The Prognostic Value of Comprehensive Geriatric Assessment on the Management of Older Patients With Small Cell Lung Cancer

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Research Article

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Abstract

Background The prognostic value of a comprehensive geriatric assessment (CGA) for the management of older cancer patients remains to be established. This study investigated the association of each CGA variable with overall survival (OS) in older small cell lung cancer (SCLC) patients.

Methods A retrospective cohort enrolled 21 older SCLC patients over 65 years from March 2018 to 2019 at the Yonsei Cancer Center. The CGA was performed before treatment and included the following instruments: Frailty, a circumference of arm/calf, body mass index (BMI), sarcopenia (e.g., Timed Up and Go test [TUG], grip strength), comorbidity, polypharmacy, function, nutrition, depression, and cognitive function. The correlations of oncological and geriatric variables with OS were determined. The log-rank test and a Cox model were used for the analysis. Prognostic factors of OS were examined by using the Kaplan-Meier method.

Results The median age was 75 years (range 67-85). All patients had the Eastern Cooperative Oncology Group performance status (ECOG PS) 0-2. The median survival was 9.93 months (1.53-36.30). Among CGA parameters, activities of daily living (ADL) and nutritional status had significant differences in OS in univariate analysis. In multivariate analysis, only nutritional status was independently associated with survival (HR 0.17 [95% CI 0.05-0.57]). Median OS for low nutritional status was 5.63 months and the normal nutrition group was 15.5 months ($p = .004$).

Conclusions Geriatric assessment detects more information than routine oncological evaluation alone, such as ECOG PS. Pre-treatment nutritional status measured by CGA appears to be a predictor of OS in older SCLC patients. A prospective study with larger sample size is desirable in the future.

Background

As life expectancy increases, the number of older cancer patients is also expected to gradually increase. Lung cancer, in particular, is the leading cause of cancer-related deaths in the older population. Small cell lung cancer (SCLC) is a neuroendocrine tumor, accounting for approximately 15% of all lung cancers[1]. Unlike the recent development of a various treatment that immunotherapy or target therapy for non-small cell lung cancer (NSCLC), it is true that there is no significant change in treatment for SCLC. Moreover, the median age at diagnosis of SCLC is over 65 years old, which is a cancer that mainly occurs in smokers and older populations. Although chemotherapy and radiation therapy for SCLC is very burdensome for older patients, older patients with SCLC are underestimated when making treatment decisions in the clinical setting. Specialized assessment of overall health status and full support and management for the older SCLC patients is very important. This is a different concept from palliative care and requires an independent approach by geriatric professionals.

Older cancer patients are a very heterogeneous group of patients in terms of geriatric syndromes including decreased physiological reserves, comorbidities, cognitive impairment, and disability. Older age negatively affects treatment tolerance, which in turn affects the prognosis. Therefore, a comprehensive

approach to older cancer patients is essential. Several studies have investigated the effects of comprehensive geriatric assessment (CGA) on overall survival (OS), in-hospital mortality, hospitalization, adverse events, quality of life, and treatment allocation, suggesting that the CGA more accurately determine the health status of older cancer patients compared to the Eastern Cooperative Oncology Group performance status (ECOG PS) which is commonly used function measuring score in the current clinical setting[2, 3]. In other words, successful treatment of older cancer patients requires overall management of physical, cognitive, emotional, nutritional status, and medication history. For this reason, a formal geriatric assessment has been developed for older adults[4–6]. However, studies specifically examining the relationship between CGA and OS in older SCLC patients are lacking. Therefore, this study aimed to estimate the prognostic role of various CGA domains on OS in older patients with SCLC. This will enable appropriate predictions and interventions to determine whether to treat chemotherapy and manage it during chemotherapy in older SCLC patients.

