How to optimize cancer treatment in older patients: an overview of available geriatric tools

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Abstract:
Cancer is a disease of older people, but this age group has often been excluded from clinical trials of cancer, which leads to poor transportability of standardized treatments in older cancer patients. One of the main reasons for the exclusion is the heterogeneity of older people in several domains: social environment, comorbidities, dependency, functional status, nutritional status, cognition status and mood status. Comprehensive geriatric assessment (CGA) aims to assess this heterogeneity and has identified frequent health problems often unknown before therapeutic decisions, which allows for targeted geriatric interventions with or without follow-up and appropriate cancer treatment selection. Several tools and scores have been developed for a complementary approach. These tools screen for vulnerability to select patients who may benefit from a CGA; are predictive tools for survival, post-operative complications, or chemotherapy-related toxicity; are decisional algorithms for cancer treatment; or define a core set of geriatric data to be collected in clinical cancer trials. Here, we present an overview of the geriatric tools that were published in PubMed from 2000 to 2017, that could help in the therapeutic decision-making for older cancer patients.

Key Words:
Comprehensive Geriatric Assessment, Clinical Decision-Making, Risk Factors, Clinical Trials, Neoplasms

1. INTRODUCTION

With the ageing of world's population, the incidence of cancer in old people aged 70 years and over has increased markedly [1]. However, older cancer patients have often been excluded from clinical trials of treatment that sets the standards of care in oncology, and the extrapolation of results from younger patients to older cancer patients remains difficult [2]. When considering the heterogeneity of older people, chronological age remains insufficient to assess their health status. Indeed, comorbidities, functional status, nutritional status, mood, cognition and social environment can all interfere with cancer treatment tolerance or compete with cancer as a cause of death.

Ageing is also associated with an increasing risk of frailty. Frailty is defined as an excess vulnerability to stressors, with reduced ability to maintain or regain homeostasis after a destabilizing event. Frailty results from a decrease in physiological functional reserves [3]. It is associated with the risks of disability, institutionalization, unplanned hospitalization, falls, and early death [3]. The support of frailty determinants could reduce or delay the consequences [4].

The assessment of frailty in older cancer patients could help oncologists determine the most appropriate treatment and better assess the benefit/risk balance of performing or omitting specific oncologic interventions. The main goal is to reduce over and under-treatment in old er cancer patients. Consequently, scientific societies and health authorities have recommended the implementation of a comprehensive geriatric assessment (CGA) before the cancer treatment decision [5].

Other tools have been recently developed as a complementary approach in order to help with the therapeutic decision. These are screening tools for vulnerability to select older cancer patients who may benefit from a CGA [6] and prognostic scores of survival, post-operative complications, chemotherapy-related toxicity and decisional algorithms for management in older cancer patients. To date, because of the numerous tools and due to the lack of recommendations, the choice of tools and prognostic scores in the geriatric oncology setting depends on the preferences and habits of clinicians, and the local availability of geriatric expertise.

This narrative review focuses on tools and prognostic scores used in current practice (published on PubMed between 2000 and 2017) to help with the therapeutic decision-making in older cancer patients.

2. CGA IN OLDER CANCER PATIENTS

CGA is a multidimensional and multidisciplinary assessment approach that has been progressively used for older cancer patients in the last decade. CGA aims to detect and treat some unknown issues that commonly occur in older patients and interfere with the natural course of cancer and anticancer treatment [7]. CGA identifies frequent health problems often unknown before the therapeutic decision, which allows for targeted geriatric interventions with or without follow-up and appropriate cancer treatment selection [8]. Usually, CGA assesses the following domains: social environment, functional status (mobility and autonomy), nutritional status, cognitive status, mood status, comorbidities and their related polypharmacy [5,9]. For each domain, many reproducible tools are available; there were first validated in a geriatric population, then studied in older cancer patients [10]. A recent systematic review of prospective observational and interventional studies assessing CGA in older cancer patients and published on PubMed between 2000 and 2014, the authors found that GA revealed the high frequency of impaired geriatric domains: 25% to 75% patients with dependency, 35% to 55% with mobility disorders and/or fall risk, up to 80% with malnutrition, up to 40% with cognitive impairment, up to 65% with mood impairment, up to

80% with more than three comorbidities and up to 40% with inappropriate social environment [11]. Moreover, in a large observational study involving 1967 older cancer patients (median age 76 years) with various sites and stages of cancer, CGA revealed unknown geriatric impairments before the therapeutic decision, that were unknown to the oncologist in 51.2% of patients [12].

