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Long-Term Survival and Risk of Institutionalization in Onco-Geriatric Surgical Patients: Long-Term Results of the PREOP Study

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OBJECTIVES: To evaluate long-term survival and institutionalization in onco-geriatric surgical patients, and to analyze the association between these outcomes and a preoperative risk score.

DESIGN: Prospective cohort study with long-term follow-up.

SETTING: International and multicenter locations.

PARTICIPANTS: Patients aged 70 years or older undergoing elective surgery for a malignant solid tumor at five centers (n = 229).

MEASUREMENTS: We assessed long-term survival and institutionalization using the Preoperative Risk Estimation for Onco-geriatric Patients (PREOP) score, developed to predict the 30-day risk of major complications. The PREOP score collected data about sex, type of surgery, and the American Society for Anesthesiologists classification, as well as the Timed Up & Go test and the Nutritional Risk Screening results. An overall score higher than 8 was considered abnormal.

RESULTS: We included 149 women and 80 men (median age = 76 y; interquartile range = 8). Survival at 1, 2, and 5 years postoperatively was 84%, 77%, and 56%, respectively. Moreover, survival at 1 year was worse for patients with a PREOP risk score higher than 8 (70%) compared with 8 or lower (91%). Of those alive at 1 year, 43 (26%) were institutionalized, and by 2 years, almost half of the entire cohort (46%) were institutionalized or had died. A PREOP risk score higher than 8 was associated with increased mortality (hazard ratio = 2.6; 95% confidence interval [CI] = 1.7-4.0), irrespective of stage and age, but not with being institutionalized (odds ratios = 1 y, 1.6 [95% CI = .7-3.8]; 2 y, 2.2 [95% CI = .9-5.5]).

CONCLUSION: A high PREOP score is associated with mortality but not with remaining independent. Despite acceptable survival rates, physical function may deteriorate after surgery. It is imperative to discuss treatment goals and expectations preoperatively to determine if they are feasible. Using the PREOP risk score can provide an objective measure on which to base decisions. **J Am Geriatr Soc 00:1-7, 2020.**

Keywords: survival; institutionalization; postoperative outcome; onco-geriatric patients; risk assessment

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INTRODUCTION

The older population is growing worldwide and is expected to exceed 1 billion by 2020.[1] Given that solid tumors mainly affect patients aged 65 years or older,

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leaders in the field of geriatric oncology have recently sought to emphasize that chronological age per se should not be considered a contraindication to surgical treatment.[2-5] Nevertheless, older patients with cancer still often receive substandard treatment compared with their younger counterparts.[6] For example, it was shown that older women are offered surgical treatment less often for breast,[7] pancreatic,[8] and ovarian cancer.[9]

Researchers have suggested that surgical oncologists deviate more often from standard treatment protocols in the older population. This may be because they fear the higher risk of troublesome postoperative outcomes or because they lack certainty about the potential benefits to survival and quality of life.[10] However, data are lacking as to why standard treatment is withheld from this cohort, leaving doubt as to whether such decisions are justifiable.[7-9] Most studies in onco-geriatric surgery have also been limited to focusing on short-term outcomes, despite the reality that most patients will die outside of the immediate postoperative period.[11,12] Additionally, long-term loss of independence in older patients remains only partially explored, an important omission because the preservation of preoperative functional status was shown to be among the most important patient-centered outcomes.[13]

Outcome prediction in onco-geriatric surgical patients has gained research interest in recent years. Several studies have evaluated the ability of time-saving and easy-to-administer geriatric screening tools to predict the risk of postoperative complications.[14-16] The Preoperative Risk Estimation for Onco-geriatric Patients (PREOP) study identified that using the Timed Up & Go (TUG) test and Nutritional Risk Screening (NRS) as part of a risk score offered easy and quick tools for predicting major 30-day postoperative complications in onco-geriatric surgical patients.[17]

The primary aim of the current study was to provide data on long-term survival and institutionalization after surgery in onco-geriatric patients. Furthermore, we hypothesized that impairments in specific geriatric domains might be associated with impaired long-term outcomes, so we analyzed the association between the PREOP risk score and long-term survival and institutionalization rates. We anticipate that gaining a better understanding of long-term outcomes will help improve preoperative decision making.