Methods

Patients

This retrospective cohort study enrolled 291 patients aged over 65 years diagnosed with cancer at Yonsei Cancer Center between March 2018 and March 2019. Patients who were not available to receive CGA or aged under 65 years were excluded. Of these, 21 patients were diagnosed with SCLC and completed CGA before treatment. Their survival was followed until August 2021. Apart from the CGA, ECOG PS was also measured. We aim to analyze the CGA domain associated with OS in older SCLC patients. Informed consent was waived by the Institutional Review Board of Yonsei University's Health System in the ethics approval and consent to participate for this study as all the data was obtained from medical records (IRB number: 4-2021-1348).

Statistical analysis

The Cox regression test was used for univariate and multivariate analyses using the Cox proportional hazards model to evaluate the prognostic value of CGA domains. The log-rank test was used to evaluate survival differences between the groups according to CGA scores. Cumulative survival rates were calculated by the Kaplan-Meier method. Confidence intervals at the 95 % level [95% CI] were calculated, and statistical significance was considered with P-values less than 0.05. All analyses were performed using SPSS for Windows, version 25 (SPSS Inc, Chicago, IL).

Comprehensive geriatric assessment

All participants underwent the CGA by trained geriatric nurses before the starting of chemotherapy. The CGA consisted of the following domains: basic items, physical activity, functional status, frailty, nutritional status, cognition, and depression. Basic items consisted of medical history including comorbidity, medications being taken, Timed Up and Go test (TUG test), grip strength, and lifestyle habits such as smoking. Comorbidity was evaluated by Charlson's comorbidity index (CCI)[4], summing up the

data regarding myocardial infarction, congestive heart failure, peripheral vascular disease, cerebral vascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, diabetes, and so on. Since we only enrolled the SCLC patients, all patients scored 6 points in CCI, and 9 points were set as cut-offs for analysis[4]. The number of medications was analyzed by dividing 5 drugs as a cut-off value[7]. The clinical significance of sarcopenia is increasingly recognized as a component of cancer cachexia syndrome, and with this increasing awareness, a recent international consensus has established sarcopenia as the major diagnostic criterion for cancer cachexia[8]. Therefore, we included circumference of arm and calf[9], TUG test, and grip strength in the CGA parameters to evaluate sarcopenia. Circumference of arm and calf means the amount of muscle mass. Since muscle mass itself may not indicate reliable muscle function, we further measured the TUG test and grip strength. In the TUGtest, the patient was observed and timed while standing up from the chair, walking three meters, turns walking back, and sitting down again[10]. Patients who were able to complete the task in less than 12.6 seconds were considered to have good mobility. The cut-off value of hand grip strength was based on the consensus of the Asian Working Group for Sarcopenia (AWGS): 26.0 kg for male and 18.0 kg for female patients, respectively[11]. Additionally, body mass index (BMI) was also measured. Level of Frailty was assessed by the FRAIL scale, which was translated into Korean from Morley et al.'s FRAIL scale[12]. This self-reported five-item tool includes fatigue (F), resistance (R), ambulation (A), illnesses (I), and loss of weight (L). The total score (0-5) can be categorized into three: robust (0), pre-frail (1-2), frail (3-5). Functional statuswas evaluated by assessing Activities of Daily Living (ADL)[13] and Korean Instrumental Activities of Daily Living (IADL)[14]. Six items of ADL included dressing, eating, walking on a corridor, toilet use, bathing, fecal and urinary continence. Older adults with at least one dependency in ADL category were considered as ADL dependent. IADL included eight items which were shopping, housekeeping, ability to handle finances, ability to prepare food, traveling via car or public transportation, doing laundry, ability to use the telephone, and medication use. Older adults with at least one dependency in IADL category were assessed as IADL dependent. Nutritional status was assessed by the short version of the Mini Nutritional Assessment (MNA)[15]. It consists of 6 questions: decreased food intake, weight change, exercise capacity, medical history, cognitive impairment, and BMI. The MNA score (range 0-14) of over 12 was evaluated as normal nutritional status, a score of 8-11 as a risk of malnutrition, and a score of 0-7 as a stage of malnutrition. Cognitive function was assessed using the Korean version of the Mini-Mental Status Examination for Dementia Screening (MMSE-DS). This 30-item tool indicated decrease in cognitive capacity with lower score[16]. A score below 17 denotes impairment, a score from 17 to 24 denotes mild impairment, and a score of 25 or more denotes normal in cognitive capacity[17]. The Korean version Short Form of the Geriatric Depression Scale (GDSSF-K) was used to assess depression. This 15-item tool (range 0-15) indicated the risk of depression when the score is more than five points[18].

