GOSAFE - Geriatric Oncology Surgical Assessment and Functional rEcovery after Surgery

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GOSAFE - Geriatric Oncology Surgical Assessment and Functional rEcovery after Surgery: early analysis on 977 patients

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Abbreviations and Acronyms: ADL, Activities of Daily Living; ASA, American Society of Anesthesiologists; CACI, Charlson Age Comorbidity Index; ECOG PS, Eastern Collaborative Oncology Group Performance Status; ERAS, Enhanced Recovery After Surgery; ESSO, European Society of Surgical Oncology; FR, Functional Recovery; fTRST, Flemish version of the Triage Risk Screening Test; G8, Geriatric 8; MDT, Multidisciplinary Team; NRS, Nutritional Risk Screening; PROMs, Patient Reported Outcome Measures; QoL, Quality of Life; RCT, Randomized Control Trial; SIOG, International Society of Geriatric Oncology; TUG, Timed up and Go test; VAS, Visual Analogue Scale.

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ABSTRACT

Objective: Older patients with cancer value functional outcomes as much as survival, but surgical studies lack functional recovery (FR) data. The value of a standardized frailty assessment has been confirmed, yet it's infrequently utilized due to time restrictions into everyday practice. The multicenter GOSAFE study was designed to (1) evaluate the trajectory of patients' quality of life (QoL) after cancer surgery (2) assess baseline frailty indicators in unselected patients (3) clarify the most relevant tools in predicting FR and clinical outcomes. This is a report of the study design and baseline patient evaluations.
Materials & Methods: GOSAFE prospectively collected a baseline multidimensional evaluation before major elective surgery in patients (≥70 years) from 26 international units. Short−/mid−/long-term surgical outcomes were recorded with QoL and FR data.
Results: 1003 patients were enrolled in a 26-month span. Complete baseline data were available for 977(97.4%). Median age was 78 years (range 70–94); 52.8% males. 968(99%) lived at home, 51.6% without caregiver. 54.4% had ≥ 3 medications, 5.9% none. Patients were dependent (ADL < 5) in 7.9% of the cases. Frailty was either detected by G8 ≤ 14(68.4%), fTRST ≥ 2(37.4%), TUG > 20 s (5.2%) or ASAIII-IV (48.8%). Major comorbidities (CACI > 6) were detected in 36%; 20.9% of patients had cognitive impairment according to Mini-Cog.
Conclusion: The GOSAFE showed that frailty is frequent in older patients undergoing cancer surgery. QoL and FR, for the first time, are going to be primary outcomes of a real-life observational study. The crucial role of frailty assessment is going to be addressed in the ability to predict postoperative outcomes and to correlate with QoL and FR.

"…They want to know if they are treated, just how sick they will get from the treatment. They want to know if they will still be able to function"…. "They want to know if they can still be socially active and if their memory will be intact. Eighty percent of our older patients say they would rather maintain their memory than survive…"

[Arti Hurria, MD]

1. Introduction

Progressive aging of the world population has become one of the most significant challenges for national health care systems. With aging, the incidence and prevalence of cancer increases: it has been estimated that in 2020 >60% of all malignancies will occur in patients aged 70-years and older [1]. At the same time, progress in medical knowledge has had a positive impact in clinical practice. In particular, significant improvements in perioperative care with standardized pathways, intraoperative care with minimally invasive surgery, and postoperative care with the introduction of multimodal pain control and enhanced recovery pathways have made oncologic surgery feasible for a larger proportion of patients. Nevertheless, several studies have shown that senior adults affected by cancer are often sub-optimally treated, based on chronological age alone [2,3].

Chronic conditions that often affect the older population put this group of patients at a higher risk of postoperative complications [4], resulting in a higher incidence of long-term mortality independent of cancer stage [5]. Preoperative assessment of functional status is fundamental to identify fit, vulnerable and frail individuals in order to avoid under- or over-treatment. While the PACE [6] and the PREOP [7,8] studies showed how simple, surgeon-friendly tools can be used to achieve an accurate prediction of postoperative complications, very little data have been reported to date on one of the most relevant patient outcomes: the ability to regain functionality.

Loss of independence, which may occur as a consequence of major cancer surgery, is a devastating life change for older adults and functional recovery (FR) has been shown to be of critical value in the older population since restoration/conservation of independence has been found to be as important as survival for these patients [9].

Table 1
Recruiting international centers.

