Three Years Survival of Elderly Cancer Patients in Indonesia: Do We Need a Different Approach?

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ABSTRAK

Latar belakang: *jumlah populasi usia lanjut semakin meningkat di Indonesia. Di lain sisi, prevalensi kanker pada pasien usia lanjut juga meningkat. Akan tetapi, studi mengenai faktor klinis terkait kesintasan pasien kanker usia lanjut masih terbatas. Studi ini bertujuan untuk mengevaluasi kesintasan pasien kanker usia lanjut dan faktor-faktor terkait.* ***Metode:*** *studi ini adalah kohort retrospektif. Subyek adalah pasien kanker usia lanjut berusia > 60 tahun yang berobat pada tahun 2013 – 2015 di RS Kanker Dharmais. Data diambil dari rekam medis, terdiri dari jenis kelamin, usia, jenis kanker, stadium, status performa ECOG, indeks massa tubuh, Charlson Comorbidity Index, dan jenis terapi. Analisis kesintasan menggunakan analisis Cox regression untuk mengidentifikasi faktor prognostik independen.* ***Hasil:*** *sejumlah 249 pasien dilibatkan dalam studi; median usia adalah 66 tahun dengan rentang usia 60 – 85 tahun. Jenis kanker terbanyak adalah paru, diikuti dengan payudara, kolorektal dan ginekologi. Median waktu kesintasan adalah 24 bulan. Analisis multivariat dilakukan dengan stratifikasi berdasarkan jenis kelamin. Kanker stadium lanjut (III-IV) adalah variabel yang bermakna pada kelompok perempuan (hazard ratio [HR] 2.72; 95% confidence interval [CI] 1.53–4.80; p = 0.001), sedangkan status performa (ECOG 2 – 4) merupakan faktor risiko pada kelompok laki-laki (HR 1.82; 95% CI 1.01–3.24; p = 0.04).* ***Kesimpulan:*** *kesintasan pasien kanker usia lanjut dipengaruhi berbagai faktor prognostik tradisional. Kanker stadium lanjut merupakan faktor prognostik bermakna pada perempuan, sedangkan status performa merupakan faktor prognostik pada laki-laki.*

Kata kunci: *usia lanjut, kanker, kesintasan.*

ABSTRACT

Background: *the number of elderly people in Indonesia is increasing. Additionally, cancer prevalence among older patients is also increasing. However, studies assessing clinical factors associated with the survival of elderly patients with cancer are still lacking. This study aimed to investigate the survival of geriatric patients with cancer and associated factors.* ***Methods:*** *this was a retrospective cohort study. Subjects were geriatric patients with cancer aged >60 years, enrolled between 2013 and 2015 in Dharmais Cancer Hospital. Data were retrieved from medical records and consisted of gender, age, cancer type, stage, Eastern Cooperative Oncology Group (ECOG) performance status (PS), body mass index (BMI), Charlson Comorbidity Index, and type of treatment. Cox regression analysis was used to identify independent prognostic factors for survival.* ***Results:*** *a total of 249 patients were enrolled, with a median age of 66 (60–85) years. The most common cancer was of the lung, followed by breast, colorectal, and uterine cervical cancers. The median survival time was 24 months. Cox multivariate analysis was performed by gender stratification. Advanced stage cancer (III-IV) was identified as the risk factor for mortality in female patients (hazard ratio [HR] 2.72; 95% confidence interval [CI] 1.53–4.80; p = 0.001),*

while poor performance status (ECOG 2 – 4) was the risk factor in male group (HR 1.82; 95% CI 1.01–3.24; p = 0.04). ***Conclusion:*** *the survival of elderly patients with cancer is affected by traditional prognostic factors. Advanced cancer stage was significant independent prognostic factor in female patients, while poor performance status was significant in male patients.*

Keywords: *elderly patients, cancer, survival.*

INTRODUCTION

The number of elderly people (aged 60 years and above) is increasing rapidly in Indonesia. Approximately 8.97% (23.4 million) of elderly people were estimated in the country in 2017, a percentage that is expected to increase to 15% in 2035.[1] On the other hand, the prevalence of non-communicable diseases associated with aging − including cancer − is also increasing. Among Western populations, and the median age of diagnosis of common cancers, such as breast, colon, and prostate, is mostly above 60 years.[2] This demographic change carries the challenge of managing cancer in elderly patients and led to the emergence of geriatric oncology.[3]