Results

Patients Characteristics

Of the 21 older SCLC patients, 20 were males, and 1 was female (Table 1). The median age of the patients was 75 years old (range, 67-85). Nineteen patients were initially at the extensive stage; 2 patients were at the limited stage. Of the 21 patients, 20 (95.24%) patients had ECOG PS 0 or 1. Treatment of SCLC was classified as combined chemoradiation (sequential or concurrent), chemotherapy alone, and best supportive care. The recommended chemotherapy for SCLC in this study was carboplatin-etoposide. Nine patients underwent combined chemoradiation therapy including radiation to the lung, and only one of them received radiation to the metastatic lesion of the pelvic bone. Nine patients received chemotherapy alone, one patient was not treated due to spondylitis and the other patient was due to a urinary tract infection. Only one patient received prophylactic cranial irradiation (PCI). Six patients with brain metastases underwent the whole brain radiation therapy, and 15 patients were without brain metastases. The median OS was 9.3 months (1.53-36.30 months) (Table 1).

Table 1
Characteristics of Patients

		N	%
Age at CGA	Median, year (Range)	75 (67-85)	
Gender	Male	20	
	Female	1	
Treatment	Combined chemoradiation (sequential or concurrent)	9	42.86%
	Chemotherapy alone	9	42.86%
	Best supportive care	2	9.52%
	Follow up loss	1	4.76%
ECOG PS	0	12	57.14%
	1	8	38.10%
	2	1	4.76%
Stage	Extensive	19	90.48%
	Limited	2	9.52%
PCI	Done	1	
Brain metastases	Yes*	6	28.57%
	No	15	71.43%
OS	Median, month (Range)	9.33 (1.53-36.30)	

*All patients with brain metastases received whole brain radiation therapy.

N, Number of included patients; *ECOG PS*, the Eastern Cooperative Oncology Group performance status; *PCI*, prophylactic cranial irradiation; *OS*, Overall survival

Baseline Cga Results

Results regarding the relationship between the CGA domains and OS are summarized in Table 2. In univariate analysis, the level of frailty did not affect OS. The median arm circumference of the patients was 24 cm and the median calf circumference was 30.5 cm, which also did not affect OS. Seven patients with BMI over 25 kg/m^2 were defined as obese, 6 patients with BMI over 23 kg/m^2 were overweight, and 8 patients with BMI less than 23 kg/m^2. Differences by BMI were also insignificant. There were 8 patients with normal TUG, 5 patients with prolonged TUG, and 8 patients who did not perform the test. TUG also did not affect OS. A minimum score of 6 points on CCI was the baseline score for patients diagnosed with SCLC, and 10 patients with a total score of over 9 points, including other chronic diseases, did not

affect OS. Ten patients were taking more than 5 drugs, and this also did not affect OS. There were 6 patients with current smokers, 14 patients with ex-smokers, and 1 patient with never-smoker. Smoking history did not affect OS. Eleven patients with a depression-related GDS score of over 5 and 11 patients with IADL dependency were measured, but none of them significantly affected OS. The MMSE defined cognitive impairment based on a score of less than 24, with only 1 patient scoring less than 24 and all other patients being normal. Therefore, MMSE did not affect survival. Finally, in univariate analysis, ADL and nutritional status significantly affected the survival of SCLC patients ($p = 0.017$, $p = 0.025$, respectively). There were 7 patients with ADL dependency, 11 patients with normal nutritional status with an MNA score of over 12, 8 patients with 8-11 points, and 2 patients with 0-7 points. It showed that the better the nutritional status, the longer the survival. In multivariate analysis, adjusted for sex and age, only nutritional status had a significant effect on OS. Those with an MNA score of over 12 had significantly longer survival than those with an MNA score of less than 12 (median survival 5.63 vs 15.50, $p = 0.004$, HR 0.17 [95% CI 0.05-0.57]) **(Figure 1).**

