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Systematic review

Significance of the comprehensive geriatric assessment in the administration of chemotherapy to older adults with cancer: Recommendations by the Japanese Geriatric Oncology Guideline Committee

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ABSTRACT

Introduction: The number of older patients with cancer is expected to continue to increase owing to the aging population. Recently, the usefulness of geriatric assessment (GA) conducted by multiple staff members from different medical backgrounds has been reported; however, a consensus on the effectiveness of GA has not yet been achieved.

Materials and Methods: We, as the Japanese Geriatric Oncology Guideline Committee for elderly patients with cancer, conducted a literature search of randomized controlled trials published before August 2021 that used GA or comprehensive GA (CGA) as an intervention for patients with cancer undergoing chemotherapy. As the key outcomes for answering the clinical question, we focused on survival benefit, adverse events, and quality of life (QOL). After a systematic review of these studies, the expert panel member developed recommendations according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.

Results: For older patients with cancer, GA or CGA is suggested during or before chemotherapy (weakly recommended). Chemotherapy-induced adverse events were significantly reduced by GA/CGA interventions without any adverse effects on survival. Health-related QOL tended to improve with the GA/CGA interventions.

Discussion: Although, in our opinion, GA/CGA does require time and resources, it poses no harm patients. Therefore, we suggest expanding the human resources and educating skills of medical providers for clinical implementation of GA/CGA.

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1. Introduction

The incidence of cancer among people aged 65 and over worldwide is estimated to be approximately 60% and is expected to increase further owing to the aging population [1]. Japan has the highest percentage of older adults in the world, and older adults develop cancer more often than the younger population; 73% of patients newly diagnosed with cancer and 87% who die of cancer are 65 years old or older [2,3]. Cancer can be considered a chronic malignant disorder in older patients. However, we still seek to develop standardized cancer treatment for older patients, especially for vulnerable patients. Despite this strong demand, advances in cancer treatment for older adults remain limited. This is partly due to the low accrual of older participants in clinical trials, as such patients are often excluded from trials based on the study protocol or physicians' judgement [4]. It is ideal to conduct clinical trials that specifically focus on older populations. Older adults are often excluded from studies because of their multiple inherent conditions, which include age-related organ dysfunction, comorbidities, poor nutritional status, cognitive impairment, and need for psychosocial support [5]. Importantly, it should be noted that there are significant individual differences among older patients [6]. Thus, vulnerable older adults with cancer are likely to be overtreated, while healthy (fit) patients may be undertreated [7,8]. Performance status (PS) scores do not seem to accurately predict the adverse events of chemotherapy in older adults with cancer; therefore, new evaluation methods are needed [9].

Recently, geriatric assessment (GA) and interventions based on GA results undertaken by a multidisciplinary medical team was shown to be useful for clinical practice [10,11]. The American Society of Clinical Oncology (ASCO) guidelines recommend the use of GA to identify vulnerability in patients with cancer aged 65 years and older undergoing chemotherapy [12]. The National Comprehensive Cancer Network (NCCN) guidelines also recommend performing pretreatment assessment using comprehensive geriatric assessment (CGA) for all older patients with cancer [13]. CGA is defined as a multidimensional assessment of physical function, cognitive function, emotions, motivation, social skills, and nutritional status, although other reports also indicate that continuous assessment of these issues is required [14]. In clinical trials involving older patients with cancer and requiring chemotherapy, methods for assessing GA were markedly heterogeneous [15], and the definitions of CGA and GA were ambiguous. Therefore, in this study, we conducted a literature search and systematic review to develop Japanese Geriatric Oncology Guidelines, focusing on the outcomes of older patients with cancer from interventional studies using either GA or CGA.

2. Methods

2.1. Literature search strategy

We independently performed a comprehensive literature search using the PubMed database, supported by the Japan Medical Library Association (Tokyo, Japan), to examine manuscripts published through August 2021. The database search terms used are listed in Table S1. We also reviewed abstracts and presentations from the proceedings of all relevant major conferences, including those held by ASCO, the European Society for Medical Oncology, and the International Society of Geriatric Oncology, published through June 2021.