A major issue in the management of elderly patients with cancer is the intensity of optimal treatment. Elderly patients are a heterogeneous group and little information is available regarding their ability to tolerate the toxicity of certain anticancer regimens.[4] A study found that elderly patients are submitted to less surgery, more frequent single-agent hormonal treatment, and less adjuvant systemic treatment compared with younger patients. Moreover, elderly patients have shorter relative survival than their younger counterparts.[5]

Although developments in medicine and socioeconomics have reduced the mortality associated with other conditions, cancer death remains high. The cancer mortality rate is also higher in older than in younger patients. The age-based cancer mortality for patients over 65 years (1,068/100,000) is higher than that of younger patients (67/100,000). These data showed that the cancer mortality rate was 16 times higher in advanced age than in younger ages. More than 70% of mortality related to solid cancers, such as prostate, bladder, colon, uterus, pancreas, stomach, rectum, and lung, occurs in patients over 65 years of age.[6] Another study by Bourdel et al.[7] found that 1-year mortality rate in elderly patients with cancer older than 70 years was 43.89%.

Recent data from Indonesia showed that the cancer prevalence increased from 1.4‰ in 2013 to 1.8‰ in 2018.[8] Together with the increasing life expectancy, geriatric patient management will soon be a new challenge for medical professionals. However, appropriate training and clinical geriatric oncology practice are still limited in Asian countries, including Indonesia.[9] The increasing prevalence of cancer and elderly patients, along with the high associated mortality rate, argue in favor of more geriatric oncology research. Until now, studies investigating factors associated with the survival of elderly patients with cancer in Indonesia were lacking. Therefore, this study aimed to evaluate the survival of elderly patients with cancer and associated factors.

METHODS

This was a retrospective cohort study included patients from Dharmais Cancer Hospital (DCH), in Jakarta. Elderly patients between January 2013 and December 2015 were enrolled based on medical record assessments. The elderly were defined as patients aged >60 years, based on World Health Organization criteria for developing countries.10 This study was approved by the DCH Ethical Committee on April 4, 2018, with the ethical clearance number 048/KEPK/IV/2018.

Clinical Assessment

Clinical data were obtained from patients' medical records and included age at diagnosis, performance status (PS), comorbidities, type of cancer, histopathology, stage at diagnosis, and type of treatment. The clinical outcome assessed was 3-year survival, defined as the time between the date of diagnosis and death from any cause.

Patients were censored if they were lost to follow-up (observed until December 31, 2018).

Criteria for Nutritional Status

Based on the body mass index (BMI) criteria for the Asian population, patients were classified according to nutritional status as underweight (BMI <18.5 kg/m^2), normal-weighted (BMI= 18.5–22.9 kg/m^2), overweight (BMI = 23.0–24.5 kg/m2), and obese (BMI >25.0 kg/m^2).11 Comorbidities were assessed using the Charlson Comorbidity Index (CCI) as the total number of non-cancer chronic conditions.[12] Performance status was assessed based on the Eastern Cooperative Oncology Group (ECOG) PS, scored from 0 to 4.[13]

Statistical Analysis

Demographic and clinical variables were descriptively presented. Differences in overall survival between subgroups were calculated using the Kaplan–Meier survival analysis.[14] The log-rank test was used to evaluate the equality of survival distributions across different subgroups; a p value <0.05 was considered statistically significant. The Cox proportional hazards model was developed to identify independent prognostic factors for overall survival, and expressed as the hazard ratio (HR) and corresponding 95% confidence interval (CI).[15] Statistical analyses were performed using Stata version 12.0 for Windows PC.

RESULTS

A total of 249 patients were enrolled in this study, 60% of which were female. The patients' median age was 66 years, ranging from 60 to 85 years. A total of 233 solid and 16 blood/lymphoid tumors were identified. The most common solid cancer was of the lung, followed by breast, colorectal, and uterine cervical cancers. Most patients were diagnosed at advanced stages (III or IV). Other clinical characteristics are shown in **Table 1**.

Survival Analysis

A total of 173 deaths were recorded during the study period. The median 3-year survival was 24.00 (21.24–26.76) months (**Figure 1**).

