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The incremental value of a geriatric assessment-derived three-item scale on estimating overall survival in older adults with cancer

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ABSTRACT

Objective: A geriatric assessment (GA) assesses functional age of older patients with cancer and is a well-established tool predictive of toxicity and survival. The objective of this study was to investigate the prognostic value of individual GA items.
Materials and Methods: 546 patients with cancer ≥ 65 years completed GA from 2009 to 2014 and were followed for survival status for a median of 3.7 years. The GA consisted of function, nutrition, comorbidity, cognition, psychological state, and social activity/support domains. GA items with $p < 0.05$ in univariable analyses for overall survival (OS) were entered into multivariable stepwise selection procedure using a Cox proportional hazards model. A prognostic scale was constructed with significant GA items retained in the final model.
Results: Median age was 72 years, 49% had breast cancer, and 42% had stage 3–4 cancer. Three GA items were significant prognostic factors, independent of traditional factors (cancer type, stage, age, and Karnofsky Performance Status): (1) "limitation in walking several blocks", (2) "limitation in shopping", and (3) "≥ 5% unintentional weight loss in 6 months". A three-item prognostic scale was constructed with these items. In comparison with score 0 (no positive items), hazard ratios for OS were 1.85 for score 1, 2.97 for score 2, and 8.67 for score 3. This translated to 2-year estimated survivals of 85%, 67%, 51% and 17% for scores of 0, 1, 2 and 3, respectively.
Conclusions: This three-item scale was a strong independent predictor of survival. If externally validated, this could be a streamlined tool with broader applicability.

1. Introduction

An accurate estimate of overall survival is essential for shared decision-making between patients with cancer and clinicians. Survival of patients with cancer is typically estimated based on cancer type, disease stage and oncology performance status measures, such as Karnofsky Performance Status (KPS) or Eastern Cooperative Oncology Group (ECOG) performance status, regardless of age [1,2]. A concern is that these performance status measures do not address the heterogeneity in health status of older adults with cancer [3]. Geriatric assessment (GA) is a helpful tool to identify multidimensional impairments in older patients which are potentially associated with adverse outcomes (i.e., treatment-related toxicities, postoperative complications and functional decline) and survival [4]. The routine use of GA in older adults with cancer is recommended by the International Society of Geriatric Oncology (SIOG) and U.S. National Comprehensive Cancer Network (NCCN); however, there is no consensus on a standard GA tool [5,6]. Partially because of differences in the GA tools used in various studies, the GA variables identified as prognostic for survival have not been consistent across studies [7–10]. Further, the prognostic value of individual items in each GA domain has not been elucidated as most prior studies have focused on associations between GA domains and survival.

In the U.S., the cancer-specific GA developed by Hurria et al. has been the most studied, and its feasibility and utility in routine practice and clinical trials has been demonstrated [11–14]. Using this particular GA, a "chemotherapy toxicity risk score" (CTRS) for older adults with patients receiving chemotherapy was developed and validated [15,16]. Building on prior CTRS research, the aim of this study was to evaluate the prognostic value of individual items in the cancer-specific GA for survival, independent of traditional factors such as cancer type, disease stage, treatment, age, and performance status. Prognostic factors identified as significant were used to construct a scale to predict survival in older adults with cancer.

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2. Methods

2.1. Patient Population

The "Carolina Senior Registry" (CSR) is a cross-sectional study of patients with cancer 65 years or older who completed a cancer-specific GA regardless of cancer type, stage or treatment status (CSR; ClinicalTrials.gov identifier NCT01137825); the sample method is a non-probability sampling [13]. Informed consent had been obtained from all patients prior to participation in the Registry. Eligibility was restricted to patients able to speak and read English. For the present study, we limited analysis to 546 patients in the CSR who were recruited at the North Carolina Cancer Hospital, a large academic medical center, between October 2009 and September 2014 and whose records were linked to the North Carolina Central Cancer Registry (NCCCR) [17]. Survival status was determined through linking to the National Death Index, Social Security Death Index, and North Carolina State Center for Vital Statistics, and was available through August 2015. The patients who remained alive on August 31, 2015, were censored. The NCCCR collects data on all cancers diagnosed in the state of North Carolina including date of diagnosis, cancer type, stage, all-cause and cancer-specific mortality. If there were unspecified cancer-related variables (e.g. cancer type and stage) in the dataset, medical records were reviewed for clarification. Treatment data were extracted from medical records and summarized as curative or palliative intent treatment. The study protocol was approved by the UNC Institutional Review Board.