2.2. Study selection

We focused on trials that used GA- or CGA-based interventions in chemotherapy for older patients with cancer. We included all randomized controlled trials (RCTs) that assessed outcomes, such as efficacy and safety, and classified them according to the outcomes of interest. Study results reported in conference meetings and not in journals were adopted only when they had a significant impact on daily clinical practice in Japan. For the purpose of this study, GA was defined as a functional assessment of older adults using a defined method, and included CGA as well. CGA is a multidimensional assessment of activities of daily living (ADLs), cognitive function, emotions, motivation, social skills, and nutritional status and includes treatment plan and follow-up for detected problems. GA is often referred to as limited screening of the functional assessment of older adults [10].

Two investigators (KN and DI) independently searched the databases and participated in the trial selection process. Study quality was also formally assessed for all included studies by the two investigators and two reviewers (KT and HI), independently. The risk of bias in each trial was evaluated using the Cochrane risk of bias tool for RCTs [16].

2.3. Process of guideline development

The expert panel of the Japanese Geriatric Oncology Guideline Committee consisted of oncologists, medical doctors, surgeons, geriatricians, radiologists, psychiatrists, pharmacists, nurses, and representatives from patient advocacy groups. Their positions are disclosed in Table S2, and their conflicts of interest were strictly controlled according to the regulations of the Japanese Association of Supportive Care in Cancer. Initially, they developed a clinical question (CQ) and collected evidence. Evidence was systematically reviewed by outcomes, and committee members determined the strength of evidence on a four-point scale (A to D), with A being the highest and D being the lowest. Considering this strength of evidence and other factors (i.e., risk-benefit balance and social values), we determined the final recommendation based on input from all committee members. Guidelines were developed in accordance with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [17]. The consensus recommendations were determined based on voting by each committee member with an agreement of 70% or more using the GRADE grid method [18].

2.4. Key outcomes of interest

In this review, we set the CQ: "Should older patients with cancer be evaluated by GA or CGA when they receive anticancer chemotherapy?" As the key outcomes for assessing the CQ, we focused on survival benefit, adverse events, and quality of life (QOL). Other outcomes, such as patient satisfaction and treatment completion rate, were also evaluated and discussed by expert panels to examine the recommendation levels. Due to the difficulty in analyzing cost-effectiveness under the national health insurance system in Japan, the impact of treatment costs was not considered in this guideline.

3. Results

3.1. Characteristics of the identified studies

During our database search, we examined 560 publications and identified 24 relevant RCTs conducted in many countries following abstract or full-text review (Fig. 1). Among them, we mainly evaluated RCTs in which GA or CGA were used as interventions when administering anticancer therapy (mainly chemotherapy), and, finally, twelve trials (fourteen publications) that met the CQ were identified (Table 1). The quality assessments of all included interventional studies are provided in Table S3. The sample sizes of the included trials ranged from 61 to 718, and there was heterogeneity in patient characteristics such as cancer types and conditions among the trials. One notable RCT was excluded from further review because it had a different aim than this CQ, that is, a comparison of treatment failure-free survival between regimens based on CGA and those based only on age and PS [19].