METHODS

Study Design and Participants

The current research concerns the long-term follow-up of the prospective international multicenter PREOP cohort study designed by the surgical task force of the International Society of Geriatric Oncology.[17-19] The original aim was to investigate the predictive ability of geriatric screening tools in terms of their 30-day postoperative outcomes by assessing all domains recommended for geriatric assessment (Supplementary Table S1 summarizes the assessed tools). Patients aged 70 years or older who underwent elective surgery for suspected malignant solid tumors were enrolled between September 2008 and October 2012. The PREOP study was approved by the appropriate ethics committees and registered with the Dutch trial registry (Trial ID NTR1567). All patients gave written informed consent in accordance with the ethical standards of local ethics committees.

Whereas previous analyses of the PREOP study focused on short-term outcomes,[17-19] the current research focused on the long-term outcomes. Centers that participated in the PREOP study were asked to collect additional postoperative data for up to 2 years on survival and living situations. These long-term follow-up data were collected between January 2015 and August 2016. Patients were only included for analysis if postoperative histology had confirmed a malignant tumor because we wanted the data set to be affected by the presence of malignancy.

End Points

The primary end point in the current study was long-term survival, as expressed by the postoperative survival rate at

Table 1. Baseline Variables of Onco-Geriatric Surgical Patients

Variable	Current cohort (N = 229)	Original cohort (N = 276)	*P* value
Sex, n (%)			
Female	149 (65)	174 (63)	.6
Male	80 (35)	102 (37)	
Age, y, n (%)			
70-74	83 (36)	100 (36)	.998
75-79	71 (31)	89 (32)	
80-84	52 (23)	60 (22)	
≥85	23 (10)	27 (10)	
Living situation, n (%)			
Independent/Family	226 (99)	272 (99)	.85
Residential care/ Nursing home	2 (1)	2 (1)	
Surgery, n (%)			
Minor	88 (38)	97 (35)	.45
Major	141 (62)	179 (65)	
Cancer site, n (%)			
Breast	67 (29)	75 (27)	.96
Colorectal	81 (35)	105 (38)	
Gastric	15 (7)	21 (7.5)	
Gynecologic	13 (6)	14 (5)	
Pancreas and biliary tract	23 (10)	21 (7.5)	
Remaining	8 (3)	11 (4)	
Renal and bladder	9 (4)	14 (5)	
Soft tissue and skin	13 (6)	15 (6)	
Tumor stage, n (%)			
Stage 1/2	132 (60)	158 (57)	.79
Stage 3	47 (22)	65 (24)	
Stage 4	40 (18)	53 (19)	
PREOP risk score, n (%)			
≤8	155 (68)	163 (65)	.42
>8	74 (32)	89 (35)	

The data compare the current cohort (five centers, 229 patients) with those from the original PREOP study (eight centers, 276 patients). Patients had a confirmed diagnosis of cancer.

Abbreviation: PREOP, Preoperative Risk Estimation for Onco-Geriatric Patients.

6 months and at 1, 2, and 5 years. The secondary end point was the long-term institutionalization rate, as expressed by the change in living situation at 1 and 2 years postoperatively. The living situation was defined as independent, assisted living, or nursing home, and the status before and after surgery was compared.

PREOP Risk Score

The PREOP risk score was derived by multivariable logistic regression analysis for the occurrence of major 30-day postoperative complications and comprises five variables. Two are common geriatric screening tools, the TUG and the NRS scores.[17] The other three are sex, type of surgery, and American Society for Anesthesiologists (ASA) classification. The TUG assesses the time a patient needs to get up from a chair, walk 3 m, turn around, walk back, and sit down again.[20] The NRS assesses recent weight loss, overall condition, and reduction of food intake.[21] To calculate the PREOP risk score, patients are assessed on these items and scored as follows:

- Sex: female = 0; male = 3
- Type of surgery: minor = 0; major = 4
- TUG: ≤20 s = 0; >20 s = 3
- ASA: <3 = 0; ≥3 = 3
- NRS: normal = 0, impaired = 3

The area under the receiver operating characteristic curve (AUC) indicated an optimal cutoff point of higher than 8, with a higher PREOP risk score corresponding to a higher risk of major complications.[17] We therefore compared high (>8) with low (≤8) PREOP risk scores.