Institution	Department	City	Country	Activation date
Ospedale "per gli Infermi" AUSL Romagna (Coordinating Center)	U.O. Chirurgia Generale	Faenza (RA)	Italy	15-Feb-17
Ospedale "GB. Morgagni-L. Pierantoni" AUSL Romagna	U.O. Chirurgia Generale e Terapie Oncologiche Avanzate	Forlì (FC)	Italy	15-Feb-17
Ospedale "Ceccarini", AUSL Romagna	U.O. Chirurgia Generale	Riccione (RN)	Italy	09-May-17
AUSLPiacenza, PO Piacenza	U.O. Chirurgia generale	Piacenza	Italy	11-July-17
Humanitas Clinical and Research Center	Division of Colon and Rectal Surgery,	Rozzano (MI)	Italy	14-July-17
Ospedale "S. Matteo degli Infermi" AUSL Umbria-2	General, Minimally Invasive and Robotic Surgery	Spoleto (PG)	Italy	26-July-17
Brigham and Women's Hospital	Thoracic Surgery	Boston (MA)	USA	11-Oct-17
Clinica S. Rita	Department of Colorectal Surgery	Vercelli	Italy	18-Oct-17
Istituto Tumori Giovanni Paolo II IRCCS	Department of Surgical Oncology	Bari	Italy	22-Nov-17
University of Pennsylvania, Perelman School of Medicine	Department of Surgery	Philadelphia (PA)	USA	22-Nov-17
University Medical Center Groningen	Department of Surgical Oncology	Groningen	Netherlands	30-Nov-17
ASST Grande Ospedale Metropolitano Niguarda	Chirurgia generale Oncologia e Mininvasiva	Milano	Italy	29-Nov-17
Jagiellonian University Medical College	Department of General, Oncologic and Geriatric Surgery	Krakow	Poland	12-Dec-17
Ospedale Policlinico S. Martino IRCCS	OU General and Oncologic Surgery	Genova	Italy	06-Dec-17
Oslo University Hospital	Department of Surgery	Oslo	Norway	12-Dec-17
ASST Monza - Ospedale di Desio	General and Emergency Surgery	Desio (MB)	Italy	18-Dec-17
Aristotle University of Thessaloniki, Medical School	4th Surgical Department	Thessaloniki	Greece	23-Jan-18
Hospital Universitario y Politécnico La Fe	General and Digestive surgery	Valencia	Spain	09-Feb-18
Roger William Medical Centre Providence	Surgical Oncology	Providence (RI)	USA	27-Feb-18
Sapienza University of Rome, Sant'Andrea University Hospital	Emergency Surgery Unit	Roma	Italy	27-Mar-18
Hospital Sao Francisco Xavier	General Surgery	Lisbona	Portugal	04-Apr-18
Rabin Medical Center	Department of Geriatrics	Tel Aviv	Israel	26-Apr-18
Ospedale Policlinico S. Martino IRCCS	Department of Surgical Sciences and Integrated Diagnostics (DISC)	Genova	Italy	14-May-18
Hospital General Universitario de Elche, Universidad Miguel Hernández	Colorectal & Gastrointestinal Department	Alicante	Spain	21-May-18
Manchester Royal Infirmary, University of Manchester	HPB Unit	Manchester	UK	16-July-18
Cleveland Clinic Foundation	Department of Colorectal Surgery	Weston (FL)	USA	11-Jan-19

Personalization of onco-geriatric patients' care is closely related to the preservation of functional capacity [10,11].

The goal of the Geriatric Oncology Surgical Assessment and Functional rEcovery after Surgery (GOSAFE) study was to obtain prospective data on both quality of life (QoL) and FR after surgery.

The GOSAFE Study was promoted by Local Health Authority (AUSL) of Romagna in collaboration with Cancer Institute of Romagna, Italy, and developed by the collaboration of a multidisciplinary group from the European Society of Surgical Oncology (ESSO) and the International Society of Geriatric Oncology (SIOG) Surgical Task Force.

While many contributed to the study design, the inspiration by Arti Hurria about the pivotal role of frailty assessment in the surgical population resonated with the entire collaborative group. Indeed, Dr. Hurria envisioned the importance of patients' experience and patients-reported outcomes measures (PROMs) as a means to improve scientific research and the quality of care: "*Historically, research left out people who were older and more experienced, which doesn't make much sense. We are changing that. Older people have much to teach us*".

The problem we face when describing the role of QoL or other PROMs is that these are not routinely primary endpoints of any