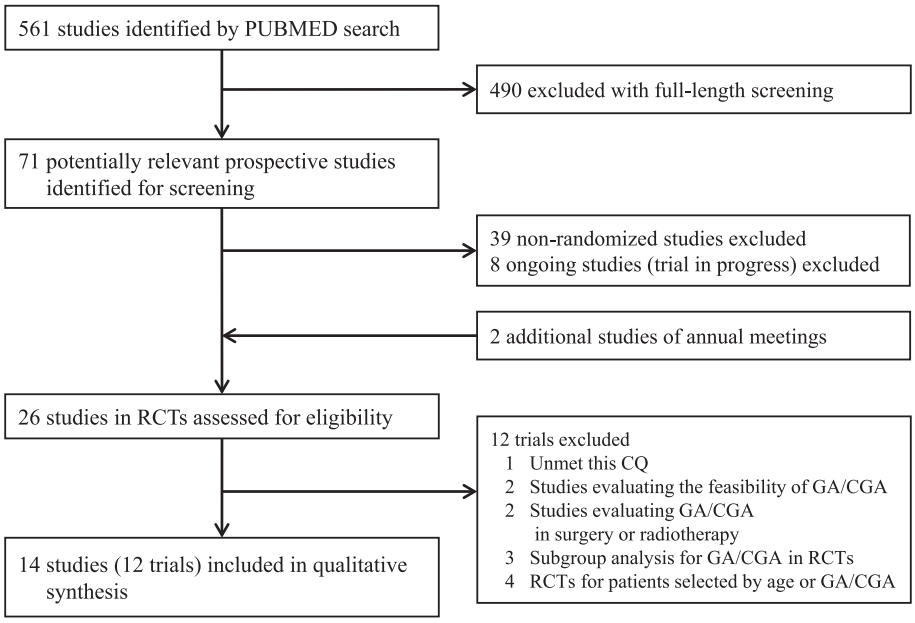

Fig. 1. Flowchart of study selection.
CGA, comprehensive geriatric assessment; CQ, clinical question; GA, geriatric assessment; RCT, randomized controlled trial.

Table 1
Study characteristics.

Study	Design	No.	Eligibility Criteria	Intervention	Comparison
Rao AV et al., 2005 [22]	Randomized 2 × 2 trial (subgroup)	99	Hospitalized, frail patients with cancer, aged ≥65 years, after stabilization	Care in 1) a geriatric inpatient unit a) a geriatric outpatient clinic	Care in 2) a usual inpatient unit b) a usual outpatient clinic
Nadaraja S et al., 2020 [24]	RCT	96	Patients with cancer, aged ≥70 years	Treatment decision based on the G8 screening and MDT	Treatment decision based on the oncologist's clinical judgement
Lund CM et al., 2021 (GERICO) [25]	RCT (Phase 3)	142	Aged ≥70 years with CRC, vulnerable (G8 score ≤ 14 points)	CGA-based interventions	Standard of care
Mohile SG et al., 2021 (GAP70+) [26]	Cluster-randomized trial	718	Aged ≥70 years with incurable solid tumors or lymphoma, at least 1 impaired GA domain	Oncologists received a tailored GA summary and recommendations	GA summary or recommendations were not provided
Li D et al., 2021 (GAIN) [27]	RCT (Phase 3)	600	Aged ≥65 years with a solid malignant neoplasm, completed GA	Geriatrics-trained MDT reviewed GA results and implemented interventions	Standard of care
Magnuson A et al., 2018 [28]	RCT	71	Patients with stage III/IV solid tumor malignancies	GA with management interventions	Usual care
Soo WK et al., 2020 (INTEGERATE) [29]	RCT	154	Aged ≥70 years with solid cancer or DLBCL	Integrated oncogeriatric care	Usual care
Puts M et al., 2021 (5C) [30]	RCT (Phase 3)	351	Aged ≥70 years referred for chemotherapy, ECOG-PS 0 to 2	CGA plus follow-up by geriatric trained team	Usual care
Puts MTE et al., 2018 [31,32]	RCT	61	Aged ≥70 years with stage II-IV gastrointestinal, genitourinary, or breast cancer	GA and integrated care	Usual care
Mohile SG et al., 2020 (COACH) [33,34]	Cluster-randomized trial	541	Aged ≥70 years with an advanced solid tumor or lymphoma, at least 1 impaired GA domain	Oncologists received a tailored GA summary with recommendations	Alerts only for patients meeting criteria for depression or cognitive impairment
Jolly TA et al., 2020 (GARRT) [35]	RCT	138	Aged ≥70 years with malignancy, non-electively hospitalized,	GA report provided to their treating clinicians	GA report not provided
Ørum MA et al., 2021 [36]	RCT	363	Aged ≥70 years with HN, lung cancer, UGI cancer, and CRC.	Tailored follow-up by MDT	No geriatric follow-up

Abbreviations: CGA, comprehensive geriatric assessment; CRC, colorectal cancer; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; GA, geriatric assessment; HN, head and neck cancer; MDT, multidisciplinary team; PS, performance status; RCT, randomized controlled trial; UGI, upper gastrointestinal tract.

