



# Characteristics and Assessment of Frailty as Risk Factor of Therapy-Related Acute Toxicities and Delayed Overall Treatment Time in Elderly Patients Treating with External Beam Radiation Therapy at Indonesia Top Referral Hospital

Steven Octavianus<sup>1\*</sup>, Handoko Handoko<sup>1</sup>, Tiara Bunga Mayang Permata<sup>1</sup>, Gatot Purwoto<sup>2</sup>, Marlinda Adham<sup>3</sup>, Sonar Soni Panigoro<sup>4</sup>, Siti Setiati<sup>5</sup>, Soehartati Gondhowiardjo<sup>1</sup>

<sup>1</sup>Department of Radiation Oncology, Faculty of Medicine, Universitas Indonesia, Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia; <sup>2</sup>Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Faculty of Medicine, Universitas Indonesia, Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia; <sup>3</sup>Department of Otorhinolaryngology, Faculty of Medicine, Universitas Indonesia, Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia; <sup>4</sup>Department of Surgery, Division of Oncology Surgery, Faculty of Medicine, Universitas Indonesia, Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia; <sup>5</sup>Department of Internal Medicine, Division of Geriatric, Faculty of Medicine, Universitas Indonesia, Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia

## Abstract

**BACKGROUND:** Older patients are at a higher risk of being frail. Frailty implies that even a minor stressor can have major negative implications on physical, psychological domains. Geriatric-8 (G-8) screening tool shows good screening properties for identifying vulnerable elderly patients with cancer.

**AIM:** We, therefore, decided to investigate the utility of G-8 associated with acute toxicity and prolonged overall treatment time (OTT) in elderly cancer patients treated with radiotherapy (RT).

**MATERIALS AND METHODS:** A prospective observational cohort study is performed. Eligible subjects are patients aged  $\geq 60$  years and were referred for curative or palliative RT. We use the G-8 questionnaire for consecutive patients before starting RT. We recorded acute toxicity and OTT and identified potential predictors.

**RESULTS:** A total of 52 consecutive geriatric patients were included with an average age of 67 years. Of all those subjects, 21% had head-and-neck cancers, 29% gynecology cancers, 23% breast cancers, and 27% other cancers. According to the G-8, 65% of the patients were potentially frail. Toxicity Grade  $\geq 3$  was observed among 32% of subjects who were potentially frail according to the G-8 and 0% of the subject who was fit ( $p = 0.007$ ). Prolonged OTT was observed in 61.8% of potentially frail and 27.8% of the subjects who were fit ( $p = 0.020$ ). On multivariate analysis, only chemoradiation was strongly associated with acute toxicity Grade  $\geq 3$  odds ratio 11.1 (95% confidence interval 1.4–83.6;  $p = 0.019$ ).

**CONCLUSION:** The utility of G-8 in daily practice seems to be limited. Only concurrent chemoradiation was associated with acute toxicity. Future prospective studies should investigate whether the G-8 is a good predictor for other relevant clinical outcomes and survival in our local settings.

**Edited by:** Ksenija Bogoeva-Kostovska  
**Citation:** Octavianus S, Handoko, Permata TB, Purwoto G, Adham M, Panigoro SS, Setiati S, Gondhowiardjo S. Characteristics and Assessment of Frailty as Risk Factor of Therapy-Related Acute Toxicities and Delayed Overall Treatment Time in Elderly Patients Treating with External Beam Radiation Therapy at Indonesia Top Referral Hospital. Open-Access Maced J Med Sci. 2022 Jul 28; 10(B):1806-1812. https://doi.org/10.3889/oamjms.2022.9709  
**Keywords:** Cancer; Frailty; Geriatric 8; Overall treatment time; Radiotherapy; Toxicity  
**\*Correspondence:** Steven Octavianus, Department of Radiation Oncology, Faculty of Medicine Universitas Indonesia - Dr. Cipto Mangunkusumo Hospital, Jl. Pangeran Diponegoro No 71, Jakarta, Indonesia. E-mail: dr.octavianussteven@gmail.com  
**Received:** 08-Apr-2022  
**Revised:** 12-May-2022  
**Accepted:** 19-Jul-2022  
**Copyright:** © 2022 Steven Octavianus, Handoko, Tiara Bunga Mayang Permata, Gatot Purwoto, Marlinda Adham, Sonar Soni Panigoro, Siti Setiati, Soehartati, Gondhowiardjo  
**Funding:** This research did not receive any financial support  
**Competing Interest:** The authors have declared that no competing interest exists  
**Open Access:** This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0)

## Introduction

One of the health problems in the elderly is cancer. Cancer risk increases with age and more than 60% of new cancer cases are diagnosed in patients over 60 years of age [1], [2]. Berger *et al.* reported that the incidence of cancer increased 10 times and the mortality rate was 16 times higher in the elderly compared to the younger age [3]. According to GLOBOCAN 2020, lung, colorectal, prostate, breast, and gastric cancers are cancers with the highest incidence and leading cause of death in patients aged  $>60$  years [4].

