Predictive Value of Geriatric Oncology Screening and Geriatric Assessment in Older Patients with Solid Cancers

Protocol for a Danish prospective cohort study (PROGNOSIS-G8)

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Predictive Value of Geriatric Oncology Screening and Geriatric Assessment in Older Patients with Solid Cancers: Protocol for a Danish prospective cohort study (PROGNOSIS-G8)

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ABSTRACT

Introduction: Older patients with cancer constitute a heterogeneous group with varying degrees of frailty; therefore, geriatric assessment with initial geriatric oncology screening is recommended. The Geriatric 8 (G8) and the modified Geriatric 8 (mG8) are promising screening tools with high accuracy and an association with survival. However, evidence is sparse regarding patient-centered outcomes. This protocol describes a study, which aims to address the predictive and prognostic value of the G8 and mG8, with quality of life (QoL) as the primary outcome.

Materials and methods: In this single-center prospective cohort study, patients, age ≥70 years with solid malignancies, will be screened with the G8 and mG8 prior to receiving 1st line antineoplastic treatment. Patients will contribute medical record data including; cancer type, Charlson comorbidity index score, performance status, and treatment intent, type, and dosage, at baseline. Patients will complete QoL questionnaires (EORTC QLQ-C30 and ELD-14) at baseline, 3, 6, 9, and 12-months follow-up. Two functional measurements (the 30-s chair stand test and the handgrip strength test) will be conducted at baseline to assess the added predictive and prognostic value. At 12 months follow-up, initially administered treatment and treatment adherence will be recorded and assessed with generalized linear models, while overall survival and cancer-specific survival will be assessed using survival analysis models with time-varying covariates. The relationship between frailty (G8 ≤ 14, mG8 ≥ 6) and QoL within 12 months will be examined using mixed regression models.

Discussion: Geriatric oncology screening may identify a subgroup of older patients with frailty, at risk of experiencing diminishing QoL and poor treatment adherence. With the proposed screening program, patients who require treatment modification and additional support to maintain their QoL may be identified. It is our hope, that these insights may facilitate the formation of national guidelines for the treatment of older patients with cancer.

Registration: NCT04644874

1. Introduction

Cancer has been the leading cause of death in Denmark since 2000 [1]. Age is the strongest risk factor for developing cancer, and with the increasing longevity of the population, an increased incidence of cancer is anticipated. Today almost half of all patients with cancer are 70 years or older at diagnosis [1]. However, due to underrepresentation in oncological clinical trials, there is less evidence to guide treatment decisions

Abbreviations: G8, Geriatric 8; mG8, modified Geriatric 8; CGA, Comprehensive Geriatric Assessment; QoL, Quality of life; CST, Chair Stand Test; HGST, Handgrip Strength Test; OUH, Odense University Hospital.

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for older adults [2]. A focus on older persons with cancer is, therefore, a highly relevant public health issue.

Older adults with cancer often have a decline in functional reserve of multiple organs and varying degrees of comorbidity, constituting a heterogeneous group with some being fit, some vulnerable, and some frail [3]. Frailty has been shown to affect quality of life (QoL), survival, as well as the ability to tolerate chemotherapy [4–7]. Chronological age does not account for the non-uniformity of the aging process, and therefore a systematic, evidence-based method of describing the heterogeneity is needed to guide oncology treatment decisions [8].

Traditionally, oncologists use performance status to decide, whether a person is fit or unfit for treatment. However, performance status may not capture important deficits associated with an increased risk of treatment-related complications, functional decline, and poorer survival [9]. Furthermore, treatment goals may also differ because older persons with cancer often value maintained QoL and independence, over prolonged survival [10,11].