3.2. Recommendations

CQ: Should older patients with cancer be evaluated using GA or CGA when they receive anticancer chemotherapy?

Answer: GA or CGA was suggested during or before chemotherapy (weakly recommended).

The following outcomes were shown for the GA/CGA interventions during chemotherapy.

(1) Low impact on survival (strength of evidence: B).
(2) Reduction in adverse events due to chemotherapy (strength of evidence: B).
(3) Tendency to improve or maintain health-related QOL (strength of evidence: C).

3.3. Systematic review for each outcome

3.3.1. Survival (evidence level B)

No trials have been conducted testing GA/CGA interventions with survival outcomes as the primary endpoint. Five RCTs that assessed survival effects were identified as secondary or exploratory outcomes. Older American veteran patients with frailty, defined by the presence of two or more geriatric problems, were assigned to one of four groups (2×2 design): the geriatric ward group or the general ward group for inpatient care and the geriatric outpatient group or the general outpatient group for outpatient follow-up [20].

Rao et al. reported that their subgroup analysis of 99 patients with cancer showed no clear difference in one-year survival rates among the four groups with different geriatric management, although the details of therapeutic interventions were not assessed [21].

Nadaraja et al. reported that 96 patients aged ≥70 years with advanced solid tumors were studied to compare patients who received intervention based on the G8 geriatric health screening results [22] obtained before treatment to those of usual care. In the exploratory analysis, there was no difference in progression-free survival (PFS) or overall survival (OS) (adjusted OS-hazard ratio [HR] 1.24; 95% confidence interval [CI]: 0.68–2.24) [23].

In the GERICO trial, which compared a group of 142 patients with colorectal cancer aged ≥70 years scheduled for chemotherapy who underwent CGA and were provided intervention with the usual care group, there was no difference in disease-free survival (DFS), PFS, or OS (colorectal cancer-related mortality 0.98, 95%CI: 0.56–1.72) [24].

A cluster randomized trial, GAP70+, was conducted to compare the experimental group, in which primary care physicians were informed of the GA results and were given recommended interventions based on the GA results, with the control group of usual care. This study included patients aged ≥70 years with incurable tumors or lymphoma who had at least one geriatric condition. A total of 718 patients were enrolled at 41 sites, and the secondary endpoint of six-month survival was 72% vs. 75% ($P = 0.38$) for patients who received GA interventions vs. usual care, respectively, with no difference between the two groups, nor was there a difference in institution-adjusted OS at one year (adjusted OS-HR 1.05, 95%CI: 0.85–1.29) [25].

The GAIN trial, which conducted a 2:1 randomized comparison between GA-based intervention and usual care in 613 patients with solid tumors aged ≥65 years who were chemotherapy-naïve and evaluated using GA before treatment, showed no difference in OS between the two groups ($P = 0.55$, log-rank test) [26].

Thus, five trials evaluated survival outcomes (Table 2), and GA/CGA interventions did not appear to affect survival outcomes, or at least did not shorten survival outcomes. Two of the five trials were exploratory analyses with fewer than 100 patients and insufficient power, and each trial had some indirect problems, such as bias toward disease and stage.

3.3.2. Adverse events (evidence level B)

Two trials evaluated whether GA/CGA reduced the adverse events associated with chemotherapy as the primary endpoint.

