



Research Article

Patient-Reports of Fatigue and Cognitive Changes in Cancer Survivors

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Conclusion: High proportions of old-old cancer survivors may experience perceived cognitive change and pervasive fatigue after cancer treatment and reports may be common in patients treated with radiotherapy. Supportive care in survivorship should include focus on factors that may influence these symptoms, including anxiety, sleep disorders and fear of recurrence. These findings may also inform patient counseling prior to cancer treatment.

Introduction

As life expectancy in the United States increases, more and more elderly persons develop and survive cancer, going on to join a growing population of elderly cancer survivors [1]. This group is relatively poorly understood, particularly those 75 years and older [2]. As this population grows, the oncologic community is faced with numerous challenges, including understanding the complex intersection of cancer biology and aging, the efficacy of various treatments in this unique population and the management of their survivorship.

Patient-reported outcomes are a unique way of assessing patient needs, with increasing evidence supporting their use [3]. Patient-reported outcomes may be difficult to obtain, particularly for underserved groups such as old-old cancer survivors, but may shed particular light on certain clinical issues that are most difficult for clinicians to assess. Among these are the subjective complaints of perceived cognitive changes and pervasive fatigue [4]. Clinicians know that many cancer patients and survivors report these findings, but they can be difficult for clinicians to assess and document and are likely under-reported in the general literature. These symptoms may be multi-factorial in nature and be associated with mental health concerns (anxiety and depression), sleep and circadian disruptions, medical illness, pharmacologic issues and general illness. Elderly cancer survivors may encounter (or have recently encountered), each and every one of these issues and are thus at high risk for development of cognitive change and fatigue. This study was undertaken to understand the incidence of these complaints in older survivors, particularly those who have received radiotherapy.

Methods

Older cancer survivors utilized an Internet-based resource for creation of survivorship care plans by their own volition, creating a convenience sample frame. The care plan program allows patients to answer a series of questions in order to generate a detailed survivorship care plan, the details of which have been described previously [5]. Created in 2007 by a team of oncology nurses and physicians, the tool has undergone several revisions and modifications to include questions regarding patient-related outcomes and late sequela in order to provide more focused information for the user. Survivors are queried regarding their experience with perceived cognitive changes via the question "are you concerned about cognitive changes, such as memory loss, difficulty with short-term memory, concentration, or learning new skills?" and about pervasive fatigue via the question "Are you experiencing fatigue (overwhelming physical, mental or emotional

Abstract

Background: The population of elderly cancer survivors living in the United States continues to increase. Here, we examine perceived cognitive change and pervasive fatigue as reported by a group of "old-old" (75 years or older) cancer survivors.

Methods: A convenience sample was gathered from users of an Internet-based tool for creation of survivorship care plans. Survivors utilized the care plan tool voluntarily, providing data regarding demographics, cancer diagnosis and treatments received, as well as late effects experienced.

Results: 174 old-old survivors utilized the tool to create care plans over a 12-month period. Median diagnosis age was 79 years and median current age 80 years, with a median of 1 year since diagnosis. Breast cancer, lung and gastrointestinal cancers were the most common diagnoses and over half of users had received radiotherapy, most commonly to chest wall, lung and pelvis. Perceived cognitive changes were reported by 38% of the total population and was highest in the group receiving radiation, as well as those <1 year from cancer diagnosis and those 80 years or older. Pervasive fatigue was reported by 46% and reports were highest in the group receiving radiation, those >1 year from diagnosis and those 80 years or older. Radiation appeared to be associated with increased reports of cognitive change and fatigue regardless of site irradiated.

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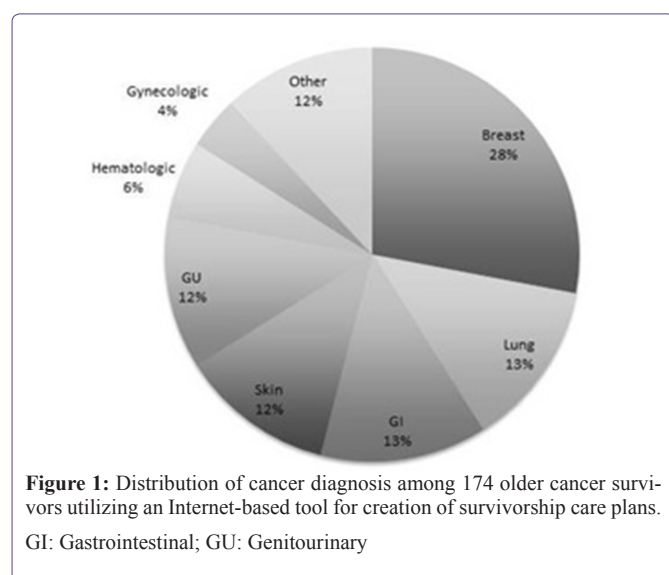
Citation: Frick M, Vachani C, Bach C, Arnold-Korzienowski K, Metz J, et al. (2018) Patient-Reports of Fatigue and Cognitive Changes in Cancer Survivors. J Gerontol Geriatr Med 4: 018.