Statistical Analysis

Descriptive data are reported as absolute numbers and as percentages for categorical data. Overall survival was analyzed by survival analysis as the primary end point. Median follow-up time was calculated by the Kaplan-Meier estimate of potential follow-up method.[22] Proportional hazards assumptions were evaluated graphically, using log minus log Cox regression curves. Cox regression was then used to

Table 2. Survival by Disease Stage and PREOP Risk Score

	Survival			
	6 mo (SE)	1 y, % (SE)	2 y, % (SE)	5 y, % (SE)
Stage				
1/2	96% (2)	95 (2)	91% (3)	73 (5)
3	91% (4)	77 (6)	75 (7)	44 (8)
4	78% (7)	58 (8)	38 (8)	11 (5)
PREOP risk score				
≤8	95% (2)	91 (2)	87 (3)	68 (4)
>8	84% (4)	70 (5)	56 (6)	30 (6)

Abbreviations: PREOP, Preoperative Risk Estimation for Onco-geriatric Patients; SE, standard error.

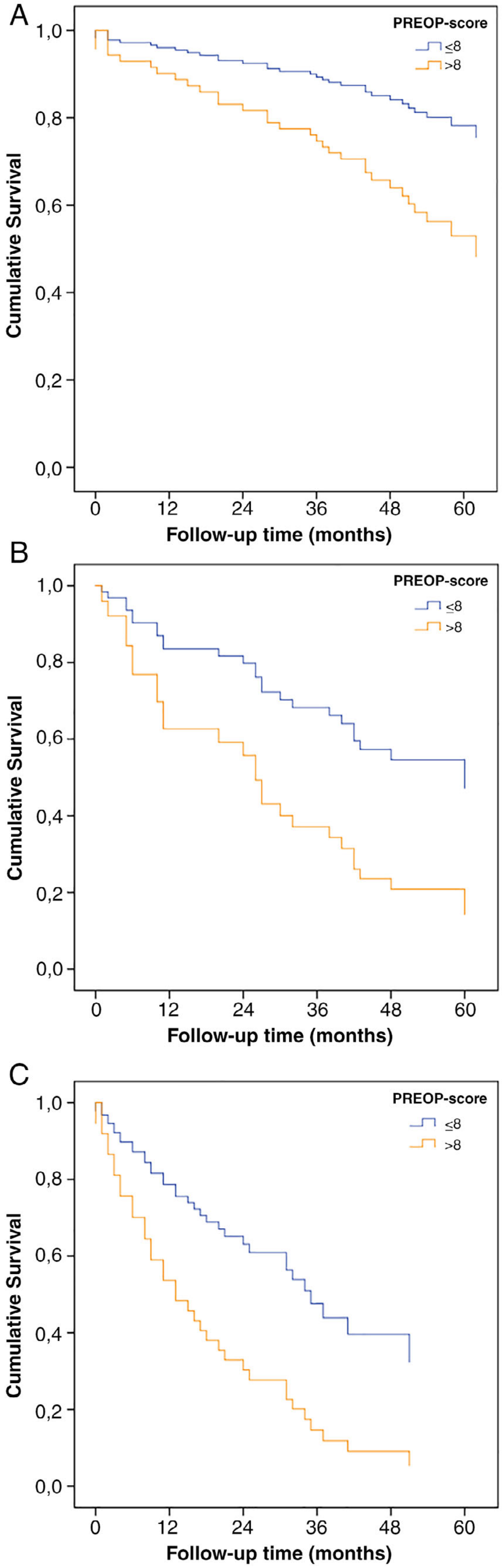

Figure 1. Survival functions for the PREOP risk score per disease stage. (A) Patients with stage 1/2 disease. (B) Patients with stage 3 disease. (C) Patients with stage 4 disease.

