new) staff. Moreover, it was checked if possibly eligible patients coming to the hospital, were indeed screened for participation. The mentioned measures, among others, increased inclusion rates but also caused an increased time investment and consequently extra financial resources for staff costs.

Samenvatting

Een postoperatief delier is een veelvoorkomende complicatie bij oudere patiënten. Het leidt tot slechtere uitkomsten na een operatie. De meeste studies ter preventie van een delier bij ouderen zijn gericht op orthopedische patiënten (meestal patiënten met een heupfractuur) of patiënten met interne aandoeningen die in het ziekenhuis worden opgenomen via de spoedeisende hulp. Het doel van dit proefschrift is om beter inzicht te krijgen in de preventie van postoperatief delier bij kwetsbare oudere onco-chirurgische patiënten. Deze populatie werd gekozen omdat kanker een ziekte is van de oudere mens: meer dan 50% van de solide tumoren en meer dan 80% van de sterfgevallen aan kanker komen voor bij patiënten ouder dan 65 jaar.

In **hoofdstuk 2** wordt onderzocht welke risicofactoren voorspellend zijn voor een postoperatief delier bij patiënten ouder dan 65 jaar die een electieve operatie ondergaan voor een solide tumor. In een observationele, retrospectieve, multicenter studie werden de medische statussen van 251 patiënten gescreend op het doormaken van een postoperatief delier. Hiervoor werd gebruik gemaakt van een gestandaardiseerd meetinstrument. Vierenzestig patiënten ontwikkelden een postoperatief delier (18.3%). Er werd vastgesteld dat het preoperatief cognitief functioneren (OR: 23.36; 95% CI: 5.33-102.36) en de zwaarte van de operatie onafhankelijke risicofactoren waren voor een postoperatief delier. Het risico op een postoperatief delier was significant vergroot bij gemiddeld grote chirugische ingrepen (OR: 15.44, 95% CI: 1.70-140.18) en grote chirurgische ingrepen (OR: 45.01, 95%CI: 5.22-387.87) in vergelijking met kleine ingrepen. Deze studie suggereert dat interventies ter preventie van een postoperatief delier in de klinische praktijk gericht zouden moeten zijn op ouderen die een gemiddeld grote - tot grote operatie ondergaan met extra aandacht voor diegenen waarbij het cognitief functioneren gestoord is.
Momenteel is er geen overeenstemming over de beste preventiestrategie voor een delier. Dit heeft te maken met het ontbreken van een algemeen risicoprofiel voor het ontwikkelen van een delier in verschillende patiënten populaties en onder verschillende omstandigheden en de onduidelijkheid met betrekking tot de pathosfysiologische route die leidt tot een delier. Zowel farmacologische- als non-farmacologische interventies worden toegepast.

In **hoofdstuk 3** worden de resultaten beschreven van een meta-analyse. Deze had tot doel te onderzoeken of (non-)farmacologische interventies ter preventie van een delier effectief zijn en te exploreren welke factoren de effectiviteit van deze interventies verbeteren. Er werden zestien relevante studies geïncludeerd. In negen van de studies werd een farmacologische

interventie getest. Globaal, toonden de geïncludeerde studies een positief resultaat voor elke interventie ter preventie van een delier (gepoolde OR 0.64; 95% CI 0.46-0.88). Het grootste effect werd gezien in studies waarbij de delier incidentie in de controle groep hoger was dan 30% (gepoolde OR 0.34; 95%CI 0.16-0.71 versus 0.76; 95%CI 0.60-0.97). Interventies lijken effectiever te zijn wanneer de delier incidentie in de onderzochte populatie hoger is dan 30%. Om de mogelijkheden voor een kosteneffectieve delier preventiestrategie te optimaliseren, zou het nuttig kunnen zijn om de interventie alleen toe te passen op een geselecteerde hoog risico populatie.

In **hoofdstuk 4a** worden de korte termijn resultaten van de Liaison Intervention in Frail Elderly (LIFE) studie gepresenteerd. Dit is een klinisch, gerandomiseerde, multicenter studie. Het doel van deze studie was om het effect van een geriatrische liaison interventie op de incidentie van postoperatief delier te onderzoeken in vergelijking met reguliere zorg bij kwetsbare oudere oncologische patiënten die werden behandeld middels electieve chirurgie voor een solide tumor. De interventie bestond uit een preoperatief geriatrisch consult, een individueel behandelplan gericht op risicofactoren voor delier en dagelijkse visites door een geriatrie verpleegkundige gedurende de ziekenhuisopname. De verpleegkundige gaf advies aan het behandelteam op de afdeling ten aanzien van eventuele problemen. In totaal werden de data van 260 patiënten geanalyseerd. Bij 31 patiënten (11.9%) trad een delier op. Er was geen significant verschil in de delier incidentie tussen de interventie groep en de controle groep (9.4% vs. 14.3%, OR: 0.63, 95% CI: 0.29-1.35). Bepaalde beperkingen van de studieopzet, zoals patiëntenselectie, kunnen een rol hebben gespeeld bij deze uitkomsten.

