UNIVERSITA' DEGLI STUDI DI GENOVA

DOTTORATO DI RICERCA IN
MEDICINA INTERNA CLINICO-SPERIMENTALE

Direttore Chiar.mo Professore M. Bagnasco

TESI DI DOTTORATO

Il ruolo del geriatra nella gestione del paziente oncologico anziano

Candidata : Dott.ssa Chiara Russo

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CHAPTER 1

INTRODUCTION

The risk of cancer increases with age[1] and the population growth will lead to an increased incidence of cancer in the elderly.

In the USA the elderly population is increasing: from 25 million in 1980 to 72 million estimated in 2030.[2] Italy is one of the countries with the highest old-age index in the world, equal to 157.7 in 2015 (vs. 138.1 in 2005). In 2005, the elderly population was 19.5% but in 2015 it was 21.7%, with a growth expectation of 32.6% in 2065. In 2015, the oldest old people represented 3.2% of the population but in 2065 it should be 10%.[2]

The incidence of cancer is increasing worldwide. In 2013, 14.9 million malignant neoplasms were diagnosed compared to 8.5 million in 1990,[3] with estimates of growth of up to 26 million in 2030 according to the International Agency for the Research on Cancer.[4] Every day in Italy, about 1000 people receive a diagnosis of cancer and, in 2016, a total of 365,000 new diagnoses were estimated. The most frequent was colorectal (52,000), followed by the breast (50,000), lung (40,000), prostate (35,000) and bladder (26,000) cancer.[5]

Already as of today, more than half of the patients who are newly diagnosed with cancer are older than 65 and this percentage is projected to increase to 70% by 2030.[6,7]

Epidemiological data from the National Cancer Institute Surveillance, Epidemiology and Results Program show that 71% of cancer deaths occur in people over 65, demonstrating that cancer is primarily an old age disease.[8]

Presently, faced to emerging demands on health care, improvement of life expectancy, and concomitant development of procedures, this "oncogeriatric" population will benefit from innovative therapies or surgical procedures, which will, however, require specific clinical management.[9]

The management of elderly patients suffering from cancer remains challenging and complex. Many specific issues may influence cancer treatment decision including the physicians' propensity to consider an old age as an obstacle to provide an optimal treatment, and to fear an increased disability and worsening of chronic conditions occurring with cancer and its treatment.[10]

In geriatric oncology it's very important to stratify older patients according to their biological status, to be able to recommend the most appropriate type of treatment in a personalized fashion. Therefore, the optimal management should involve tumour assessment and careful geriatric evaluation.[11,12]

Geriatric Assessment (GA) is a multidisciplinary approach, originally developed by geriatricians to define the global health status in elderly and to establish a suitable care plan.

Since the 1990s, oncologists and geriatricians recognized the importance of integrating a Comprehensive Geriatric Assessment (CGA) with oncology.[12-18]

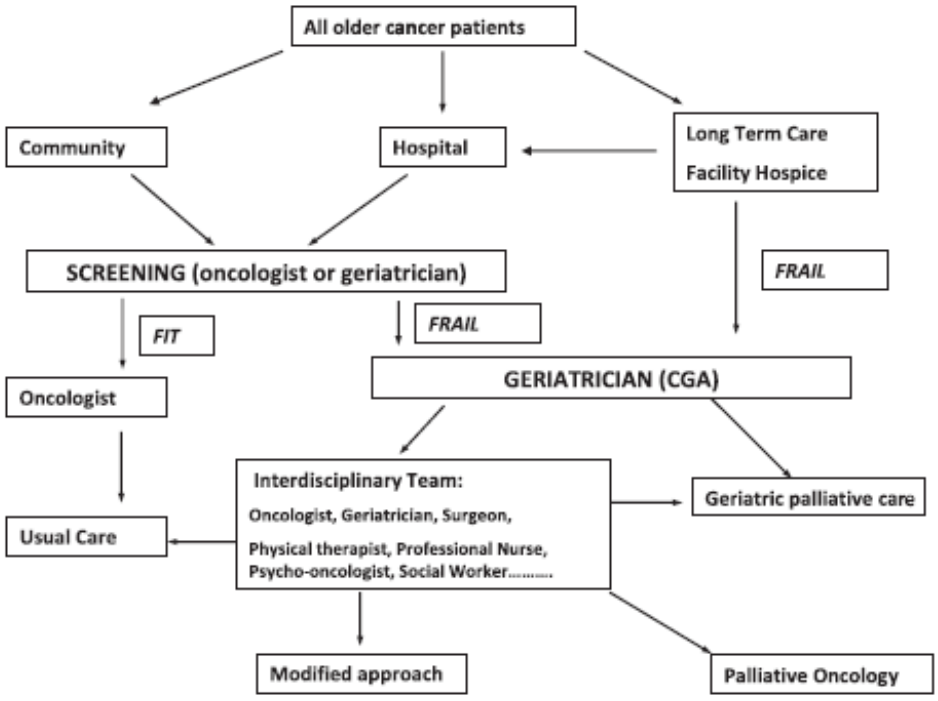
CGA provides an evaluation of the main geriatric domains including cognition, psychological, functional and nutritional status, social situation, associated diseases, and patient's medications.[14,15] CGA may assist in early identification of patients' strengths and weaknesses, geriatric problems requiring specific interventions, and may lead to the development of individual plans in order to facilitate cancer treatment program.[16-18] Geriatric evaluation can help to determine which patients

are candidates to effective standard cancer treatment, to personalized approach, and those for whom palliative care would be the best option.[19] Moreover, CGA should be seen as a dynamic tool able to progressively integrate new specific instruments to better assess the risk of treatment procedures.[20]

According to the International Society of Geriatric Oncology (SIOG), the Comprehensive Geriatric Assessment remains the gold standard for defining the presence and or the degree of frailty in elderly cancer patients.[12,15] Its widespread use is recommended, particularly since the CGA was shown to improve patient overall survival, functional status, and quality of life.[12,15] In geriatric oncology frailty's evaluation is mainly focused on person's ability to tolerate cancer treatment; frailty is also associated with a worse quality of life.

However, the CGA is time and resource-consuming and requires the expertise of geriatricians who are not always available in standard cancer clinics. Thus, it remains poorly incorporated in routine clinical practice.

Consensus guidelines from the National Comprehensive Cancer Network (NCCN),[21] the European Organization for Research and Treatment of Cancer (EORTC),[22] and the SIOG,[23] consider a "two-step approach" as a reasonable strategy, where the first step involves a geriatric screening test to identify patients who are at high risk of being frail and the second step foresees a complete CGA to be performed by geriatricians.[1, 24-27]



Management of older cancer patient

Since the 2005 SIOG guidelines, a total of 17 different tools have been studied in 44 different trials to evaluate the best screening test in oncogeriatrics.[23] These include G8, Oncogeriatric screen (OGS), Abbreviated Comprehensive Geriatric Assessment (aCGA), Senior Adult Oncology Program (SAOP) 2, Gerhematolim, the Vulnerable

Elders Survey-13 (VES-13) and Flemish version of the Triage Risk Screening Tool (fTRST) . So far, although the G8, the VES-13 and fTRST tools have shown the best clinometric properties in elderly patients,[23] there remains a substantial uncertainty as to which test most adequately identifies frailty in at risk older cancer populations.[28]

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CHAPTER 2

INTRODUCTION

During my PhD I participated to several research projects in oncogeriatrics at the Hospital Policlinic San Martino, in Genoa, Italy, and at the Comprehensive Cancer Center Lèon Bèrard, in Lyon, France. Two studies were completed and published:

- Geriatric assessment in oncology: moving the concept forward. The 20 years of experience of the Centre Léon Bérard geriatric oncology program.
- Performance of two frailty screening tools in older patients with solid cancer: a comparison of SAOP2 and G8.

The others studies are still in progress:

- **PREPARE**: Assessment of the effectiveness of a geriatrician intervention in the management of elderly cancer patients compared to 'standard care' (treatment according to ongoing standards in Oncology).
- **PRIORITY**: Description of the priorities of elderly cancer patients receiving initial medical treatment.
- **MEQAPAG**: Impact on quality of life of melatonin supplementation in elderly metastatic patients.
- **NutriAgeCancer**: Assessment of nutritional status in elderly cancer patients.

CHAPTER 3

GERIATRIC ASSESSMENT IN ONCOLOGY: MOVING THE CONCEPT FORWARD. THE 20 YEARS OF EXPERIENCE OF THE CENTRE LÉON BÉRARD GERIATRIC ONCOLOGY PROGRAM

ABSTRACT

Objectives: The management of cancer in aging people remains a challenge for physicians. Specialists agree on the assistance provided by a Multidimensional Geriatric Assessment (MGA) to guide the cancer treatment decision making process. We aim to explore the use of MGA in treatment decision and to identify MGA parameters likely to influence the planned cancer treatment.
Material and Methods: We conducted a single-site retrospective study in patients older than 65 years suffering from various types of cancer who underwent MGA before cancer treatment decision. Logistic regression analyses were used for identification of predictive variables.
Results: In the 266 patients' population, the mean age was 75.8 ± 7.4 years and 155 (58%) patients were men. Patients had solid tumors (95.4%) or hematologic malignancies (4.6%). Most of patients were in advanced setting
(57%). The MGA revealed malnutrition (47%), cognitive/mood impairment (48%), functional decline (53%), and led to adjust medical care through reinforcing health status and fostering successful completion of cancer treatment plan for 259 (97%) patients. The MGA changed cancer treatment in 47 (18%) patients. Functional and/or cognitive impairment, risk of falls, and polypharmacy were associated with treatment change in univariate analysis. No multivariate model was possible.
Conclusions: MGA leads to modification of treatment in only few patients. However, MGA enables a better understanding of patients' strengths and weaknesses essential to improve care management. Further improvements with integration of innovative specific tools are warranted to help decision-process in the increasing complexity of treatment plans available in older adults.