Although the incidence of cancer in the elderly continues to increase, there are still large gaps in how to properly risk stratify older patients according to their biological state. This stratification is very important and aims to be able to recommend the most appropriate type of treatment in a personalized way [5]. There are several methods to assess the risk of a condition in the elderly before making oncological treatment decisions. Risk stratification of a condition of frailty or vulnerability in the elderly can use between the comprehensive geriatric assessment (CGA)/geriatric assessment (GA), and geriatric screening [6]. However, not all patients are older people with cancer who require complete CGA. CGA should be focused on specific at-risk patients, such

as those with multiple chronic diseases or with complex conditions. In addition, a complete CGA also takes time and resources. Therefore, the International Society of Geriatric Oncology (SIOG) recommends the use of the geriatric-8 (G-8) screening instrument to identify elderly patients with cancer who would benefit from CGA, not only according to their clinical judgment [7], [8], [9].

The G-8 is the first screening instrument specifically designed for elderly patients with cancer. The G-8 consists of eight questions, the total G-8 rating ranges from 0 (very frail) to 17 (no disturbance at all), with the threshold value for potential frailty being  $\leq 14$  [8]. In addition to helping oncologists to make treatment plan decisions by identifying in patients requiring CGA (score 14), the G-8 can predict treatment-related complications and survival through a low G-8 score [10].

Radiotherapy (RT) is one of the main modalities in cancer management, where more than 50% of cancer patients will require RT as part of their cancer management [11]. RT is an attractive treatment option and is often the main choice for elderly patients, especially if surgery and chemotherapy would be expected to pose too great a risk [12]. However, in reality, certain groups of elderly people undergoing RT are highly susceptible to significant toxicity and many will eventually require hospitalization [13]. This is because vulnerable elderly patients may not fully recover from RT/chemoradiation-induced toxicity. The acute toxicity experienced during the radiation process has a direct impact and can immediately reduce the quality of life. This condition will be positive if the patient will fully recover and have a long enough life expectancy as the outcome of the therapy plan. However, for debilitated patients, both may not be obtained.

Thus, in this study, the authors wanted to know the characteristics and role of G-8 screening as a risk factor for acute toxicity due to moderate-to-severe radiation and delayed completion of radiation treatment time in elderly cancer patients undergoing external radiation.

## Materials and Methods

### Patients

Patients were eligible if aged  $\geq 60$  years and diagnosed with cancer and had no previous history of RT. They were referred for RT with curative or palliative intent in the Department of Radiotherapy, Dr. Cipto Mangunkusumo Hospital, between February 2021 and June 2021. Patient baseline characteristics were collected by nurses and physicians. Performance status and G-8 screening were as assessed by an attending physician, and the results of G-8 scores did not influence treatment decisions. The treatment strategies and dosage of RT or concurrent chemoradiation were determined

by comprehensive assessment. RT treatments were performed according to institutional protocols. Written informed consent was obtained from all study participants. The study protocol and ethical approval were approved by the responsible ethics committee (The Ethics Committee, Faculty of Medicine, Universitas Indonesia – Dr. Cipto Mangunkusumo Hospital, Number: KET-143/UN2.F1/ETIK/PPM.00.02/2021).

### Data collection

Baseline data collection was completed before the initiation of RT. Recorded variables were age, sex, Karnofsky Performance Status (KPS) score, body mass index (BMI) [14], hemoglobin (Hb) level, number of comorbidities (Charlson comorbidity index [15]), type of primary cancer (classified as head and neck, breast, gynecology, and other cancer), stage at diagnosis (according to AJCC 8<sup>th</sup> stage grouping or FIGO for gynecology cancer [16], [17], [18]), treatment history before RT, concurrent chemoradiation, RT technique, and total dose of RT. During treatment, patients were monitored weekly for signs of acute toxic effects. Acute treatment-related toxicities were evaluated according to Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer [19]. Acute treatment-related toxicities were evaluated according to Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer with grade 0: absence of radiation effect; grade 1: mild; grade 2: moderate; grade 3: major toxicity; grade 4: severe toxicity, and grade 5: Effect led to death [19]. The most severe grade among the organ/tissue-specific measures at the two assessment times (weekly during RT, on the last day of RT) was taken as an overall measure of the severity of acute toxicity. Delayed OTT was defined as treatment days missed related to acute toxicity. Scheduled days missed due to holidays, machine downtime, or were not recorded.

### Geriatric-8

The G-8 is a geriatric screening tool introduced by Bellera *et al.* that was originally designed to assess elderly cancer patients who could benefit from a CGA [8]. The G-8 consists of the eight questions regarding the history of anorexia, weight loss in the past 3 months, physical mobility, psychological status, BMI, number of medications, self-perception of health, and age at the assessment. The G-8 provides a numerical score with a maximum score of 17 (fit) and a minimum of 0 (very frail). A score of  $\leq 14$  is considered as potentially frail. This cutoff was also applied in our study.