estimate hazard ratios (HRs) and 95% confidence intervals (CIs) that were adjusted for each center. In the multivariable Cox regression analysis, the HR for the PREOP risk score regarding mortality was adjusted for cancer stage, age, and center. The AUC was calculated to assess the discriminative value of the selected PREOP risk score cutoff in the survival model. The AUC was reflected by the Harrell C-statistic. Internal validation of the multivariable Cox regression model was performed by bootstrapping with 500 resamples. The living situation at 1 and 2 years after surgery was compared with that before surgery (ie, deterioration to being institutionalized after surgery compared with still living independently or improvement to independent living after surgery). Logistic regression analysis was used to estimate odds ratios (ORs) and 95% CIs, which were adjusted for each center.

Missing values for the geriatric screening tools before surgery were handled by multiple imputation after the assumptions for performing multiple imputation were checked and met.[17,19] The PREOP risk scores were calculated based on these imputed data sets that were then used in the current analyses. Overall, values were considered statistically significant at $P \leq .05$. Statistical analyses were completed with IBM SPSS v.23 and Stata/SE v.14.2.

RESULTS

Description of Cohort

Of the 328 patients in the original study, 276 were eligible for this study after excluding patients with benign pathologies. However, we lost another 47 of these patients (17%) to follow-up because only five centers agreed to collect long-term follow-up data. Two centers were unable to collect data due to a lack of clerical help, and one center did not respond to our invitation. Thus we were left with a final cohort of 229 patients for the present study. As shown in Table 1, the baseline variables were comparable between the cohorts with proven malignancy, with exclusion of the three nonparticipating centers having no major effect.

Survival

The median follow-up time was 55 months (95% CI = 54-56 mo), and the overall postoperative survival at .5, 1, 2, and 5 years was 91%, 84%, 77%, and 56%, respectively. The overall survival rates by disease stage and PREOP risk score are shown in Table 2. Disease stage