In the GAP70+ trial, the frequency of grade 3 adverse events from chemotherapy was 51% in the GA intervention group and 71% in the control group, and the difference was significant (adjusted relative risk 0.74, 95%CI: 0.64–0.86; $P = 0.0001$). Dose modification of chemotherapy at the start of treatment was more common in the GA group than the control group (48.7% vs. 35.0%, respectively) [25].

The GAIN trial also assessed the frequency of grade 3 or higher adverse events from chemotherapy, which was 50.5% in patients with GA-based intervention and 60.6% in those of the usual care, a significant difference (difference − 10.1%, 95%CI: −1.5–-18.2%, $P = 0.02$). There were no significant differences in the following parameters between the two groups: dose modification or discontinuation of chemotherapy, emergency visits, and unscheduled hospitalization, although chemotherapy dose modifications tended to be more common in the GA group vs. the usual care group (54.2% vs. 46.8%, respectively) but not significantly ($P = 0.08$) [26].

There were three RCTs that presented adverse events as a secondary outcome.

Magnuson et al. reported a small trial comparing GA-based intervention with usual care in patients with stage III/IV solid cancers ($n = 71$), and the frequency of grade 3 or higher adverse events was 57% vs. 61%, respectively, with no statistically significant difference ($P = 0.74$). In this study, patients with both instrumental activities of daily living (IADL) impairment and high Cancer and Aging Research Group toxicity scores were significantly skewed toward the GA-based intervention group, which might have influenced the results [27]. Nadaraja et al. reported that the frequency of grade 3 or higher adverse events tended to be lower in GA-based interventions vs. usual care (20% vs. 38%, respectively, $P = 0.55$) [23]. In the GERICO trial, the frequency of serious adverse events was 28% vs. 39%, with a trend toward fewer serious adverse events in the CGA-based intervention vs usual care, respectively ($P = 0.156$) [24].

Table 2
Summary of survival outcomes.

Study	Endpoint	Results (CGA-based intervention vs control)
Rao AV et al. [22]	OS	There was no effect on mortality. (1-year survival 59.6%)
Nadaraja S et al. [24]	OS	median 19.1 vs 14.2 months, crude HR 0.97, 95%CI: 0.57–1.65, $P = 0.911$, adjusted HR 1.24, 95%CI: 0.68–2.24, $P = 0.484$
Lund CM et al. (GERICO) [25]	OS	HR 1.13, 95%CI: 0.68–1.87
	CRC-related mortality	HR 0.98, 95%CI: 0.56–1.72
Mohile SG et al. (GAP70+) [26]	OS rate at 6 months	72% vs 75%, $P = 0.38$
		adjusted HR 1.13, 95%CI: 0.85–1.50, $P = 0.39$
	OS rate at 1 year	adjusted HR 1.05, 95%CI: 0.85–1.29, $P = 0.68$
Li D et al. (GAIN) [27]	OS rate at 6 months	84% vs 83%
	OS rate at 1 year	66% vs 64%, $P = 0.55$ (log-rank)

Abbreviations: CGA: comprehensive geriatric assessment; CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Table 3
Summary of adverse event outcomes.

Study	Endpoint	Results (CGA-based intervention vs control)
Mohile SG et al. (GAP70+) [25]	Any grade 3–5 toxic effects over 3 months (**primary**)	51% vs 71%, adjusted RR 0.74, 95%CI: 0.64–0.86, $P =$ **0.0001**
	Hematological	adjusted RR 0.85, 95%CI: 0.70–1.04, $P = 0.11$
	Non-hematological	adjusted RR 0.72, 95%CI: 0.52–0.99, $P = 0.045$
Li D et al. (GAIN) [26]	Grade ≥ 3 chemotherapy-related toxic effects (**primary**)	50.5% vs 60.6% 10.1% reduction, 95%CI: 1.5–18.2%, $P =$ **0.02**
	Hematologic only	11.2% vs 19.2%
	Non-hematologic only	18.4% vs 26.6%
	Both	20.9% vs 14.8%
Magnuson et al. [27]	Grade 3–5 chemotherapy toxicity	57% vs 61%, $P = 0.74$
Nadaraja S et al. [24]	Grade 3–5 toxicity	20% vs 38%, $P = 0.55$
Lund CM et al. (GERICO) [25]	Grade 3–5 toxicity	28% vs 39%, $P = 0.156$

Abbreviations: CGA: comprehensive geriatric assessment; CI: confidence interval; RR, relative risk.