### Statistical analysis

Demographics and treatment characteristics were reported as descriptive statistics. Potential

predictors of acute toxicity measured at baseline RT including G-8 were compared between patients with major toxicities and prolonged overall treatment time (OTT) and those without using Chi-square tests or Fisher's exact test for categorical variables and *t*-test for continuous variables.  $p < 0.05$  was considered statistically significant. All statistical analyses were conducted using SPSS version 25 software (IBM SPSS Statistics for Macintosh, Version 25.0. Armonk, NY: IBM Corp).

## Results

Between February and June 2021, a total of 52 consecutive geriatric patients are included in the study. Subject characteristics are shown in Table 1. A total of 38.5% of the subjects were male and 61.5% were female. The median age was 67 years (mean: 67; range: 60–81 years); KPS was  $\geq 90$  for 69.2% of the patients, 70–80 for 30.8%, and no one had KPS performance status below 70. Half of the patients have normoweight regarding the BMI, 11.5% underweight, and 36.5% are overweight. About 55% of patients reported had one or more comorbidities with hypertension which was the most reported comorbidity, reported by 42.3% of the patients, followed by diabetes (21%). About 75% of subjects are patients with locally advanced cancer and 80% of RT was intended for curative purposes with 30.8% of subjects receiving concurrent chemoradiation. About 63% had a history of therapy before RT including surgery, chemotherapy, and a combination of surgery + chemotherapy.

### Frailty

Based on the G-8 assessment, 34 (65.4%) elderly subjects were potentially frail (score  $\leq 14$ ) and 18 (34.6%) were fit. About 81% of the head-and-neck cancer patients, 41% of the breast cancer patients, 66% of gynecology cancer, and 71% of the other cancer patients were classified as potentially frail according to their G-8 assessment. Regarding comorbidities, 55% of susceptible potentially frail subjects had one type of comorbidity and 72.7% of susceptible potentially frail subjects had two comorbidities compared to fit elderly (Table 2).

### Acute toxicity and overall treatment time

All study subjects completed RT according to the therapy plan. Acute toxicity assessment was completed for 52 patients. No RT-related toxicity was observed in 2 (3.8%) subjects. Grade 1 in 17 (32.7%), Grade 2 in 22 (42.3%), Grade 3 in 8 (15.4%), Grade 4 toxicity in 3 (5.8%), and no Grade 5 toxicity

**Table 1: Subject and treatment characteristics**

Variable	n (%)
Sex	
Male	20 (38.5)
Female	32 (61.5)
Age	67.27 $\pm$ 5.069
Age classification (year old)	
60–69	40 (77)
70–79	11 (21.1)
$\geq 80$	1 (1.9)
KPS	
$\geq 90$	36 (69.2)
70–80	16 (30.8)
BMI	
Underweight (BMI $\leq 18.49$ )	6 (11.5)
Normoweight (BMI 18.5–25.0)	27 (51.9)
Overweight (BMI $\geq 25.1$ )	19 (36.5)
Hemoglobin level	
$< 11$ g/dL (male), $\leq 10$ g/dL (female)	9 (17.3)
$\geq 11$ g/dL (male), $> 10$ g/dL (female)	43 (82.7)
Cancer site	
Cervix	10 (19.2)
CNS	2 (3.8)
Endometrium	4 (7.7)
Gastrointestinal	1 (1.9)
Liver	3 (5.8)
Hypopharynx	1 (1.9)
Larynx	7 (13.5)
Lymphoma	4 (7.7)
Nasopharyngeal	3 (5.8)
Lungs	1 (1.9)
Breasts	12 (23.1)
Prostate	2 (3.8)
Rectum	1 (1.9)
Vulva	1 (1.9)
Stage	
Stage 1	8 (15.4)
Stage 2	5 (9.6)
Stage 3	22 (42.3)
Stage 4	17 (32.7)
Treatment history before external radiation	
Surgery	17 (32.7)
Chemotherapy	3 (5.8)
Surgery+chemotherapy	10 (19.2)
Hormonal therapy	1 (1.9)
Chemotherapy+targeted therapy	2 (3.8)
No treatment	19 (36.5)
Number of comorbidities	
No comorbid	23 (44.3)
1	18 (34.6)
2–3	10 (19.2)
$> 3$	1 (1.9)
Comorbid type	
Hypertension	22 (42.3)
Diabetes mellitus without complications	11 (21.1)
Chronic kidney failure	5 (9.6)
Congestive heart failure	1 (1.9)
Cerebrovascular disease	3 (5.7)
Mild liver disease	2 (3.8)
Coronary heart disease	2 (3.8)
Dementia	1 (1.9)
Purpose of external radiation	
Curative	42 (80.8)
Palliative	10 (19.2)
Concurrent chemotherapy	
Yes	16 (30.8)
No	36 (69.2)
External radiation technique	
3D-CRT	9 (17.3)
IMRT	38 (73.1)
SBRT	4 (7.7)
SRT	1 (1.9)
Total dose of external radiation (Gy)	
$< 50$	15 (28.8)
50–59	17 (32.7)
60–69	14 (26.9)
$\geq 70$	6 (11.5)