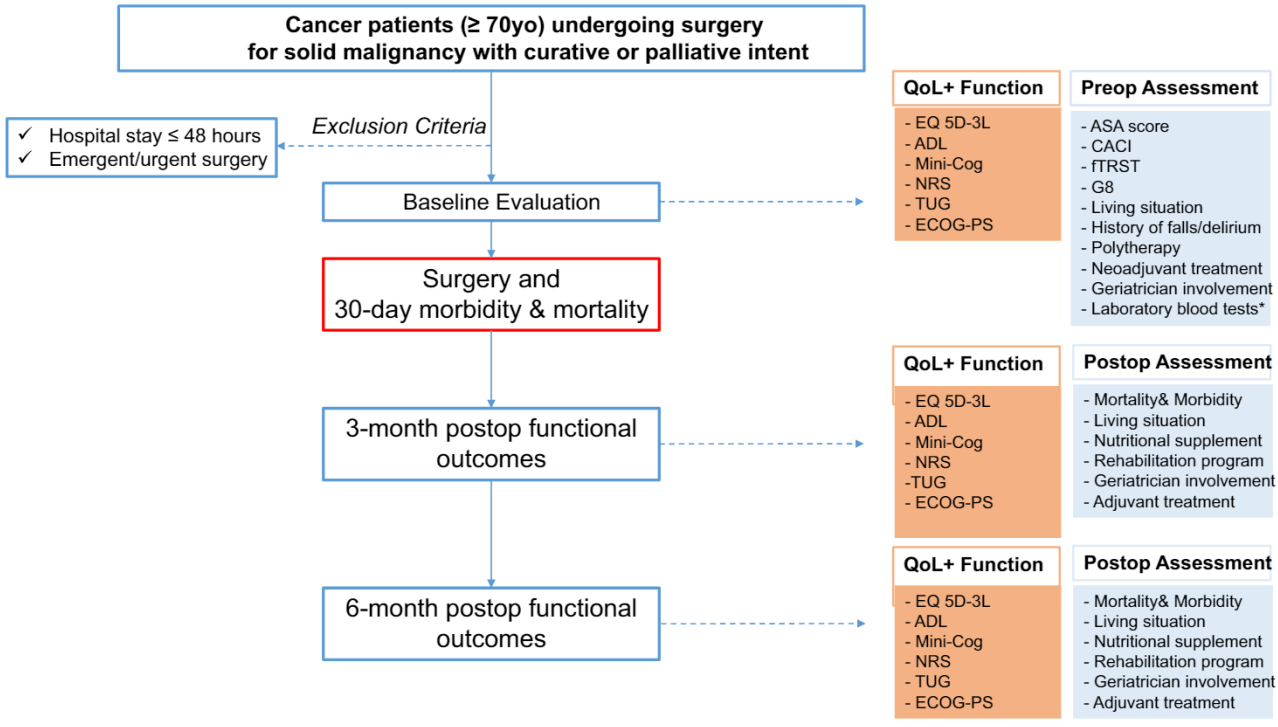

Fig. 1. Study Flow Diagram.

Table 2
Functional assessment indicators.

Test	Acronym	Range of possible scores	Frailty indicator threshold	Purpose
EQ 5D-3L [13–15]	EQ 5D-3L Index	0–1	Not applicable	Evaluation of QoL assessing patient's mobility, self-care, usual activities, pain and anxiety, includes a visual scale
EQ 5D-3L [13–15]	EQ 5D-3L VAS	0–100	Not applicable	
Eastern Collaborative Oncology Group Performance Status [22,23]	ECOG PS	0–4	≥1	Evaluation of cancer burden on functional status
Katz Activities of Daily Living [24]	ADL	0–6	<5	Evaluation of functional independence
Mini-Cog [26,27]	Mini-Cog	0–5	≤2	Detection of cognitive impairment in older adults therefore suitable for a more thorough evaluation.
Flemish version of the Triage Risk Screening Test [28,29]	fTRST	0–6	≥2	Detection of hospitalized geriatric patients at risk for frailty
Timed Up & Go Test [7,8,30,31]	TUG	Not applicable	≥20 s	Three-meters walking test to evaluate functional status
G8 [32]	G8	0–17	≤14	Detection of onco-geriatric patients who may benefit from comprehensive geriatric assessment
Nutritional Risk Screening [33]	NRS	Normal to severely impaired nutritional status	Moderately to severely impaired	Evaluation of nutritional status taking into account BMI, weight loss and food intake
American Society of Anesthesiology score [34]	ASA	1–5	Not applicable	Evaluation of preoperative general clinical condition and estimation of anesthesiologic risk
Charlson Age Comorbidity Index [35,36]	CACI	0–42	≥6	Evaluation of cumulative burden of patient's comorbidities

prospective randomized controlled trial (RCT). This is even more relevant for senior adults who are rarely included in RCTs [12]. Furthermore, because of the lack of solid information about these endpoints, the majority of clinicians continue applying knowledge obtained from younger patients to older, vulnerable individuals.

The aim of this study is to gain robust and reliable knowledge about real-life, long-term postoperative outcomes in older patients with cancer with a particular emphasis on QoL and FR: the correlation between frailty assessment and PROMs will enable clinicians to deliver personalized treatment and to identify better strategies to improve both clinical and functional outcomes. This is a report of the study design and baseline patient evaluations.

2. Methods and Study Design

The GOSAFE study is a multicentre international prospective observational cohort study carried out in 26 hospitals world-wide as detailed in Table 1. This study was approved at every center's Institutional Review Board and Ethics Committees according to local regulations. The study has been registered on clinicaltrials.gov (Identifier: NCT03299270).

2.1. Inclusion criteria

All patients aged ≥70 years and undergoing elective major surgical procedures with curative or palliative intent for a solid malignancy were considered eligible for the study. All major procedures including any resection for any cancer via any operative approach (open, minimally invasive, robotic) were included. As the goal was to obtain information about real-life practices caring for older adult patients, cognitive impairment was not considered an exclusion criterion if informed consent was obtained by the appropriate health care proxy.

2.2. Exclusion criteria

Patients undergoing emergent/urgent surgical procedures or planned hospital stay <48 h were excluded from the study.

Centers who could not provide the minimum 20 consecutive patients required for participating in the study were excluded from the analysis of the primary and secondary outcome.

