

## Geriatric 8 screening of frailty in patients with prostate cancer

(前立腺癌患者のフレイル評価における Geriatric 8 スクリーニング)

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# Geriatric 8 screening of frailty in patients with prostate cancer

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**Running Head:** Frailty screening in prostate cancer

## Abstract

**Objectives:** To evaluate the association between the score of geriatric 8 (G8) and treatment by disease stages in patients with prostate cancer (PC).

**Methods:** Between January 2017 and June 2019, we prospectively evaluated the G8 in 540 PC patients who were treated with robot-assisted radical prostatectomy (RARP), radiotherapy (RT), androgen deprivation therapy alone (ADT-alone), and standard of care for metastatic hormone-naïve prostate cancer (mHNPc) or castration-resistant prostate cancer (mCRPC). The primary purpose was the association between the frailty ( $G8 \leq 14$ ) and RARP, RT, ADT-alone, and metastatic diseases. Secondary purposes included a comparison of the G8 scores among the disease status and the influence of G8 score on overall survival.

**Results:** The median age was 75 years.  $G8 \leq 14$  were seen in 36% of RARP ( $n = 78/214$ ), 57% of RT ( $n = 119/209$ ), 91% of ADT-alone ( $n = 19/21$ ), and 70% of metastatic diseases ( $n=67/96$ ). The median G8 score in patients treated with RARP, RT, ADT-alone, and metastatic diseases was 15.0, 14.0, 12.0, and 12.8, respectively. The median G8 score was significantly higher in the metastatic disease than that in localized disease (14.5 vs 12.8, respectively). The patients with RARP had a significantly higher G8 score than that of RT with the cutoff value of  $<14.5$ . The overall survival was significantly different between the  $G8 \leq 13$  and  $>13$  in the mHNPc patients, and between the  $G8 \leq 12$  and  $>12$  in the mCRPC patients.

**Conclusion:** The G8 score was significantly associated with treatment by disease stages in patients with PC.

**Keywords:** frailty; geriatric screening, G8, prostate cancer; prognosis

## INTRODUCTION

Frailty screening in patients with cancer has clinical value, but a full geriatric assessment of all candidates is time-consuming and not feasible in practice.<sup>1-10</sup> Several simple measures are available, including the Fried frailty phenotype criteria, modified frailty index, and the geriatric 8 (G8) screening tool.<sup>6, 11</sup> A recent systematic review found that the G8 was one of the most robust screening tools currently available and was associated with improved survival and decreased treatment-related complications.<sup>12</sup> Prostate cancer (PC) is the most frequently diagnosed male cancer in the USA, Europe, and Japan,<sup>13-21</sup> and treatment includes concerns of frailty because most patients are elderly and androgen deprivation therapy (ADT) can lead sarcopenia.<sup>22, 23</sup> As treatment of advanced PC often includes ADT plus steroid medications,<sup>24, 25</sup> management should include consideration of individual health status and frailty. However, not enough evidences are available supporting the usefulness of the G8 in PC patients.<sup>26, 27</sup> Therefore, we investigated the utility of the G8 to determine the prevalence of frailty in patients with localized and metastatic PC.

## **METHODS**

### **Ethics Statement**

This study was performed following the ethical standards of the Declaration of Helsinki and was approved by the ethics review board of the Hirosaki University School of Medicine (authorization number: 2014-297). All participants provided written or verbal informed consent. The study was registered on the UMIN-CTR (UMIN000025057).

