Clinical Oncology xxx (2018) 1–12

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Older Age, Early Symptoms and Physical Function are Associated with the Severity of Late Symptom Clusters for Men Undergoing Radiotherapy for Prostate Cancer

A. Lemanska *, D.P. Dearnaley †, R. Jena ‡, M.R. Sydes §, S. Faithfull *

* School of Health Sciences, Faculty of Health and Medical Sciences, University of Surrey, Guildford, UK
† Institute of Cancer Research and Royal Marsden NHS Trust, London, UK
‡ Cambridge University Hospitals, Addenbrookes Hospital, Cambridge, UK
§ MRC Clinical Trials Unit at UCL, Institute of Clinical Trials and Methodology, London, UK

Received 31 August 2017; received in revised form 15 December 2017; accepted 22 December 2017

Abstract

Aims: To identify symptom clusters and predisposing factors associated with long-term symptoms and health-related quality of life after radiotherapy in men with prostate cancer.

Materials and methods: Patient-reported outcomes (PROs) data from the Medical Research Council RT01 radiotherapy with neoadjuvant androgen deprivation therapy trial of 843 patients were used. PROs were collected over 5 years with the University of California, Los Angeles Prostate Cancer Index (UCLA-PCI) and the 36 item Short-Form Health Survey (SF-36). Symptom clusters were explored using hierarchical cluster analysis. The association of treatment dose, baseline patient characteristics and early symptom clusters with the change in severity of PROs over 3 years was investigated with multivariate linear mixed effects models.

Results: Seven symptom clusters of three or more symptoms were identified. The clusters were stable over time. The longitudinal profiles of symptom clusters showed the onset of acute symptoms during treatment for all symptom clusters and significant recovery by 6 months. Some clusters, such as physical health and sexual function, were adversely affected more than others by androgen deprivation therapy, and were less likely to return to pretreatment levels over time. Older age was significantly associated with decreased long-term physical function, physical health and sexual function ($P < 0.001$). Both baseline and acute symptom clusters were significant antecedents for impaired function and health-related quality of life at 3 years.

Conclusions: Men with poorer physical function and health before or during treatment were more likely to report poorer PROs at year 3. Early assessment using PROs and lifestyle interventions should be used to identify those with higher needs and provide targeted rehabilitation and symptom management.

Keywords: Acute symptoms; late symptoms; PROs; prostate cancer; radiotherapy; survivorship; symptom clusters

Introduction

Prostate cancer (PCa) survival has improved significantly over the last decade. More than 84% of men now survive 10 years or more in the UK [1] and the number of survivors is growing by 3% every year [2]. Globally, more than 1.1 million cases of PCa were recorded in 2012. This constitutes 8% of all cancers and 15% of cancers in men, making PCa the second most common cancer in men [3]. With increasing survival, cancer-related symptoms and treatment-related toxicity can affect men's long-term health-related quality of life (HRQOL) [4]. Common side-effects after prostate radiotherapy include decreased urinary, bowel and sexual functions and these affect supportive care needs of men [5]. Population-based studies of long-term functional outcomes after PCa suggest that at 12 years from treatment, 87% of men will have erectile dysfunction or sexual inactivity, 20% urinary incontinence and 14% bowel problems [6]. These figures are substantially lower in men without cancer and of a similar age (62, 6 and 7%, respectively). Androgen deprivation therapy (ADT) is commonly used with radical

Author for correspondence: A. Lemanska, School of Health Sciences, Faculty of Health and Medical Sciences, University of Surrey, Guildford GU2 7XH, UK. Tel: +44-1483689384.
E-mail address: a.lemanska@surrey.ac.uk (A. Lemanska).

https://doi.org/10.1016/j.clon.2018.01.016
0936-6555/

radiotherapy for intermediate- or high-risk PCa. It allows for better long-term PCa control than with radiotherapy alone. However, it can add fatigue, hot flushes or muscle and bone loss to the spectrum of expected side-effects [7,8].

The prevalence of long-term side-effects from radiotherapy depends on many factors. Treatment factors, such as total dose or fractionation schedule, and individual factors, such as age, comorbidities or medical history (e.g. previous surgery), can all affect late toxicity [9]. Patients undergoing radiotherapy experience groups of symptoms called clusters in response to cancer or treatment. Symptom clusters were first defined in cancer by Miaskowski *et al.* in 2004 [10]. They are groups of symptoms with similar prevalence rates and related by a common aetiology or by influencing similar patient outcomes. Since then the concept has served as a basis for the assessment and management of multiple symptoms. There has been substantive research into defining and identifying symptom clusters in a variety of cancers and oncology treatments [11]. Fatigue, insomnia, pain and depression constitute the most prevalent symptom cluster in cancer [12]. Synergy of symptoms in clusters has been studied and the effect on HRQOL, functional status and survival has been described [13,14].