In this review, we identified five trials that examined the impact of GA/CGA on the outcome of chemotherapy-induced adverse events (Table 3). Two large trials showed as the primary outcome that interventions using GA/CGA significantly reduced adverse events caused by chemotherapy. However, there are several limitations to this issue, including the lack of clarity on how to intervene in managing the physical, cognitive, psychosocial, or other problems identified by GA/CGA and the detailed dosing of antineoplastic agents. The other three small RCTs also showed a tendency toward reduced adverse events.

In summary, these results are inconsistent with regard to the relationship between GA/CGA ratio and adverse events associated with chemotherapy.

3.3.3. *Quality of life (evidence level C)*

Two trials were conducted to investigate QOL as a primary endpoint in relation to GA/CGA intervention.

The INTEGERATE trial compared GA-based interventions with usual care in 154 patients aged ≥70 years with solid tumors and diffuse large B-cell lymphoma before systemic therapy. The mean health-related QOL (HRQoL) score using the Elderly Functional Index as the primary endpoint was 71.4 vs. 60.3 (difference 11.1, 95%CI: 3.5–18.7) at 12 weeks, 72.0 vs. 58.7 (difference 13.4, 95%CI: 5.5–21.2) at 18 weeks, and 73.1 vs. 64.6 (difference 8,5, 95%CI: 0.5–16.5) at 24 weeks for GA-based intervention vs. usual care, indicating that HRQoL was maintained better with the GA-based intervention than with usual care. Compared to the usual-care group, the intervention group also showed significant improvements in the following QOL domains: functioning, mobility, burden of illness, and future worries. However, global QOL was not improved on the EORTC QLQ-C30, and the score at enrollment (at week 0) was also higher in the intervention group than the usual care group (mean 79.2 vs. 73.4, respectively) [28].

A 5C study was conducted to compare CGA-based interventions and geriatric follow-up with usual care in 351 patients aged ≥70 years with cancer scheduled for chemotherapy. The twelve-month EORTC QLQ-C30 better HRQoL score as the primary endpoint was +0.45 (95%CI: −3.42–4.32) in the intervention group and + 0.71 (95%CI: −3.19–4.61) in the usual care group, with no significant difference [29].

As a secondary or exploratory evaluation, five RCTs assessing QoL with CGA interventions were included. Rao et al. reported that HRQoL scores using the SF-36 at discharge and after twelve months were higher in geriatric units for several endpoints, including improvement of pain [21]. In the GERICO trial, there was no difference in global QOL scores on the EORTC QLQ-C30, although some QOL domains showed improvement [24]. The GAM study compared GA-based interventions with usual care in 61 patients with stage II-IV solid tumors aged ≥70 years who received chemotherapy. The HRQoL score by EORTC QLQ-C30 at three months was −2.08 in the intervention group and − 6.50 in the usual care group [30]. In this study, the median HRQoL index at three months using the EQ-5D-3L questionnaire was 0.82 in the intervention group and 0.78 in the usual care group, and the GA-based intervention tended to maintain better QOL [31].

The COACH trial was a cluster-randomized trial comparing patients aged ≥70 years with advanced solid tumors and malignant lymphomas who had problems with at least one GA item and were randomized to the group that was informed of the GA results and recommended interventions depending on the results or to the group with no such intervention. The study enrolled 541 patients at 31 sites, and the six-month HRQoL score by FACT was not different between the two groups ($P = 0.82$) [32].