### **Study Population and Treatment Protocol**

This prospective observational study included 544 patients with localized (M0) or metastatic (M1) PC who were treated at the Hirosaki University Hospital and Mutsu General Hospital between January 2017 and June 2019. The definition of M1 disease was the presence of metastatic prostate cancer at G8 evaluation. Eligible patients with localized PC and treated by robot-assisted radical prostatectomy (RARP), radiotherapy (RT), or androgen deprivation therapy alone (ADT-alone) depending on eligibility for surgery or patient preference. Eligible patients with metastatic PC were metastatic hormone-naïve prostate cancer (mHNPC) or metastatic castration-resistant prostate cancer (mCRPC) given a standard of care (SOC) treatment. The G8 score was evaluated at the initial visit to our hospitals before treatments. Some patients with mHNPC and all patients with mCRPC were treated with the short-term primary ADT or primary ADT ± alternative anti-androgen therapy, respectively. Patients with PC who could not be evaluated for frailty using the G8 and those with insufficient treatment information were excluded.

Treatment options were discussed, and recommendations made at weekly department medical conferences.

RARP was indicated for men with non-metastatic, localized PC with an acceptable lifetime expectancy (approximately >10 years). Contraindications included a history of extensive abdominal or pelvic surgery, severe comorbidities that prevent general anesthesia, morbid obesity, or patient refusal for surgery.

Treatment modality (RARP or RT) was recommended as often as possible for patients with localized PC.

Selection of treatment modalities was by shared decision making.

### **Patient Variables**

The patient variables evaluated at diagnosis were age, sex, serum prostate-specific antigen (PSA), hypertension (HTN), cerebro- or cardiovascular disease (CCVD), diabetes mellitus (DM), chronic respiratory disease (CRD), instrumental activities of daily living (IADL), Gleason score, clinical stage, D'Amico risk group, metastatic tumor burden, and metastatic disease status (mHNPC or mCRPC). Tumor stage and grade were assigned based on the 2009 TNM classification of the Union of International Cancer Control. Metastatic status was evaluated by conventional imaging modalities. Bone metastatic volume was evaluated by the extent of disease on bone scintigraphy. The high-volume disease was defined by the risk criteria of Chemo-hormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) trial in PC.<sup>17</sup>

### **Assessment of Frailty**

We assessed frailty by the patient's G8 score. The G8 includes eight items in multiple geriatric assessment domains and was administered at the initial outpatient clinic visit. The G8 score ranges from 0 to 17 with a frailty cutoff of  $\leq 14$ . IADL was assessed by the Tokyo Metropolitan Institute of Gerontology Index of Competence (TMIG) index.<sup>28</sup> The TMIG score ranges from 1–13. Functional capacity impairment (low IADL) was a score of  $< 11$  (an IADL of  $< 80\%$ ). We evaluated both the G8 and Fried phenotype criteria in 101 of 540 PC patients (19%). The five Fried phenotype criteria are weight loss, exhaustion, low physical activity, slowness, and weakness. Non-frail patients experienced from none to two characteristics (score 0–2); frail patients experienced three or more (score  $\geq 3$ ).<sup>6</sup>

## **Outcomes**

The primary purpose was to evaluate the association of frailty ( $G8 \leq 14$ ) with treatment by disease stages among the patients treated with RARP, RT, ADT-alone, and standard of care for M1 diseases. Secondary purposes included the comparison of the G8 scores among the disease status and the influence of G8 score on overall survival (OS). G8 cutoff score for the RARP and RT groups was estimated by receiver operating characteristic (ROC) curve analysis and the area under the curve (AUC). Multivariate logistic regression analysis was performed to identify the optimal cutoff value of frailty for poor OS in patients with mHNPC or mCRPC. Exploratory purpose included the association of the G8 score and Fried phenotype criteria for the definition of frailty.