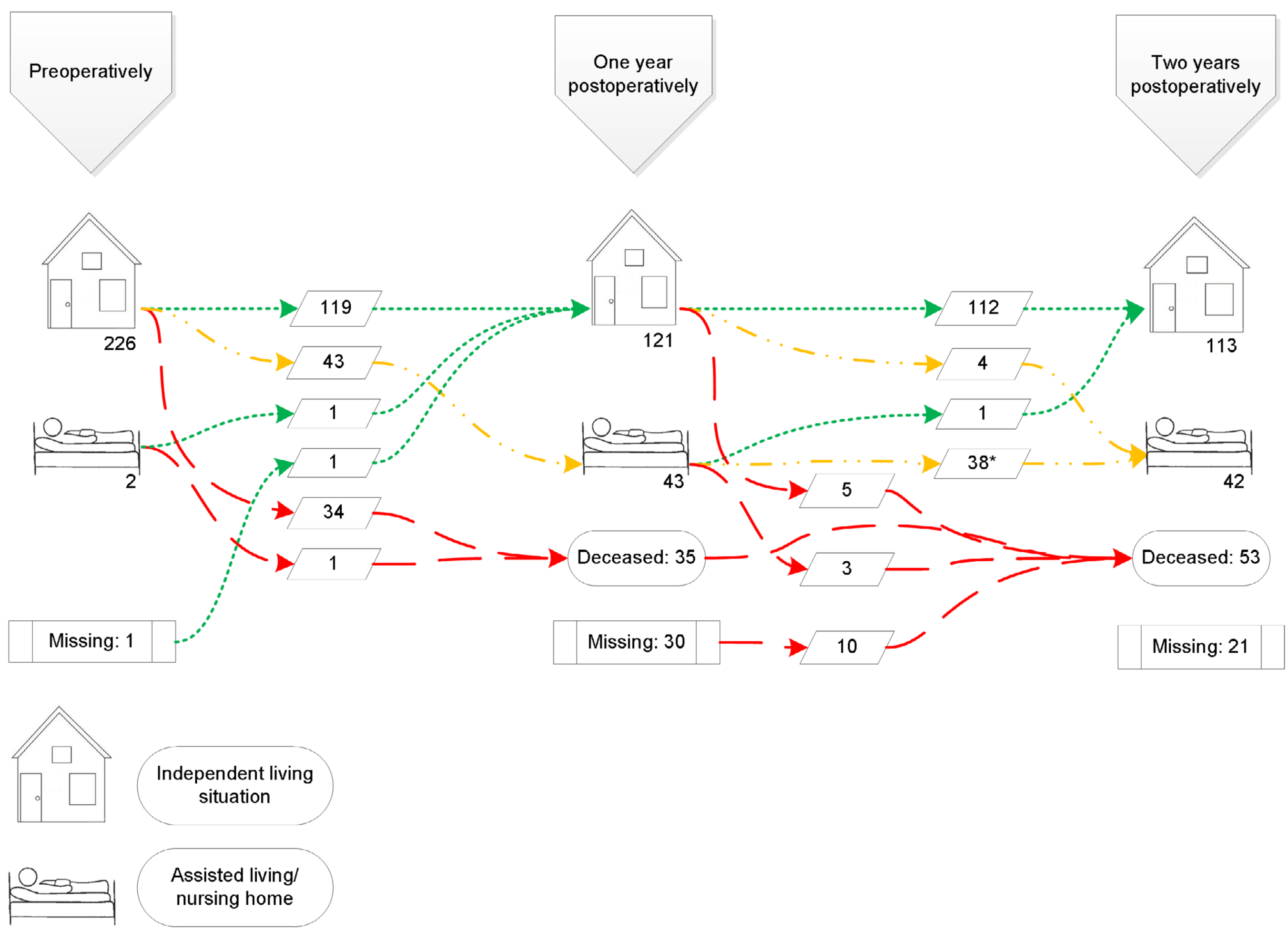

Figure 2. Living situation preoperatively and at 1 and 2 years postoperatively. *From 1 to 2 years postoperatively five patients deteriorated, one of whom moved from assisted living to a nursing home (so not shown in flowchart).

Table 3. Association of Preoperative Variables with Deterioration in Living Situation at 1 Year[a]

	Living situation		
	IndependentN (%)	InstitutionalizedN (%)	OR (95% CI)[b]
Age, y			
70-74	46 (38)	12 (28)	1
75-79	40 (33)	10 (23)	1.7 (.5-5.6)
80-84	27 (22)	15 (35)	**5.0 (1.5-16.2)**
≥85	8 (7)	6 (14)	**6.1 (1.5-25.5)**
Sex			
Female	81 (67)	32 (74)	1
Male	40 (33)	11 (26)	.7 (.3-1.8)
Disease stage			
1/2	85 (73)	28 (65)	1
3	21 (18)	8 (19)	.9 (.3-2.7)
4	10 (9)	7 (16)	3.6 (.7-17.5)
Type of surgery			
Minor	61 (50)	19 (44)	1
Major	60 (50)	24 (56)	1.1 (.5-2.6)
PREOP risk score[c]			
≤8	93 (77)	30 (70)	1
>8	28 (23)	13 (30)	1.6 (.7-3.8)
NRS			
Normal	92 (76)	32 (74)	1
Impaired	29 (24)	11 (26)	1.1 (.4-2.9)
TUG test			
≤20	112 (93)	33 (77)	1
>20	9 (7)	10 (23)	**4.5 (1.5-13.4)**
ASA			
<3	71 (59)	16 (37)	1
≥3	50 (41)	27 (63)	**3.3 (1.4-7.9)**

Abbreviations: ASA, American Society for Anesthesiologists [classification]; CI, confidence interval; OR, odds ratio; NRS, Nutritional Risk Screening; PREOP, Preoperative Risk Estimation for Onco-Geriatric Patients; TUG, Time Up & Go.

Figures shown in boldface are statistically significant.

[a]Because the deterioration in living situation occurred mainly during the first postoperative year, results for this end point were shown.

[b]Univariable OR, adjusted for center.

[c]PREOP risk score includes sex, type of surgery, TUG, ASA, and NRS.