The highest mortality was found among patients with lung cancer (84.8%), followed by

Table 1. Characteristics of study subjects (n = 249)

Variables	n (%)
Gender (n, %)	
- Male	100 (40.2)
- Female	149 (59.8)
Educational level	
- <12 years (finished high school or less)	190 (76.3)
- >12 years (graduate and postgraduate)	59 (23.7)
Nutritional status	
- Underweight	39 (15.7)
- Normal weight	89 (35.7)
- Overweight	49 (19.7)
- Obesity class I	52 (20.9)
- Obesity class II	20 (8.0)
Anatomical origin of primary tumor	
- Lung	66 (26.5)
- Breast	64 (25.7)
- Gastrointestinal	37 (14.9)
- Gynecological	37 (14.9)
- Blood and lymphoid	16 (6.4)
- Urological	15 (6.0)
- Head and neck	11 (4.4)
- Skin	2 (0.8)
- Neurological	1 (0.4)
Stage (n, %)	
- I–II	55 (22.1)
- III–IV	194 (77.9)
Comorbidity	
- CCI 0 – 1	204 (81.9)
- CCI 2 – 4	45 (18.1)
ECOG PS	
- 0 – 1	192 (77.1)
- 2 – 4	57 (22.9)

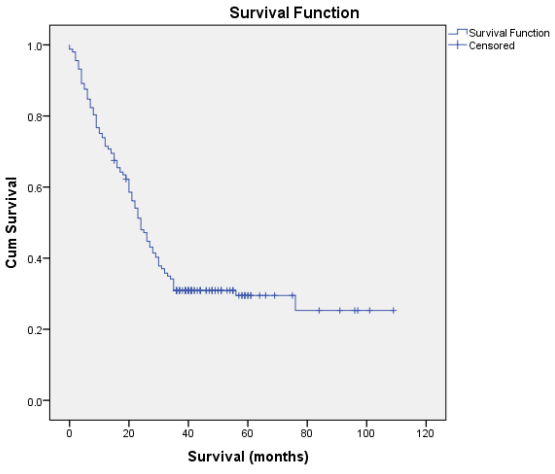

Figure 1. Kaplan-Meier survival curves of 3-years overall survival.

those with head and neck cancers (27.3%), and digestive cancers (27.0%). Univariate analysis found that older age (>75 years old), underweight (BMI <18.5 kg/m^2), poor performance status, advanced stage disease and single treatment significantly associated with lower overall survival (**Table 2**). Kaplan-Meier curve for each significant variable was shown in **Figure 2** – **Figure 7**.

Table 2. Univariate analysis

Variables	HR (95% CI)	P
Male	1.40 (1.04-1.89)	0.029
Age >75 years	1.57 (1.05-2.34)	0.028
BMI <18.5 kg/m2	1.64 (1.11-2.42)	0.013
ECOG PS 2-4	1.63 (1.16-2.30)	0.005
Stage III-IV	2.97 (1.89-4.65)	<0.001
Single treatment	1.35 (0.99-1.84)	0.05
CCI	0.89 (0.45-1.74)	0.73

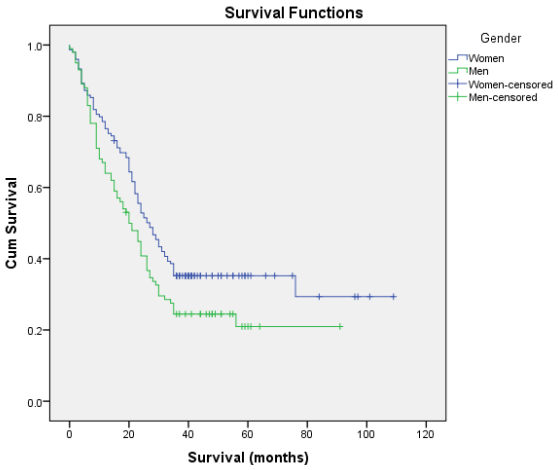

Figure 2. Kaplan-Meier survival curves of 3-years overall survival based on sex.

All data were treated as closed cohort with 36 months observation. After data management and categorizing all independent variables, it was found that gender did not meet the Cox proportional assumptions. Therefore, multivariate analysis with Cox regression was carried out by gender stratification. All variables with p<0.20 in univariate analysis were conducted to univariate and multivariate analysis in each group. Advanced stage cancer (III-IV) was identified as the risk factor for mortality in female patients (hazard ratio [HR] 2.72; 95%