Received: October 12, 2017; **Accepted:** April 27, 2018; **Published:** May 11, 2018

exhaustion)?" Responses to these questions included "yes," "no," and "don't know" and were collapsed into two categories ("yes" versus "no" and "don't know") for analysis. Survivors also provide information on demographics (age, race, gender), cancer diagnosis and cancer treatments received. We used Fisher's exact tests to assess the statistical significance of comparisons; statistical significance was defined as $p < 0.05$. Institutional Review Board approval was obtained prior to any study proceedings. For this study, data were obtained from the survivor user database for all survivors with a diagnosis age of 75 years or older.

Results

Over a 12 month period (October, 2014 - October, 2015), 4309 care plans were created by survivors using this tool. Of these, 174 were created by persons age 75 years or older at the time of cancer diagnosis. Older cancer survivors ranged in age from 75-99 years at the time of cancer diagnosis (median 79 years) and from 76 - over 100 years at the time of care plan completion (median 80 years). The median time from diagnosis was 1 year, with a maximum time of 16 years. Older survivors were 68% female ($n = 118$) and 83% white ($n = 144$). The most common cancer diagnosis was breast cancer ($n = 48$, 28%), followed by lung and gastrointestinal cancers (each $n = 22$, 13%) and skin and genitourinary cancers (each $n = 21$, 12%) (Figure 1). Approximately half (52%, $n = 91$) of this group of survivors was treated with radiotherapy, most commonly to the intact breast or chest wall (32%, $n = 29$), thorax in the setting of lung cancer (12%, $n = 11$), or pelvis (11%, $n = 10$) for prostate, gynecologic, or gastrointestinal cancers; only one user reported having received cranial radiotherapy. Many survivors reported having received multimodality therapy, with 68% ($n = 118$) having undergone surgical treatments and 49% ($n = 85$) having received chemotherapy. Demographics and treatment characteristics are further summarized in table 1.



Of the entire group, 38% ($n = 66$) of older survivors noted perceived cognitive changes occurring since cancer diagnosis and treatment. The incidence of this complaint was highest in the group having received radiotherapy (46%, $n = 41$), compared to chemotherapy (38%, $n = 32$) and surgery (32%, $n = 38$) ($p =$ Not Significant [NS]

and 0.04, respectively). Pervasive fatigue or tiredness was noted by 53% ($n = 92$) of the entire group of older survivors. The incidence of fatigue was highest in the group treated with chemotherapy (61%, $n = 52$) versus 51% ($n = 46$) of those who had received radiotherapy and 45% ($n = 53$) who underwent surgery ($p =$ NS and 0.02, respectively).

Survivor Characteristics	N (%)
Gender	
Male	56 (32%)
Female	118 (68%)
Race	
Caucasian	144 (83%)
African-American	13 (2%)
Other	7 (4%)
Age	
Diagnosis	
Median	79 years
Range	75->100 years
Current	
Median	80 years
Range	76->100 years
Time Since Diagnosis	
Median	1 year
Range	<1-16 years
Treatments Received	
Radiation	91 (52%)
Breast/chest wall	30 (32%)
Thorax	11 (12%)
Pelvis	10 (11%)
Head and neck	6 (3%)
Skin	6 (3%)
Brain	1 (1%)
Other	27 (30%)
Chemotherapy	85 (49%)
Surgery	118 (68%)

Table 1: Characteristics of "old-old" cancer survivors utilizing an Internet-based tool for creation of survivorship care plans and providing patient-reported information on late effects.