In this review, we identified seven trials that assessed QOL outcomes with GA/CGA interventions (Table 4). The two trials assessed differences in changes in HRQoL as the primary endpoint; however, both trials had several limitations and did not show clear improvements in HRQoL by GA/CGA interventions. The other five trials showed that GA/CGA interventions potentially improved or maintained HRQoL with no harm to the patients. QOL appears to be an outcome indicator characterized by a complex combination of various assessment indices. In addition, the assessment tools used were different from those used in the study, making it difficult to analyze and understand the results. In summary, this review suggests that interventions using GA/CGA may play a role in improving or maintaining HRQoL through qualitative evaluation.

Table 4
Summary of the impact on quality of life.

Study	Endpoint	Results (CGA-based intervention vs control)
Soo WK et al. (INTEGERATE) [29]	Health-related QOL (ELFI, **primary**)	71.4 vs 60.3 at 12w (difference 11.1, 95%CI: 3.5–18.7) 72.0 vs 58.7 at 18w (difference 13.4, 95%CI: 5.5–21.2) 73.1 vs 64.6 at 24w (difference 8,5, 95%CI: 0.5–16.5)
Puts M et al. (5C) [30]	Health-related QOL (EORTC QLQ-C30, **primary**)	Not significant difference between the two groups Intervention: +0.45 (95%CI: −3.42–4.32) Control: +0.71 (95%CI: −3.19–4.61)
Rao AV et al. [22]	Health-related QOL (SF-36)	No difference in SF-36 scores between the two groups (Improvement in the item “pain”)
Lund CM et al. (GERICO) [25]	Health-related QOL (EORTC QLQ-C30)	Change 0–6 months (SD) +3.14 (20.23) vs +0.82 (22.56), $P = 0.669$
Puts MTE et al. 31,32	Health-related QOL (EORTC QLQ-C30)	Change in mean QOL from baseline (SD): −2.08 (30.04) vs −6.50 (33.17), $P = 0.66$
	Health-related QOL (EQ-5D-3L)	At 3 months: 0.82 (IQR = 0.29) vs 0.78 (IQR = 0.15)
Mohile SG et al. (COACH) [33]	FACT-G scale (over 6 months)	No significant difference between the two groups difference (SE), −0.23 (1.03); $P = 0.82$

Abbreviations: CGA: comprehensive geriatric assessment; ELFI, Elderly Functional Index; EORTC, European Organization for Research and Treatment of Cancer; EQ-5D-3L, EuroQoL 5 dimensions 3-level; FACT, Functional Assessment of Cancer Therapy; IQR, interquartile range; QLQ, questionnaire core questionnaire; QOL, quality of life; SD, standard deviation; SE, standard error.

3.3.4. *Other interest outcomes*

The COACH trial showed that presenting GA results and recommending interventions to the physician who took care of the patients led to an increased chance of communicating with the patients and caregivers about aging-related concerns. The patients experienced significantly better satisfaction [32]. In addition, this study also showed a 2.4-fold increase in the rate of realizing comorbidity concerns by GA-based intervention [33]. In contrast, the GARRT trial enrolled 138 patients with malignancies aged ≥70 years who required unplanned hospitalization and received inpatient care. The admitted patients were divided into two groups. One group was given GA results, while the other group was not. The referral of the former group to the appropriate department to cope with geriatric problems was expected to increase compared with the latter group. However, the referral rate in each group was 9% for patients with GA results vs. 6% for those without ($P = 0.53$) [34].

RCTs have also been conducted to evaluate CGA interventions to improve chemotherapy treatment completion rates. Ørum et al. compared close follow-up by geriatricians with usual care in 363 patients with solid tumors aged ≥70 years, for whom CGA-based chemotherapy was planned. In this study, the treatment completion rate within 90 days was evaluated as the primary endpoint. The intervention group had close follow-up by the geriatricians with a tendency toward higher completion rates up to 61%, compared to 52% in the usual care group, but no significant difference was noted (risk rate 1.16, 95% CI:0.95–1.42, $P = 0.14$) [35]. Nadaraja et al. reported that CGA-based interventions did not improve the treatment completion rate (48% vs. 54% for CGA vs. usual care, respectively) [23].