The American Society for Clinical Oncology (ASCO) and the International Society of Geriatric Oncology (SIOG) recommend the incorporation of geriatric assessment in oncologic care to evaluate the overall health of older persons [8,12]. However, a comprehensive geriatric assessment (CGA) is an intensive, multidisciplinary assessment with interventions and follow-up. This is time and resource-consuming and may not be needed for all older patients with cancer. Therefore, SIOG recommends a two-step approach starting with a screening tool to identify those at risk of geriatric deficiencies, who would potentially benefit from a CGA [13].

The Geriatric 8 (G8) has been described in multiple systematic reviews as a robust and validated screening tool [14–16]. In reference to CGA (the gold standard for assessing frailty), the G8's diagnostic performance shows strong sensitivity and good specificity (85% and 64%) [15]. However, despite being a well-established geriatric oncology screening tool, evidence is limited when concerning the predictive value for patient-centered outcomes, such as changes in QoL. To our knowledge, only a head and neck cancer study has investigated possible associations between QoL and G8 frailty in older patients with cancer. Herein, it was reported, that contrary to fit patients, G8 frail patients did not regain baseline QoL after treatment [17].

G8 prognostic findings are conversely more investigated. Although only 15 out of 24 studies (63%) have found an association between the G8 and survival, associations are more pronounced (85%) when focusing on studies, wherein patients have received varied cancer treatments vs. chemotherapy or surgery alone. Nonetheless, associations between the G8 and treatment-related complications, have only been reported in 43% of studies [15].

The modified G8 (mG8) is a newer and less investigated screening tool developed based on the G8 [18]. However, the mG8 displays promising clinical utility, reporting similar sensitivity and better specificity than the original G8, as well as an association with short and long-term survival [18–20].

Weakness is one of the defining criteria of frailty and can be quantified by measuring muscle strength [21]. Handgrip strength has been shown to predict abnormal CGA in older adults with hematological malignancies [22]. Meanwhile, poor performance on the chair stand test (CST), which tests patients' lower body strength, has been associated with a decline in activities of daily living in older community dwellers [23,24]. In patients with non-small cell lung cancer, preliminary data suggests that adding a handgrip strength test (HGST) to the G8 may give a better prediction of survival [25]. However, these findings have yet to be validated in other cancer types.

Thus, although there is some knowledge about geriatric oncology screening, the evidence is not entirely consistent, and there is a need for further investigation and validation, before implementation in clinical practice. This will be carried out in a large sample of Danish patients with cancer.

As the primary objective, this prospective cohort study aims to determine whether older patients with cancer and frailty (G8 ≤ 14), experience declining QoL (Global health status/ QoL) within 12 months, in comparison to patients without frailty. The secondary objectives are to determine whether frailty, identified with the G8 and mG8 (mG8 ≥ 6), is associated with: 1) declining health-related QoL within 12 months using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire- Core 30 and Elderly cancer patient 14 (EORTC QLQ-C30 and ELD14); 2) decreased cancer-specific and overall survival at 12 months; 3) less often receiving standard 1st line palliative or curative antineoplastic treatment; and 4) poorer adherence to 1st line palliative or curative antineoplastic treatment. An additional secondary objective will determine whether the addition of a functional measure (the handgrip strength test or the 30-s chair stand test) can increase the predictive and prognostic value of the G8 and mG8.

2. Methods: Participation, Assessments, and Outcomes

2.1. Study Setting and Design

This is a single, academic-center, prospective cohort study including older patients with solid malignancies. Patients are referred to the outpatient clinic for an oncologist consultation concerning the initiation of antineoplastic treatment and screened with the G8 and mG8 between June 1, 2020, and November 30, 2021. The Department of Oncology at Odense University Hospital (OUH) performs highly specialized antineoplastic treatments, and therein, receives widespread patient referrals (averaging approx. 6000 patients annually).

2.2. Eligibility Criteria

Inclusion criteria

- Patients age 70 or more with solid malignancies (not hematological malignancies nor non-melanoma skin cancer).