Thus, CGA is able to estimate the strengths and weakness of older patients that could interfere with cancer treatment or that could have an independent prognostic value on mortality. CGA may help oncologists select older patients for a standard treatment, those for an adapted treatment, or exclusive supportive cares. Indeed, CGA modifies the therapeutic decision in older cancer patients in 21% to 60% of cases [10–15]. Some studies highlighted domains of CGA that were independently associated with modification of the therapeutic decision in older cancer patients, functional status and nutritional status being the most important [13,14]. In addition, numerous prospective observational and multi-centric studies highlighted the importance of geriatric domains to predict survival in older cancer patients [15]. Indeed, severe comorbidities, malnutrition, dependency in activity of daily living and mobility impairment assessed by the Timed Get Up and Go test (TGUG) were independently associated with the 1-year mortality after a CGA [16]. A slow gait speed, < 0.8 m/s, was also a predictive factor of early death during the 6 months after a CGA, regardless of treatment modalities (i.e., exclusive supportive cares or not) [17].

Furthermore, CGA allows for personalized patient-tailored geriatric interventions in older cancer patients. These geriatric interventions are frequent and various, with mainly nutritional support (70% of cases), social support (46%), psychological support (36%) or cognitive support (21%) [14]. However, few studies have assessed the benefit of geriatric interventions based on CGA results. Nevertheless, it seems that a support and a geriatric monitoring by a nurse may increase the survival in older cancer patients undergoing surgery [18], may result in more appropriate cancer management [19] or may increase the quality of life in older inpatients [20]. Recently, it was highlighted that geriatric interventions based on CGA results were found to increase the completion of chemotherapy and reduce treatment adaptations in older cancer patients [21].

3. SCREENING TOOLS FOR FRAILTY IN OLDER CANCER PATIENTS

Because CGA is time-consuming, and with the limited number of geriatricians trained in oncology, the assessment is not implementable for all older cancer patients and is probably not necessary for the most robust of them. Conversely, the most vulnerable patients remain the target for the implementation of CGA. Thus, the International Society of Geriatric Oncology (SIOG) recommends a two-step approach, starting with screening older cancer patients who need a CGA [6,22]. According to the SIOG guidelines, this screening should be done before a therapeutic decision, should be easy and quick, and should target a high sensitivity and negative predictive value [6]. To date, and because of the lack of consensual definition of vulnerability in geriatric oncology, available screening tools have defined vulnerability by the number of impaired geriatric domains in the CGA. Thus, the definition of vulnerability across studies varies from 1 and 2 impaired geriatric domains [22]. Moreover, the number of geriatric domains used varies widely across studies (3-8), as does the number of tools used in each geriatric domain (4-10). Consequently, the diagnostic performance of screening tools for vulnerability is heterogeneous (Table 1) [22–39][23–40].

A recent update of the SIOG guidelines reported that the most-used screening tools for vulnerability were the Geriatric 8 index (G8 index), the Vulnerable Elders Survey-13 (VES-13) and the Eastern Cooperative Oncology Group Performance Status (ECOG-PS) [6]. The ECOG-PS is the most familiar tool for oncologists to estimate the performance status of their

older patients. However, Repetto L et al [41] showed the lack of accuracy of this tool in 363 older cancer patients (median age 72 years) with solid cancers or hematological malignancies. Indeed, in this study, patients with a good ECOG-PS (i.e., score < 2) had at least two comorbidities, and 9.3% and 37.7% were dependent in activities of daily living (ADL) and in instrumental ADL (IADL), respectively [41]. The G8 index should be preferred according to the SIOG recommendations, the French National Institute of Cancer and the French Society of Geriatric Oncology. Indeed, the G8 index is one of the rare screening tools specifically designed in a population of older patients with cancer [23]. It has been validated in a large independent cohort of 1435 analyzed patients (1674 included) with solid cancer and non-Hodgkin's lymphoma [24]. The G8 index is easy and quick to administer and its diagnostic performance is acceptable, with sensitivity 76.5% (95% confidence interval [CI]: 73.9-78.9) and specificity 64.4% (95% CI: 58.6-70.0) to detect at least one impaired geriatric domain.