OBJECTIVE

The objective of this retrospective study is to assess the global health status in older outpatients with cancer, to report uncovered problems or dysfunctions requiring targeted geriatric interventions, to identify Multidimensional Geriatric Assessment (MGA) parameters likely to influence planned cancer treatment, and finally to report our experience from our almost 20-year Geriatric Oncology Program.

MATERIALS AND METHODS

Study design and data collection

Patient population

This retrospective analysis explored data of patients treated from 1999 to 2012 at the Comprehensive Cancer Centre Léon Bérard, aged 65 years and over, with a diagnosis of solid cancer or hematologic malignancy,arbitrarily referred to the Geriatric Oncology Program by their oncologist-in-charge at early or advanced stage to evaluate the suitability of standard cancer treatment. The ethics committee (CPP LYON-Sud-Est IV) was consulted for study approval.

Geriatric assessment

The MGA procedure was exclusively conducted with the existing multidisciplinary team headed by a geriatrician, including a social worker, a dietician, a physiotherapist, a pharmacist, and a research nurse contributing together in a multidimensional data collection. Based on a 90-120-minute evaluation, including a joint interrogation and clinical examination, the geriatrician provided conclusions on the patient's health status, guidelines on the management plan, and recommendations for specific geriatric interventions. MGA enables the geriatrician to evaluate the eligibility of a patient for the standard cancer treatment, or to decide if the patient should benefit from a more personalized approach, or should be referred to palliative care.[1-3] MGA results and intervention plan were systematically sent to the patient's general practitioner.

Data collection

Demographic data (age, gender), Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) and Karnofsky score (KPS), tumour characteristics (site, local or metastatic), cancer treatment initially proposed, geriatric variables, overall management recommended by the geriatrician, and treatment plan modifications when available were collected. Tests and scales for cognitive impairment (Mini Mental State Examination-MMSE),[4] depression (Geriatric Depression Scale-GDS with total score range from 0 to 30),[5] functional status (Basic Activities of Daily Living-ADL and Instrumental Activities of Daily Living-IADL) were currently used for both men and women in daily practice.[6,7] Mobility was defined as the risk of falls by the occurrence of at least one fall in the last year,[8] or five or more anomalies detected with the Performance-Oriented Assessment of Mobility test (POMA score $\geq$5/22).[9,10] Nutritional status was assessed according to the Clinical Practice Guidelines from the French Health High Authority, and malnutrition defined as the presence of at least one of the following criteria: weight loss of at least 5% in the last three months or 10% in the last six months, Body Mass Index (BMI) lower than 21 Kg/m^2, Mini Nutritional Assessment (MNA) score lower than 17/30,[11] or serum albumin level lower than 35 g/l.[12,13] Impairment was assessed through the identified fourteen comorbidities' categories of the Cumulative Illness Rating Scale for Geriatrics (CIRS-G), calculating the number of grade 3 or 4 (severe or very severe) comorbidities, and the global score (range 0-56).[14] Social issues addressed basic key questions such as the presence of caregiver, existence of financial problems, or legal protection. Risk for drug interactions (polypharmacy) was defined as taking five or more drugs a day. Patients with too many missing data (>10%), especially between 2008 and 2011, were not considered in the analysis.

Statistical analysis

Qualitative variables were described using frequencies and percentages, and compared between subgroups using the chi-square test. Quantitative variables were described using median (range), or mean and standard deviation (SD), and were compared between subgroups using the Student's t-test.
Potential predictors selected for clinical relevance were first described and tested in univariate analyses according to treatment change or not. Variables significant at a 15% level in univariate analyses were selected for the multivariate model. To note, factors significant at a 15% level with too many missing data (>10%) were not selected for multivariate analysis. A backward selection procedure was then used to keep only variables significant at a 5% level in the final multivariate model. Statistical analyses were performed using SAS (version 9.3).

RESULTS

Patient population

In the 266 patients' population, the median age was 75.8 ±7.4 years, and 155 patients (58.3%) were male. A solid tumour was diagnosed in 95.4% of patients and hematologic malignancy in 4.6% of subjects. The main solid tumour localisations were genitourinary (38.5%), breast (15.8%), gastrointestinal (13.1%), and head & neck sites (11.5%) (Table 1). At the time of the evaluation, most of the patients were in advanced setting (57.5%). 174 (66%) patients had an ECOG-PS <2 and the mean KPS Index was 80.5 ±25.0.

Geriatric assessment

Geriatric evaluation's results are listed in Table 2. No difference according to gender was observed in our series, especially regarding the IADL score.

Table 1: Patient demographic and clinical characteristics.

Patient characteristics	N = 266	
Demographics		
Gender, male	155	(58.3%)
Mean age (SD), years	75.8	(±7.4)
Solid tumour		
Genitourinary	100	(38.5%)
Breast	41	(15.8%)
Gastrointestinal	34	(13.1%)
Head & Neck	30	(11.5%)
Lung	10	(3.8%)
Skin	8	(3.1%)
Gynecologic	6	(2.3%)
Others[a]	19	(7.3%)
Unknown primary site	6	
Hematologic malignancy	12	(4.6%)
Disease stage		
Local	81	(33.5%)
Locally advanced	22	(9%)
Metastatic	139	(57.5%)
Missing data	24	
Performance Status		
ECOG PS <2	174	(66%)
Mean KPS (SD)	80.5	(±25)

Abbreviations: ECOG-PS: Eastern Cooperative Oncology Group Performance Status; KPS: Karnofsky Performance Status.

Qualitative data are *n* (%) and quantitative data were described using mean and standard deviation (SD).

[a] bone, Ewing sarcoma, penile, testicular cancer.

Table 2: Multidimensional Geriatric Assessment results.

Parameters	Patients N = 266	
Cognition		
Cognitive decline (MMSE≤24)	125	(47.5%)
Normal cognition (MMSE>24)	138	(52.5%)
Missing data	3	
Median score (range)	25	0–30
Depression		
Normal (GDS<10)	130	(50.2%)
Depression (GDS ≥10)	129	(49.8%)
Missing data	7	
Median score (range)	9	0–30
Functional status		
Functional decline (ADL score < 6)	140	(52.5%)
Normal (ADL score = 6)	126	(47.5%)
Missing data	0	
Median score (range)	5	0–6
Functional decline (IADL score < 8)*	210	(79.5%)
Normal (IADL score = 8)	54	(20.5%)
Missing data	2	
Median score (range)	5	0–8
Mobility		
Fall in the last year	47	(31.5%)
Missing data	117	
POMA test		
Risk of falls (POMA score ≥ 5)	88	(35.9%)
Missing data	21	
Median score (range)	1	0–22
Nutrition		
HAS recommendations		
Weight loss		
5% weight loss in 3 months	92	(35.4%)
No weight loss	168	(64.6%)
Missing data	6	
Mean BMI (SD)	24.2	(±4.9)
MNA		
Malnourished MNA <17	43	(16.2%)
At risk for malnutrition 17 < MNA < 23.5	124	(46.8%)
Normal 24 < MNA < 30	98	(37%)
Missing data	1	
Median score (range)	22	7–30
Social status		
Presence of caregiver	184	(70.5%)
Missing data	5	
Financial problems	7	(2.6%)
Missing data	1	
Legal protection	2	(0.8%)
Missing data	1	
Comorbidity		
CIRS-G: median global score (range)	12	2–29
CIRS-G: at least one grade 3/4 comorbidity	188	(70.7%)
Polypharmacy		
Mean number of medications/day (SD)	5	(±3.2)

Abbreviations: MMSE: Mini Mental State Examination; GDS: Geriatric Depression Scal
ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; POMA: Perfo
mance-Oriented Assessment of Mobility Instrument; HAS: French Health High Authorit
MNA: Mini Nutritional Assessment; BMI: Body Mass Index; CIRS-G: Cumulative Illne
Rating Scale for Geriatrics.

MGA newly uncovered unknown problems, mainly malnutrition (47%), cognitive and/or mood impairment (cognitive, depression, anxiety, insomnia) (48%), and functional impairment (53%). The MGA led the geriatrician to provide targeted interventions for 259 patients (97%), predominantly nutritional care (69%), changes in prescribed medications (57%), requirement for further investigations (57%), and comorbid conditions diagnosis and monitoring (52%). The geriatrician might also specifically recommend for 40% of the patients an extensive medical management and contingently an orientation to a closer geriatric resource.
The cancer treatment initially planned was presented in Table 3. 47 (18%) patients had their initial cancer treatment plan changed based on MGA results.

Table 3: Cancer treatment plans and change based on MGA results.

Planned cancer treatment program		
Treatment options	Number of patients considered for each treatment option	Number of patients with no modification
		N = 219 (82.3%)
Standard chemotherapy	98	78 (79%)
Surgery	50	34 (68%)
Radiotherapy	42	39 (93%)
Hormonal therapy	26	24 (92%)
Combination of two treatments:	22	16 (73%)
Chemotherapy + Radiotherapy	12	11
Chemotherapy + Surgery	2	1
Radiotherapy + Surgery	5	1
Radiotherapy + Hormonal Therapy	3	1
Watchful waiting	22	22 (100%)
Palliative care	6	6 (100%)

Modifications included changes in treatment intensity (15%), in administration schedule (17%), or in the initially proposed regimen (11%). Based on MGA, the final cancer treatment included surgery in 34 (68%) patients, radiotherapy in 39 (93%) patients, hormonotherapy in 24 (92%) patients, and standard chemotherapy in 78 (79%) patients. Three patients were not eligible for surgery, two patients underwent a modified surgery (cholecystojejunostomy, hysterectomy) and 11 patients were referred to a medical treatment (chemotherapy or hormonotherapy). Eight (40%) patients received a reduced dose of the chemotherapy initially proposed, 4 (20%) patients received the treatment with a longer time interval, 3 (15%) patients received another regimen with a more manageable tolerance profile, and chemotherapy was definitively cancelled in 5 (25%) patients (Table 3).
The univariate analysis showed that ADL, Karnofsky Index, MMSE, number of medications, and POMA were variables potentially involved in treatment modifications with the 15% significance level. No multivariate model can be achieved with these data. No significant predictive factor was identified in our series (Table 4).