2.3. Outcomes measures

The primary outcome of the study was to evaluate the change in QoL following surgery as scored using a validated self-reported QoL assessment tool (EQ 5D-3L) 13,14].

Table 3
Demographic data.

Variable	Overall $n = 977$ (%)
Gender	
Male	516 (52.8)
Female	461 (47.2)
Age	
Median, [range]	78 [70–95]
Age	
≥70 and <75	311 (31.8)
≥75 and <80	307 (31.4)
≥80 and <85	239 (24.5)
≥85	120 (12.3)
Living situation	
Home independent	504 (51.7)
Home with family/caregiver	464 (47.5)
Residential care	8 (0.8)
Missing	*1*
Polipharmacotherapy	
None	58 (5.9)
Number of drugs, median [range]	4 [1–28]
Missing	*1*
History of falls 6 months prior to operation	97 (9.9)
Previous delirium	54 (5.5)
Smoking habits	
Yes	80 (8.2)
No (former)	419 (43.0)
No (never)	476 (48.8)
Missing	*2*
Cancer site	
Endocrine (Thyroid, adrenal)	6 (0.8)
Upper GI (Esophagus, stomach, small bowel)	93 (11.8)
Lower GI (Colon and rectum, anus)	537 (68.1)
HBP (pancreas, duodenum, liver, biliary tree)	86 (10.9)
Soft tissue/Bone	13 (1.6)
Head & neck	2 (0.3)
Thoracic (Lung, mediastinum and pleura)	27 (3.4)
Genito-urinary (kidney/ureter, testis, bladder, prostate)	8 (1.0)
Gyn (Uterus, ovary, Vulva)	2 (0.3)
Other (intra abdominal sarcoma, spleen, pelvic recurrence of rectal adenocarcinoma, colon cancer with gastric infiltration)	14 (1.8)

Table 4
Baseline frailty screening.*

G8 score – Variables	Overall n = 977 (%)	fTRST – Variables	Overall n = 977 (%)
Food intake		Presence of cognitive impairments	48 (4.9)
Severe decrease in food intake	71 (7.3)	Lives alone or no caregiver	366 (37.5)
Moderate decrease in food intake	271 (27.8)	Difficulty with walking, or transfer, or falls in the last 6 months	209 (21.4)
No decrease in food intake	633 (64.9)	Hospitalized in the last 3 months	270 (27.7)
Missing	*2*	Polypharmacy >5 medication	367 (37.6)
Weight loss		Total score	
Weight loss >3 kg	245 (25.1)	0	238 (24.4)
Does not know	70 (7.2)	1	372 (38.2)
Weight loss 1–3 kg	203 (20.8)	≥2	365 (37.4)
No weight loss	457 (46.9)	Missing	2
Missing	*2*	ADL SCORE	
Mobility		<5	77 (7.9)
Bed or chair bound	16 (1.6)	≥5	892 (92.1)
Able to get out of bed/chair but does not go out	111 (11.4)	Missing	8
Goes out	848 (87.0)	MINICOG Total score	
Missing	*2*	0–2 positive screen for dementia	201 (20.9)
Neuropsychological problems		3–5 negative screen for dementia	759 (79.1)
Severe dementia or depression	27 (2.8)	Missing	17
Mild dementia or depression	107 (11.0)	PS ECOG	
No neuropsychological problem	841 (86.2)	ECOG 0	538 (55.6)
Missing	*2*	ECOG 1	284 (29.3)
BMI (Only male patients)		ECOG≥2	146 (15.1)
BMI < 18.5	3 (0.6)	Missing	9
BMI 18.5 to <21	42 (8.2)	ASA score	
BMI 21 to 23	73 (14.2)	1–2	488 (51.2)
BMI ≥ 23	396 (77.0)	3–4	466 (48.8)
Missing	*2*	Missing	23
BMI (Only female patients)		Charlson Age comorbidity index	
BMI < 18.5	15 (3.3)	3–6	625 (64.0)
BMI 18.5 to <21	49 (10.7)	≥7	352 (36.0)
BMI 21 to 23	76 (16.5)	Timed up and Go	
BMI ≥ 23	320 (69.5)	≤ 20 s	820 (94.8)
Missing	*1*	>20 s	45 (5.2)
>3 prescription drugs per day	530 (54.4)	Nutritional status score	
How patient consider health status		Normal	622 (64.9)
Not as good	132 (13.6)	Mildly impaired	240 (25.1)
Does not know	123 (12.6)	Moderately impaired	70 (7.3)
As good	421 (43.2)	Severely impaired	26 (2.7)
Better	298 (30.6)	Missing	19
Missing	*3*	Laboratory tests	Median (range)
G-8 Total score		Albumine (g/l)	40 (20–70)
Median (range)	13 (3–17)	Haemoglobin (g/dl)	12.3 (6.10–17.4)
G-8 ≤ 14	667 (68.4)	Creatinine (mg/dl)	0.9 (0.15–11.3)
G-8 > 14	308 (31.6)		
Missing	*2*		

Legend: G8, Geriatric 8; BMI, body mass index; fTRST, Flemish version of the Triage Risk Screening Test; ADL, activities of daily living; ECOG, Eastern Collaborative Oncology Group Performance Status; ASA, American Society of Anesthesiologists.
* Please see Table 2 for frailty screening thresholds and tests' meanings.