Table 2
Domains explored by comprehensive geriatric assessment

			Univariate analysis			Multivariate analysis		
			p value	Exp(B)	95% CI	p value	Exp(B)	95% CI
Frail	0-2	14	*0.437*	1.51	0.54-4.24			
	3-5	7						
Circumference of arm (cm)	median	24	*0.400*	0.91	0.74-1.13			
	range	21-28.5						
Circumference of calf (cm)	median	30.5	*0.909*	0.99	0.84-1.17			
	range	26.5-38.8						
BMI	< 23 kg/m^2	8	*0.146*	0.85	0.68-1.06			
	≥ 23 kg/m^2	6						
	≥ 25 kg/m^2	7						
TUG (Second)	normal	8	*0.507*	0.66	0.20-2.24			
	Higher (≥12.6s)	5						
	not done	8						
Grip strength (kg)	normal	13	*0.694*	0.82	0.29-2.26			
	low(<26kg in men; <18kg in women)	8						
CCI	< 9	11	*0.456*	1.46	0.54-3.93			
	≥ 9	10						
Drug	≥ 5	11	*0.875*	1.08	0.40-2.93			
	< 5	10						

			Univariate analysis			Multivariate analysis		
Smoking	never-smoker	1						
	ex-smoker	14	*0.273*	0.30	0.04-2.59			
	current-smoker	6	*0.545*	0.50	0.06-4.65			
MNA	≥12	11	*0.025*	0.30	0.11-0.86	*0.004*	0.17	0.05-0.57
	8-11	8						
	0-7	2						
GDS	≥ 5	11	*0.619*	0.76	0.26-2.21			
	< 5	9						
	Unknown	1						
ADL	Impaired	7	*0.017*	3.78	1.27-11.22			
IADL	Impaired	11	*0.458*	1.46	0.54-3.94			
MMSE	< 24	1	*0.100*	0.13	0.01-1.48			
	≥ 24	16						
	unknown	4						

BMI, Body Mass Index; *TUG*, Timed Up and Go test; *CCI*, Charlson Comorbidity Index; *MNA*, Mini Nutritional Assessment; *GDS*, Geriatric Depression Scale; *ADL*, activities of Daily Living; *IADL*, Instrumental Activities of Daily Living; *MMSE*, Mini-Mental State Exam

Discussion

CGA has important prognostic information. This can be helpful to predict survival and life expectancy in older people, which is crucial for oncologists to know when to make treatment decisions. CGA in older cancer patients indicates previously unknown geriatric problems in many patients (up to 50%) and may alter treatment decisions in 10-20% of patients[19]. Among the domains of CGA, limitations in cognition, nutrition, function, and comorbidities have been shown to be important factors in diminishing OS in older cancer patients in several studies[20–22]. It has also been shown that specialized geriatric intervention for older cancer patients significantly improved OS and facilitated a return to their own home compared to conventional care. We recommend some form of geriatric assessment, such as CGA, in all older cancer patients for whom to make important treatment decisions, and our study began on this basis.