Nevertheless, the diagnostic performance of the G8 index to screen for vulnerability varies widely across studies (sensitivity: 65-97%, specificity: 3-100%). The main reason for this variation is probably the heterogeneity of gold standards, the number of tools used in CGA and the heterogeneity of studied populations included in clinical studies [22]. Thus, improvements in the G8 index were proposed in 2016. Results of two French cohort studies of patients ≥ 70 years old with cancer at various sites and stages were published: the modified G8 index and the G8 IADL-modified index [42,43]. These screening tools derived from the G8 index included other parameters of interest in geriatric oncology such as functional status and some comorbidities. Thus, diagnostic performance (sensitivity and specificity) was increased: for the G8 modified index, sensitivity was 89.2% (95% CI: 86.5-91.5) and specificity 79.0% (95% CI: 69.4-86.6) to detect at least one impaired geriatric domain [42]; for the G8 IADL-modified index, sensitivity was 88% (95% CI: 84-91) and specificity 69% (95% CI: 41-89) to detect at least one impaired geriatric domain [43].

Furthermore, diagnostic performance of the G8 index varied across cancer sites: sensitivity and specificity were 90% (95% CI: 82-95%) and 23% (95% CI: 5-54%) for colorectal cancer and 95% (95% CI: 88-99%) and 50% (95% CI: 7-93%) for urological malignancies [22]. These variations in diagnostic performances of the G8 index suggest the need for vulnerability screening tools adapted to cancer site and cancer treatment modality.

4. PROGNOSTIC SCORES AND MORTALITY IN OLDER CANCER PATIENTS

In practice, estimating the patient's overall survival at the time of the treatment decision may be useful but challenging. First, we retrieved numerous scores that have been validated in large epidemiologic cohorts: Carey's score [44] and Walter's score [45] for estimating overall inpatient's survival at 1 year, and Gagne's score [46] and Lee's score [47] for estimating overall outpatient survival at 3 and 4 years, respectively. All these scores consider comorbidities with cancer, nutritional status and dependency as covariates, which are variables of interest in older cancer patients. Indeed, these scores could help in estimating the patient's overall survival with and without cancer. Consequently, they could weigh the effects of ageing and comorbidities on survival at the time of the decision-making process. To our knowledge, no studies have validated these scores in the geriatric oncology setting. Of note, these scores were developed in an epidemiological context and unlike the CGA, probably do not reflect the individual variability in current practice. Second, we retrieved a recent composite score specifically developed for older cancer outpatients for predicting 1-year mortality: the Onco-Multidimensional Prognostic Index (onco-MPI) [48]. This score, based on the CGA before a therapeutic decision, was developed in 658 newly diagnosed outpatients (mean age 77.1 years) with cancer at various sites and various stages, Besides age, cancer site and stage, other variables of interest in geriatric oncology were included: body mass index,

dependency (ADL and IADL scores), ECOG-PS, comorbidities (Cumulative Illness Rating Scale-Geriatric [CIRS-G] score), number of drugs, cognition (Mini Mental State Examination [MMSE] score) and social environment. Use of the Onco-MPI classified patients into three groups at risk of death during the 1-year follow-up: low, medium and high risk. To our knowledge, the Onco-MPI was not externally validated. Table 2 summarizes the prognostic performance of these scales based on area under the receiver operating characteristic curve (AUC) or survival c-index. The choice of score depends on preferences and habits of clinicians and the local availability of geriatric expertise.

5. TOOLS FOCUSING ON RISK OF POST-OPERATIVE COMPLICATIONS IN OLDER CANCER PATIENTS

Surgery remains the cornerstone of treatment for localized cancers [49]. Despite the improvements in surgical management of cancers, post-operative complications are highly prevalent in older patients (35–50%), of which half of complications will be major [47–49][48–50][48–50]. In a large survey of 939 150 US patients (two-thirds aged 65 years and over) hospitalized for a major cancer surgery (gastrointestinal tract, genitourinary tract, breast and prostate), 9.2% experienced at least one geriatric event (dehydration, delirium, pressure ulcers, falls and fractures) during the hospitalization. These complications more often concerned the oldest patients (age ≥ 75 years) with a Charlson's comorbidity score ≥ 2, and with bladder, ovary, colorectal, pancreas or stomach cancer [51].

Accordingly, pre-surgery assessment of older patients is needed to limit post-operative complications. Thus, the SIOG recommends the implementation of a multidimensional pre-operative assessment in cancer patients aged 70 years and older when surgery is indicated, named Preoperative Assessment in Elderly Cancer Patients (PACE). PACE includes numerous tools that are summarized in Table 3 [51–58][52–59]. In a study conducted by a SIOG surgical task force, involving 460 patients with mean age 76.9 years and various cancer sites (breast, gastrointestinal tract, urinary tract), the PACE was used before surgery [50]. Among tools used, the American Society for Anaesthesiologist scale (ASA) ≥ 2 was the only tool predicting post-operative complications, whereas 30-day mortality was associated with post-operative complications, cancer extension, and major surgery. Moreover, in this study, ADL, IADL and ECOG-PS were independently associated with a long hospitalization. To our knowledge, the PACE has not been externally validated, and no score to predict post-operative complications has been specifically developed in older patients undergoing surgery for cancer.