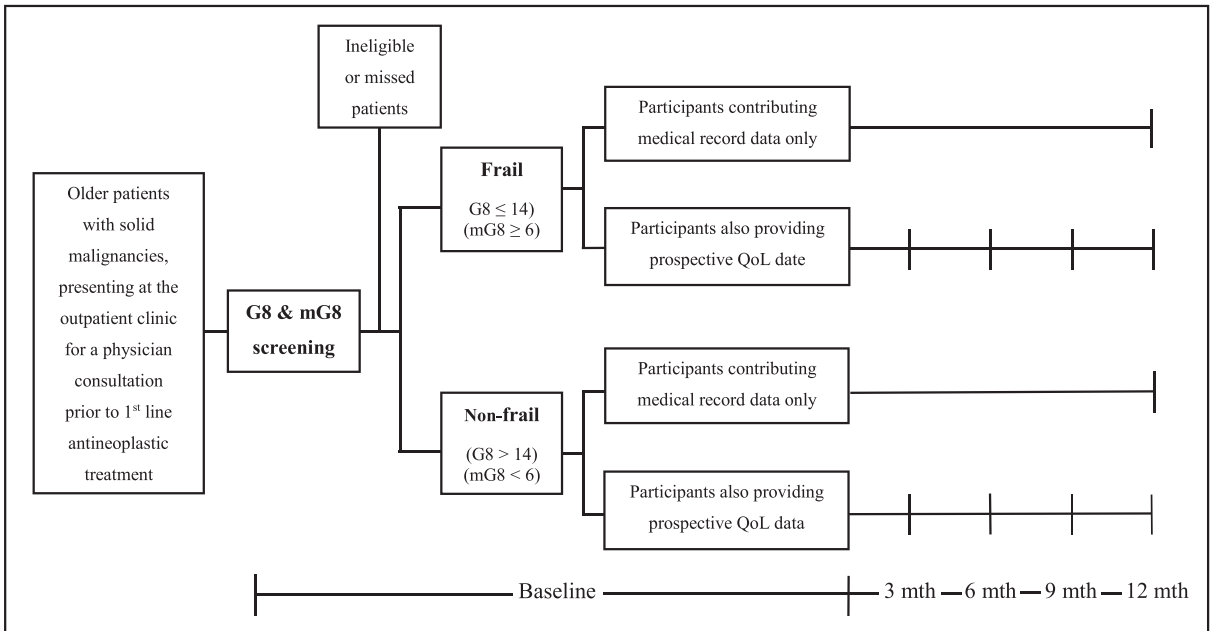
Exclusion criteria

- Patients who are unable to give informed consent.
- Patients who do not speak Danish or English.
- Patients who have received antineoplastic treatment for another cancer diagnosis within the past year.
- Patients who have begun antineoplastic treatment (except endocrine or radiation therapy) for the referred cancer diagnosis more than 48 h prior to the time of consent.
- Patients who have begun radiation therapy for the referred cancer diagnosis more than 7 days prior to the time of consent.

2.3. Recruitment and Consent Procedures

The G8 and mG8 screening will be conducted using non-probability sampling to screen, all eligible older patients with cancer, in accordance with standard departmental procedure to evaluate patient health. One-year medical record data will be obtained from all older patients, seen in the outpatient clinic at the Department of Oncology, Odense University Hospital between June 1, 2020, and November 30, 2021.

Patients will only be approached regarding participation in the prospective QoL and functional measure -part of the study, as approval has been obtained from the Region of Southern Denmark to disclose medical record data to this study and therefore, does not require patient consent. Patients wishing to participate in the prospective aspects of this study will receive written and oral information (in person in conjunction with treatment initiation, and/or via telephone), before providing written consent. Screening scores alongside medical record data will