3.4. Expert panel meeting

Based on these results, an expert panel meeting was held. No consensus was reached in the first round of voting for implementing GA/CGA in patients with cancer who were scheduled to receive chemotherapy. More than half of the members stated that GA/CGA should be strongly recommended because it would help improve the quality of medical care and cancer care, while others pointed out that there were some issues, such as the lack of clear information on supportive care and dose modification of chemotherapy resulting from GA/CGA results. Some members were also concerned about the insufficient evidence regarding the effectiveness of GA/CGA in improving QOL or ADL/IADL, because no studies have clearly demonstrated this as a primary endpoint in RCTs, although the INTEGERATE trial suggested the improvement of several QOL domains [28]. In the second round of voting, the above critical discussion resulted in a consensus opinion, with >70% of the participants agreeing with the suggestion to conduct GA/CGA before the start of chemotherapy. The vote by the expert panel for this CQ is presented in Table S4.

4. Discussion

Several prospective observational studies previously showed that GA can identify older patients at high risk of toxicity and mortality from chemotherapy [36–38]. However, these were not sufficient to recommend the application of GA/CGA in clinical practice. Recently, several systematic reviews have shown that GA/CGA interventions reduce chemotherapy-associated adverse events [15,39]. In this systematic review, we finely summarized several RCTs in which GA or CGA was used as an intervention for supportive care, primarily during chemotherapy. In several trials, GA/CGA interventions reduced chemotherapy-related adverse events without adverse effect on survival. Reduction of adverse events might be caused not only by a lower dose intensity of chemotherapy [25], but also by the intensification of supportive care [26]. This review comprehensively evaluated the multiple outcomes demonstrated by GA/CGA interventions through a panel of experts across a variety of professions, again demonstrating the high clinical significance of GA/CGA. This guideline is novel compared to others in that a formal bias risk assessment was conducted for all trials and the results were agreed upon through multiple panel experts. In Japan, the implementation of GA/CGA is not yet fully widespread in the field of medical care for older adults with cancer. Therefore, we suggest expanding the human resources and education of medical providers for the clinical implementation of GA/CGA.

The evidence reviewed in this guideline had several limitations. First, there were large variations in the type of cancer and treatment in each trial, which may have affected the results. The non-directiveness of each trial is summarized in Table S3 as the Risk of Bias; in particular, the study by Rao et al. did not focus on chemotherapy and was rated as poor. Second, the cost of GA/CGA implementation and burden on healthcare providers were not considered. Although some GA tools can be used even in busy oncology clinics [10,40], there is still an urgent need to develop tools that are easy to implement. Above all, it is important to build a multidisciplinary team that can adequately address the challenges of GA/CGA in older patients with cancer. Third, the contamination bias would need to be considered in each trial conducted with GA/CGA as an intervention. Most trials did not assess the treatment administered to older patients in the non-intervention group, which may have conversely weakened the impact of the intervention. Finally, this review only included RCTs published before August 2021, and results from more recent RCTs may lead to different interpretations.

The recommendations derived from this systematic review must have an impact on cancer care in older adults. However, it should be widely implemented in clinical practice, and real-world data needs to be collected and analyzed to validate the usefulness of GA/CGA. This process can only improve cancer and medical care for older patients with cancer.

Author Contributions

KN and DI independently performed and interpreted the comprehensive literature search; KT reviewed the contents of that literature search. All authors participated in the expert meeting, and review committee members (except KT, CKI and TS) voted on the decision of the recommendations. All authors read and approved the final manuscript.

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Declaration of Competing Interest

The authors whose names are listed immediately below report the following details of affiliation or involvement in an organization or entity with financial or non-financial interest in the subject matter or materials discussed in this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2023.101485.

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