Nevertheless, numerous impaired geriatric domains were found independently associated with post-operative complications in older cancer patients. Indeed, in a recent systematic review, the authors retrieved 17 observational cohort studies conducted between 2004 and 2015 in older patients undergoing surgery for cancer [60]. Functional status including mobility, nutritional status, comorbidities and cognition predicted post-operative complications: overall mortality, disease-specific survival, major Clavien-Dindo score (i.e., ≥ 3 complications during the post-operative 90 days), and discharge to nursing home [60]. More recently, in a study of 263 consecutive older patients (median age 76 years) undergoing elective surgery for solid cancers (breast, thyroid, gastrointestinal, genitourinary), 19.5% of patients experienced a major complication (Clavien-Dindo score ≥ 3) during the post-operative 30 days [61]. In this study, TGUG score > 20 s and ASA scale score ≥ 3 were independently associated with major post-operative complications and a prolonged hospital stay. Impaired geriatric domains were also found specifically associated with post-operative delirium. Indeed, in a recent study of 416 consecutive old patients (median age 80 years) undergoing major carcinologic surgery (gastro-intestinal, hepatobiliary, genitourinary, head and neck), 19% experienced post-

operative delirium according to the confusion assessment method. Charlson's comorbidity score ≥ 3, IADL dependency and history of fall in the last 6 months were independently associated with post-operative delirium (AUC: 0.63) [62]. In another study, for 118 consecutive patients aged 75 years and over and undergoing major abdominal surgery, post-operative delirium occurred in 24%. ASA scale score ≥ 3, TGUG score > 20 s and post-operative tramadol administration were independently associated with post-operative delirium [63].

Furthermore, in one study conducted in Korean people, the authors proposed a 1-year post-operative mortality prognostic index, specifically developed in older patients with and without cancer and undergoing surgery [64]. In this study, a multidimensional frailty score (MFS) based in part on CGA domains was established in 275 consecutive older patients with mean age 75.2 years and before surgery, including 53.8% with malignant disease. The MFS involved nine items: malignant disease, Charlson's comorbidity index; albumin level, Mini Nutritional Assessment score, and mid-arm circumference for nutritional status; ADL and IADL scores for functional status; MMSE score; and nursing delirium screening for cognition [64]. The MFS was independently associated with 1-year post-operative mortality and discharge to a nursing facility but not post-operative complications. In addition, the MFS was a better discriminative score by comparison with the ASA scale regardless of outcome (AUC = 0.82 for 1-year mortality, AUC = 0.72 for post-operative complications and AUC = 0.77 for discharge to a nursing facility). In contrast, the AUC values with the ASA scale were 0.64, 0.57 and 0.59, respectively [64]. Nevertheless, and to our knowledge, this index was not externally validated in older cancer patients and in Western countries.

Post-operative risk depends on the type of surgery, and homogenization of this risk with a single score in older cancer patients remains difficult. Further studies are needed to validate a good prognostic score to predict post-operative complications in older cancer patients.

6. TOOLS FOCUSING ON THE RISK OF CHEMOTHERAPY-RELATED TOXICITY IN OLDER CANCER PATIENTS

Estimating the patient's toxicity risk (≥ grade 3) related to chemotherapy is one of the main issues in older cancer patients scheduled for chemotherapy. Indeed, patients aged 65 years and older more commonly experience chemotherapy-related toxicity than do younger patients [65]. This fact could be explained by the heterogeneity of older patients [66]. Like post-operative risk, chemotherapy-related toxicity was found associated with numerous CGA components in older cancer patients. The geriatric domains poor functional status, comorbidities, polypharmacy, malnutrition, cognitive impairment, depressive mood, inappropriate social environment, and frailty assessed by Fried's criteria were independently associated with chemotherapy-related toxicity in most observational cohort studies conducted in older cancer patients [66].