KPS: Karnofsky Performance Status, RT: Radiotherapy, 3D-CRT: 3D conformal RT, IMRT:

Intensity-modulated RT, SBRT: Stereotactic body radiation therapy, SRT: Stereotactic radiation therapy,

BMI: Body mass index, CNS: Central nervous system.

was observed. Of the 11 subjects with  $\geq$  Grade 3 toxicities, seven had head-and-neck cancer, three had gynecology cancer, and one subject had lung cancer. Head-and-neck cancer patients had the highest incidence of toxicity Grade 3 (63.6%) and gynecology cancer (20%) in the second places. Patients treated with concurrent chemoradiation (CCRT) had a higher percentage of Grade  $\geq 3$  toxicities 56.6% compared to

**Table 2: Geriatric 8 among subjects**

Variable	Potentially frail, n (%)	Fit, n (%)
Sex		
Male	14 (70)	6 (30)
Female	20 (62.5)	12 (37.5)
Age classification (year old)		
60–69	26 (65)	14 (35)
70–79	7 (63.6)	4 (36.4)
≥ 80	1 (100)	0 (0)
BMI	22.58 ± 3.89	26.66 ± 3.27
Hemoglobin level	11.94 ± 1.51	11.78 ± 1.47
Cancer site		
Head and neck	9 (81.8)	2 (18.2)
Breast	5 (41.7)	7 (58.3)
Gynecology	10 (66.7)	5 (33.3)
Others	10 (71.4)	4 (28.6)
Stage		
Stage 1	4 (50)	4 (50)
Stage 2	2 (40)	3 (60)
Stage 3	14 (63.6)	8 (36.4)
Stage 4	14 (82.4)	3 (17.6)
Number of comorbidities		
No comorbid	16 (69.6)	7 (30.4)
1	10 (55.6)	8 (44.4)
≥ 2	8 (72.7)	3 (27.3)
Overall treatment time		
Delay	21 (61.8)	5 (27.8)
No delay	13 (38.2)	13 (72.2)
Number of delay days		
N/A	13 (38.2)	13 (72.2)
≤ 3	11 (32.4)	4 (22.2)
> 3	10 (29.4)	1 (5.6)

BMI: Body mass index, N/A: Not available.

5.6% for patients with RT only OR 21.85 (95% CI: 3.8 to 123,  $p < 0.0001$ ). For prolonged OTT, 50% of subjects completed the radiation process as scheduled without delay, 28.8% of subjects with a delay of 3 days, 21.2% a delay of more than 3 days, and the largest delay of 40 days due to COVID-19.

### Frailty, toxicities, and overall treatment time

Eleven of the 34 subjects (32.4%) who were potentially frail according to G-8 developed toxicity Grade 3 and none of the fit patients developed Grade 3 acute toxicity,  $p = 0.007$  (Table 3). Twenty-one subjects (61.8%) who were potentially frail on G-8 had prolonged OTT and 5 subjects (27.8%) patients in the fit group had prolonged OTT (odds ratio [OR] 4.2; 95% confidence interval [CI] 1.21–14.54;  $p = 0.020$ ). In the potentially frail group, 11 (32.4%) subjects had a delay of 3 days and 10 (29.4%) had a delay of >3 days. Meanwhile, in the fit group, there were 4 (22.2%) subjects with a delay of 3 days and only 1 (5.6%) subject who experienced prolonged OTT for more than 3 days.

**Table 3: Toxicity Grade ≥ 3 and overall treatment time according to G8 test results**

Variable	Yes, n (%)	No, n (%)	p
Acute toxicity ≥ Grade 3			
Potentially frail	11 (32.4)	23 (67.6)	0.007*
Fit	0	18 (100.0)	
Prolonged OTT			
Potentially frail	21 (61.8)	13 (38.2)	0.020*
Fit	5 (27.8)	13 (72.2)	

OTT: Overall treatment time.

### Univariate and multivariate analysis

Univariate analyses were performed for the entire variables to screen potential factors which predict acute toxicity ≥Grade 3 and prolonged OTT including sex, age, KPS, Hb level, BMI, number of comorbidities,