## **Statistical Analysis**

Statistical analysis was performed with GraphPad Prism 5.03 (GraphPad Software, San Diego, CA, USA), BellCurve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan), and R 3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were compared using Fisher's exact test or the  $\chi^2$  test. Quantitative variables were expressed as means  $\pm$  standard deviation. The significance of between-group differences was determined by Student's *t*-test for normally distributed data or the Mann–Whitney *U* test for non-normally distributed data. The Kruskal–Wallis test was used to analyze differences between the three groups. OS was estimated using Kaplan–Meier analysis and compared by logrank test. A *P*-values  $< 0.05$  were considered statistically significant. Agreement of the frailty definitions determined by the two assessment tools was assessed using Cohen's  $\kappa$  coefficient with  $< 0$  for poor,  $0-0.2$  for slight,  $0.21-0.4$  for fair,  $0.41-0.6$  for moderate,  $0.61-0.8$  for substantial, and  $\geq 0.81$  for nearly perfect agreement.<sup>29</sup> Hazard ratios with 95% confidence intervals (95% CI) were calculated using multivariate Cox regression model for OS after controlling for potential confounders including frailty (G8  $\leq 14$ ,  $< 13$ ,  $< 12$ , or  $< 11$ ) and metastatic disease.

## RESULTS

### Patient Characteristics

Of 544 patients, we excluded 4 patients who did not fill out the full G8 questionnaires. The answer recovery rate was 99.3% ( $n = 540/544$ ) in this study. Of 540, 444 and 96 patients with M0 and M1



diseases were included (**Fig. 1A**). The patient characteristics are shown in **Table 1**. Of the 444 patients with M0 disease, 214 received RARP, 209 received RT, and 21 received ADT-alone. Of the 96 patients with M1 disease, 55 and 41 were diagnosed with mHNPc and mCRPC, respectively. The median age was significantly younger in the patients treated by RARP than those treated with non-surgical therapies (RT, ADT-alone or M1 disease) ( $P < 0.001$ ).

### **Primary Outcome**

The patients with frailty ( $G8 \leq 14$ ) in the RARP, RT, ADT-alone, and M1 disease were 36%, 57%, 91%, and 70%, respectively (**Fig. 1B**). The number of patients with frailty was significantly lower in the patients treated with RARP than those treated with RT ( $P < 0.001$ ), ADT-alone ( $P < 0.001$ ), and the M1 disease ( $P < 0.001$ ).

### **Secondary Outcomes**

The G8 score was significantly higher in the M0 than in the M1 group (14.5 vs 12.8, respectively;  $P < 0.001$ ; **Fig. 2A**). The G8 score was significantly higher in the RARP compared with the RT and ADT-alone groups (median score 15 vs 14 vs 12, respectively,  $P < 0.001$ , Kruskal–Wallis test; **Fig. 2B**). The optimal G8 cutoff score for the RARP and RT groups was  $<14.5$ , with an AUC of 0.623, the sensitivity of 67%, and specificity of 58% (**Fig. 2C**). We defined frailty as  $G8 \leq 14$  in the M0 group based on the median G8 score. OS was not significantly different between the  $G8 > 14$  and  $G8 \leq 14$  in patients treated with RARP (**Fig. 2D**) and RT (**Fig. 2E**). The G8 scores of patients with mHSPC and mCRPC were

not significantly different (12.0 vs 13.0,  $P = 0.891$ , **Fig. 3A**). The time trend analysis of G8 score in patients with mCRPC showed no significant association of G8 and time from mHNPC in patients with mCRPC (**Fig. 3B**). Tumor volume (CHAARTED criteria) was not significantly associated with frailty (**Fig. 3C**). Castration-resistant status adjusted Cox regression analysis for OS in the M1 disease showed G8  $\leq 13$ ,  $\leq 12$ , and  $\leq 11$  showed a significant association with a poor OS (**Fig. 3D**). We defined frailty as G8  $\leq 13$  in the mHNPC, and G8  $\leq 12$  in the mCRPC based on the prognostic viewpoint. A significant difference was observed in OS between the G8  $\leq 13$  and  $>13$  in the patients with mHNPC (**Fig. 3E**) and between the G8  $\leq 12$  and  $>12$  in the patients with mCRPC (**Fig. 3F**).