Measures	Acquisition method	Baseline	3-month follow-up	6-month follow-up	9-month follow-up	12-months follow-up
G8 and mG8 screening	Physician/ nurse administered	√				
Sociodemographic information	Medical records	√				
Cancer diagnosis, stage, and comorbidities	Medical records	√				
Treatment plan administered at initial physician consultation	Medical records	√				
Functional measurements (CST and HGST)*	Study personnel administered	√				
Quality of Life (EORTC QLQ-C30 & QLQ-ELD14)*	Patient self-administered	√	√	√	√	√
Treatment adherence (including dosage reductions, delays, and discontinuations)	Medical records					√
Overall survival and cancer-specific survival	Medical records					√

Fig. 1. Participant timeline and data collection.
Footnote: *Data collected from patients who have given written consented to provide prospective data. Abbreviations: (QoL) quality of life, (mth) months, (CST) chair stand test, (HGST) handgrip strength test, (EORTC) European Organization for Research and Treatment of Cancer (QLQ-C30 and ELD14) Quality of Life Questionnaire- Core 30 and Elderly cancer patient 14.

be obtained from a total of 1250 patients, of which approximately half are expected to provide QoL data and functional measurements (Fig. 1).

2.4. Assessments

2.4.1. Geriatric Oncology Screening Tools

The G8 is an eight-item screening tool, developed for older patients with cancer. In addition to age, the G8 consists of seven items, including appetite changes, weight loss, mobility, neuropsychological problems, body mass index, medication intake, and self-reported health. Overall, the G8 score ranges from 0 (heavily impaired) to 17 (not at all impaired), with a cut-off for potential frailty at ≤14 [12]. The mG8 is a 6-item screening tool consisting of weight loss, neuropsychology, medication intake, self-reported health, performance status, and past heart failure or coronary artery disease. The mG8 score ranges from 0 (not at all impaired) to 35 (heavily impaired), with a cut-off for potential frailty at ≥6 [13]. Both screening tools are easy and quick to administer (median time of 5 min).

2.4.2. Functional Measures

The HGST is a physical test measuring muscle strength in the dominant hand [26]. Patients are instructed to sit with their shoulder adducted, forearm in a neutral position, and asked to squeeze a dynamometer as hard as possible, taking short breaks in between repetitions. HGST is recorded, as the mean of three measurements.

The CST is a physical test assessing lower limb muscle strength and endurance. In the 30 s CST, the patient raises from sitting in a chair to a standing position as many times as possible within 30 s without using their arms for support [23]. The 30 s CST is a validated test, with low test-retest variability [27].

2.5. Primary Outcome

2.5.1. Global Health Status/ QoL

The primary outcome will be assessed at baseline, and at 3, 6, 9, and 12 months follow-up using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire core 30 (EORTC QLQ-C30) [28]. The Global health status/ QoL is a subscale comprised of two questions (questions 29 and 30) concerning overall health and quality of life during the past week. Answers are given using a seven-point Likert scale, and results are represented as a score ranging from 0 to 100. A significant change in Global health status/ QoL is defined as a difference of ≥10 points between scores [29].

2.6. Secondary Outcomes

2.6.1. Health-Related QoL

Health-related QoL will also be described using the EORTC-QLQ-C30 summary score and the functional and symptom subscales of the EORTC-QLQ-ELD14 at baseline and at 3, 6, 9, and 12 months follow-up. The EORTC-QLQ-C30 summary score includes all scales from the QLQ-C-30 except for the Global health status/ QoL and financial difficulties. The functional and symptom subscales of the EORTC-QLQ-ELD14 include all scales, and like the summary score, is represented as a score ranging from 0 to 100.

2.6.2. Receiving Guideline 1st Line Oncologic Treatment

Information regarding initially prescribed 1st line antineoplastic treatment, treatment intent, cancer diagnosis, and stage will be collected from medical records and compared with current guideline treatment recommendations, to determine whether patients have received guideline treatment.