In PCa there have been only two studies examining symptom clusters related to the early stage disease or its treatment [15,16]. Maliski *et al.* [15] found that fatigue and emotional distress were common in this group of patients and they clustered together with urinary, bowel and sexual symptoms. Capp *et al.* [16] only explored rectal symptoms in their longitudinal study. They found that symptom clusters were stable over time and that rectal urgency and pain were the core drives of symptom clustering [16]. A different longitudinal study of Knapp *et al.* [17] explored trajectories and predictors of radiotherapy-related PCa symptoms over 25 weeks. They found that pain, fatigue, insomnia and diarrhoea were highly prevalent and related to symptom distress. Only a limited number of longitudinal studies are available in PCa and none report symptom clusters over a 5 year trajectory. A limitation of studies that analyse radiotherapy-related data in a cross-sectional manner is that the effect of baseline symptoms on time trajectory is not considered and it may be attributed to radiation toxicity.

It is important to consider baseline symptoms when assessing treatment-related side-effects. This is because both baseline and acute symptoms have been found to be a precursor of late symptoms. This has been termed as consequential late effects [18,19]. In addition, treatment factors (ADT, radiotherapy dose or fractionation) have been found to directly affect acute and late symptoms [20]. However, the research into treatment side-effects is now complemented by the evidence of an indirect effect of patient characteristics, such as age, functional status or comorbidities [21–23]. Despite the increasing interest and growing body of evidence, identification and prediction of long-term symptom clusters in PCa, to establish links between symptoms and the role of other contributing factors, remains a challenge. Men with PCa could benefit from this through targeted symptom management approaches that address multiple symptoms and risk factors.

Materials and Methods

Study Design and Research Questions

Longitudinal profiles of patient-reported outcomes (PROs) were explored and symptom clusters investigated using well-established symptom clustering methodologies [24,25]. Patterns in PROs data, reported up to 5 years after treatment by men in the Medical Research Council (MRC) RT01 clinical trial were investigated to study: (i) which PROs were associated and formed symptom clusters, to investigate what symptom clusters are experienced by men with PCa during and after radiotherapy; (ii) how symptom clusters change over time, to investigate the effect of ADT and radiotherapy treatment on the trajectory of symptom clusters during the 5 years of follow-up; (3) the association of treatment, demographics, medical history, i.e. comorbidities, and baseline and acute symptom clusters with the change in symptom clusters over 3 years, to investigate potential risk factors contributing to late symptom clusters. Secondary data analysis was agreed by the MRC RT01 trial team and received appropriate ethical approval.

Dataset and Patients

We used the MRC RT01 trial (ISRCTN47772397), which is a dataset of 843 patients [20,26]. It was a UK-led, multicentre, randomised controlled trial that investigated standard (64 Gy/32 fractions) versus escalated (74 Gy/37 fractions) conformal radiotherapy with neoadjuvant ADT for patients with localised PCa. Eligible men had histologically confirmed PCa and prostate-specific antigen <50 ng/ml, no previous PCa treatment and no significant medical history that excluded them from radical radiotherapy. Men were followed in the study for up to 5 years. PROs were recorded with the University of California, Los Angeles Prostate Cancer Index (UCLA-PCI), which also included the RAND 36 item Short-Form Health Survey (SF-36). A detailed study design, patient eligibility criteria and main results have been published [27,28].

Measurements and Outcome Variables

Patient baseline characteristics are presented in Table 1. Information includes treatment group, age, tumour stage, Gleason score, prostate-specific antigen, comorbid conditions (diabetes, hypertension, inflammatory bowel, haemorrhoids) and medical history, such as type of biopsy, previous pelvic surgery or previous transurethral resection of the prostate. PROs were collected before ADT (baseline), during radiotherapy (acute) and until 5 years after radiotherapy (long-term). PROs included 20 items of the UCLA-PCI [29] measuring function and symptom bother in the three PCa primary concern areas (urinary, bowel and sexual scales); and 36 items of the SF-36 measured HRQOL

Please cite this article in press as: Lemanska A, et al., Older Age, Early Symptoms and Physical Function are Associated with the Severity of Late Symptom Clusters for Men Undergoing Radiotherapy for Prostate Cancer, Clinical Oncology (2018), https://doi.org/10.1016/j.clon.2018.01.016