Table 4: Univariate analysis comparing MGA results and cancer treatment changes.

Variable	No treatment change	Treatment change	p-value**
Patient characteristics	219 (82.3%)	47 (17.7%)	
Demographics			
Gender, male	128 (58.4%)	27 (57.4%)	0.9
Mean age (SD), years	75.5 (±7.2)	77.1 (±8.0)	0.165
Solid tumour			
Genitourinary	85 (39.9%)	15 (32%)	
Breast	37 (17.4%)	4 (8.5%)	0.083
Gastrointestinal	27 (12.7%)	7 (14.9%)	
Head &Neck	22 (10.3%)	8 (17%)	
Lung	9 (4.2%)	1 (2.1)	
Skin	7 (3.3%)	1 (2.1%)	
Gynecologic	5 (2.4%)	1 (2.1%)	
Others*	15 (7%)	4 (8.5%)	
Unknown primary site	6	0	
Hematologic malignancy	6 (2.8%)	6 (12.8%)	
Disease stage			
Local	65 (32.7%)	16 (37.2%)	0.659
Locally advanced	17 (8.5%)	5 (11.6%)	
Metastatic	117 (58.8%)	22 (51.2%)	
Missing data	20	4	
Performance status			
ECOG PS <2	150 (70.5%)	24 (53.3%)	0.33
Mean KPS (SD)	82.0 (±24.0)	73.6 (±28.8)	0.04
Geriatric parameters			
Cognition			
MMSE ≤24/30	98 (45.2%)	27 (58.7%)	0.095
MMSE >24/30	119 (54.8%)	19 (41.3%)	
Median score (range)	26 (0–30)	22.5 (14–30)	0.06
Missing data	2	1	
Depression			
GDS <10/30	107 (50.2%)	23 (50%)	0.837
GDS ≥10/30	106 (49.8%)	23 (50%)	
Median score (range)	9 (0–30)	9.5 (1–24)	0.848
Missing data	6	1	
Functional status			
ADL median score (range)	5 (0–6)	5 (0–6)	0.11
IADL median score (range)	5 (0–8)	4 (0–8)	0.172
Mobility			
POMA score ≥ 5	68 (33.2%)	20 (50%)	0.042
POMA score < 5	137 (66.8%)	20 (50%)	
Median score (range)	1 (0–22)	3.5 (0–21)	0.438
Missing data	14	7	

Nutrition			
Weight loss			
5% weight loss in 3 months	74 (34.4%)	18 (40%)	
No weight loss	141 (65.6%)	27 (60%)	0.476
Missing data	4	2	
MNA			
Malnourished MNA < 17	35 (16.1%)	8 (17%)	
At risk for malnutrition 17 < MNA < 23.5	103 (47.2%)	21 (44.7%)	0.95
Normal 24 < MNA < 30	80 (36.7%)	18 (38.3%)	
Median score (range)	22 (8–30)	22 (7–29)	0.763
Missing data	1	0	
Social status			
Presence of caregiver	148 (69.2%)	36 (76.6%)	
No caregiver	66 (30.8%)	11 (23.4%)	0.311
Missing data	5	0	
Comorbidity			
CIRS-G: at least one grade 3/4 comorbidity	151 (68.9%)	37 (78.7%)	0.182
No grade 3/4 comorbidity	68 (31.1%)	10 (21.3%)	
Polypharmacy			
Mean number of medications/day (SD)	5.0 (±3.0)	5.9 (±3.5)	0.061

Abbreviations: ECOG-PS: Eastern Cooperative Oncology Group Performance Status; KPS: Karnofsky Performance Status; MMSE: Mini Mental State Examination; GDS: Geriatric Depression Scale; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; POMA: Performance-Oriented Assessment of Mobility Instrument; MNA: Mini Nutritional Assessment; BMI: Body Mass Index; CIRS-G: Cumulative Illness Rating Scale for Geriatrics.

[a] Bone, Ewing, sarcoma, penile, testicular cancer.

[b] Chi-square test or Fisher's exact test.

DISCUSSION

MGA offers a more accurate picture of the general health status of older patients with cancer and provides a reliable help in cancer treatment decision. Most of these older patients (66%) had an ECOG-performance status <2 and a mean Karnofsky index of 80.5%. These patients were considered as healthy enough to receive a cancer treatment and consequently referred to our tertiary cancer center. However, MGA highlighted unknown geriatric problems. We frequently identified functional decline (53%), malnutrition (47%), cognitive impairment and depressive disorders (48%). Indeed, the performance status does not appear to be a reliable parameter in the older population, and this highlights the requirement of variables specifically dedicated to older people.[15,16] The MGA identified problems and/or dysfunctions in geriatric domains similar to those reported in previous publications, with the limitation of indirect comparisons,[17,13,18-21] despite the different patients' population attending a regional comprehensive cancer centre or a geriatric hospital. In addition, the geriatric assessment varies according to the organization of the unit and the MGA instruments used.[17,13,18-21]

We initially supposed that the geriatric assessment would have greater influence on cancer treatment decision whereas only a limited number of patients (47 patients, 18%) have their treatments changed in our series. These findings are nonetheless consistent with the literature. The prospective Elderly Cancer Patient (ELCAPA) study showed a modification of the initial cancer treatment plan in 20.8% of the patients, and identified impaired ADL score and malnutrition as factors independently associated.[13]

Different factors were reported to be associated with cancer treatment modification. A reduced BMI and the absence of depressive symptoms were factors reported to be associated with treatment changes in 39% of patients.[17] Age, performance status, comorbidities, and polypharmacy were reported to be significantly associated with treatment changes in 42% of patients.[21] Severe comorbidities and dependence for at least one ADL were associated with treatment modifications and cancer treatment changed in 49% of patients.[18] MMSE impairment was significantly correlated with treatment modification in older patients with primary lung cancer.[20] In our series, POMA, ADL, Karnofsky Index, MMSE, and number of medications were identified as potentially associated factors with cancer treatment changes with the 15% significance level in univariate analysis. However, the multivariate model failed to identify significant predictive factors at a 5% significance level. These findings might indicate that MGA has to be considered in its entirety and isolated geriatric variables should not be powerful enough to influence cancer treatment plans in this population of patients with different cancer stages and tumour types. Indeed, isolated parameters such as cognitive decline, even severe, does not systematically preclude older patients from undergoing surgery in breast cancer, or radiation therapy in prostate cancer.[22,23] Only a global assessment would help the orientation to the best therapeutic option.

While modifications are scarce, geriatric recommendations were corrective recommendations generated for almost all patients (97%). They mainly focused on nutrition and comorbidity, the two major domains previously known to have a high impact on patient's survival.[24,25] Indeed, in our series, around two-thirds of the patients were at risk of malnutrition or already malnourished, and the median global score of comorbid conditions was 12 (2-29). Moreover 70% of the patients had at least one CIRS-G grade 3 or 4 comorbidity. Geriatric recommendations consequently

included nutrition care, comorbidity monitoring, and changed concomitant medications with a view to optimizing the patient's overall health status, and therefore ensuring a proper implementation of the cancer treatment plan.

In the 1990s, oncologists started to use a multidimensional geriatric assessment in the cancer treatment decision-making process. Our results illustrating the use of the standard MGA in a regional cancer centre are consistent with the literature. The growing incidence of tumours in older adults, their emerging demands of health care, and the development of refined surgical procedures, innovative therapies, and a rising number of complex treatments available therefore lead the MGA to be more flexible so as to adjust to the evolution of the demands in the current medical context. Based on our twenty-year experience, MGA should rather be considered as a dynamic procedure progressively integrating innovative instruments addressing the needs of patient and better assess the risk of proposed treatment procedures, especially in the field of surgery or chemotherapy. Refined MGA may provide a support to the oncologist in complex treatment decision-making process.

The American College of Surgeons National Surgical Quality Improvement Program Calculator (ACS NSQIP),[26-28] the Cardiac Risk Index, the postoperative pneumonia risk index,[29,30] and the DELirium Prediction based on Hospital Information (Delphi) score[31] were subsequently included to better assess the surgical risk.[32]

To assist personalized treatment-decisions and to anticipate serious adverse effects, Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH),[33] and Cancer and Aging Research Group (CARG),[34,35] have been integrated in our standard procedure.

Our study has several limitations. Our study aims to appreciate the help that the MGA may provide in the specific context of oncology, and we do not intend to assess an evaluation of MGA. A psychometric evaluation study would be required to demonstrate its validity, consistency, and reliability.

We report a retrospective data collection, and missing data in the geriatric management were frequently observed. The pilot project initiated in our Geriatric Oncology Program exclusively referred patients aged 65 years and over to the geriatrician who were arbitrarily selected by the oncologist-in-charge to assist their decision-making process; no specific screening instruments or ECOG-PS were used. In addition, patients' evaluation was limited by the consulting schedule of only one dedicated geriatrician providing services for a half a day per week in our institution. To note, all the source patients' evaluations were not initially accessible as electronic files. However, an upward trend was seen in the last two years and the rate of patients referred to the geriatric oncology program was twice in the last two years compared to that observed at the initiation of the study with 33.1 % of patients referred 2011-2012. Moreover, the selection inherent to a regional comprehensive cancer centre prompted us to recruit older patients with different cancer (stage, localization), prognoses and therapeutic approaches. Further analyses in subgroups warrant to be explored. Indeed, the failure to identify predictive factors could be related to the small sample size, or to the heterogeneity in terms of cancer stages and tumor types in the present population.

This local initiative based on substantive data collection across years provides a novel insight in the management of older people in the specific context of oncology. Uncovered parameters warrant to be explored and further implementation of the current MGA would be helpful to assess specific information and thereby deliver a more personalized approach in this specific population. Our results contribute to the

global international collaborative effort essential to improve the global care in older patients with cancer.

Our results, in accordance with the literature, showed the value of the standard MGA in cancer treatment decision-making.[17,13,18,20,21] Besides a better description of patient's strengths and weaknesses, MGA pointed out the necessity of targeted geriatric interventions that aimed at improving health conditions for older patients to receive the cancer treatment.