Secondary outcomes were 1) FR in terms of restoration of daily activities, nutritional status, and cognitive status and 2) three- and six-month postoperative morbidity and mortality.

In addition, 3) the correlation between several risk factors (including data resulting from the frailty assessment tools) and postoperative outcomes, QoL and FR were evaluated.

2.4. Study Design and Baseline Assessment

The study flow diagram is reported in Fig. 1. In order to obtain a comprehensive assessment, every geriatric domain was evaluated with validated and easy-to-administer tests (Table 2). Baseline evaluation takes approximately 20 min on average to complete and can be carried out by trained health care providers such as attending surgeons, surgical residents, senior medical students, geriatricians, nurses or physician assistants in the outpatient clinic. The tests were part of the routine preoperative evaluation.

2.5. Testing

Pre- and postoperative testing are described in Table 2 including the specific threshold scores that indicate frailty reported from the literature and from expert opinions [15]. Appendix 1 also reports the integral version of the tests as they were performed.

The Eastern Collaborative Oncology Group Performance Status (ECOG PS) [16,17] was chosen to evaluate performance status and cancer impact on patient daily life while the level of independence was assessed through the Katz Activities of Daily Living (ADL) [18].

Cognitive function is relevant for the ability to consent and understand treatment discussions, and it is associated with clinical and functional outcomes [19]. Cognitive impairment is easily missed without objective testing. Furthermore, patients with cognitive impairment have been excluded from clinical trials. In order to increase the detection of cognitive impairment and implement knowledge of its effect on the postoperative outcomes, the three-minute Mini-Cog [20,21] test was chosen due to its simplicity and effectiveness.

The multimodal frailty assessment was also carried out with three additional tests that have complementary features. The 5-item Flemish version of the Triage Risk Screening Test (fTRST) [22,23] was chosen to identify patients with a high-risk profile. As the importance of objective performance tests in identifying frailty have become more evident over the recent years, we added the The Timed Up & Go (TUG) test [7,8,24,25]. Finally, the geriatric 8 (G8) [26] specifically designed to be used in the oncology setting, was assessed.

Every patient was also screened to identify malnourishment using the Nutritional Risk Screening (NRS) [27]. American Society of Anaesthesiologists (ASA) score [28] and Charlson Age Comorbidity Index (CACI) [29,30] were used to evaluate pre-operative anaesthesiologic risk and the cumulative burden of comorbidities. Baseline evaluation further included information about living situation before surgery, polypharmacy, history of falls and delirium, history of neoadjuvant chemotherapy and/or radiation therapy and geriatrician involvement in the perioperative care. Finally, for every patient preoperative haemoglobin, albumin and creatinine levels were recorded.

Details about data collection, outcome measures, and statistical analysis are reported on Appendix 2.

3. Results

Data from 26 centers were prospectively collected from February 2017 to April 2019.

Complete clinical data were obtained from 977/1003 patients (97.4%) in a 26-month span.

Four patients had incomplete baseline data, 21 were excluded because not meeting inclusion criteria (no malignancy was found, no major surgery was performed or LOS was shorter than 48 h), one patient died after the prop-evaluation and before surgery.

There were 516 men (52.8%) and the median age was 78 (range 70–95) years. Analysis of the preoperative living situations shows that 51.7% of patients lived alone and 47.5% were at home with family or caregivers while only eight patients (0.8%) resided in residential care facilities before the surgery.

Demographic data including cancer subtypes are reported in Table 3.

Preoperative frailty assessment is reported in Table 4. The number of patients with positive indicators of frailty varied according to the different tools. Three-hundred-forty-two patients had a CACI≥7 (36%) while 68.4% had a G-8 score ≤ 14. In 37.4% of patients, the fTRST score was ≥2, and an ECOG ≥1 was detected in 44.4% of patients. Independence in ADL (ADL ≥ 5) was found in 92.1% of patients. Despite being only partially appreciated by patients, caregivers and perhaps physicians; cognitive impairment was quite frequently detected using the Mini-Cog. Cognitive impairment was only detected in 2% of patients using the CACI and 12% by the G8 score (mild to severe dementia/depression). When using the Mini-Cog test, a low score of 0–2, indicating cognitive impairment, was reported in 201/977 patients (20.9%). Nutritional data before surgery are reported in Table 4. Mild to severe nutritional impairment, was detected, according to the NRS in 35.1% of the study population.

QoL questionnaire EQ-5D was completed in 94.9% of cases by the patients themselves while the specifically designed version was completed by the healthcare proxy because of severe cognitive impairment for 50 patients (5.1%).

While only 5.9% of patients did not take any medication, 54.4% of the study population was prescribed more than three drugs per day, and the majority of these patients used five drugs or more. Ninety-seven patients (9.9%) had a history of falls in the six months before admission, and 5.5% a past history of delirium.