De facto, CGA remains a cornerstone to assess pre-therapeutic vulnerabilities when chemotherapy is considered. Nevertheless, two prognostic scores were specifically developed to predict chemotherapy-related toxicity in older cancer patients to help oncologists with therapeutic decision-making. The first score, published and validated in 500 older patients (mean age 73 years) with various solid cancers (lung, gastrointestinal, gynecologic, breast and genitourinary) at various stages (I to IV) was the Cancer and Aging Research Group (CARG) toxicity tool (Table 4) [67]. This score was compared with the Karnofsky performance status and showed better discrimination according to the AUC (0.72 vs 0.53, respectively). The second score, the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH), was validated in 518 older patients (mean age 75.5 years) with various solid cancers (lung, breast, colorectal, bladder) at various stages (I to IV), and hematological malignancies (Table

5) [68]. In contrast to the CARG toxicity tool only considering the overall risk of toxicity, the CRASH estimates hematological and non-hematological toxicity risk. In addition, the CRASH takes into account the type of chemotherapy, whereas the CARG toxicity tool considers single versus poly-chemotherapy. To date, no external validation and no comparison of prognostic performance between both scores are available, and the choice of score depends on the preferences and habits of clinicians. Use of the CRASH also depends on the local availability of geriatric expertise since it uses numerous geriatric tools. Whatever the tool used, the adaptation of chemotherapy in older cancer patients is still not consensual and is based on two practical attitudes: secondary adaptation to tolerance of first cycles or immediate dose reduction and then strengthening of chemotherapy dose-adjusted to patient tolerance. Overall, joint monitoring (oncologists and geriatricians) should be implemented for older vulnerable cancer patients scheduled for chemotherapy.

7. DECISION TREES FOR MANAGEMENT FOR OLDER CANCER PATIENTS

Different decision-making trees for management for older cancer patients have been proposed (Table 6). The first algorithm for therapeutic decision-making in geriatric oncology based on the CGA findings was suggested by Balducci L and Belghe C [69]. This algorithm classified older cancer patients as "robust patients" for whom a standard strategy against cancer was proposed, "vulnerable patients" for whom an adapted strategy was proposed, or "frail patients" for whom exclusive supportive care was proposed [69]. Another classification was suggested by Droz et al. and was used in the SIOG guidelines for older men with prostatic cancer (SIOG-1) [70]. This last classification was updated with inclusion of the G8 index (SIOG-2) [71]. These classifications are based on clinical expertise and consensus.

Recently, a new statistical approach based on latent classes analysis (LC) classified patients into homogeneous health groups according to CGA domains [72]. Four phenotypes were identified: relative good health, malnourished, cognitive and/or mood impaired, and globally impaired. More recently, the four classifications (i.e., Balducci, SIOG-1, SIOG-2, and LC) were compared in a study of 763 older patients (mean age 80 ± 5.7 years) with solid cancers and hematological malignancies [73]. All four classifications had good prognostic performance in predicting 1-year mortality and 6-month unplanned hospitalizations. They showed variation in performance across tumor sites, with lower discrimination in colorectal cancer and better discrimination in breast and prostate cancer.

To date, because of lack of sufficient scientific data, consensus is lacking on an algorithm for decision-making about cancer treatments and for stratifying older patients with cancer in clinical trials. One clinical trial compared a standard strategy for chemotherapy allocation based on age and the ECOG-PS to an experimental strategy based on Balducci's classification in older patients with advanced lung cancer. In this clinical trial, the use of an algorithm based on geriatric domains assessed by a pneumologist without geriatric interventions was amenable to reduce chemotherapy-related toxicity but did not affect overall survival [74].

8. GERIATRIC MINI DATASET FOR CLINICAL TRIALS

The collection of a minimum dataset of geriatric data should be encouraged in clinical trials. It may provide a clearer description of characteristics of older patients enrolled in clinical trials, with a better chance to extrapolate the applicability of results to standard practice. Moreover, it may be essential for comparing and merging data from different studies.

The European Organisation for Research and Treatment of Cancer recommended the use of a standardized minimum dataset for assessing the global health and functional status of older populations [75]. This minimum dataset (minDS) consisted of the G8 index, IADL questionnaire, Charlson's Comorbidity Index, and data on social situation. Hurria et al. [76] developed a tool, the geriatric assessment for the Cancer and Leukemia Group B trial (CALGB) based on 75 items, primarily patient self-administered, and with only a small part requiring the assistance of a healthcare provider. The approach and the scientific method used to define the minDS or CALGB were not clearly explained, and the appropriation of the minDS for target users was not studied. By a Delphi consensus method followed by an international survey, Paillaud et al. developed a user-friendly tool (Geriatric COre Data sEt [G-CODE]) that can be used by any cancer health professional for collecting geriatric data in cancer clinical trials at baseline in the curative or palliative setting regardless of tumor type [77].

CONCLUSIONS:

During the last twenty years, CGA has become a reference to help with the therapeutic-decision making in older cancer patients. Several tools were developed in a complementary approach to select patients who may benefit from a CGA, to predict treatment complications and survival, and to promote clinical cancer trials in older cancer patients.

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