2.2. Cancer-specific Geriatric Assessment (GA)

The cancer-specific GA used in the CSR was developed by Hurria et al. and is comprised of validated measures [11]. The section of the GA completed by a health-care professional (clinical staff or research assistant) includes the following measures: Karnofsky Performance Status (KPS), Timed Up and Go (TUG) test, Blessed Orientation Memory Concentration (BOMC) test, and Body Mass Index (BMI). Measures that are completed by a patient include: Activities of Daily Living (ADL, subscale of Medical Outcomes Study (MOS) Physical Health), Instrumental Activities of Daily Living (IADL, subscale of the Older American Resources and Services (OARS)), falls, vision, hearing, comorbidities, medications, nutrition, psychological state (Mental Health Inventory-17 (MHI-17)), and social support/function (MOS Social Activity/Social Support Survey).

2.3. Statistical Analysis

Patient and tumor characteristics and geriatric assessment results were summarized descriptively. The primary outcome was overall survival (OS) measured from the date of completion of the GA to date of death. Survival was estimated using the Kaplan Meier method and survival curves were compared using the log rank test.

We ran univariable Cox proportional hazards models to identify variables significantly associated with OS ($p < 0.05$). Individual GA items were dichotomized at the median or at a previously reported cut-off value [15,18]. Variables significant in the univariable analyses were selected for inclusion in a multivariable backward stepwise selection procedure, with a removal criterion of $p > 0.05$ and an entry criterion of $p < 0.025$. To address the potential for collinearity, correlations between all univariable significant items were assessed using Cramer's V; values > 0.50 were considered strong collinearity [9,19]. When there was strong correlation between two variables, the variable with the best Akaike information criterion (AIC) value was entered into the stepwise selection procedure. We included cancer type, stage, treatment, age and KPS to models, as these are traditional factors known to be associated with mortality. The treatment variable was categorical (curative or palliative intent treatment). Because the GA was administered to participants at varying times from diagnosis, time from diagnosis to completion of the GA was also included as a covariate. For sensitivity analysis, we repeated the variable selection procedure using forward stepwise selection.

A prognostic scale was constructed with variables retained in the final stepwise model. The final model was internally validated by calculating the 95% confidence intervals (CIs) for hazard ratios and C-statistic using a nonparametric bootstrap method with 1000 unrestricted random samples. The incremental value of the prognostic scale was assessed by comparing the C-statistic of a model using traditional factors only and then adding the prognostic scale to the traditional factors. We also used the net classification improvement (NRI) proposed by Pencina et al. as a further measure for quantifying the added value from the new predictors [20]. The NRI provides a more rigorous statistical approach to quantifying the correctness of reclassification or movement of predicted probabilities as a result of adding a new variable into prediction models. We used the NRI to evaluate the additive prognostic value of the scale for all-cause mortality at 1 and 2 years [21]. Calibration plots were used to evaluate the performance characteristics of the prognostic scale [22].

As there were differences among patients in time from diagnosis to completion of the GA, an exploratory subgroup analysis was performed with 179 patients who completed the GA within 3 months of their date of diagnosis (incident cancer group). We assessed the prognostic value of the scale for cancer-specific survival. Finally, we performed a subgroup analysis in patients with breast cancer as approximately 50% of patients had breast cancer in this cohort and an exploratory analysis stratified by the treatment variable (curative vs palliative).

Analyses were performed using Stata 14 software (College Station, TX: StataCorp LP) and the R package ("survIDINRI" and 'rms').

3. Results

3.1. Patient Characteristics

From October 2009 to September 2014, 703 patients age ≥ 65 years with various types of cancer were enrolled in the CSR. Of the 703 patients, 546 patients had adequate GA, tumor-specific and survival data [17]. Among the 546 patients included in our analysis, the median age of the study population was 72 years at the time of the GA (range, 65 to 100 years), and 72% of patients were female. The most common type of cancer was breast cancer (49%) and 42% of patients had a stage 3–4 cancer. Most patients had a physician-rated KPS of 80 or greater (81%), with a range of 30 to 100. More detailed patients' characteristics are shown in Table 1. The baseline characteristics of the 157 patients excluded in the process of the data linkage were similar to those included in the final dataset based on bivariable analyses: median age 73 years ($p = 0.30$), 67% female ($p = 0.20$), 87% white ($p = 0.69$), 45% breast cancer ($p = 0.32$) and 78% physician-rated KPS ≥ 80 ($p = 0.44$).

3.2. Geriatric Assessment Results

In total, 39% patients had a MOS-ADL score lower than 70, with a higher score indicating better physical capacity (Table 2). Thirty-seven percent of patients reported impairment in at least one IADL and 24% had at least one fall in the last 6 months. Unintentional weight loss ≥ 5% in the past 6 months was reported in 22% of patients. The median number of comorbidities and prescribed medications were two and five, respectively. Five percent of patients had abnormalities in cognition on the BOMC test.

3.3. Univariable Survival Analysis

The median time since the GA was conducted was 3.7 years (range 0.9 to 5.7 years). 191 patients died from any cause, with an overall 1-year risk of mortality of 20%. 143 deaths (74.9%) were attributable to cancer. Cancer-related factors (cancer type, stage and treatment

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