3 (HR = 3.1; 95% CI = 1.8-5.3) and stage 4 (HR = 6.4; 95% CI = 3.6-11.4), as well as age (HR = 1.1; 95% CI = 1.0-1.1), were statistically significant predictors of increased mortality. Moreover, a high PREOP risk score (>8) remained a statistically significant predictor of increased mortality (HR = 3.1; 95% CI = 2.0-4.7), irrespective of disease stage and age (HR = 2.6; 95% CI = 1.7-4.0). Despite excluding patients who did not survive the first postoperative year (seeking to eliminate the impact of postoperative complications), the multivariable association persisted between the PREOP risk score and mortality (HR = 2.5; 95% CI = 1.5-4.4).

The HR for high PREOP score was similar after bootstrap analysis corrected for disease stage and age (HR = 2.7; 95% CI = 1.7-4.3). Bias was considered low because the percentile CIs (1.71-4.31) and bias-corrected CIs (1.79-4.39) were comparable. The AUC of the PREOP risk score was .78 and showed fair discriminatory capacity.

The survival functions for the PREOP risk score are shown by disease stage in Figure 1. The 1-year survival rates were 70% (standard error = 5%) and 91% (standard error = 2%) for patients with PREOP risk scores higher than 8 and 8 or lower, respectively.

Deterioration in Living Situation

The postoperative living situations of older patients at 1 and 2 years are shown in Figure 2. A total of 43 patients (26%) were institutionalized by the end of the first postoperative year, compared with 42 (27%) by the end of the second postoperative year. When comparing these living situations, one patient improved (.6%) and five patients deteriorated (3%) between the first and second years. Of the two patients who had lived in a nursing home preoperatively, one was able to move to an independent living situation, and the other patient did not survive the first postoperative year.

A PREOP risk score higher than 8 was not significantly associated statistically with a higher risk for postoperative institutionalization at either 1 year (OR = 1.6; 95% CI = .7-3.8) or 2 years (OR = 2.2; 95% CI = .9-5.5); by contrast, the age, ASA classification, and TUG components of the PREOP risk score were associated with higher risk (Table 3). However, the proportion of patients living independently at home did not differ with statistical significance between patients with high and low PREOP risk scores either at 1 year (high = 68%; low = 76%; P = .36) or at 2 years (high = 63%; low = 76%; P = .13).

DISCUSSION

The overall postoperative survival rates decreased from 91% at 6 months to 56% at 5 years, and a notable difference was found in survival rates at 1 year between patients with PREOP risk scores higher than 8 and 8 or lower (70% and 91%, respectively). Among the patients alive at 1 year, 1 in 4 were institutionalized, and at 2 years, almost one-half of the entire cohort (46%) were institutionalized or had died. Overall, the PREOP risk score was associated with survival, irrespective of disease stage and age, but not with the risk of institutionalization.

Short-term and long-term survival rates in our study were comparable with those reported in other cohorts of older patients.[11,23-26] A study by Ommundsen et al is one of only a few to have focused on long-term survival in older patients, specifically those with colorectal cancer, and noted a 5-year survival rate of 48%.[23] As with our results, they also noted that frailty was accompanied with decreased survival, irrespective of disease stage, reporting 5-year survival rates of 24% in frail patients and 66% in non-frail patients.[23] Postoperative survival rates at 1 year in our cohort were 70% and 91%, respectively. The PREOP risk score itself was associated with the observed long-term survival. Ommundsen et al further reported that nutritional status, instrumental activities of daily living, and comorbidities were each predictive of long-term survival, independent of disease stage.[23] However, a systematic review produced conflicting results concerning survival prediction.[27] In most studies, irrespective of the definitions used, frailty and comorbidity are statistically and significantly associated with survival, whereas functional status and nutritional status are not typically associated. The presence of frailty, whether established by a formal assessment tool or by clinical judgment, may account in other research for the numbers of older people considered undertreated compared with younger peers.[7-9]

The long-term use of post-acute care services (eg, specialist nursing or long-term care facilities) is high among older adult cancer patients undergoing surgery when compared with those who have no cancer.[28] By 2 years postoperatively in the current study, approximately 1 in 5 patients was institutionalized, one-quarter had died, and one-half were living independently at home. A deterioration in living situation can be considered a proxy for functional status,[29] with an increased level of dependency in both activities of daily living and instrumental activities of daily living being precursors to institutionalization. Although a postoperative deterioration in functional status is frequently observed, the prevalence varies from 3% to 69% depending on the population under study, the type of end point, and the follow-up duration.[30-33] Although partial recovery can be observed during the postoperative course, overall functional status scores at 1 year rarely return to preoperative levels.[31] This deterioration occurs predominantly in older patients,[33,34] especially in those who are frail.[34] These results indicate that older patients are at increased risk of permanent, or at least long-term, functional decline after surgery.