Despite the high chronological age and the limited use of chemotherapy or radiation in the preoperative setting (i.e. rectal cancer, esophageal cancer, metastatic disease), 139/977 (14.2%) patients underwent preoperative chemotherapy and 111 (11.4%) had neoadjuvant radiation treatment.

4. Discussion

In the prospective GOSAFE study, during a 26-month period, 1003 patients were enrolled from 26 centers and baseline evaluation of preoperative frailty was completed in 977/1003 patients. This is one of the largest, prospectively evaluated, cohorts of geriatric patients undergoing major surgery for solid cancer. Median age (78 years old) and the number of patients older than 80 years (339) is, once again, remarkable evidence that cancer surgery in senior adults is possible and that age alone should no longer be considered a contraindication to surgery. In brief, the main goal of the GOSAFE study is to highlight the role of frailty and other preoperative variables in affecting postoperative QoL, FR, morbidity and mortality.

While the scientific community agrees that optimal oncological results should be obtained via a personalized treatment approach, we still lack the actual data supporting this vision, above all in the surgical field. In recent years terms like 'precision medicine' and 'targeted therapy' have been often exploited to identify optimized care for single patients, but very little literature has been produced regarding what patients really want: to remain independent.

Disability and lack of independence in ADLs seem to impact patients with cancer more than the cancer prognosis per se. Banks et al. [31] were able to analyze self-reported questionnaire-based data from 89,574 Australian men and women with cancer sampled from the Medicare database. In their study, they concluded that, although approximately 8% of people suffer from severe psychological distress, *'the risk of psychological distress in individuals with cancer relates much more strongly to their level of disability than it does to the cancer diagnosis itself'*. This has been also shown in a survey by the Macmillan cancer support group in the UK. *'Although maintaining health is listed as the most important priority for most people living with cancer, this changes for the older retired group, who state that continued independence (44%) is just as important as maintaining health (43%)'* [32].

In our study, a large number of patients presented features of frailty, based on the preoperative evaluation. This makes the previous report by the Macmillan support group particularly relevant, as those are at higher risk of losing independence as a consequence of cancer treatments.

Our initial analysis shows that routine frailty evaluation is feasible, even in a large population, but also that additional work is needed in order to define the optimal screening tool for frailty. While 36–37% of patients could be considered 'frail' based on the fTRST and the CACI, this number rises to 68.4% based on the G-8. Other frailty indicators such as the TUG and the ADL offer a more 'optimistic' view with 94.8% and 92.1% of patients being able to walk proficiently and being independent in their daily activities respectively. This is not dissimilar to what was found in a comparable cohort of patients from the PREOP study where 85% had a TUG<20 s [8] and from the PACE study with 15% of patients showing signs of dependence in ADL[6].

It will be interesting to evaluate, once the 6-month follow-up is completed, one of the secondary endpoints of the GOSAFE: identifying which one, or which combination of screening tools, will be able to better predict the risk of poor QoL outcomes and disability.

The lack of understanding of the individual patient's frailty [33] seems to prevent cancer specialists from determining the appropriate treatment in order to take care not only of the tumor, but of the single patient with cancer. This could possibly be one of the main reasons for the undertreatment of solid cancer in senior adults. It has been shown by De Angelis et al. [2] at a European level in 2014 and was demonstrated once again by the United Kingdom (UK) National Cancer Intelligence Network [34]: older patients with cancer have worse oncological outcomes as they receive less surgery when compared to their younger counterparts. Again, what is striking us about these publications is not just the poor outcomes, but the lack of complementary frailty data as to highlight once again that frailty assessment is still widely underutilized in clinical practice.

This demographic baseline analysis of the GOSAFE dataset also showed a significant discrepancy in detecting cognitive impairments/dementia between family/physicians and the Mini-Cog test. This has been shown by the fact that while only 2%–12% of patients/families reported a condition of cognitive disorders or dementia (based on the CACI and G8 score) the Mini-Cog, performed in the preoperative period, showed a result consistent with a significant impairment in >20% of the cases. Once again, the value of screening-detected cognitive disease will be assessed based on the possible correlation with postoperative outcomes and functional recovery. In any case, awareness of cognitive impairment in older patients diagnosed with cancer and in need of surgical treatment has implications for patient consent, information needs, and follow-up.

The impact of nutritional status on post-treatment outcome has also been shown to be crucial and our cohort confirms that a large number of patients 336/958 (35%) experience a degree of weight loss and nutritional imbalance before surgery, of which about 10% have moderate-to-severe nutritional impairment. While the role of prehabilitation is becoming more and more relevant before cancer surgery [35], our study confirms that there is a large group of people (96/977–9.8%) who could be considered for preoperative optimization including nutritional counseling and preoperative implementation [36,37].

In conclusion, the GOSAFE study shows that a large collaboration among international centers can be effective in gathering substantial prospective information on senior adults with cancer in a short period of time. QoL and FR, outcomes that have been shown to be important patients, are going to be, for the first time, the main endpoints of a multicenter, real-life observational study that includes all patients with cancer older than 70 years, including patients with cognitive impairment. Our baseline data are useful in better understanding the main characteristics of a non-randomly selected cohort of surgical patients. The crucial role of frailty assessment is going to be addressed not only in the ability to

predict postoperative complications, but also to correlate with postoperative short and long-term quality of life and functional recovery.