Based on our 20-year experience, MGA should be seen as a dynamic process that must integrate new tools in order to address the complex issues that the innovative cancer care procedures involve with older patients. The geriatric evaluation procedure should be adapted to the cancer type, stage and related treatment plan, and ideally personalised for each patient. Thus, specific tools should be added to the common assessment core to assist oncologists in treatment decision. To achieve this objective, a strong collaboration between oncologists and geriatricians built on their complementary knowledge and skills is necessary.

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POSTER

- ***Copenaghen, October 2013, International Meeting of the International Society of Geriatric Oncology, SIOG 2013***: "Multidimensional geriatric assessment influences planned cancer treatment and detects unknown geriatric problems". C Russo, G Albrand, S Perrin, C Terret.

ORAL COMMUNICATION

- ***Naples, November 2015, National Meeting of the Italian Society of Geriatrics and Gerontology, SIGG 201*5:** "Nel paziente oncologico anziano la valutazione multidimensionale influenza le scelte terapeutiche ed evidenzia problemi geriatrici sconosciuti". C Russo.

PUBLICATION

- Russo C, Terret C, Cropet C, Albrand G. Geriatric assessment in oncology: Moving the concept forward. The 20 years of experience of the Centre Léon Bérard geriatric oncology program. J Geriatr Oncol. 2018; 9(6):673-678.

CHAPTER 4

PERFORMANCE OF TWO FRAILTY SCREENING TOOLS IN OLDER PATIENTS WITH SOLID CANCER: A COMPARISON OF SAOP2 AND G8

ABSTRACT

Objectives: Comprehensive Geriatric Assessment (CGA), the gold standard for detecting frailty in elderly cancer patients, is time-consuming and hard to apply in routine clinical practice. Here we compared the performance of two screening tools for frailty, G8 and Senior Adult Oncology Program (SAOP2) for their accuracy in identifying vulnerable patients.
Material and Methods: We tested G8 and SAOP2 in 282 patients aged 65 or older with a diagnosis of solid cancer and candidate to undergo surgical, medical and/or radiotherapy treatment. CGA, including functional and cognitive status, depression, nutrition, comorbidity, social status and quality of life was used as reference. ROC curves were used to compare two screening tools.
Results: Mean patient age was 79 years and 54% were female. Colorectal and breast cancer were the most common types cancer (49% and 24%). Impaired CGA, G8, and SAOP2 were found in 62%, 89%, and 94% of the patients, respectively. SAOP2 had a better sensitivity (AUC 0.85, $p<0.032$) than G8 (AUC 0.79), with higher performance in breast cancer patients (AUC 0.93) and in patients aged 70-80 years (AUC 0.87).
Conclusions: G8 and SAOP2 both showed good screening capacity for frailty in the cancer patient population we examined with SAOP2 showing a slightly better performance than G8.

OBJECTIVE

The primary outcome was to assess the diagnostic accuracy of Senior Adult Oncology Program (SAOP2) and G8 screening tool, with reference to Comprehensive Geriatric Assessment (CGA), in detecting patient's clinical vulnerability.

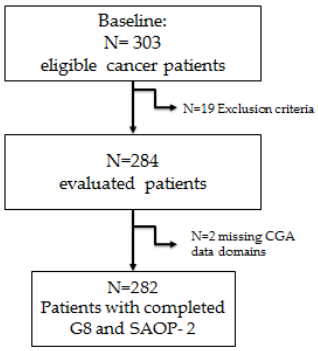
MATERIALS AND METHODS

Study design and population

This prospective study was performed at the Ospedale Policlinico San Martino, Genoa, Italy, from January 2015 to May 2017.
Inclusion criteria were all patients over 65 years with a first diagnosis of solid tumour, who qualified for surgery and/or chemotherapy, adequate understanding of the Italian language and ability to sign an informed consent.
Exclusion criteria were: palliative care patients; severe dementia or pre-existing major neurological and/or psychiatric disorders.

The study was approved by the ethical committee of the participating hospital, and written informed consent was obtained by all subjects or their next to kin.
Patients were simultaneously tested for G8 and SAOP2 questionnaire and comprehensive geriatric assessment, before oncological treatment (surgery, neoadjuvant or adjuvant chemotherapy), by an expert geriatrician.
First visit also included the Short Form 36[1,2] to assess quality of life.
Demographic data (age, gender), tumour characteristics (site, local or metastatic), proposed chemotherapy and/or surgery, geriatric recommended clinical interventions were also collected.

Figure 1: Study sample design.



Test methods

G8 screening tool

The G8 screening tool was developed to identify elderly unfit cancer patients, eligible for geriatric assessment.
The G8 test consists of the following eight items: chronological age (<80, 80–85, >85 years) and seven clinical items including the Mini Nutritional Assessment, a questionnaire dealing with food intake, weight loss, mobility, neuropsychological comorbidity, body mass index, prescription drug, and self-perception of health status.[3,4,5]
The total score can range from 0 to 17. A score of ≤14 is considered abnormal, indicating a clinical vulnerability profile.
The G8 was compared in terms of clinometric properties with CGA in eight different studies, that cumulatively included 3816 patients.[5-12] Sensitivity ranged from 65% to 92%, specificity ranged from 3% to 75% and negative predictive value (NPV) from 8% to 78%.[13]

Senior adult oncology program (SAOP) 2

The SAOP2 screening tool was developed by the multidisciplinary clinical team of the SAOP at Moffitt Cancer Centre. In addition to functional status, depression, and cognitive screening, the tool includes the assessment of health-related quality of life, self-rated health, falls, nutrition, sleep, multiple medications, and social issues (drug

payment and reimbursement and caregiver availability).[14]
If 1 item is impaired, the respective specialist is called in, with potential secondary referral to other team members. If several items are impaired, the multidisciplinary team is called along with the geriatric referral for CGA assessment. SAOP2 is a sensitive tool, with low internal specificity, addressing the importance of a multidisciplinary team approach.[15-17]

Comprehensive geriatric assessment (CGA)

An expert geriatrician administered the CGA assessment in an average time of 50 minutes. It evaluates the following tools to assess several clinical domains: cognitive status (Mini Mental State Examination, MMSE[18] and Clock Drawing Test, CDT[19]), psychological status (Geriatric Depression scale, GDS 15 items),[20] functional status (Instrumental Activities of Daily Living, IADL, of Lawton[21] and Barthel Index[22]), postural stability (Tinetti Scale),[23] risk of falls (Morse Scale),[24]) physical performance (Timed "Up & Go" test, TUG),[25,26] nutritional status (Mini Nutritional Assessment),[27] social vulnerability (Gijon Scale),[28] physical burden of illness (Cumulative Illness Rating Scale, CIRS: Illness Severity Index-SI, and Co-morbidity Index-CI.[29,30] Patients were categorized as impaired if the CGA ≥3 deficits.[31]
Pain was assessed using the Numeric Rating Scale (NRS).[32,33] Polypharmacy was also collected.

Table 1: CGA assessment, clinical domain and cut-offs.

Tool	CLINICAL DOMAIN	NUMBER OF ITEMS	RANGE	CUT-OFF *
IADL	FUNCTIONAL STATUS	8	0-8	≤ 7
BARTHEL	FUNCTIONAL STATUS	10	0-100	< 50
MORSE SCALE	RISK OF FALL	6	0-125	≥ 25
TINETTI SCALE	POSTURAL STABILITY	16	0-28	≤ 18
CIRS SEVERITY COMORBIDITY	COMORBIDITY	19	0-37 0-5 0-13	 >3
MMSE	COGNITIVE STATUS	7	0-30	<24
CDT	COGNITIVE STATUS	1	1 -6	≥ 3
GDS	PSYCHOLOGICAL STATUS	15	0-15	≥ 5
MNA	NUTRITIONAL STATUS	18	0-30	< 23
NRS	PAIN	1	0-10	≥ 3
GIJON SCALE	SOCIAL STATUS	5	5-25	≥ 10
CGA	-	-	-	≥ 3

Abbreviations: I-ADL: Instrumental Activities of Daily Living; CIRS: Cumulative Illness Rating Scale; SI: Illness Severity Index; CI: Co-morbidity Index; MMSE: Mini Mental State Examination; CDT: Clock Drawing Test Shulman; GDS: Geriatric Depression Scale; MNA: Mini Nutritional Assessment; NRS: Numeric Rating Scale; CGA: Comprehensive Geriatric Assessment.
* Cut-off score.

Statistical analysis

The descriptive analysis for quantitative variables was expressed as mean and standard deviation (SD) or median and interquartile range (IQR).
Sensitivity and specificity of both screening tools were calculated using the pre-specified cut-offs from literature.
Further receiver operating characteristic (ROC) curves were used to compare G8 and SAOP2 screening tools.
If present, indeterminate results were considered as false-positive or false-negative and incorporated into the final analysis. For example, an indeterminate result in a patient found to be frailty according to CGA was considered to have had a negative test result.
Areas under the curves (AUC) with 95% CI were reported. AUCs were compared using chi-square test.
A non-parametric Mann Whitney test was used to compare two variables.
A p-value <0.05 was considered statistically significant.
Stata (v.14; function “roccomp”; StataCorp) was used for the computation.

RESULTS

Patients’ clinical characteristics

Three hundred three eligible cancer patients were evaluated at the Ospedale Policlinico San Martino in Genoa, Italy, between January 2015 and May 2017. For two patients, clinical data collection was not completed and therefore they were not

included in the study. Nineteen patients did not meet the inclusion criteria. Thus, 282 eligible patients were evaluated in the study. Mean patient's age was 79.02 years ± 5.87 (range, 65-93 years) and about 40% of the patients were >80 years old. 54% of the patients were female and 46% were male. Colorectal cancer and breast cancer were the most common types of neoplasms for which patients were being treated, accounting for 50% and 24% of the patients, respectively.
Patients' clinical characteristics, screening tools and CGA assessment are illustrated in Table 2 and 3.

Table 2: Patient's demographic and clinical characteristics.