2.6.3. 1st Line Antineoplastic Treatment Adherence

Deviations from the initial antineoplastic treatment plan will be obtained through medical record data at 12- months follow-up. Data will include dosage reductions, dosage delays, and discontinuation of 1st line antineoplastic treatment. Dosage reductions will be represented as the administered dosage, recorded as a percentage of the planned dosage. Dosage delays will be measured in days, excluding delays ≤5 days, to disregard deferrals due to holidays and departmental scheduling. Discontinuations will be measured as the number of given cycles divided by the number of planned cycles, excluding cycles not administered due to progressive disease.

2.6.4. Overall Survival and Cancer-Specific Survival

Survival data will be collected from medical records at 12-months follow-up. Overall survival and cancer-specific survival will be measured from the date of G8 and mG8 screening at physician consultation until the time of death. Death in patients with residual cancer will constitute a cancer-specific death.

2.6.5. The Added Value of Functional Measures

The CST and HGST will be measured at baseline and grouped into abnormal or normal scores. HGST measurements will be obtained using a digital Jamar® dynamometer, with the mean strength, of three repetitions, recorded in kilograms [26]. HGST cut-off values for frailty will be determined based on Danish normative data [30,31]. The CST will be conducted using a chair with a seat height between 42 and 44 cm [32]. CST cut-off values for frailty will be dependent on patients' age and sex [33].

2.7. Patient Characteristics

Baseline characteristics will be collected on age, sex, G8 and mG8 scores, Body Mass Index (BMI), Performance Status (WHO/ECOG), and comorbidity using the Charlson Comorbidity Index based on ICD-10 classifications [34,35].

2.8. Data Management

Meta-data concerning recruitment procedures will be stored in a restricted Sharepoint managing platform. Participant data collected from medical records, clinical measurements, and QoL responses will be stored in a designated REDCap Database, in agreement with the Danish Data Protection Agency's laws.

2.9. Sample Size and Power

2.9.1. Quality of Life

Mean normative data for the Global health status/ QoL, is 60.6, with a standard deviation (SD) of 25, for patients with cancer age 70 years or more. With a power of 80%, a significance level of 5% (alpha = 0.05), and a loss to follow-up of 20%, a total of 240 participants are needed to detect the minimal clinically important difference of 10 [29].

2.9.2. Survival

With a significance level of 5%, a ratio of frail(G8≤ 14) to non-frail (G8 > 14) at 0.51, we estimate the survivor function for the non-frail group to be 0.7 at one year, 0.5 at 1.5 years, and 0.3 at two years [36]. With survival data available for 1250 participants, we expect to have a statistical power of 90% to detect hazard ratios of death ranging from 1.3 to 1.9 comparing frail with non-frail.

Although our primary objective only requires 240 participants, to obtain significant findings on all study objectives, including survival, the sample size of this study will consist of 1250 participants.

2.10. Data Analysis

Statistical analysis will be conducted using STATA. The study population will be described using standard statistical descriptive analysis using baseline data.

2.10.1. Quality of Life Analysis

Quantitative variables will be described as means ± SD or medians (25th–75th percentiles) according to their distribution. To determine between-group differences (frail vs. non-frail) in QoL, and in-group differences between QoL responses will be analyzed via mixed model regression. Potentially confounding variables will be included in mixed model regression analyses (e.g. age, comorbidity, cancer diagnosis, treatment modality) taking individual outcome trajectories, baseline assessments, and drop-out into account.

2.10.2. Treatment and Adherence Analysis

Qualitative variables (receiving guideline treatment vs. not receiving guideline treatment, and treatment adherence vs. non-adherence) will also be analyzed by generalized linear regression models.

2.10.3. Survival Analysis

Overall survival and cancer-specific survival between patients with and without frailty will be assessed using survival analysis models with time-varying covariates.

2.10.4. Functional Measures

To assess the added predictive and prognostic value, baseline CST and HGST scores (normal vs. abnormal scores) will be grouped with G8 and mG8 screening outcomes (frail vs. non-frail). Survival analysis models will be used to assess potential improvements in associations with survival. Between-group differences (i.e. CST/HGST abnormal + G8 frail vs. CST/HGST normal + G8 non-frail vs. mixed findings) in QoL and treatment adherence will be analyzed by mixed model regression and generalized linear regressions models, respectively.