Disclosures and Conflict of Interest Statements

The authors team have nothing to disclose related to this manuscript.

Contributors

GU, IM, AS, GE, MJ, SR, PS, BvL, NdL, NS, FG and RA conceived and designed the study;
All authors and *SIOG surgical task force/ESSO GOSAFE study group* contributed to data acquisition; FF CZ, BV and ON performed quality control of data and algorithms, and statistical analysis; IM, GU, SR, BvL, NdL, NS, FG, FF, CZ, ON and RA performed data analysis and interpretation; IM, GU, NS, FG, FF, CZ and RA prepared the manuscript; IM, GU, AS, GE, SR, PS, BvL, NdL, NS, FG, FF, CZ, MJ, ON and RA performed manuscript editing and review;
All authors reviewed the draft, provided detailed comments and input, and contributed to the final draft.

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Appendix 1. Frailty evaluation

GO SAFE Study

APPENDIX 1

Frailty evaluation

Sex: ☐ Male ☐ Female

Living situation: ☐ home independent ☐ home with family/care giver ☐ residential care

Polipharmacotherapy (total number of medications): _____

History of falls in the 6 months prior to the operation ☐ No ☐ Yes (total number_____)

Previous delirium during illness or hospital admission: ☐ Yes ☐ No

Smoking habit: ☐ Yes ☐ No (former) ☐ No (never)

Preoperative chemotherapy: ☐ Yes ☐ No

Preoperative radiation therapy: ☐ Yes ☐ No

Geriatrician involved in preoperative management? ☐ Yes ☐ No

PREOPERATIVE SCREENING

TUG test first trial _____ (sec)	TUG test second trial _____ (sec)

ASA score (1-5)	

LABs

Albumin ___.___ (g/dL)	Haemoglobin ___,__ (g/L)	Creatinin ___,___ (mg/dL)

GO SAFE Study

Age adjusted Charlson Comorbidity Index*

Condition	Pts
40 ≥ Age	0
50≥Age>40	1
60≥Age>50	2
70≥Age>60	3
80≥Age>70	4
Age>80	4
Myocardial Infarction	1
Congestive Heart Failure	1
Periferal Vascular Disease or by-pass	1
Cerebrovascular disease	1
Hemiplegia	2
Chronic Pulmonary disease	1
Diabetes mellitus without end organ damage	1
Diabetes mellitus with end organ damage	2
Renal disease	2
Mild liver disease	1
Moderate liver disease	3
Peptic ulcer disease	1
Lymphoma	2
Leukemia	2
Any malignancy	2
Metastatic solid tumor	6
Dementia	1
Rheumatic disease	1
AIDS	6
TOTAL SCORE (0-41)	

***As published in PLoS One:**
Adjusted Age-Adjusted Charlson Comorbidity Index Score as a Risk Measure of Perioperative Mortality before Cancer Surgery.Chang CM et al. PLoS One. (2016)

G-8

Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties?	0 = severe decrease in food intake 1 = moderate decrease in food intake 2 = no decrease in food intake
Weight loss during the last 3 months?	0 = weight loss >3 kg 1 = does not know 2 = weight loss between 1 and 3 kg 3 = no weight loss
Mobility?	0 = bed or chair bound 1 = able to get out of bed/ chair but does not go out 2 = goes out
Neuropsychological problems?	0 = severe dementia or depression 1 = mild dementia or depression 2 = no neuropsychological pèroblems
BMI?	0 = BMI < 18,5 1 = BMI 18,5 to <21 2 = BMI 21 to <23 3 = BMI ≥23
Takes more than three prescription drugs per day?	0 = yes 1 = no
In comparison with other people of the same age, how does the patient consider his/her health status?	0.0 = not as good 0.5 = does not know 1.0 = as good 2.0 = better
Age	0 = >85 1 = 80–85 2 = <80
Total Score (0-17)	

GO SAFE Study

EQ-5D-3L and VAS

https://euroqol.org/

MINI-COG

https://mini-cog.com/

GO SAFE Study

ADL

BATHING	I = Receives no assistance (gets in and out of bath or shower by self if bath is usual means of bathing) I = Receives assistance in bathing only one part of the body (such as back or leg) D = Receives assistance in bathing more than one part of the body (or not bathed)
DRESSING	I = Gets clothes and gets completely dressed without assistance I = Gets clothes and gets completely dressed without assistance except for assistance in tying shoe laces D = Receives assistance in getting clothes or in getting dressed, or stays partly or completely undressed
TOILET	I = Goes to "toilet room", cleans self, and arranges clothes without assistance (may use object for support such as cane, walk frame, or wheelchair and may manage night bedpan or commode, emptying same in morning) D = Receives assistance in going to "toilet room" or in cleaning self or in arranging clothes after elimination or in use of night bedpan or commode D = Doesn't go to room termed "toilet" for the elimination process
TRANSFER	I =Moves in and out of bed as well as in and out of chair without assistance (may be using object for support such as cane or walk frame) D = Moves in and out of bed or chair with assistance D = Doesn't get out of bed
CONTINENCE	I = Controls urination and bowel movement completely by self D = Has occasional "accidents" D = Needs supervision for urine or bowel control; catheter is used, or is incontinent