Cognitive changes were noted more frequently in users <1 year from diagnosis ($n = 88$), who admitted to cognitive changes in 41% ($n = 36$) of cases - this was compared to 29% ($n = 25$) of users noting perceived cognitive changes one or more years from cancer diagnosis ($n = 86$) ($p = 0.07$). In contrast, the group <1 year from diagnosis noted pervasive fatigue less often than the group diagnosed >1 year prior (42% ($n = 37$) vs 62% ($n = 53$), $p = 0.005$).

Incidence of perceived cognitive change and pervasive fatigue were separately analyzed according to current age of user (those aged 75-79 years ($n = 81$), compared to those 80 years and older ($n = 93$). Incidence of both perceived cognitive changes and pervasive fatigue was higher in older survivors, regardless of treatment modality (32% and 48% in those less than 80 years versus 46% and 60% in those 80 years or older, respectively, $p = 0.05$ and $p = 0.04$). In the younger group (those ages 75-79), treatment with radiation was associated with increased report of fatigue compared to those not receiving

radiation (53% vs 44%, $p = 0.04$), but rates of perceived cognitive change were similar in those having received radiation and those not (31% vs 33%, $p = \text{NS}$). In the older group (80 years and older), treatment with radiation was associated with increased report of both fatigue (65% vs 57%, $p = 0.06$) and perceived cognitive change (60% vs 31%, $p = 0.03$) compared to those not receiving radiation. Reports of cognitive changes and fatigue are further summarized in figure 2.

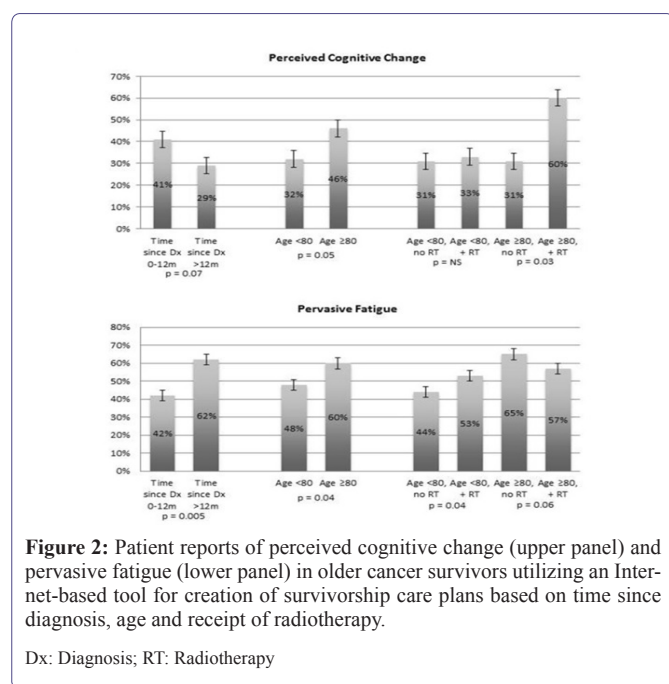


Figure 2: Patient reports of perceived cognitive change (upper panel) and pervasive fatigue (lower panel) in older cancer survivors utilizing an Internet-based tool for creation of survivorship care plans based on time since diagnosis, age and receipt of radiotherapy.

Discussion

In this paper, we report high incidence of patient-reported cognitive change and pervasive fatigue in a group of older cancer survivors. This group is increasingly being recognized as its numbers increase, both due to the general aging of the United States population (with persons over 65 years accounting for 60% of all new cancer diagnoses) and to improved rates of cancer survival [6]. As the number of elderly cancer survivors in the United States increases, particular attention must be turned to the unique needs of this population, both during selection of treatment options and during management of overall health after a cancer diagnosis. Treating and curing, cancer in this select population requires clinicians to be aware of multiple competing forces: first, the avoidance of “ageism” that may prevent cancer patients above a certain age from participating in clinical trials, or influence their care providers to offer less aggressive treatment simply because of age [7]. Minimal evidence exists to support the suggestion that elderly cancer patients cannot tolerate aggressive cancer treatment simply because of age, however, suggesting that this group of patients should generally be offered standard treatments. Having said this, clinicians must be aware of unique needs for supportive care, the effects of co-morbidities and unique survivorship risks as they counsel and care for elderly patients.