3. Ethics and Dissemination

This cohort was reported to the Danish National Committee on Health Research Ethics, which determined that this study did not require formal ethical approval, as it is purely observational, and does not fall under the Medical Research Involving Human Subjects Act. The study is approved by the Danish Data Protection Agency (20/17768), and the Region of Southern Denmark [21/19375] has approved the disclosure of medical record date for research purposes.

The study will be conducted following the Helsinki Declaration and the International Conference on Harmonization (ICH-GCP), Research Ethics Committee regulations, and applicable government regulations. Participation will be voluntary. Declined participation or withdrawal may take place at any time and will have no resulting consequences. Participants will be covered by the Danish "Complaint and compensation law in health care."

The study has been registered at clinicaltrials.gov [NCT04644874]. Study findings will be presented at national and international conferences, as well as published in peer-reviewed scientific journals in accordance with STROBE guidelines [37], irrespective of the findings.

3.1. Patient Population Involvement

This study was designed in collaboration with older members of OUH's Oncologic Patient Panel and OUH's Geriatric Patient Panel. Panel members were asked about potential treatment situations, and what they would value most. Panel members placed much emphasis on the importance of maintaining QoL, which shifted the primary focus of this study. Furthermore, during our initial pilot study, participant feedback was instrumental in fine-tuning our study setup, particularly in relation to patient recruitment.

4. Discussion

This prospective cohort will to our knowledge, be the first to investigate, whether G8 and mG8 identified frailty is associated with declining QoL in older patients with various site solid malignancies. We will explore associations between G8 and mG8 screening outcomes (frail vs. non-frail) and initial administered antineoplastic treatment (guideline vs. less than guideline treatment), treatment adherence, and survival. Additionally, the added predictive and prognostic value of the 30 s CST and the HGST in geriatric oncology screening will be displayed.

Personnel-administered, geriatric oncology screening is an important step in identifying patients, who require additional care and may otherwise be overlooked. Frailty can be subtle and may remain undetected in self-assessment and clinical judgment by the treating oncologist [38–40]. There is often a poor association between the cancer specialist's clinical judgment and frailty found through geriatric assessment [41]. Furthermore, there is also considerable assessor variability between physicians, in the clinical judgment of frailty in older patients with cancer [40]. This can lead to an increased risk of adverse advents from antineoplastic treatment [7]. Moreover, even when potential frailty is apparent, patients are rarely referred to a CGA in Danish clinical practice [42].

A CGA can help oncologists better understand the overall health status of the patient, and possibly identify previously unknown health issues, which may influence treatment decisions. As geriatric assessment may be unnecessary for the fittest of older patients with cancer, and because this may also be immensely costly for the healthcare system [43], a screening tool is needed to streamline frailty assessment and geriatric referrals.

4.1. Methodological Considerations

This cohort will include screening scores, QoL data, and functional measurements from a substantial population of older patients with various site solid malignancies. Study inclusion was preceded by a two-month pilot study, which helped to optimize procedures for participant recruitment. G8 and mG8 screening will be performed by everyday oncologic personnel, acquainted with both screening tools, and is thus, representative of clinical practice. However, because screening will not be performed at the time of diagnosis, but during the oncologist consultation prior to potential oncologist-administered antineoplastic treatment, patient screening scores may be influenced by preceding surgery or prolonged endocrine treatment. Nonetheless, screening scores represent an accurate account of the health of the individual, on which the basis of treatment type and dosage is determined, and is therein highly relevant for the treating oncologist.