VARIABLE	N
DEMOGRAPHICS	
GENDER:	
FEMALE	*152*
MALE	*130*
MEAN AGE	*79.02 ± 5.87 (range 65–93 YEARS)*
AGE	
< 69	*14*
70 - 80	*156*
81 - 89	*101*
> 90	*11*
CANCER TYPE	
COLORECTAL	*138*
GASTRIC AND OESOPHAGEAL	*15*
PANCREAS AND BILIAR TRACT	*4*
HEAD AND NECK	*12*
BREAST	*68*
PROSTATE	*11*
GYNAECOLOGICAL	*11*
RENAL AND BLADDER	*11*
LUNG	*3*
OTHERS	*9*
DISEASE STAGE	
NON-METASTATIC DISEASE	*186*
METASTATIC DISEASE	*14*
UNCLASSIFIED	*82*

Table 3: G8, SAOP2 screening tools, CGA assessment with frequency of elders who were categorized as impaired in each domains of CGA.

SCREENING TOOLS AND CGA ASSESSMENT	CLINICAL DOMAIN	CUT-OFF *	IMPAIRED %	MEAN SCORE ± SD
G8		≤14	74	*12.23 ± 2.75*
SAOP2		>2	78	*2.73 ± 1.32*
MMSE	COGNITIVE STATUS	<24	20	*26.65 ± 3.88*
CDT (SCHULMAN)	COGNITIVE STATUS	≥ 3	48	*2.54 ± 1.40*
MNA	NUTRITIONAL STATUS	< 23	44	*22.62 ± 3.91*
IADL	FUNCTIONAL STATUS	≤ 7	39	*6.83 ± 2.02*
BARTHEL INDEX	FUNCTIONAL STATUS	< 50	3,5	*95.98 ± 11.64*
CIRS COMORBIDITY SEVERITY	COMORBIDITY	>3	63	*4.23 ± 1.83* *1.96 ± 0.38*
N° OF DRUGS	-	≥ 3	57	*4.48 ± 2.75*
GDS	PSYCHOLOGICAL STATUS	≥ 5	30	*3.92 ± 3.34*
TINETTI SCALE	POSTURAL STABILITY	≤ 18	16,5	*24.02 ± 5.74*
MORSE SCALE	RISK OF FALL	≥ 25	29	*23.44 ± 19.94*
GIJON SCALE	SOCIAL STATUS	≥ 10	35	*8.77 ± 2.29*
SF-36	*QoL*			*0.68 ± 0.21*
*CUT OFF CGA***		≥ 3	62	*3.77 ± 2.56*

Abbreviations: SAOP2: Senior Adult Oncology Program (SAOP) 2; MMSE: Mini Mental State Examination; CDT: Clock Drawing Test; MNA: Mini Nutritional Assessment ; I-ADL: Instrumental Activities of Daily Living; CIRS: Cumulative Illness Rating Scale; GDS: Geriatric Depression Scale; SF-36: Short Form 36; QoL: Quality of life; CGA: Comprehensive Geriatric Assessment.

* Cut-off score.

** cumulative number of impaired CGA domains.

Overall, 175 out of 282 patients (62%) showed problems in at least 3 CGA clinical domains, thus resulting as frail. This clinical vulnerability was mainly characterized by multimorbidity; initial functional decline and malnutrition risk (Table 3). In addition, patients reported a poor perception of the quality of life according to Short Form 36 (SF-36).

Notably, based on the CGA assessment, a G8 impairment mostly reflected an increased malnutrition risk (Mini Nutritional Assessment-MNA) (U 642, $p<0.05$) (Table 4).

Table 4: Comparison of CGA domains in patients aged between 70 and 80 years with impaired G8 and SAOP2, respectively.

CLINICAL DOMAIN AND TOOL MEAN SCORE (±SD)	N 156	G8 ≤ 14 N 114	SAOP ≥ 2 N 131	P value [b]
COGNITIVE STATUS MMSE	27.29±2.95	26.93±3.25	26.85±3.16	ns
FUNCTIONAL STATUS BARTHEL	97.01±9.48	95.75±11.47	96.03±10.75	ns
FUNCTIONAL STATUS IADL	7.16±1.67	6.83±1.95	6.91±1.86	ns
PHYSICAL PERFORMANCE TUG	10.15±4.27	10.80±4.87	10.77±4.60	ns
NUTRITIONAL STATUS MNA	22.53±4.91	20.85±4.76	21.76±4.88	U 642, p<0.05
PSYCHOLOGICAL STATUS GDS	3.89±3.44	4.45±3.70	4.54±3.62	ns
SOCIAL STATUS GIJON SCALE	8.53±2.36	8.99±2.44	9.02±2.39	ns
COMORBIDITY CIRS CI	4.05±1.83	4.43±1.91	4.40±1.85	ns
QOL SF-36	0.69±0.21	0.65±0.22	0.65±0.22	ns

[b] non-parametric Mann–Whitney U test.
Abbreviations: CGA: Comprehensive Geriatric Assessment; SAOP2: Senior Adult Oncology Program (SAOP) 2; MMSE: Mini Mental State Examination; I-ADL: Instrumental Activities of Daily Living; TUG: Timed "Up & Go" test; MNA: Mini Nutritional Assessment; GDS: Geriatric Depression Scale; CIRS: Cumulative Illness Rating Scale; CI: Co-morbidity Index; QoL: Quality of life; SF-36: Short Form 36.

Frail patients (based on CGA assessment) scored positive according to G8 in 89% and to SAOP2 in 94% of the cases, respectively (Table 5).

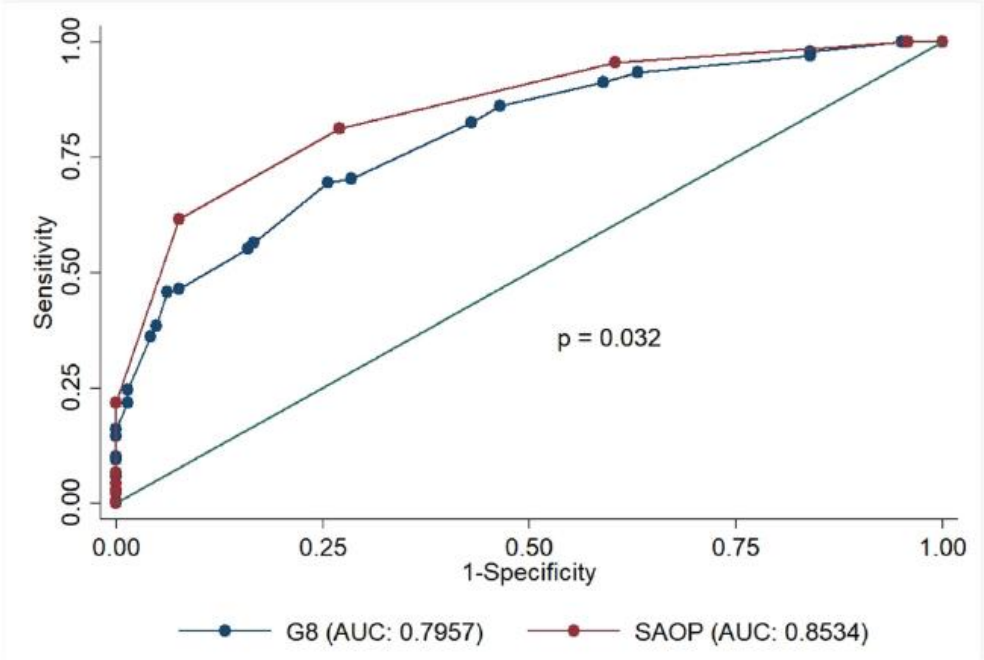
Table 5: Comparison between G8 and SAOP2 diagnostic accuracy with reference to the gold standard CGA.

	Sensitivity	Specificity	PPV	NPV
G8	89%	49.5%	73.9%	73.6%
SAOP2	94%	46.9%	74%	81%

Abbreviations: CGA: Comprehensive Geriatric Assessment; SAOP2: Senior Adult Oncology Program (SAOP) 2; PPV: positive predictive value; NPV: negative predictive value.

The comparison between G8 and SAOP2 diagnostic accuracy showed that SAOP2 had fair specificity, lower than G8.
A pairwise comparison between SAOP2 (n=282; AUC 0.85; 95% CI: 0.0215-0.81130) and G8 (n=282; AUC 0.79; 95% CI: 0.0260-0.74478) with reference to CGA using ROC curves showed a higher accuracy in differentiating patients with abnormal CGA for the SAOP2 screening tool (p<0.032) (Figure 2).

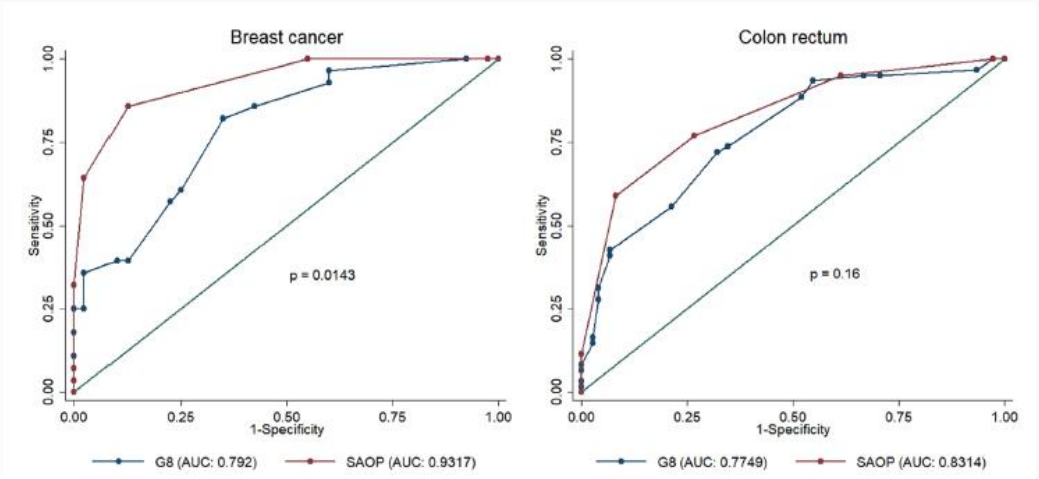
Figure 2: ROC curve diagnostic accuracy comparison between G8 and SAOP2 screening tools with reference to CGA.