### **Exploratory Outcome**

A subset of 101 patients was evaluated by the G8 and Fried phenotype criteria, including 64 with M0 and 37 with M1 disease. A waterfall plot of G8 (**Fig. 4A**) showed that 56 of those patients (56%) were identified as frail (G8  $\leq 14$ ). Fried phenotype criteria indicated that 19 of those patients (19%) were frail ( $\geq 3$ ) (**Fig. 4B**). The agreement for the definition of frailty (G8  $\leq 14$ ) versus Fried phenotype criteria ( $\geq 3$ ) was slight (Cohen's  $\kappa = 0.166$ ;  $P = 0.022$ , **Fig. 4C**). The agreement for the definition of frailty (G8  $\leq 13$ ) versus Fried phenotype criteria ( $\geq 3$ ) was fair (Cohen's  $\kappa = 0.268$ ;  $P = 0.007$ , **Fig. 4D**).

## **DISCUSSION**

This prospective observational study found that the G8 score was significantly different not only in the metastatic status but also treatment selection. More than half of patients had frailty in the patients with ADT-alone (91%), followed by M1 disease (70%) and RT (57%). Our results showed that patients with ADT-alone had highest prevalence of frailty ( $G8 \leq 14$ ) than that with the M1 disease. It might be in line with a clinical experience because we selected ADT-alone for severe frail patients who were not indicated for RARP and RT. The median G8 score was significantly higher in the patients with RARP than that with the RT (15.0 vs 14.0, respectively), and the optimal cutoff value between the RARP and RT was  $<14.5$ , suggesting the feasibility of cutoff  $\leq 14$  as general frailty in Japanese patients with localized PC. This observation was also acceptable because we selected RT in patients who were not eligible for surgery such as the presence of CCVD and low-IADL (**Fig. S1**). Our finding suggested frailty had significant influence on treatment selection in patients with localized disease.

We found a significant difference in the G8 scores of patients with M0 and M1 diseases (**Fig. 2A**). However, the G8 scores of patients with mHNPc or mCRPC were not significantly different (**Fig. 3A**). Our analysis also showed no significant association of G8 and time from mHNPc in patients with mCRPC (**Fig. 3B**). This finding suggests that the effect of ADT on the frailty of patients with mHNPc might not be reflected in the G8 score although a previous study reported a negative

association of ADT and sarcopenia.<sup>23</sup> A comprehensive geriatric assessment might be necessary to detect the frailty in those patients. Further study is necessary to validate our findings.

The general cutoff of  $G8 \leq 14$  was not significantly associated with poor prognosis in the M0 and M1 patients. This discrepancy might be short follow up periods and ethnic differences in the Japanese population. The death events in the RARP, RT, and ADT-alone groups were 1 (non-cancer death), 0, and 0, respectively. Therefore, longer follow-up is necessary to evaluate the effect of frailty on prognosis in the M0 group. Also, there are concerns to accommodate of  $G8 \leq 14$  for frailty in Japanese patients because of the assumed body mass index (BMI) range. As the median BMI in the Japanese population is reported as  $23 \pm 3.2$ , approximately one-third of the patients could lose 1–2 points in their G8 score despite not being frail. We found a significant association of G8 cutoff  $\leq 13$  and  $\leq 12$  in the prediction of poor OS in patients with mHNPC and mCRPC. Although the previous study suggested the feasibility of  $G8 \leq 14$  for poor prognosis in several cancers,<sup>12, 30</sup> the cutoff of  $G8 \leq 13$  and  $\leq 12$  may be useful for the prediction of poor OS in patients with mHNPC and mCRPC, respectively. However, further study is necessary to find specific G8 cutoff scores for the type and stage of cancers.