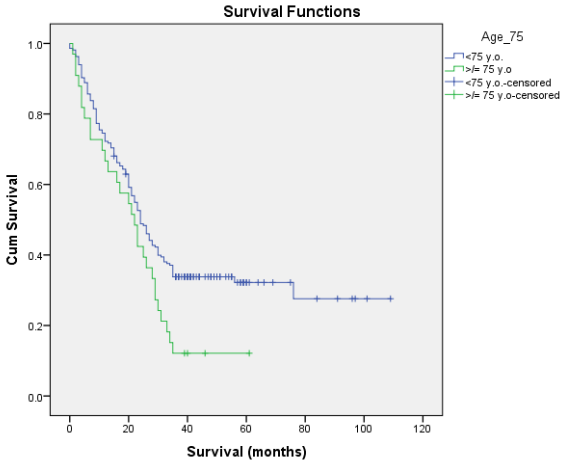

Figure 3. Kaplan-Meier survival curves of 3-years overall survival based on age group.

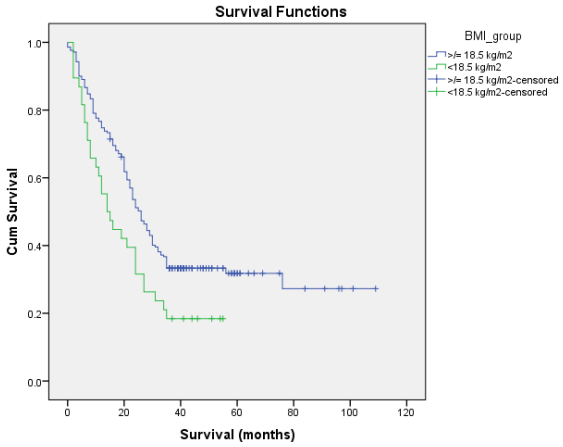

Figure 4. Kaplan-Meier survival curves of 3-years overall survival based on BMI group.

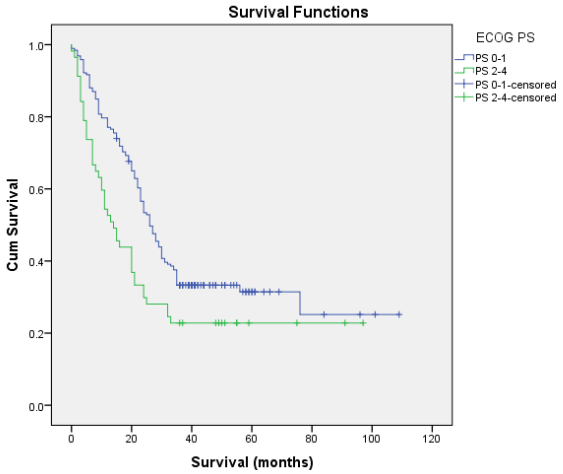

Figure 5. Kaplan-Meier survival curves of 3-years overall survival based on performance status group.

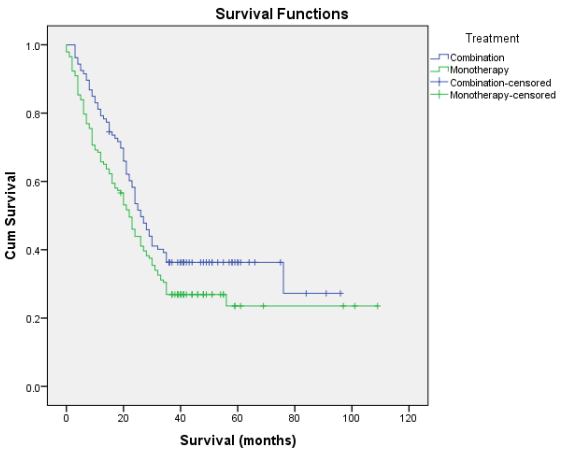

Figure 6. Kaplan-Meier survival curves of 3-years overall survival based on treatment group.

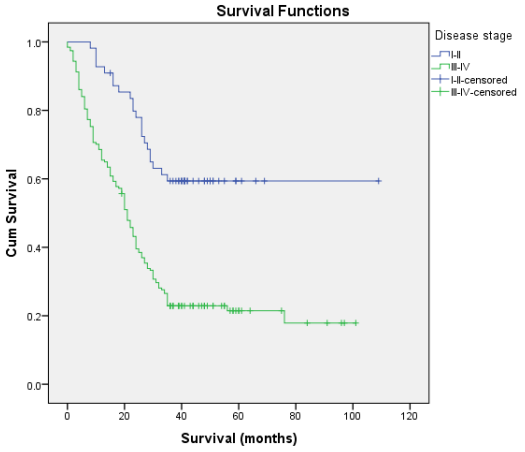

Figure 7. Kaplan-Meier survival curves of 3-years overall survival based on disease stage.

confidence interval [CI] 1.53–4.80; p = 0.001) (**Table 4**), while poor performance status (ECOG 2 – 4) was the risk factor in male group (HR 1.82; 95% CI 1.01–3.24; p = 0.04) (**Table 6**).