GO SAFE Study

NUTRITIONAL RISK SCREENING

Weight in kg: __ __ __ . __ Height in cm: __ __ __ . __ BMI:__ __ (weight/height x height)

Mildly impaired nutritional status: >5% weight loss in 3 months or food intake below 50-75% of normal requirement in preceding week Moderately impaired nutritional status: >5% weight loss in 2 months or BMI 18.5-20.5 + impaired general condition or food intake 25-60% of normal requirement in preceding week Severely impaired nutritional status: >5% weight loss in 1 month (>15% in 3 months) or BMI <18.5 + impaired general condition or food intake 0-25% of normal requirement in preceding week	<table><tr><th>Nutritional Status</th><th>Score</th></tr><tr><td>Normal</td><td>0</td></tr><tr><td>Mildly impaired</td><td>1</td></tr><tr><td>Moderately impaired</td><td>2</td></tr><tr><td>Severely impaired</td><td>3</td></tr></table> Instructions: circle appropriate score

ECOG Performance Status*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

***As published in Am. J. Clin. Oncol:**

Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655

Appendix 2. Data collection, outcome measures, and statistical analysis.

- Data Collection

Clinical Reporting Forms (CRF) were to be completed through OpenClinica [38], an open source clinical trial software for Electronic Data Capture (EDC) available on-line. The database is certified, highly secured and it is stored in an encrypted server that meets all the requirements for data safety and privacy set by international law. All patients' information has been kept private and anonymized.

Surgical data analysis, including detection of postoperative complications, required the supervision of a staff surgeon.

- Assessment/Comparison of Quality of Life and Functional Recovery

QoL analysis was performed by calculating and comparing the EQ 5D-3L index [39–41]. In addition, VAS scores were used to compare QoL before and after surgery. A threshold of VAS ≥ 60 was determined to define fair QoL.

EQ-5D-3L consists of five questions, each assessing problems in one of these dimensions: mobility, selfcare, usual activities, pain/discomfort, and anxiety/depression. Each dimension is assigned a level using a 3-point scale: no problems, some or moderate problems, and extreme problems. The test is designed to assess five domains on a scale from one to three (where three represents the worst scenario) and it complements with a visual scale that goes from one to 100 representing the level of fitness perceived by the patient on the very day of the testing.

The test has been shown to be reliable in a multitude of countries (around the world) and applicable (in a modified version) to assess QoL in patients with cognitive impairment [42,43].

With five dimensions and three levels, 243 potential health profiles were possible for each patient. A profile of '11111' represents the best possible health state, while the profile '33333' represents the worst possible health state.

These health profiles have been valued by representative samples of the general population: from their values, a value set has been derived allowing the calculation of a score for any health profile. We used the value set derived from preferences of the general population of Europe to calculate reference scores [44].

Functional recovery was defined as a composite measure taking into account the combination of three systems required for patient independence: ADL, Mini-Cog and TUG.

Complete FR (cFR) was defined as preservation or improvement of baseline results of all the three reported tests from the preoperative period to three and six months after surgery. With the same algorithm, partial FR (pFR) was defined as preservation or improvement of at least two out of the three functional assessment tests. Functional deterioration (FD) was defined by the decline of at least two of three domains after 3 or 6 months from the procedure.

- Operative details and early post-operative outcomes

Cancer site, type of procedure, approach and intent were recorded for each patient. Palliative procedures were considered eligible for inclusion when at least one surgical resection was performed (i.e. partial gastrectomy/colectomy in a metastatic patient with obstructive symptoms). Duration and type of anaesthesia were recorded together with need for post-operative Intensive Care Unit and/or blood transfusions. Post-operative length of stay was registered and study participants were asked to define the facility/living situation the patient was discharged to. Tumor-Node-Metastasis (TNM) status and cancer stage were reported according to the 7th edition of TNM cancer staging system [45].

One-month postoperative complications were reported according to the Clavien Dindo Classification [46]. In case of death, cause and living situation at that time were asked to be specified.

- Long term follow-up

Three and six months postoperatively, EQ 5D-3L and functional assessment tests (ADL, TUG, ECOG, mini-Cog and NRS) were repeated to evaluate effects of surgery on QoL and FR. Data about adjuvant treatments, living situation, rehabilitation (both physical and nutritional), morbidity and mortality were also collected.

- Statistical Analysis

Descriptive analysis was performed for demographic, health and clinical variables. For the primary analysis, evaluable patients are required to have a pre-surgery EQ-5D-3 L assessment and a three- and six-month assessment. The observed change in QoL before and after surgery will be determined by comparing the EQ index scores at 3 months to the pre-surgery EQ index score, and paired *t*-test will be used to assess the statistical significance of the change between the two time-points.

All statistical analyses were performed using Stata/SE version 15.0 for Windows (StataCorpLP, College Station, TX, USA).

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