All patients presenting in the outpatient clinic will be screened. Thus, the study population will represent various stages of cancer treatment, such as neoadjuvant, adjuvant, and treatment for metastatic disease and patients may receive curative, palliative, or no treatment. Predictive findings will, therefore, be indicative of a wide range of patients, but the sample size may not be sufficiently large enough to draw conclusions specific to each subgroup. Nevertheless, time of inclusion and planned treatment has not been previously associated with baseline QoL in a study of G8 frail patients [44].

Although we intend to include all patients age 70 years or more, we cannot rule out that selection bias may occur, due to competing clinical trials at the oncology department. Fit patients, receiving curative or palliative treatment, can be offered to take part in such trials, and may not be allowed to participate in our cohort. On the other hand, patients who are too frail to receive treatment may be less likely to be screened with the G8 and mG8.

The G8's well-established, strong diagnostic performance [16,45–47] and successful application in previous departmental research [48,49], made the G8 our primary choice of geriatric oncology screening tool. However, as the G8 is developed based on the Mini Nutritional Assessment, much emphasis is placed on food intake and weight loss. Thus, patients with certain cancers, such as gastrointestinal cancers, tend to be overrepresented with G8 frailty, as these patients often experience weight loss [50]. Contrarily, the modified G8 contains only one question on nutrition, making it also a screening tool of interest [18].

SIOG recently suggested that health-related QoL should be as highly prioritized in geriatric oncology research as traditional outcomes measures [51]. The EORTC-QLQ-C30 is used worldwide to measure QoL and has been extensively validated in various cancer patient populations. Although it can be argued that the QLQ-C30 summary score may be more reliable [52,53], the Global health status/QoL is more commonly used to represent health-related QoL. Moreover, it focuses directly on patients' perceived health and quality of life and was, therefore, selected as this study's primary outcome [17,28].

4.2. Comparison to Other Studies

A large multicenter cohort recently reported that health-related QoL (measured by the Global health status/ QoL) improved at 3 months for the majority (35% of 2972 participants) of G8 frail patients with cancer, whilst declining for 28% [44]. This indicates that oncological treatment may improve short-term QoL for patients with frailty, which should be a highly valued treatment goal. Though, it is unclear if this pertains exclusively to patients with frailty, and whether this improvement may be sustained long-term.

Age, performance status, functional status, pain, fatigue, mental status, and nutritional status are all factors, which have been shown to influence baseline QoL [44,54–59]. As many of these factors are represented in the G8 and mG8, there may likely be an association between these screening tools and baseline QoL. Indeed, the G8 been has shown to predict quality-adjusted survival in head and neck cancer patients [17] however, no association was found in a study of 134 patients with breast and colorectal cancer [60]. To our knowledge, possible associations between QoL and the mG8 have yet to be investigated.

Following SIOG's recommendations, some European countries have begun implementing geriatric oncology screening with subsequent CGA in clinical practice. However, such guidelines have yet to be established in Denmark. Factors contributing to this may include the varying screening methodologies, their ambiguous predictive application in clinical practice, and the unclear effects of CGA when including prior patient selection. It is our hope that the knowledge generated from this study may help illuminate such queries and facilitate the formation of national guidelines.

5. Conclusion

To individualize cancer treatment and improve patient-centered outcomes, it is essential to identify non-frail, older patients, who can receive the recommended standard treatment, and those who are too frail and may require additional support or treatment modifications. We hope that insights obtained from this study may help to formulate guidelines for geriatric oncology screening and geriatric assessment.

Ethical Approval and Consent

Approval waived by the Danish National Committee on Health Research Ethics.

Patient Consent for Publication

Not applicable.

Data Sharing Statement

Not applicable.

Funding Statement

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Authors' Contributions

HMD, AKWG, JR, ME, CML, PP, TLJ, HJD, were involved in the conception and design of the study. ME, HJD, TLJ and HMD wrote the grant applications with input from AKWG, JR, TLJ, CML. HMD wrote the manuscript draft with senior contributions from ME. AKWG, JR, ME, CML, AM, PP, TLJ, HJD reviewed and critiqued the manuscript and approved the final published version.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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