Radiotherapy and Oncology 113 (2014) 240–247

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Phase III randomised trial

Effects of a dietary intervention on gastrointestinal symptoms after prostate cancer radiotherapy: Long-term results from a randomized controlled trial

Anna Pettersson [a,*], Peter Nygren [a], Christina Persson [a], Anders Berglund [b], Ingela Turesson [a,1], Birgitta Johansson [a,1]

[a] Department of Radiology, Oncology and Radiation Science, Uppsala University; and [b] Pfizer AB, Sollentuna, Sweden

ARTICLE INFO

Article history:
Received 28 July 2014
Received in revised form 22 October 2014
Accepted 12 November 2014
Available online 29 November 2014

Keywords:
Prostate cancer
Radiotherapy
Dietary intervention
Long-term gastrointestinal symptoms

ABSTRACT

Background and purpose: To evaluate the long-term effects of dietary intervention on gastrointestinal symptoms after highly dose-escalated radiotherapy for localized prostate cancer, using boost with protons or high-dose-rate brachytherapy.

Materials and methods: Patients were randomized to an intervention group ($n = 64$) advised to reduce insoluble dietary fiber and lactose intake, or to a standard care group ($n = 66$) advised to continue their usual diet. Gastrointestinal symptoms, other domains of health-related quality of life (HRQOL), and dietary intake were evaluated for $\leqslant$24 months post-radiotherapy with the European Organization for Research and Treatment of Cancer quality-of-life questionnaires QLQ-C30 and QLQ-PR25, Gastrointestinal Side Effects Questionnaire, and Food Frequency Questionnaire. The effect of the intervention on gastrointestinal symptoms was evaluated using generalized estimating equations.

Results: Dietary intervention had no obvious effect on long-term gastrointestinal symptoms or HRQOL. The intervention group markedly reduced their dietary fiber and lactose intake during radiotherapy, but adherence tended to decline over time. The vast majority of long-term gastrointestinal symptoms were reported as 'a little', with a noticeable difference from pre-treatment only for unintentional stool leakage, limitations on daily activities, and mucus discharge.

Conclusion: Long-term gastrointestinal symptoms were predominantly mild, and dietary intervention was not superior to a usual diet in preventing these symptoms.

Although recent improvements in radiotherapy have lowered the risks of severe long-term gastrointestinal complications, a proportion of patients still have persistent, notable symptoms after radiotherapy for prostate cancer [1–6]. Estimates of the occurrence of gastrointestinal symptoms vary owing to the different definitions, grading scales, and reporting methods used. Persistent gastrointestinal symptoms include increased frequency and urgency of defecation, diarrhea, mucus discharge, pain, bloating, and bleeding [7,8]. The incidence and severity of long-term symptoms depends on a complex interaction between treatment, physical, genetic, and patient-related factors [9]. Patient-related risk factors include age, smoking, diabetes mellitus, pre-existing gastrointestinal symptoms, and inflammatory bowel disease [10–14]. In addition, the degree of acute radiation effects is associated with the risk of permanent symptoms, a phenomenon known as a 'consequential late effect' [15,16].

Altered bowel habits can lead to significant distress, which negatively affects patients' health-related quality of life (HRQOL) [7,17]. In addition, malnutrition is associated with a higher risk of gastrointestinal toxicity [18]. Modification of one's diet may help to reduce undesirable bowel disturbances. Previously reported nutritional interventions for the prevention and management of gastrointestinal symptoms after radiotherapy include modification of lactose, fat, and dietary fiber intake [19–22]. Although nutritional interventions may be beneficial, the evidence is inconclusive, and adherence issues pose problems for clinical implementation [23]. We recently reported a non-significant trend towards lower prevalence of acute gastrointestinal symptoms after curative radiotherapy in prostate cancer patients in relation to a dietary intervention aimed at reducing the intake of insoluble dietary fiber and lactose [24]. The present

* Corresponding author at: Department of Radiology, Oncology and Radiation Science, Section of Oncology, Uppsala University, SE-751 85 Uppsala, Sweden.

E-mail addresses: anna.pettersson@onkologi.uu.se (A. Pettersson), peter.nygren@medsci.uu.se (P. Nygren), rc.persson@telia.com (C. Persson), ab@uppstat.se (A. Berglund), ingela.turesson@gmail.com (I. Turesson), birgitta.johansson@onkologi.uu.se (B. Johansson).

[1] Shared senior authorship.

http://dx.doi.org/10.1016/j.radonc.2014.11.025
0167-8140/

study reports the long-term effects of this dietary intervention on gastrointestinal symptoms experienced by the same cohort of patients up to 2 years after completing radiotherapy.