Our work examines the incidence of two patient-reported outcomes that have been previously demonstrated to impact survivor quality of life and which are difficult, if not impossible, to measure

based on clinician report. Cognitive changes have long been associated with cranial radiotherapy and certainly continue to be; however, the association of cognitive change with chemotherapy, aggressive medical care and co-morbidities such as anxiety, depression and fear of recurrence, is only beginning to be understood [8,9]. In our study, approximately one-third of older cancer survivors reported perceived cognitive change a median of 1 year from diagnosis. This risk appeared to be highest, approaching 50%, in patients who had received radiotherapy as compared to other treatment modalities, despite radiation being delivered to non-cranial sites in >99% of subjects. Cognitive changes appeared to be more common in patients who had more recently been diagnosed with cancer, as well as those 80 years and older. Interestingly, in the oldest group of patients (those >80), 60% of users having received radiotherapy reported perceived cognitive change compared to 30% of those who did not receive radiation.

Certain of these findings are less surprising than others, especially as many studies have demonstrated that older patients are at greater risk of overall treatment toxicity [10]. For example, increasing age may be expected to be associated with increased risk of perceived cognitive changes, such as difficulty with short-term memory. It may also be the case that by nature of age, older patients may have less cognitive reserve and therein have a lower threshold before experiencing post-treatment cognitive decline [11]. The association of cognitive change with a more recent cancer diagnosis may be associated with anxiety and/or fear of recurrence, both have which have been previously demonstrated to decrease with time from diagnosis [12]. The literature on cognitive change following cancer treatment has produced broad and mixed results, likely due to differences in patient populations, treatment modalities, assessment instruments and other aspects of study methods [9]. By any means, what these studies have suggested is that certain subgroups of patients experience post-treatment cognitive deficits and in conjunction with our results, provide reason for further exploration of cognitive decline in the subgroup of elderly cancer survivors [9,11,13-17].

The finding that non-cranial radiotherapy may be associated with increased reports of perceived cognitive change, both in the entire group and when age is accounted for, is more difficult to explain based on our current understanding of radiobiology and absence of clinical exploration. This finding, however, remains important in terms of patient counseling and survivor management. It is possible that improved supportive care (nutrition, sleep and management of co-morbidities) could improve quality of life for elderly survivors who perceive cognitive changes and further investigations using detailed psychometric evaluation are certainly warranted.

Fatigue after cancer diagnosis and treatment is also increasingly recognized as an important quality of life issue and can persist long after treatment termination [18-22]. Certainly, fatigue may influence cognition and cognitive perception and vice versa, and this has been more clearly demonstrated in non-oncologic populations [23,24]. Our study shows a higher overall incidence of patient reported fatigue than perceived cognitive change in this population of older survivors, with over half describing overwhelming fatigue or tiredness when queried. Interestingly, fatigue was more common in survivors who had been diagnosed over a year before care plan completion and in those who were older. Additionally, fatigue was associated with receipt of radiotherapy in all survivors in this study, both those 75-79 years and those 80 and older. This is in contrast to studies in younger survivor

populations which have shown recovery from fatigue to baseline approximately seven months after radiotherapy [25].

Again, findings of pervasive fatigue are certainly important in patient counseling and, perhaps more importantly, in support of elderly cancer survivors. Elderly persons are recognized to have different circadian needs compared to younger persons, and clinical management of sleep disorders in elderly persons requires a unique set of understanding and skills [26]. Additionally, pervasive fatigue often occurs in a cluster alongside pain, insomnia and mood disturbance in the elderly patient, the combination of these negatively influencing functional status and quality of life [19]. The relationships between these symptoms, including cognitive change, are complex and multi-factorial with certain aspects likely unique to the elderly population [27]. Recognizing that these symptoms occur collectively highlights the importance of a comprehensive assessment of the elderly cancer survivor and integrated approach in intervention.

The data presented here represent an initial analysis of patient-reported outcomes in an under-represented population and should be considered hypothesis-driving. The data are limited by their convenience sample frame and by the relative simplicity of the questions posed to users regarding fatigue and cognitive change; however, the high incidence of reports of both symptoms, as well as their association with non-cranial radiotherapy, warrants further investigation. Future directions will include more detailed assessment of both cognitive concerns and fatigue using longer assessments. In the meantime, these authors support use of curative cancer therapy for patients who can tolerate these, regardless of age; however, we recommend additional counseling, concern and management of both fatigue and cognitive concerns for aging patients, particularly those who have received radiotherapy.

Conflicts of Interest

There are no conflicts of interest to disclose on the part of any author.

Acknowledgment

This work was funded in part by a grant from the LIVESTRONG Foundation.

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