We analyzed retrospectively enrolled data to investigate the prognostic significance of the CGA domain and identified that low MNA scores and impaired ADL were significant indicators of poor OS in patients with SCLC. In multivariate analysis, only malnutrition, independent of PS, was associated with poor OS. Our results are consistent with previous studies examining CGA parameters associated with changes in cancer treatment. In cancer treatment, malnutrition is known as a practical parameter to consider, as it is associated with therapeutic toxicity and mortality[23]. In several studies, a low BMI of less than 21 kg/m^2 was related to a modification of the cancer treatment regimen[24]. According to another study, malnutrition as assessed by MNA, BMI, weight loss, and low serum albumin was also related to changes in cancer treatment, mostly a decrease in treatment intensity[25]. In comparative studies of biochemical markers, anthropometric measures, and the MNA, the MNA was found to be strongly correlated with baseline weight loss in cancer patients and was recommended as a nutritional assessment tool. This suggests that early intervention and treatment of malnutrition in older cancer patients might be particularly important for improving OS. Malnutrition screening in older cancer patients enables preventive actions early stage of malnutrition in their cancer treatment[26]. Nutritional supplementation may be beneficial for older patients. A meta-analysis of 55 clinical trials showed the benefit of oral supplementations on OS in older patients. They reported that malnourished older patients benefit from oral supplementations when taking oral supplementation compared to patients not taking it (OR 0.66 [95% CI 0.49-0.90]) with reduced mortality[27]. In line with our findings, it appears that malnourished older cancer patients might also be able to improve their OS with oral supplementation, which requires further research.

A recent meta-analysis study has been reported that sarcopenia affects the survival rate of lung cancer patients[28], but our study did not show a significant difference. While most of these studies performed survival analysis by measuring muscle size via Computer Tomography (CT), our study analyzed survival by assessing muscle function (i.e., TUG and grip strength). There are some studies on the effect of muscle function assessment on survival, but it is still insufficient[29]. In addition to sarcopenia, there are studies on the effects of ADL and IADL assessment on survival, but data are still lacking. In our study, the ADL dependency was found to affect survival in a univariate analysis. In other words, CGA has the potential to be a useful evaluation tool to predict the prognosis for older cancer patients in various aspects.

However, it is not easy to apply CGA to clinical practice. Implementation of CGA in various clinical environments can pose significant challenges due to the lack of specific information about CGA tools. For example, what is the exact question for a particular geriatric assessment tool, what cutoff scores are used within a particular scale, how the results should be interpreted, and whether this scale has been validated in oncology. To overcome these limitations, the National Comprehensive Cancer Network (NCCN), the European Organization for Research and Treatment of Cancer (EORTC), and the International Society of Geriatric Oncology (SIOG) guidelines are proposing a ‘two-step’ approach with screening tools for early risk detection. Through the G8 questionnaire[30], the presence of risk factors is initially screened to select older cancer patients in need of geriatric assessment, and CGA and geriatric interventions are

performed. The G8 questionnaire is currently known as one of the best screening tools to identify older cancer patients due to its high sensitivity and independent 1-year survival rate.

Our study has several limitations to be noted. First, it was conducted at a single institution with a relatively small sample size of 21 patients. Also, since only patients suitable for chemotherapy were initially enrolled, there is a possibility that only patients with relatively good cognitive function or performance status were selected. Therefore, the interpretation of our results should be cautious, and a prospective study with larger sample size is desirable in the future. Despite the above limitations, this is an important study to suggest the prognostic implications of CGA in older patients with SCLC.

Conclusions

Geriatric assessment detects more information than routine oncological evaluation alone, such as ECOG PS. Pre-treatment nutritional status measured by CGA appears to be a predictor of OS in older SCLC patients. Further studies are required to verify the prospective role of CGA on older cancer patients.

Abbreviations

ADL: Activities of Daily Living

BMI: Body Mass Index

CCI: Charlson Comorbidity Index

CGA: Comprehensive Geriatric Assessment

ECOG PS: Eastern Cooperative Oncology Group performance status

EORTC: European Organization for Research and Treatment of Cancer

GDSSF-K: Korean version Short Form of the Geriatric Depression Scale

HR: Hazard Ratio

IADL: Instrumental Activities of Daily Living

MMSE: Mini-Mental State Exam

MNA: Mini Nutritional Assessment

NCCN: National Comprehensive Cancer Network

NSCLC: Non-Small Cell Lung Cancer

OS: Overall Survival

PCI: Prophylactic Cranial Irradiation

SCLC: Small Cell Lung Cancer

SIOG: International Society of Geriatric Oncology

TUG: Timed Up and Go test

Declarations

Ethics approval and consent to participate

Ethical approval for this study was obtained from the Institutional Review Board of Yonsei University's Health System (IRB number: 4-2021-1348) and adhered to the tenets of the Declaration of Helsinki. Informed consent was waived by the IRB of Yonsei University's Health System for this study as all the data was obtained from medical records.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to the ethics approval for this study. However, the data are available from the corresponding author on reasonable request.