**Table 4: Univariate and multivariate analysis of acute toxicity ≥ Grade 3**

Risk factors	Acute toxicity ≥ Grade 3			
	Univariate OR (95%CI)	p	Multivariate	p
Sex				
Female	Reference		1.69 (0.1–27)	0.709
Male	6.4 (1.4–28.5)	0.01		
Age				
< 70	Reference			
≥ 70	1.3 (0.2–6.0)	0.71		
KPS				
> 90	Reference			
70–80	3.7 (0.9–14.8)	0.06		
BMI				
Overweight	Reference			
Underweight	8.5 (0.9–74)	0.053		
Normoweight	2.4 (0.4–13.6)	0.313		
Pre-RT hemoglobin levels				
> 11 g/dL (male), >10 g/dL (female)	Reference			
< 11 g/dL (male), < 10 g/dL (female)	1.07 (0.1–6.1)	0.93		
Comorbidities				
No	Reference			
Yes	1.69 (0.4–6.4)	0.44		
Cancer site				
Other cancer	Reference		3.2 (0.17–60.9)	0.427
Head-and-neck cancer	16.1 (3.2–80.5)	0.001		
CCRT				
No	Reference		11.1 (1.4–83.6)	0.019
Yes	21.8 (3.8–123)	<0.001		
External radiation technique				
IMRT	Reference			
Non-IMRT	1.07 (0.19–6.1)	0.93		
Total RT dose (Gy)				
< 60 Gy	Reference		1.06 (0.09–11.8)	0.961
≥ 60 Gy	6.4 (1.4–28.5)	0.014		

KPS: Karnofsky Performance Status, RT: Radiotherapy, CCRT: Concurrent chemoradiation, IMRT: Intensity-modulated radiation therapy, BMI: Body mass index, OR: Odds ratio, CI: Confidence interval.

cancer site, CCRT, and total RT dose (Tables 4 and 5). As predicted, apart from the elderly with vulnerable potential based on G-8, the related factors are sex (male), head-and-neck cancer, CCRT, and total dose of RT. Multivariate analysis showed that only the administration of CCRT was an independent prognostic factor affecting the outcome of acute toxicity Grade 3 in the elderly undergoing RT with an OR of 11.1 (1.4–83.6;  $p = 0.019$ ).

**Table 5: Univariate and multivariate analysis of prolonged overall treatment time**

Risk factors	Prolonged OTT			
	Univariate OR (95% CI)	p	Multivariate	p
Sex				
Female	Reference			
Male	1.9 (0.6–6.0)	0.25		
Age				
<70	Reference			
≥ 70	0.4 (0.1–1.5)	0.19		
KPS				
> 90	Reference			
70–80	2.08 (0.6–6.9)	0.23		
BMI				
Overweight	Reference			
Underweight	8.5 (0.8–89)	0.07		
Normoweight	1.8 (0.5–6.1)	0.31		
Pre-RT hemoglobin levels				
> 11 g/dL (male), > 10 g/dL (female)	Reference			
< 11 g/dL (male), < 10 g/dL (female)	4.42 (0.8–23)	0.08		
Comorbidities				
No	Reference			
Yes	1.6 (0.5–4.8)	0.40		
Cancer site				
Other cancer	Reference			
Head-and-neck cancer	3.4 (0.7–14.7)	0.10		
CCRT				
No	Reference			
Yes	3.08 (0.8–10.7)	0.07		
External radiation technique				
IMRT	Reference			
Non-IMRT	2.3 (0.5–10.4)	0.28		
Total RT dose (Gy)				
< 60 Gy	Reference			
≥ 60 Gy	1.0 (0.3–3.05)	1.00		

KPS: Karnofsky Performance Status, RT: Radiotherapy, CCRT: Concurrent chemoradiation, IMRT: Intensity-modulated radiation therapy, BMI: Body mass index, OR: Odds ratio, CI: Confidence interval.

## Discussion

The purpose of RT is to maximize the therapeutic ratio by delivering the highest possible dose to the tumor while minimizing the dose to surrounding normal tissue [20]. Radiation toxicity is often a consideration for a radiation oncologist in planning therapy for all cancer patients. This is because radiation-induced toxicity to healthy tissue cannot be avoided in every administration of radiation therapy. In the elderly with cancer, there is a possibility that their organs and physiological reserves are not functioning optimally, so they have the potential to show more toxicity or have a higher risk of complications from RT and the combination of multimodality therapy with chemotherapy (fatigue, mucositis, xerostomia, dehydration, infection, cognitive decline, and increased risk of falls). On the other hand, elderly patients at the same time have a less functional capacity to cope with these side effects thereby increasing the risk of interruption/increasing duration of therapy, repopulation of cancer cells, or even failure of therapy [21], [22], [23]. In addition, this assumption has a significant impact. For example, Markopoulos *et al.* confirmed that the addition of chronological age is one of the factors in predicting deviations from the guidelines for all treatment modalities [24].

The G-8 was the first screening instrument specifically designed for oncology and is one of the best screening instruments. Another advantage of G-8 is that it can predict survival and complications related to treatment [10], [25]. The low G-8 value in this study can predict complications related to RT in the form of acute toxicity  $\geq$  Grade 3 and delays in completing radiation on time. Rates of acute toxicity  $\geq$  Grade 3 in our study were low (21%). This number is not different from the research conducted by Middelburg *et al.* with a total of 21.6% in the elderly with potentially frail [26]. However, the proportion of radiation delay in this study was quite high where the rate of elderly experiencing delays was 50%, especially in the potentially vulnerable group of elderly who experienced delays  $>3$  days reaching 30%. This needs special attention because an increase in OTT can affect the success of the overall treatment plan by supporting the acceleration of cancer cell proliferation, thereby reducing tumor control probability. Analysis by Fowler *et al.* showed that the addition of OTT led to a decrease in locoregional control by an average of 14% for every 1-week addition [27]. Meanwhile, a review by Ferreira *et al.* showed an average decrease in locoregional control ranging from 1–1.2% per day to 12–14% per week and required additional dose compensation ranging from 0.6 to 0.8 Gy/day [28].