Abbreviations: ROC: Receiver operating characteristic; SAOP2: Senior Adult Oncology Program (SAOP) 2; CGA: Comprehensive Geriatric Assessment

The diagnostic accuracy of both screening tools (with reference to CGA) was further assessed, separately, in patients with a diagnosis of breast cancer (n=68) versus patients with a diagnosis of colorectal cancer (n=138).
The SAOP2 showed higher accuracy in predicting patients' clinical vulnerability in breast cancer patients (n= 68; AUC 0.93; 95% CI: 0.87822-0.98518) as compared to the G8 (n=68; AUC 0.79; CI: 0.68674-0.89719) ($p<0.014$). Conversely, a comparison between SAOP2 and G8 in colorectal cancer patients did not show any difference in the ability to detect frail patients ($p<0.160$) (Figure 3).

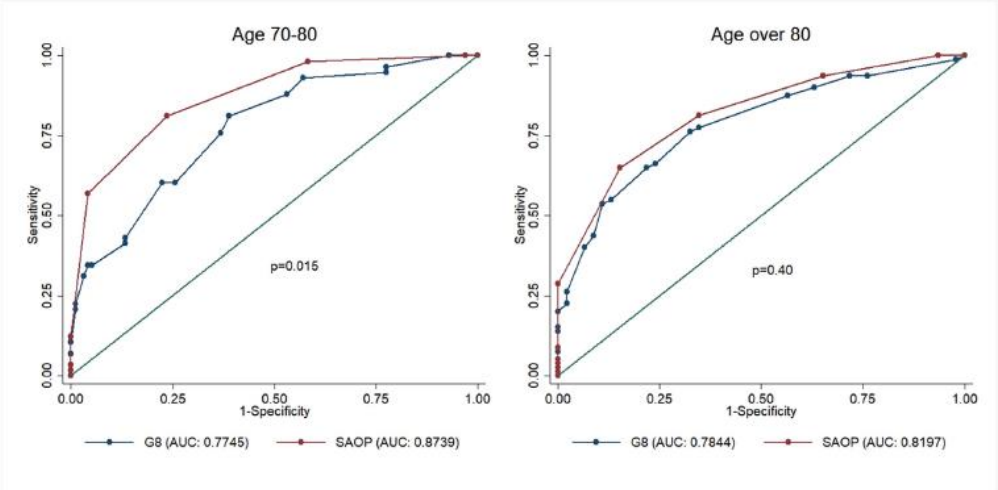
Figure 3: ROC curve comparison of G8 and SAOP2 screening tools in patients with breast cancer and colon rectal cancer respectively.



Abbreviations: ROC: Receiver operating characteristic; SAOP2: Senior Adult Oncology Program (SAOP) 2

In addition, in patients aged between 70 and 80 years, SAOP2's diagnostic accuracy (n=156; AUC 0.87; 95% CI 0.82061-0.92710) was higher as compared to G8's accuracy (n=156; AUC 0.77; 95%CI 0.70043-0.84865) (p<0.015).
Notably, both screening tools failed to accurately detect frailty in patients aged >80, with a high rate of false positive results (p<0.40) (Figure 4).

Figure 4: ROC curve comparison of G8 and SAOP2 screening tools in patients aged 70- 80 years and in patients > 80 years.



Abbreviations: ROC: Receiver operating characteristic; SAOP2: Senior Adult Oncology Program (SAOP) 2

DISCUSSION

The integration of CGA in clinical practice could help oncologists tailor clinical decisions based on the elderly patient's actual fitness. Currently, a two-step approach is recommended. Nevertheless, the best screening tool to be applied in the clinic remains to be defined.[34]

To the best of our knowledge, this is the first study to directly compare the performance of two commonly applied frailty screening tools, G8 and SAOP2, in an older cancer population.

Clearly, a high sensitivity and specificity are both desired properties of an oncogeriatric-screening tool, to limit the number of fit patients who unnecessarily undergo CGA assessment. These clinometric properties also ensure that frailty is properly recognized, thus avoiding that vulnerable subjects are over treated and exposed to the risk of treatment toxicity.[13]

Our data show that the SAOP2 has higher diagnostic accuracy as compared to the G8, especially in oncogeriatric patients who are <80 years. Conversely, both SAOP2 and G8 showed adequate sensitivity at the expense of specificity in patients older than 80 years. Furthermore, our results indicate that the SAOP2 screening tool has better screening performance than the G8 in breast cancer patients, but not in patients diagnosed with colorectal cancer.

Evidence is accumulating on the role of G8 screening tool in detecting vulnerable patients, even if with heterogeneous results.[13,35] The ONCODAGE multicentre study[7] has validated the G8 for the identification of older cancer patients eligible for CGA assessment: sensitivity varied according to tumour site and stage (head and neck cancer 94%; colon cancer 88%; metastatic stages 87%). Further, Kenis et al[6] has shown high sensitivity and moderate negative predictive value of the G8 tool in elders with metastatic breast and colorectal cancer.

Conversely, the comparison among Flemish version of the Triage Risk Screening Tool (fTRST), G8, and Groningen Frailty Index in elderly cancer patients[8] has resulted in the higher diagnostic accuracy of fTRST (sensitivity 92%) compared to G8 (sensitivity 80%). Baitar et al[9] has confirmed the higher accuracy of G8 tool in identifying vulnerable cancer patients with prevalent malnutrition.

Furthermore, in neck and head cancer patients, the G8 tool has shown better sensitivity, compared to Vulnerable Elders Survey-13 (VES-13),[10] and, similarly, Liu et al[11] has reported G8 higher sensitivity in patients with local colorectal cancer, upper digestive, hepatic tumour and in the metastatic group. In keeping with that, Pottel et al[36] has underpinned more impaired G8 scores in patients with advanced cancer, compared to early stage cancer patients.

Thus, it is plausible that subjects with more advanced cancer, and particularly with gastrointestinal and head/neck tumour are frequently comorbid for malnutrition,[4] due to the intense inflammatory response associated with anorexia and cachexia,[37] which can lead to progressive loss of skeletal muscle mass and worsen impairment of function.[38] Malnutrition has been associated with reduced ability to tolerate anti-cancer therapy, increased severe dose-limiting toxicities, lesser response rates, worse quality of life, decline in performance status, and shorter survival outcomes.[39] Thus, malnutrition turns to play a key relevant weight in informing G8 impairment.

Indeed, G8 screening tool incorporates most of the MNA items and the fact that MNA was not designed to specifically detect an abnormal CGA may probably explain the lack of specificity of the G8 as a screening instrument.[35]

Conversely, in haematological malignancies, the G8 tool didn't adequately discriminate unfit subjects eligible for CGA,[40] showing moderate diagnostic accuracy. Hamaker et al[41] has indicated lower sensitivity but better specificity (respectively 69% and 79%) of G8 screening performance due to potential higher prevalence of underdiagnosed geriatric syndromes.

This scientific background may count for the higher accuracy of SAOP2 screening in intercepting vulnerability in breast cancer patients compared to colorectal patients, as observed in the present study.

Thus, different cancer types and stages may have a different weighed impact on screening performance and overall diagnostic accuracy and the use of several validated CGA instruments and cut-off values may also add methodological biases, affecting results reliability.

Fewer evidence has shown the diagnostic accuracy of SAOP2 screening tool in different cancer population and clinical settings. However, SAOP2 tool[15] has shown adequate clinometric properties with reference to the standard geriatric assessment (sensitivity of 100% and a specificity of 40%),[16] including the assessment of key relevant issues for cancer related outcomes, such as social vulnerability, depression, quality of life and perceived health status.

Lower perceived social support is generally associated with higher depressive symptoms and lower quality of life,[42,43] especially in cancer patients compared to the general population.[42,44] Thus, social vulnerability represents a key factor for patient's compliance and the effectiveness of chemotherapy regimens.[45,46] It has also been shown that social vulnerability and frailty are related but distinct clinical constructs[47] and that the former was a significant predictor of mortality and disability, regardless of patients' frailty.[48,49]

Originally, the present findings indicate SAOP2 better performance in patients aged 70-80 years and support the diagnostic inaccuracy of oncogeriatric screenings (higher false positive screening results) in over octogenarian patients. The biological aging involves a loss of homeostasis with enhanced vulnerability to environmental stressors (surgical interventions or chemotherapy)[45,50] that may exceed patients' threshold homeostenosis, precipitating a frailty trajectory.[51] Moreover, it is likely that the highly individualized trajectory of frailty could affect the discriminative power of these screening tools, especially in the oldest old (>85 years) populations.[5,52] In turn, the time-saving potential of screening may outweigh the risk of incorrectly identifying patients, delivering inappropriate care.[52]

On the basis of our results, G8 performance seems to be outweighed by malnutrition risk in cancer patients between 70 and 80 years. Conversely, SAOP2 tool did not show any correlation with GCA domains.

Few studies have addressed the association between single geriatric domains, with reference to CGA assessment, and oncogeriatric screening performance.[52] Namely, Hamaker et al. has shown that G8 had strong predictive ability for malnutrition, but lower predictive value for geriatric conditions. In addition, VES-13 had a fair predictive value for cognitive disorders, impaired mobility, and malnutrition.[52] The association of screening tools with social support, showed a very low diagnostic accuracy (VES-13 sensitivity 33%; specificity 46%).[52-55]

In our population, SAOP2 was not statistically associated with social domains even an association trend with poorer perceived health status and lack of support was observed. This may be due to the partial diagnostic accuracy of the used Gijon Scale; in turn, the social vulnerability index (SVI),[48] may be the most appropriate tool in elderly cancer patients. However, the lack of any Italian validation hampers

the feasibility of such a tool in intercepting patients' social vulnerability.

Even preliminary in nature, SAOP2 tool seems to better predict clinical vulnerability, especially at the earlier stages of cancer. This is particularly true in ''younger'' patients with two wide prevalent cancer types.