Competing interests

The authors have no competing interests do declare.

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Authors' Contributions

YJC, KJK, COK, and MHH were involved in the study design. JYL, JWC, THK did data collection. HRK, BCC, and MHH helped on recruiting participants. YJC and JYL did data analysis. YJC did manuscript writing.

KJK, COK and MHH supervised the study and performed significant editing of the manuscript. All authors have read and approved the final manuscript.

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Figures

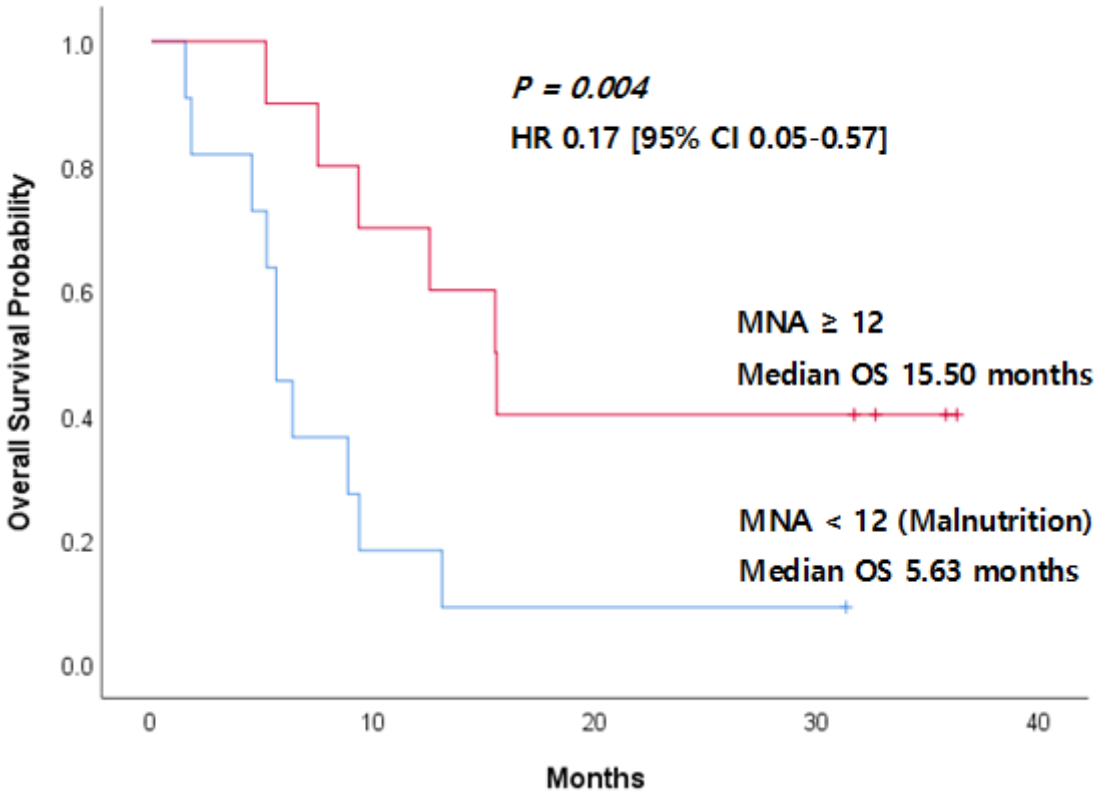

Figure 1

Overall survival according to nutritional status

The Mini Nutritional Assessment (MNA) is one of the domains of comprehensive geriatric assessment (CGA). The overall survival (OS) was longer in older small cell lung cancer (SCLC) patients with normal nutritional status or at risk of undernutrition compared to patients with malnutrition (median survival 15.50 vs 5.63, *p = 0.004*, HR 0.17 [95% CI 0.05-0.57]).