In univariate analysis, it was found that male sex and head-and-neck cancer were factors that influenced acute toxicity but were not significant predictors in further multivariate analysis. In this study, it was found that 100% of head-and-neck malignancies

in this study were male and contributed 63.6% of the total study subjects who experienced acute toxicity  $\geq$  Grade 3. This proportion is in line with the study conducted by Middelburg *et al.*, men had an OR of 1.8 (1.0–3.2;  $p = 0.04$ ) compared to women, and head-and-neck cancer was the group with the highest number experiencing acute toxicity  $\geq$  Grade 3 with 70% of subjects in the head-and-neck group experiencing acute toxicity  $\geq$  Grade 3 (OR 56 CI 15–211;  $p = 3 \times 10^{-9}$  compared with breast cancer patients) [26]. Haehl *et al.* gave a similar picture, where elderly patients with head-and-neck cancer tended to have a higher incidence of acute toxicity Grade 3 (56.1 %) [29].

CCRT administration is a treatment-related factor that influences the occurrence of acute toxicity  $\geq$  Grade 3. In particular on CCRT after multivariate analysis, CCRT still provides strong significance as a predictor in the occurrence of major acute toxicity related to RT. Van Walree *et al.*, in a systematic review of the relationship between G-8 assessments and treatment outcomes in the elderly with cancer, suggested that the elderly in the potentially frail group based on the G-8 assessment had significantly higher levels of chemoradiation-related toxicity, with relative risks varying from 1.4 to 11.3 [10]. Seeing the potential for harm that can occur, the next question is whether giving chemoradiation to elderly patients can still be recommended as a definitive treatment? Hata *et al.*, in a review of the literature on cervical malignancies, that chemoradiation can be given to elderly patients with cervical cancer with great caution [30]. Meanwhile, in head-and-neck patients, Amini *et al.* conducted a study on elderly patients with locally advanced head-and-neck cancer who received RT and chemoradiation with a total of 4042 elderly subjects  $>70$  years and 63% receiving chemoradiation. This study found that 2-year unadjusted survival was better with chemoradiation than RT alone (55.0% vs. 35.1%), and 5-year survival was 30.3% versus 15.2% (HR 0.59; 95% CI: 0.55–0.63;  $p < 0.001$ ) with undifferentiated and tolerable acute toxicity. Therefore, elderly patients with head-and-neck cancer even those  $>70$  years of age should not be denied chemoradiation based solely on age, an assessment of other factors that determine susceptibility in CGA should be considered [31].

Regarding the dose and RE technique obtained by the research subjects in this study, all of them used radiation techniques using high technology RT, especially the intensity modulated radiotherapy (IMRT) technique. In addition, there were no subjects who received the 3D technique if they received a dose of more than 60 Gy. All patients received IMRT if the prescribed dose was  $>60$  Gy. This happens not without reason that the risk of toxicity is directly proportional to the total dose and volume of the radiation area [32]. Administration of higher techniques at higher doses aims to minimize the toxicity due to therapy. The IMRT technique can modulate hotspot areas in healthy tissue

and transfer them to the target volume area and will directly reduce the distribution of high doses in healthy tissue and OAR and allow for a smaller volume of target radiation so that it can be well tolerated by elderly individuals. In line with the study by Wang *et al.*, in cervical cancer receiving chemoradiation, it was found that the incidence of hematological toxicity Grade 3 or greater was higher than in patients treated with 3D-CRT (seven subjects; 71.4%) and IMRT (17 subjects; 58.8%), but not statistically significant [33].

Our study has some limitations. First, our study was a prospective study with a small number of patients, this is due to the difficulty in recruiting research subjects due to the decrease in the number of patients undergoing cancer treatment due to the COVID-19 pandemic. Second, in potentially frail patients according to the G-8, subjects do not follow CGA examination to confirm whether the subject is frail or in a fit state. The third is that in assessing the toxicity our institution has not used CTCAE as an assessment of the degree of toxicity. However, our study is the first study to assess the impact of RT on the elderly in our country and addressed an important question regarding the toxicities of RT for elderly patients with cancer.

## Conclusion

Our results seem to suggest that the use of G-8 in daily practice is still limited. Only CCRT administration has a strong relationship to acute toxicity  $\geq 3$ . RT/CCRT could be delivered safely in elderly cancer patients (>60 years) with careful monitoring. The use of RT with high technique provides an opportunity for the elderly with cancer to get the appropriate treatment. However, it is strongly recommended that all treatment planning decisions should be discussed in a multidisciplinary team scheme, ideally in combination with any form of GA, to improve cancer treatment outcomes in the geriatric population.