Table 3. Univariate analysis in female patients (n=149)

Variables	HR (95% CI)	P
Age >75 years	1.74 (1.00-3.03)	0.048
BMI <18.5 kg/m^2	2.10 (1.22-3.60)	0.007
ECOG PS 2-4	1.58 (1.00-2.51)	0.049
Stage III-IV	3.19 (1.83-5.55)	<0.001
Single treatment	1.49 (0.99-2.24)	0.05
CCI	1.49 (0.60-3.69)	0.41

Table 4. Cox proportional hazard model in female patients (n=149)

Variables	Multivariate	
	HR (95% CI)	P
Age >75 years	1.49 (0.82-2.69)	0.19
BMI <18.5 kg/m^2	1.57 (0.87-2.81)	0.13
ECOG PS 2-4	1.42 (0.88-2.27)	0.15
Stage III-IV	2.72 (1.53-4.80)	0.001
Multiple treatments	1.51 (0.99-2.29)	0.05

Table 5. Univariate analysis in male patients (n=100)

Variables	HR (95% CI)	p
Age >75 years	1.51 (0.72-3.14)	0.27
BMI <18.5 kg/m^2	1.29 (0.74-2.25)	0.37
ECOG PS 2-4	1.86 (1.08-3.17)	0.02
Stage III-IV	2.07 (0.95-4.51)	0.07
Multiple treatments	0.96 (0.59-1.55)	0.86
CCI	0.51 (0.19-1.40)	0.19

Table 6. Cox proportional hazard model in male patients (n=100)

Variables	Multivariate	
	HR (95% CI)	p
Age >75 years	1.64 (0.77-3.50)	0.19
BMI <18.5 kg/m^2	1.13 (0.62-2.05)	0.68
ECOG PS 2-4	1.82 (1.01-3.24)	0.04
Stage III-IV	2.16 (0.98-4.73)	0.05
Multiple treatments	1.06 (-.65-1.74)	0.81

DISCUSSION

Geriatric oncology is a new field of medical research in Indonesia, and this study was a preliminary assessment of prognostic factors affecting the survival of elderly patients with cancer. In this study, cancer staging was not merely the prognostic factor assessed. Other important variables like age, nutritional status (represented by BMI) and performance status were also assessed. Aging is a complex process. Pre-treatment condition of elderly patients is very important to be assessed before giving any treatment.[16] Assessing psychosocial aspect such as level of education, family support, and psychomental state are also necessary. A recent systematic review found that advanced age, low income, low socioeconomic status, presence of comorbidities, advanced stage at diagnosis, and poor tumor grade were associated with lower survival.[17] However, since this was a retrospective study and psychosocial assessment was not routinely done, we did not do further analysis.

Age is one of the traditional factors that is commonly related to mortality in cancer. However, multivariate analysis in this study failed to find significant association between age and survival in cancer patients. This findings showed that chronological age has limitation in evaluating patient's physiological function, health and aging status, therefor it is not always significantly associated with mortality. Nowadays, biological age (estimated by biomarkers) is famously known as the "real age" which can reflect health status with aging. Further studies of elderly using biological age are needed.

Sex is an important factor in pathogenesis, diagnosis, and prognosis in many diseases, including cancer. Several studies showed that female gender was associated with longer survival.[17,18] Our study found that female had better survival than male. However, gender did not meet Cox proportional hazard assumption in further analysis. A study by Cook et al.[19] found that sex-related cancer disparities are more strongly related to etiology than prognosis.