The present study has some limitations. First, non-metastatic colorectal and breast cancer were strongly represented while patients with progression/relapse of the disease were systematically excluded. Thus, stratification of patients with different cancer types and stages is still needed. Moreover, the single centre population may represent a potential bias selection.

Notwithstanding that, the strength of the study lies on the real-world assessment of an oncogeriatric population, with the direct comparison of G8 and SAOP2 screening accuracy. Assessing this aspect would warrant more sophisticated study designs, including the feedback of a GA team, the appropriateness of the referral and the time frame of clinical interventions. In line with that, the prospective nature of the present study will help the understating of outcome measures in terms of service utilization, geriatric referrals, complications, functional independence and survival variables.

Comparing sensitivity and specificity to CGA has the advantage of feasibility in a study. However, it only indirectly addresses the question of how useful the tool is for selecting patients. Therefore, which screening tool could best suit the older cancer populations is a matter of debate. The inclusion of frailty indicators and biological markers may add knowledge to this intriguing field and is part of the observational study.

Eventually, further research is needed to optimize the use of SAOP2 screening tool. On the basis of its multidisciplinary nature and the inclusion of key relevant issues like social vulnerability, health perceived status and quality of life, it has great potential of defining clinical pathways, targeting the quality of life and the quality of care in this outgrowing number of cancer patients.[35]

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ORAL COMMUNICATIONS

- ***Brescia, June 2015, National Meeting of the Italian Polispecialistic Society of Young Surgeons, SPIGC 2015*:** "The collaboration between surgeon and geriatrician can improve the elderly colorectal cancer patient management: a pilot prospective observational study in a III level centre". C Russo, S Sambuceti, A Mazzeo, F Ruggiero, P Odetti, E Romairone, S Scabini.

- ***Genoa, June 2015, National Meeting of the Society of Italian Hospital Surgeons, ACOI 2015:*** "La collaborazione tra il chirurgo e il geriatra può migliorare la gestione del paziente anziano affetto da neoplasia colorettale: studio pilota multidisciplinare prospettico osservazionale in un centro di III livello". C Russo, S Sambuceti, A Mazzeo, F Ruggiero, P Odetti, E Romairone, S Scabini.

- ***Naples, November 2017, National Meeting of the Italian Society of Geriatrics and Gerontology, SIGG 2017*:** "Età, Comprehensive Geriatric Assessment e Rockwood Frailty Index come predittori di complicazioni chirurgiche nel paziente anziano affetto da cancro ".

POSTERS

- ***Oslo, September 2015, International Meeting of the European Geriatric Medicine Society, EUGMS 2015:*** "The relationship between oncological (ECOG PS), geriatric (Comprehensive Geriatric Assessment (CGA), and Rockwood Frailty Index (IF)) evaluation: preliminary results in a cohort of oncogeriatric patients". F Monacelli, C Russo, S Sambuceti, A Mazzeo, R Murialdo, A Nencioni, A Ballestrero, E Romairone, F DeCian, P Odetti.

- ***Prague, November 2015, International Meeting of the International Society of Geriatric Oncology, SIOG 2015:*** "The relationship between oncological (ECOG PS), geriatric (Comprehensive Geriatric Assessment (CGA), and Rockwood Frailty Index (IF)) evaluation: preliminary results in a cohort of oncogeriatric patients". F Monacelli, C Russo, A Mazzeo, S Sambuceti, R Murialdo, A Nencioni, A Ballestrero, E Romairone, S Scabini, F DeCian, P Odetti.

- ***Naples, November 2015, National Meeting of the Italian Society of Geriatrics and Gerontology, SIGG 2015*:** "La correlazione tra valutazione oncologica (ECOG PS), geriatrica (valutazione multidimensionale geriatrica (VMD)) ed indice di fragilità di Rockwood (IF): risultati preliminari di uno studio di coorte di pazienti oncogeriatrici in un centro di III livello". F Monacelli, C Russo, S Sambuceti, A Mazzeo, R Murialdo, A Nencioni, A Ballestrero, E Romairone, S Scabini, F DeCian, P Odetti.

- ***Florence, April 2016, National Meeting of the Italian Society of Psychogeriatrics, AIP 2016:"***La correlazione tra valutazione oncologica (ECOG PS), geriatrica (valutazione multidimensionale geriatrica (VMD)) ed indice di fragilità di Rockwood (IF): risultati preliminari di uno studio di coorte di pazienti oncogeriatrici in un centro di III livello". F Monacelli, C Russo, S Sambuceti, A Mazzeo, R Murialdo, A

Nencioni, A Ballestrero, E Romairone, S Scabini, F DeCian, P Odetti.

- ***Vilamoura Portugal, November 2016, International Meeting of the European Delirium Association, EDA 2016: "***Post operative delirium in a cohort of surgical oncogeriatric patients? Is it still a neglected issue?". F Monacelli, C Russo, M Canepa, T G Casaleto, A Mazzeo, S Sambuceti, R Murialdo, A Nencioni, A Ballestrero, E Romairone, S Scabini, F DeCian, F Boccardo, P Odetti.

- ***Lisbon, October 2016, International Meeting of the European Geriatric Medicine Society, EUGMS 2016:*** *"*A challenge in oncogeriatrics: is Rockwood frailty index an accurate tool to predict clinical outcomes?". F Monacelli,' C Russo, A Mazzeo, S Sambuceti, R Murialdo, A Nencioni, A Ballestrero, E Romairone, S Scabini, F DeCian, P Odetti.

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CHAPTER 5:

ROLE OF GERIATRIC INTERVENTION DURING TREATMENT OF OLDER PATIENTS WITH CANCER: THE PREPARE PHASE III RANDOMIZED STUDY

INTRODUCTION

While the population is aging, improvement of the management of older patients with cancer is becoming a major issue. Much progress has been made and we have validated tools with prognostic value to identify specific problems.[1] Still, this approach is time-consuming so that only a few teams in France can perform it in the daily routine. Finally, management strategy should be optimized.

Thanks to the Institut National du Cancer (INCa), some French teams have been designated as pilot since 2006/2007, the UPCOG (Unité Pilote de Coordination en OncoGériatrie). As a second step, in 2011, the INCa has labelled 15 UCOG (Unité de Coordination en OncoGériatrie) and some others are expected in 2012. These centres have been able to perform a first major step, a prospective trial of 1668 consecutive patients, ONCODAGE, which validated a screening tool, the G8 questionnaire, to detect elderly patients with cancer with an abnormal geriatric assessment.[2,3] It remains now to apply this screening strategy in the daily routine and to demonstrate whether intervention could improve outcome in screened patients.

Many randomized trials have already demonstrated that geriatric intervention was able to improve survival in the general elderly population[4,5] but only a small proportion of included patients had cancer so that no conclusion can be drawn in this specific setting.[6] A few randomized controlled intervention trials have been performed incancer patients. Case management - one-month nurse intervention - has shown survival improvement in firstline elderly patients in a randomized phase III trial which included 375 patients older than 60 but this benefit was restricted to the sub-population of advanced stages.[7] Further trials which tested different kinds of interventions showed benefit in various dimensions: type and use of cancer-specific therapies in 335 patients older than 65 with breast cancer with nurse-case management;[8] gains in function scores, basic lower extremity functions, physical activity, dietary behaviours, overall quality of life with 12-month, home-based tailored program of telephone counselling and mailed materials in 641 overweight long-term cancer survivors older than 65.[9] A few other trials were not restricted to elderly patients but included a significant proportion of old patients and showed: improvement of quality of life, fatigue, happiness, depression, general health, cardiovascular fitness, lean body mass with aerobic exercise in 122 lymphoma patients;[10] improvement of lean mass, muscle strength, walk time and quality of life with a resistance and aerobic exercise program in 57 prostate cancer with mean age of 70;[11] gains in practice of two or more goal behaviours, exercise minutes per week, total fat, saturated fat, BMI in 443 patients with newly diagnosed loco-regional breast or prostate cancer with a 10-month program of tailored mailed print materials.[12] At the end, only one trial showed a survival advantage in advanced cancer patients in a sub-analysis which is not sufficient to consider geriatric intervention as validated in this setting and, although these data plead for the potential validity of these approaches, none is a final demonstration.

Consequently, performance of a randomized phase III trial to test for the validity of intervention in elderly with cancer during treatment is necessary and France, with its UCOG and the experience of the ONCODAGE study, is probably in the best position to perform it.
We think that two strategies can be proposed with equivalent chances to improve prognosis of elderly patients with cancer: nurse-driven case management and geriatrician-driven assessment and intervention. Each of these two approaches is an alternate solution which the oncologists may prefer depending on the local situation and organization of their daily practice. We consequently decided to compare both strategies to standard oncological management.

OBJECTIVE

Primary objective

The primary objective of the study is twofold:
1. To assess the effectiveness of a geriatrician intervention, defined as management by the geriatrician and the oncologist, in the management of elderly cancer patients compared to 'standard care' (treatment according to ongoing standards in Oncology).
2. To assess the effectiveness of a Care manager intervention, defined as management by the coordinating nurse and the oncologist, in the management of elderly cancer patients compared to 'standard care'.
Effectiveness will be evaluated in terms of one-year overall survival (OS).
More specifically:
1. **Arm A, or 'Standard care'**, will involve treatment according to ongoing standards in oncology.
2. **Arm B1, or 'Care manager intervention'**, will involve a Multidimensional Geriatric Assessment (MGA) data collection performed by the nurse, followed by a nurse-driven patient orientation according to the predefined guidelines, to supportive care, and then to the oncologist or the geriatrician.
3. **Arm B2, or 'Geriatrician intervention'**, will involve an assessment of the patient by the geriatrician (with or without comprehensive geriatric assessment as necessary) with interventions as decided by the geriatrician.

Secondary objective

Secondary objectives include the comparison of the effectiveness of the three aforementioned treatment arms in terms of:
· 3-year overall survival;
· 3-year progression-free survival;
· 6-month overall response rate;
· grade 3-4 toxicities over 6-month time period;
· evolution of geriatric assessments at 6 months and one year:
o location (home versus nursing home or hospital);
o dependencies;
o nutritional status;
o mood status;
o physical status;
o number and type of geriatric Interventions.