In **hoofdstuk 4b** worden de lange termijn uitkomsten van de LIFE studie beschreven. Daarnaast wordt het effect van een postoperatief delier op de uitkomsten na ontslag gepresenteerd. Na drie maanden werd een follow-up meting uitgevoerd bij patiënten die deel hadden genomen aan de LIFE studie. De lange termijn uitkomsten bestonden uit: mortaliteit, heropnames, ADL functioneren, terugkeer naar de onafhankelijke preoperatieve woonsituatie, gebruik van aanvullende zorg, cognitief functioneren en gezondheid gerelateerde kwaliteit van leven. Voor geen van deze uitkomsten werd een verschil aangetoond tussen de interventie groep en de controle groep. Een postoperatief delier vergrootte het risico op achteruitgang in ADL functioneren (OR: 2.65, 95% CI: 1.02-6.88) resulterend in een toename van zorgafhankelijkheid (OR: 2.45, 95% CI: 1.02-5.87) en een afname van de kans op terugkeer naar de onafhankelijke preoperatieve woonsituatie (OR: 0.18, 95% CI

0.07-0.49). De delier incidentie was lager dan verwacht. Dit is waarschijnlijk van grote invloed geweest op de lange termijn resultaten. Het aanpassen van de criteria voor patiënten selectie kan mogelijk bijdragen aan de effectiviteit van de interventie (zie hoofdstuk 2).
Het verband tussen een postoperatief delier en functionele achteruitgang na de operatie werd bevestigd in de bestudeerde populatie. Daarom lijkt preventie van een postoperatief delier één van de manieren om functionele achteruitgang na de operatie te beperken in deze patiënten groep.

Door het verouderen van de wereldbevolking, neemt de interesse in klinische trials bij kwetsbare oudere patiënten toe. Evidence-based practice voor oudere patiënten is lastig omdat ouderen, vooral de kwetsbare ouderen, vaak geëxcludeerd worden voor klinische onderzoeken. Om deelname van kwetsbare ouderen aan klinische trials te vergemakkelijken, zouden onderzoekers meer bedacht moeten zijn op de mogelijke barrières bij het opstellen van een onderzoeksprotocol.
Hoofdstuk 5 toont een overzicht van de problemen die wij zijn tegengekomen bij het uitvoeren van de LIFE studie. Tevens wordt aandacht besteed aan mogelijke oplossingen. Achterblijvende inclusie cijfers waren het belangrijkste probleem. Dit werd veroorzaakt door door onder andere: 1) beperkte lichamelijke en mentale capaciteiten van kwetsbare ouderen waardoor deelname en extra ziekenhuisbezoeken een belasting waren voor patiënten; 2) moeilijkheden met het begrijpen van geschreven informatie en informatie verstrekt via de telefoon; en 3) onvoldoende bekendheid met de studie bij het ziekenhuis personeel. Om de inclusie cijfers te laten stijgen, werden de follow-up metingen uitgevoerd tijdens een huisbezoek. Om problemen met het begrijpen van geschreven informatie of informatie verstrekt via de telefoon voorkomen werden patiënten face to face geïnformeerd en werden vragenlijsten ingevuld tijdens een interview. Om de bekendheid van de studie te verbeteren werden posters, pennen en snoeppotten met het studielogo verspreid en werd het onderzoeksprotocol herhaaldelijk uitgelegd aan (nieuw) personeel. Verder werd gecontroleerd of potentieel geschikte patiënten, tijdens ziekenhuisbezoek, wel werden gescreend voor deelname. De bovengenoemde maatregelen, naast andere aanpassingen, zorgden voor een toename van de inclusie cijfers maar vergden ook een extra tijdsinvestering gepaard gaande met hogere personeelskosten.

Dankwoord

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List of publications

Publications related to this thesis

- Hempenius L, van Leeuwen BL, van Asselt DZB, Hoekstra HJ, Wiggers T, Slaets JPJ, de Bock GH. Structured analyses of interventions to prevent delirium. Int J Geriatr Psychiatry 2011; 26: 441-450
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Publication not related to this thesis

- Roebroeck ME, Hempenius L, van Baalen B, Hendriksen JG, van den Berg-Emons HJ, Stam HJ. Cognitive functioning of adolescents and young adults with meningomyelocele and level of everyday physical activity. Disabil Rehabil 2006; 28 (20): 1237-42

About the author

Liesbeth Hempenius was born on the 28th of December 1977 in Hurdegaryp, the Netherlands. In 1996, she graduated from secondary school at the Delta Scholengemeenschap in Leeuwarden. In the same year she started studying Human Movement Sciences at the University of Groningen, which was completed in 2000. Between January 2001 and September 2002 she worked as a PhD student at the department of rehabilitation medicine of the Erasmus University Rotterdam. In September 2002 she started studying medicine at the University Medical Center of Groningen. She obtained her medical degree in December 2005. Subsequently, she worked as resident at the department of Internal medicine and Geriatric medicine of the Medical Center Leeuwarden. In December 2007 she started her training in Geriatric medicine at the department of geriatric medicine of the Medical Center Leeuwarden. From May 2009 to July 2010 she worked on this thesis at the department of surgery at the University Medical Center in Groningen in collaboration with the department of geriatric medicine. Hereafter, she pursued Geriatric residency at the Medical Center Leeuwarden, combined with the completion of her thesis. In September 2015, she hopes to successfully finish her traineeship in geriatric medicine.
Liesbeth is together with Jeen Geertsma and they have two daughters: Renske (2009) and Hilde (2012).