The PS (Karnofsky or ECOG) is traditionally used to assess the functional status in elderly patients with cancer and determines their ability to tolerate anticancer treatments. In the last few decades, the Comprehensive Geriatric Assessment (CGA) has been added to geriatric oncology practice to evaluate the tolerability of the elderly before receiving chemotherapy. CGA also indicated that elderly patients with cancer have numerous health problems associated with survival, such as functional impairment, malnutrition, and comorbidities.[4] Growing evidence demonstrates that CGA can predict mortality in elderly patients with cancer.[20] However, as CGA is not used in our hospital, we were unable to evaluate certain aspects of geriatric patients, as social functioning, activities of daily living, and psychological function. Univariate analysis showed that subjects with worse PS (ECOG 2 – 4) had lower OS compared to subjecta with better PS. In gender-stratified multivariate analysis of this study, ECOG 2 – 4 was also associated with mortality. In general geriatric population, functional status have been found to be a predictor of survival.[21] For elderly with cancer, performance status may affect the ability and respond to treatment. Patients with poor performance status are associated with increased risk of treatment toxicity and poor outcomes compared to patients with better performance status.[22]

The correlation between cancer stage and survival has been widely investigated. As expected, survival in advanced stage cancer is lower than early stage.[23] A study in breast cancer patients showed that advanced stage were associated with higher mortality.[24] his similar finding was found in this study. In multivariate analysis, advanced stage cancer was associated with lower survival, especially in female group. In certain types of cancer that are more common in men such as prostate cancer and Hodgkin's lymphoma, stage does not significantly affect the decrease in survival.[23] This can be the reason of insignificant association between cancer stage and survival in male group.

Nutritional status is an important prognostic factor in elderly patients. The BMI is one of several methods to measure the nutritional status. In elderly people, reduced weight or BMI is a complex condition resulting from reduced dietary intake, loss of muscle mass (sarcopenia), and cachexia due to cancer, with potential prognostic implications.[25] Undernutrition can be found in 66% of elderly patients with cancer.[26] Low BMI and weight loss are associated with an increased risk of death in the elderly population.[27] Severe malnutrition has been associated with poor prognosis in colorectal cancer.[28] In the current study, patients with undernutrition status had lower survival (**Figure 4**). However, multivariate analysis failed to show prognostic role of BMI, suggesting that it was a confounding factor, affected by more advanced stage and related to poor PS. However, the use of BMI as a single nutritional status measure has a major drawback, since it cannot accurately reflect muscle mass or adiposity. In line with this finding, a study among elderly people aged ≥70 years without cancer found that obesity was inversely associated with mortality.[29] Another study among patients with non-metastatic colorectal cancer showed that low muscle mass, high adiposity, or both were associated with worse survival, with the lowest

risk of mortality found for BMI between 25 and <30 kg/m^2. In CT scan, patients in this subgroup seemed to have adequate muscle mass and low fat.[30] This could be the reason why patients with low BMI had poor survival outcomes.

The treatment of elderly patients with cancer remains a challenge due to the complexity of organ function decline, comorbidities, impairments, and social factors.[31] The toxicity of anticancer therapies is potentially higher in elderly patients,[32] but evidence is limited as most clinical trials have not enrolled elderly patients. In this study, the net effect of multimodal treatment compared with single treatment was investigated and failed to show significant association with survival. Single treatment with a cytotoxic agent is usually recommended for elderly patients with advanced disease. However, several studies showed different results. Study by Thiels et al.[33] found that multimodality treatment in elderly patients with stage III rectal cancer resulted in better outcomes. Another study by Coate et al.[34] also showed that multimodality treatment in elderly cancer patients could provide better outcomes if given to fit-elderly and for curative goals.

Based on the current results, the authors encourage adequate management of nutrition in elderly patients with cancer. Geriatric oncology team should also involve nutritionists in management of nutrition for elderly cancer patients. Whenever feasible, exercise should also be advised to increase muscle mass and reduce fat. Further studies are required to elucidate the optimal weight and body composition able to tolerate multiple treatments and produce better clinical outcomes. Contrary to current beliefs, multiple treatments with optimal regimens can be offered to this patient population, as the elderly are still responsive to anticancer treatment. Significant association between cancer stage and survival emphasizes the importance of early detection.

This study has some limitations. First, it had a retrospective design, based on medical record data. Therefore, the clinical data retrieved were limited and no further assessments could be performed regarding other characteristics of geriatric patients. However, some important prognostic factors could still be assessed and used for analysis. Second, all patients were included and a specific cancer type was not evaluated. It is possible that survival time is affected by tumor type, as observed in lung cancer, which has the highest mortality rate. Further studies with prospective design using CGA are needed.

CONCLUSION

The survival of elderly patients with cancer is affected by traditional prognostic factors. Advanced cancer stage was significant independent prognostic factor in female patients, while poor performance status was significant in male patients.

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CONFLICT OF INTEREST:

The authors report no conflict of interest regarding this study.

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