## References

1. Muss HB. Cancer in the elderly: A societal perspective from the United States. *Clin Oncol.* 2009;21(2):92-8. <https://doi.org/10.1016/j.clon.2008.11.008>  
PMid:19059768
2. Petit-Monéger A, Rainfray M, Soubeyran P, Bellera CA, Mathoulin-Pélissier S. Detection of frailty in elderly cancer patients: Improvement of the G8 screening test. *J Geriatr Oncol.* 2016;7(2):99-107. <https://doi.org/10.1016/j.jgo.2016.01.004>  
PMid:26868830
3. Berger NA, Savvides P, Koroukian SM, Kahana EF, Deimling GT, Rose JH, *et al.* Cancer in the elderly. *Trans Am Clin Climatol Assoc.* 2006;117:146-55.  
PMid:18528470
4. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, *et al.* Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer; 2020.
5. Russo C, Giannotti C, Signori A, Cea M, Murialdo R, Ballestrero A, *et al.* Predictive values of two frailty screening tools in older patients with solid cancer: A comparison of SAOP2 and G8. *Oncotarget.* 2018;9(80):35056-68. <https://doi.org/10.18632/oncotarget.26147>  
PMid:30416679
6. Festen S, Kok M, Hopstaken JS, van der Wal-Huisman H, van der Leest A, Reyners AK, *et al.* How to incorporate geriatric assessment in clinical decision-making for older patients with cancer. An implementation study. *J Geriatr Oncol.* 2019;10(6):951-9. <https://doi.org/10.1016/j.jgo.2019.04.006>  
PMid:31031193
7. Extermann M, Aapro M, Bernabei R, Cohen HJ, Droz JP, Lichtman S, *et al.* Use of comprehensive geriatric assessment in older cancer patients: Recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). *Crit Rev Oncol Hematol.* 2005;55(3):241-52. <https://doi.org/10.1016/j.critrevonc.2005.06.003>  
PMid:16084735
8. Bellera CA, Rainfray M, Mathoulin-Pélissier S, Mertens C, Delva F, Fonck M, *et al.* Screening older cancer patients: First evaluation of the G-8 geriatric screening tool. *Ann Oncol.* 2012;23(8):2166-72. <https://doi.org/10.1093/annonc/mdr587>  
PMid:22250183
9. Palmer K, Onder G. Comprehensive geriatric assessment: Benefits and limitations. *Eur J Intern Med.* 2018;54:e8-9. <https://doi.org/10.1016/j.ejim.2018.02.016>  
PMid:29472049
10. van Walree IC, Scheepers E, van Huis-Tanja L, Emmelot-Vonk MH, Bellera C, Soubeyran P, *et al.* A systematic review on the association of the G8 with geriatric assessment, prognosis and course of treatment in older patients with cancer. *J Geriatr Oncol.* 2019;10(6):847-58. <https://doi.org/10.1016/j.jgo.2019.04.016>  
PMid:31078444
11. Barton MB, Jacob S, Shafiq J, Wong K, Thompson SR, Hanna TP, *et al.* Estimating the demand for radiotherapy from the evidence: A review of changes from 2003 to 2012. *Radiother Oncol.* 2014;112(1):140-4. <https://doi.org/10.1016/j.radonc.2014.03.024>  
PMid:24833561
12. O'Donovan A, Leech M, Gillham C. Assessment and management of radiotherapy induced toxicity in older patients. *J Geriatr Oncol.* 2017;8(6):421-7. <https://doi.org/10.1016/j.jgo.2017.07.001>  
PMid:28739158
13. Keenan LG, O'Brien M, Ryan T, Dunne M, McArdle O. Assessment of older patients with cancer: Edmonton Frail Scale (EFS) as a predictor of adverse outcomes in older patients undergoing radiotherapy. *J Geriatr Oncol.* 2017;8(3):206-10. <https://doi.org/10.1016/j.jgo.2016.12.006>  
PMid:28024799
14. Kementerian Kesehatan Republik Indonesia. Tabel Batas Ambang indeks Massa tubuh (IMT) - Direktorat P2PTM. Available from: <http://www.p2ptm.kemkes.go.id/infographic-p2ptm/obesitas/tabel-batas-ambang-indeks-massa-tubuh-imt>. [Last accessed on 2021 Feb 25].
15. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis.* 1987;40(5):373-83.