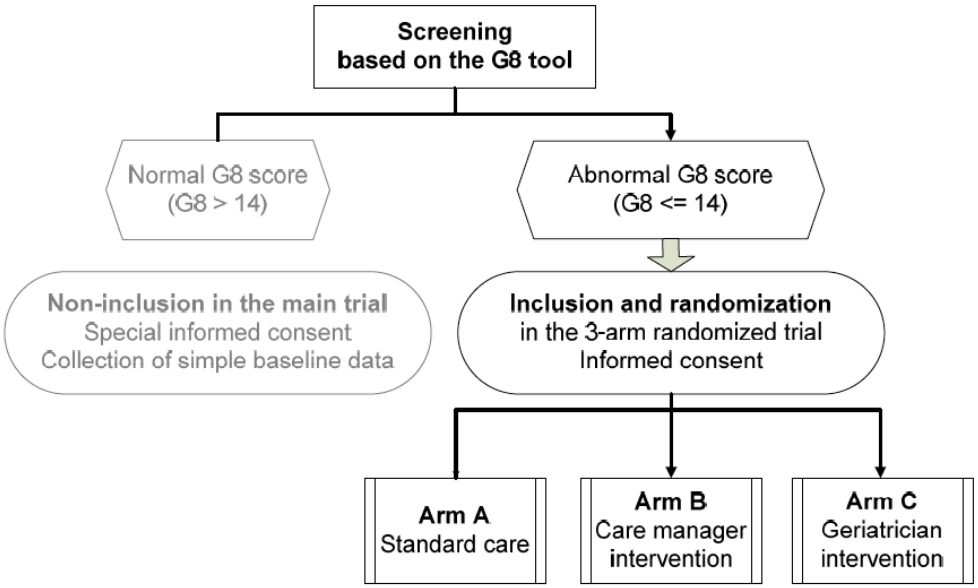
· quality of life;
· applied treatment.

MATERIALS AND METHODS

Study design

Patients will first be screened based on the G8-screening tool.
If the resulting score is normal (G8 > 14), patients will be treated according to standard management. A specific informed consent will be presented to the patients according to the French Law, and a minimal set of data will be collected (age, sex, tumour type, disease stage, PS, creatinine clearance, albumin and CRP levels mainly).
This will allow for the characterization of the population in order to compare our results to those of other published series.
If the resulting score is altered (G8 <= 14), patients will be included in the main study and randomized according to 3 modalities:
· **Arm A, or 'Standard care':** treatment according to ongoing standards in oncology.
· **Arm B1, or 'Care manager intervention':** Multidimensional Geriatric Assessment (MGA) data collection performed by the nurse, followed by a nurse-driven patient orientation according to the predefined guidelines, to supportive care, and then to the oncologist or the geriatrician.
· **Arm B2, or 'Geriatrician intervention':** assessment of the patient by the geriatrician (with or without comprehensive geriatric assessment as necessary) with interventions as decided by the geriatrician.

Fig 1. Study design



Study duration

Once the first step (elaboration of consensus protocols) will be completed for each of the three arms, the trial will be launched. It will be necessary to screen approximately 1150 patients.

· Inclusion period: 1.5 to 2 years.
· Follow-up to reach primary endpoint: 1 year.
· Follow-up to reach secondary endpoints: 3 years.
· Total study duration: 5 years.

Inclusion criteria

· Patients older than 70 years.
· With breast, colorectal, stomach, lung, prostate, bladder, ovarian and sarcoma, lymphoma, myeloma, myelodysplasia.
· Locally advanced or metastatic.
· Performance status 0 to 3 (WHO scale).
· 1st, 2nd line treatment (chemotherapy, targeted therapy, surgery, radiotherapy except hormonal therapy and best supportive care).
· Life expectancy over 6 months.
· Signed informed consent.

Non Inclusion criteria

· Patients younger than 70.
· Performance status 4.
· Patients who already received two lines of treatment.
· Patients for whom hormonal treatment will be proposed.
· Patients for whom best supportive care will be proposed.
· Presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.
· Participation at the same time in another study in which investigational drugs are used.
· Absence of prior written patient informed consent according to ICH/EU GCP, and national/local regulations.

Evaluation Criteria

Primary Endpoint

Overall survival is defined as the time from randomization to death attributable to any cause. Patients who are alive (including lost to follow-up) at the time of the analysis will be censored at the last known alive date.

Secondary Endpoint

Progression-free survival is defined as the time from randomization to progression (as per RECIST 2009) or death of any cause, whichever occurs first. Treatment safety will be assessed using the NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.
The geriatric condition will be evaluated using questionnaires:
o Assessment of comorbidities will be performed using the Cumulative Illness Rating Scale-Geriatric, or CIRS-G.[13]
o Assessement of nutritional status will be performed using the Mini Nutritrional Assessement, or MNA.[14]
o Assessment of functional status will be performed using :
-The Instrumental Activities of Daily Living questionnaire, or IADL;[15]
-The Activities in Daily Living questionnaire, or ADL.[16]
o Assessment of cognitive functions will be performed using the Mini Mental State Examination, or MMSE.[17]
o Assessment of mood disorders will be performed using the Geriatric Depression Scale, or GDS-15.[18]
o Quality of life (QoL) will be assessed using the QLQ-C30 questionnaire developed by the EORTC.[19] This validated and reliable self-report measure consists of 30 questionnaires that assess 5 aspects of patient functioning (physical, emotional, role, cognitive, and social), symptom scales (fatigue, nausea and vomiting, pain; and the global health/quality of life) and single-items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). Scale scores can be obtained for the multi-item scales.
A difference of 10 points on a 100 point scale between two treatment arms will be considered as clinically significant.

Statistical analysis

Patients included in the main study will be randomized according to 3 modalities:
· Arm A, or 'standard care'.
· Arm B1, or 'Care manager intervention'.
· Arm B2, or 'Geriatrician intervention'.
Two formal comparisons will be performed:
· Arm A versus Arm B1 in terms of one-year overall survival.
o Assuming a 90% power and a 2.5 type I error rate, 151 deaths are required to detect a difference between the 2 arms assuming 60% and 75% 1-year overall survival for arms A and B1 respectively (HR = 1.8 / log-rank test / no drop outs).
o It is necessary to include a total of 245 patients per arm to reach the 151 required deaths.
· Arm A versus Arm B2 in terms of one-year overall survival.
o Assuming a 90% power and a 2.5 type I error rate, 151 deaths are required to detect a difference between the 2 arms assuming 60% and 75% 1-year overall survival for arms A and B2 respectively (HR = 1.8 / log-rank test / no drop outs).
o It is necessary to include a total of 245 patients per arm to reach the 151 required deaths.
Thus, it will be necessary to include 245 * 3 = 735 in the randomized trial. Assuming a minimum of 5% lost to follow-up, 771 should be randomized.
It will be necessary to screen approximately 1150 patients to reach the 771 patients necessary for the 3-arm randomized trial.

Endpoint analysis

<u>Primary endpoint</u>
· The primary analysis of 1-year overall survival, will be performed when :
o Arm A versus Arm B1 comparison: approximately 151 events have occurred.
o Arm A versus Arm B2 comparison: approximately 151 events have occurred.
o In terms of one-year overall survival.
· The primary analysis of OS will be based on the ITT population.
· The statistical significance of the difference in OS between arm A and arm B1 and arm A and arm B2, will be evaluated using the Kaplan-Meier product limit estimate and the stratified log-rank test with centre and age as strata.
· Median follow-up will be calculated using the reverse Kaplan-Meier method.
· Median OS, and the OS rate at one year will be calculated using the Kaplan-Meier product limit estimate for each arm, and presented with 2-sided 97.5% confidence intervals, and the KM estimate of OS will be plotted over time.
· Cox regression model will be used to estimate the hazard ratio and its 97.5% confined interval adjusted by the aforementioned stratification factors.

<u>Secondary endpoint</u>
· Efficacy analyses will be performed on the ITT and PP populations.
· The safety analysis will be performed on the safety population.
The following statistical methods will be used depending on the type of the variable:
· Survival endpoints will be analysed using the Kaplan-Meier method. The median survival rates will be reported with a 95% confidence interval. Median follow-up will be calculated using the reverse Kaplan- Meier method. Multivariate analyses can also

be carried out based on Cox's proportional risk method and after checking the risk proportionality hypothesis.

· Quantitative variables will be described using mean and standard errors if the normality assumption is satisfied, else other descriptive statistics (median, range, quartiles) will be used.

· Qualitative variables will be described using frequency, percentage and 95% confidence interval (binomial law).

· With regard to the geriatric scales: Summary statistics of absolute scores of the scales and their changes from baseline will be calculated at each assessment time point for each intervention arm. The mean (and 95% confidence interval) and median (and inter-quartile ranges) of the absolute scores and changes from baseline will be reported.

· The EORTC QLQ-C30 questionnaire will be scores according to the EORTC CLC-C30 scoring manual.

Scales with more than 50% of the constituent items completed, a pro-rated score will be computed, consistent with the scoring manual and validation paper. For subscales with less 50% of the items completed, the subscales will be considered as missing. Summary statistics of absolute scores of the QLQ-C30 scales and their changes from baseline will be calculated at each assessment time point for each intervention arm. The mean (and 95% confidence interval) and median (and inter-quartile ranges) of the absolute scores and changes from baseline will be reported.

RESULTS

Two hundred and twelve eligible cancer patients were evaluated at the Comprehensive Cancer Center Lèon Bèrard, Lyon, France, between March 2017 and December 2018. One hundred and ninety patients did not meet the inclusion criteria (concomitant participation in another study, administration of therapy in a different institution, patient followed by another geriatrician, different therapeutic protocol). Two patients refused to participate to the study. Thus, twenty eligible patients were included in the study: 10 patients in the cohort group, 5 patients in "geriatrician intervention" arm and 5 patients in "standard care" arm. The study is ongoing.

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