The failure to show an association between the PREOP risk score and the risk of institutionalization may be due to a lack of power. A similar conclusion by Rønning et al that frailty indicators were not predictive of functional decline may also have been due to a lack of power.[33] However, a recent study by Williams et al of 125 older patients with cancer showed that (pre-)frailty and impaired functional status were associated with greater long-term care use.[35] Another possible explanation for the lack of association in our research could be that the PREOP risk score was designed to predict clinical outcomes, whereas risk of institutionalization is determined by several other nonclinical factors, such as the presence of a family and a patient's financial situation. Moreover, cultural differences in the international cohort might have obscured outcomes by influencing the destinations of patients with functional decline.[36] Finally, it is possible that factors other than the index surgery (eg, comorbidities or recurrence) led to functional decline and institutionalization.

We observed associations between long-term institutionalization and greater age, ASA classification, and TUG scores. Other studies have reported that greater age, stage, impairment in pretreatment functional status, and treatment intensity, as well as the occurrence of postoperative complications, were associated with postoperative functional decline and increased long-term care use.[28,32,34,35] Functional decline can result from a protracted postoperative course in patients with reduced physiologic reserves at the start of their treatment, and studies showed that "prehabilitation" can have a positive effect on postoperative outcomes.[37-39] This indicates scope to improve PREOP risk scores and to reduce the risk of adverse outcomes.

The current study has a few limitations. First, loss to follow-up occurred because several patients died, thereby decreasing the sample size. Although clearly inherent to this age group, this loss to follow-up limited the number of variables that could be included in the statistical models and precluded any meaningful stratified analysis by cancer site. Compounding this issue, three centers that contributed to the study of short-term outcomes did not contribute to the present research. Fortunately, patients' characteristics were similar in both cohorts. Second, no data were obtained on whether patients were treated with adjuvant chemotherapy, which is important because this can improve survival and may have affected our results. Given that long-term institutionalization is a crude measure of functional decline, we probably only included patients who deteriorated most, which will have further underestimated the magnitude of this problem. Nevertheless, the high prevalence of long-term institutionalization emphasizes the importance of this outcome measure in the onco-geriatric population. Third, external validation of the PREOP risk score is still needed to confirm its generalizability as a screening tool. Internal validation has already been performed, and the results of the bootstrap analysis in this study confirm that the obtained HR data are valid.

In the current study, we aimed to report on the long-term outcomes in onco-geriatric patients undergoing surgery for cancer, anticipating the information could be used to support shared decision making in routine clinical practice. It is with increasing conviction that we advise that advancing age, in isolation, should not be considered a sufficiently strong factor to justify withholding surgery with curative intent from older patients. Indeed, our data have shown that survival rates were rather good, with most patients able to live independently at home, despite invasive cancer treatments. Patients with a PREOP risk score of 8 or lower were most likely to have an uncomplicated course by 2 years postoperatively, whereas those with higher scores were at increased risk of a complicated postoperative course. When treating these patients, although cure may be possible, we should be aware that patients will not necessarily return to their preoperative level of function. Indeed, it is of utmost importance that both physicians and patients are aware of this before surgery. Detailed discussion of the goals and expectations of surgery is imperative, allowing us to verify their feasibility based on individualized and objective risk assessments.

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Farinella, Cirocchi, Audisio, and van Leeuwen. *Analysis and interpretation of data*: Huisman, Ghignone, Ugolini, Sidorenkov, Montroni, Audisio, de Bock, and van Leeuwen. *Preparation of manuscript*: All authors.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Supplementary Table S1: Components of the PREOP study.