The agreement of different frailty assessment tools needs mention. We determined both the G8 score and Fried phenotype criteria in 101 of 540 patients. We observed not enough agreement of the two estimates between the Fried phenotype frailty and the  $G8 \leq 14$  (Cohen's  $\kappa = 0.166$ , slight), and between the Fried phenotype frailty and the  $G8 < 13$  (Cohen's  $\kappa = 0.268$ , fair). It was not surprising because the tools

evaluate different aspects of frailty. The Fried criteria include five phenotypes associated with frailty, while the G8 screening tool is a questionnaire-based scoring system. A systematic review of studies predicting frailty in elderly patients with cancer reported that the G8 had a high sensitivity (87%) but poor specificity (61%) for frailty. Similarly, the Fried phenotype criteria had a high specificity for (91%) but poor sensitivity (31%)<sup>11</sup>. These results suggested the use of a single frailty screening tool is not sufficient to identify frail patients. As a consensus on frailty criteria is lacking, further studies are needed to identify a suitable tool for frailty assessment.

The study limitations include the small sample size, selection bias, and unmeasurable confounding factors. The results may not be generalized to other countries because of racial and regional differences. Despite these limitations, the study demonstrates the clinical value of the G8 score in patients with localized and metastatic PC. As no previous study evaluated the utility of G8 scores, our results suggested that frailty is a key factor in treatment selection in clinical practice. Further study is necessary to assess the utility and benefit of G8 for prostate cancer.

In conclusion, the G8 score was significantly associated with treatment selection by disease stages in patients with PC.

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## **Conflict of Interests**

The authors have no conflicts of interest to declare.

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## FIGURE LEGENDS

**Fig. 1. Patient selection and primary outcome measures.** The study prospectively included 540 patients with prostate cancer (PC), 444 patients with localized M0 disease and 96 with M1 metastatic disease (**A**). The prevalence of frailty (G8 score  $\leq 14$ ) in patients treated with robot-assisted radical prostatectomy (RARP), radiotherapy (RT), and androgen deprivation therapy alone (ADT-alone), and metastatic disease (M1) treated with a standard of care (SOC) are shown (**B**).

**Fig. 2. Secondary outcome measures in patients with localized diseases.** The G8 scores of patients with localized M0 and metastatic M1 disease were compared (**A**). The G8 scores of M0 patients with robot-assisted radical prostatectomy (RARP), radiotherapy (RT), and androgen deprivation therapy (ADT) alone were compared (**B**). The optimal G8 cutoff between RARP and RT patients were estimated by receiver operating characteristic (ROC) curve analysis and the area under the curve (AUC) (**C**). Overall survival was evaluated between the G8  $\geq 14$  and  $< 14$  in patients with RARP (**D**) and RT (**E**).

**Fig. 3. Secondary outcome measures in patients with metastatic disease.**

The G8 scores of M1 patients with metastatic hormone-naïve prostate cancer (mHNPC) and metastatic castration-resistant prostate cancer (mCRPC) were compared (A). The association of G8 score and time from mHNPC diagnosis in the mCRPC patients were evaluated (B). Tumor volume was compared between the CHAARTED-low and -high volumes (C). Castration-resistant status adjusted Cox regression analysis was performed to investigate the significant value of the G8 score for poor OS (D). OS was evaluated between the G8  $\leq 13$  and  $>13$  in patients with mHNPC (E), and between the G8  $\leq 12$  and  $>12$  in patients with mCRPC (F).

**Fig. 4. Exploratory outcome.** The G8 scores (A) and Fried phenotype criteria scores (B) were shown (case numbers corresponded to each other). The agreement of scores identifying frailty between a G8  $\leq 14$  and Fried phenotype criteria  $\geq 3$  was slight,  $\kappa = 0.166$ ,  $P = 0.022$  (C). The agreement of scores between a G8 score  $<13$  and Fried phenotype criteria  $\geq 3$  was fair,  $\kappa = 0.268$ ,  $P = 0.007$  (D).

**Supplementary figure**

**Fig. S1. The association of treatment and comorbidities.**

The presence of comorbidities between the patients treated with RARP and others (RT, ADT-alone, or M1 disease) were compared. Comorbidities included hypertension (HTN), cerebro- or cardiovascular disease

(CCVD), diabetes mellitus (DM), chronic respiratory disease (CRD), instrumental activities of daily living

(IADL). SOD: standard of care.