- [https://doi.org/10.1016/0021-9681\(87\)90171-8](https://doi.org/10.1016/0021-9681(87)90171-8)  
PMid:3558716
16. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, *et al.* The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin.* 2017;67(2):93-9. <https://doi.org/10.3322/caac.21388>  
PMid:28094848
17. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri. *Int J Gynecol Obstet.* 2018;143(S2):22-36. <https://doi.org/10.1002/ijgo.12611>  
PMid:30306584
18. Amant F, Mirza MR, Koskas M, Creutzberg CL. Cancer of the corpus uteri. *Int J Gynecol Obstet.* 2018;143(S2):37-50. <https://doi.org/10.1002/ijgo.12612>  
PMid:30306580
19. Cox JD, Stetz JA, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European organization for research and treatment of cancer (EORTC). *Int J Radiat Oncol Biol Phys.* 1995;31(5):1341-6. [https://doi.org/10.1016/0360-3016\(95\)00060-c](https://doi.org/10.1016/0360-3016(95)00060-c)  
PMid:77113792
20. Joiner M, van der Kogel A. *Basic Clinical Radiobiology.* 4<sup>th</sup> ed. London: HodderArnold; 2009.
21. Chang S, Goldstein NE, Dharmarajan KV. Managing an older adult with cancer: Considerations for radiation oncologists. *Biomed Res Int.* 2017;2017:1695101. <https://doi.org/10.1155/2017/1695101>  
PMid:29387715
22. Gomez-Millan J. Radiation therapy in the elderly: More side effects and complications? *Crit Rev Oncol Hematol.* 2009;71(1):70-8. <https://doi.org/10.1016/j.critrevonc.2008.11.004>  
PMid:19144538
23. Mohile SG, Heckler C, Fan L, Mustian K, Jean-Pierre P, Usuki K, *et al.* Age-related differences in symptoms and their interference with quality of life in 903 cancer patients undergoing radiation therapy. *J Geriatr Oncol.* 2011;2(4):225-32. <https://doi.org/10.1016/j.jgo.2011.08.002>  
PMid:22888384
24. Markopoulos C, van de Water W. Older patients with breast cancer: Is there bias in the treatment they receive? *Ther Adv Med Oncol.* 2012;4(6):321-7. <https://doi.org/10.1177/1758834012455684>  
PMid:23118807
25. Soubeyran P, Bellera C, Goyard J, Heitz D, Curé H, Rousselot H, *et al.* Screening for vulnerability in older cancer patients: The ONCODAGE prospective multicenter cohort study. *PLoS One.* 2014;9(12):e115060. <https://doi.org/10.1371/journal.pone.0115060>  
PMid:25503576
26. Middelburg JG, Mast ME, de Kroon M, Jobsen JJ, Rozema T, Maas H, *et al.* Timed Get Up and go test and geriatric 8 scores and the association with (Chemo-)radiation therapy noncompliance and acute toxicity in elderly cancer patients. *Int J Radiat Oncol Biol Phys.* 2017;98(4):843-9. <https://doi.org/10.1016/j.ijrobp.2017.01.211>  
PMid:28366575
27. Fowler JF, Lindstrom MJ. Loss of local control with prolongation in radiotherapy. *Int J Radiat Oncol Biol Phys.* 1992;23(2):457-67. [https://doi.org/10.1016/0360-3016\(92\)90768-d](https://doi.org/10.1016/0360-3016(92)90768-d)  
PMid:1534082
28. González Ferreira JA, Jaén Olasolo J, Azinovic I, Jeremic B. Effect of radiotherapy delay in overall treatment time on local control and survival in head and neck cancer: Review of the literature. *Rep Pract Oncol Radiother.* 2015;20(5):328-39. <https://doi.org/10.1016/j.rpor.2015.05.010>  
PMid:26549990
29. Haehl E, Rühle A, David H, Kalckreuth T, Sprave T, Stoian R, *et al.* Radiotherapy for geriatric head-and-neck cancer patients: what is the value of standard treatment in the elderly? *Radiation oncology (London, England).* 2020;15(1):31. <https://doi.org/10.1186/s13014-020-1481-z>  
PMid:32019576
30. Hata M. Radiation therapy for elderly patients with uterine cervical cancer: Feasibility of curative treatment. *Int J Gynecol Cancer.* 2019;29(3):622-9. <https://doi.org/10.1136/ijgc-2018-000077>  
PMid:30630886
31. Amini A, Jones BL, McDermott JD, Serracino HS, Jimeno A, Raben D, *et al.* Survival outcomes with concurrent chemoradiation for elderly patients with locally advanced head and neck cancer according to the National Cancer Data Base. *Cancer.* 2016;122(10):1533-43. <https://doi.org/10.1002/cncr.29956>  
PMid:26969811
32. Bentzen SM, Constine LS, Deasy JO, Eisbruch A, Jackson A, Marks LB, *et al.* Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): An introduction to the scientific issues. *Int J Radiat Oncol Biol Phys.* 2010;76(3):S3-9. <https://doi.org/10.1016/j.ijrobp.2009.09.040>  
PMid:20171515
33. Wang W, Hou X, Yan J, Shen J, Lian X, Sun S, *et al.* Outcome and toxicity of radical radiotherapy or concurrent Chemoradiotherapy for elderly cervical cancer women. *BMC Cancer.* 2017;17(1):510. <https://doi.org/10.1186/s12885-017-3503-2>  
PMid:28764676