Materials and methods

Patients diagnosed with localized prostate cancer and referred for curative radiotherapy were invited to participate during the period from January 2006 to January 2008. Totally 130 participants were recruited (Fig. 1). Exclusion criteria were previous radiotherapy to the pelvic/bowel area, inflammatory bowel disease, cognitive impairment, long-term hospitalization, and inability to speak or understand Swedish. Patients were referred to either high-dose-rate (HDR) brachytherapy ($n = 80$) or proton therapy ($n = 50$) in combination with external beam radiotherapy (EBRT). The total dose prescribed to the prostate was 70 Gy (brachytherapy 10 Gy/fraction up to 20 Gy, or proton therapy 5 Gy/fraction up to 20 Gy, in combination with EBRT 2 Gy/fraction up to 50 Gy). The equivalent dose in 2 Gy with an α/β of 3 Gy was 102 and 87 Gy, respectively. The treatment time was seven weeks. The clinical target volume was confined to the prostate gland, but EBRT also included the seminal vesicles for T3 tumors. Pelvic nodes were not irradiated. Additional details of the study procedure are available elsewhere [24]. The study was approved by the Regional Ethical Review Board. All participants provided written informed consent.

Randomization

Patients were stratified by radiation technique and randomized to receive either standard care plus the dietary intervention (intervention group; IG, $n = 64$) or standard care alone (standard care group; SCG, $n = 66$). Randomization was performed using Efron's biased coin design [25]. All patients were told which group they had been randomized to after completion of the baseline assessment. The IG was advised to avoid foods high in insoluble dietary fiber and lactose and to instead consume foods with a higher proportion of soluble fiber and a lower proportion of lactose during the entire 26-month study period. The IG received standardized dietary advice from a research dietitian in two face-to-face sessions (before radiotherapy onset and 4 weeks into the treatment period), and during a telephone session (8 weeks after radiotherapy onset). In addition, the IG received a study-specific dietary advice pamphlet at all time points, except for the final assessment. Dietary counseling was not part of the routine care procedure for prostate cancer patients in our department. Consequently, the SCG continued with their usual diet, but were able to receive counseling included in standard care when needed. On their own initiative, two SCG patients received telephone counseling (no re-appointment) from a clinical dietitian.

Data collection

The study included eight time points (Fig. 1). The follow-up completion rate was 78%. The present report focuses on long-term data collected 12, 18, and 24 months after completing radiotherapy (hereafter referred to as post-radiotherapy). Baseline demographics and clinical characteristics were collected from the medical records (Table 1). Nutritional status assessment included the scored Patient-Generated Subjective Global Assessment [26,27] and body mass index.

Gastrointestinal symptoms and other domains of HRQOL

The European Organization for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire, QLQ-C30 (version 3.0) assessed the occurrence of constipation and diarrhea, and the prostate-specific module (QLQ-PR25), assessed limitations on daily activities, unintentional leakage of stools, blood in stools, bloated abdomen and an aggregated bowel symptom scale [28–30]. The Gastrointestinal Side Effects Questionnaire (GISEQ) assessed patient-perceived changes compared with their pre-treatment status for diarrhea, constipation, blood in stools, mucus discharge, abdominal cramps, abdominal pain, intestinal gas, and flatulence [31]. Other domains of HRQOL (global health status, functional capacity, and symptoms) were assessed using both EORTC questionnaires [28–30].

Dietary intake assessment

A study-specific 61-item Food Frequency Questionnaire (FFQ) assessed dietary fiber and lactose intake. Patients indicated their average frequency of consumption during the past month on an eight-level ordinal scale ('never/less than once a month' to '$\geqslant$3 times a day'). As detailed below, food items were grouped into three food groups, and therein categorized as 'high' or 'low' based on their dietary fiber and lactose content in relation to the dietary advice given in the intervention [24,32,33].

Statistical analyses

The statistical analyses were conducted on an intention-to-treat basis, and performed using IBM SPSS Statistics (version 20.0) and STATA (version 12). All p-values were two-tailed and the level of statistical significance was set at $p < 0.05$. Missing items on multi-item EORTC scales were substituted with the mean of the patient's responses, provided that at least half of the items from the scale had been completed [34]. The responses were transformed to a 0–100 scale, with higher scores reflecting higher levels of functioning or more symptoms [34]. Note that for EORTC single symptom items, a score of 0 is equivalent to 'not at all', 33 'a little', 67 'quite a bit', and 100 'very much'. In the GISEQ, changes in symptom burden were reported on an 11-point response scale (0, 'to the same or lesser extent' to 10, 'to a much greater extent').

GEE and covariates

Statistical analyses focused on gastrointestinal symptoms. Other domains of HRQOL were checked in an exploratory manner only. The assumption of a normal distribution was not fulfilled, as a substantial proportion of patients reported no gastrointestinal symptoms over the study period. To achieve a sufficient number of events for statistical analyses, all EORTC and GISEQ scores were dichotomized according to the following thresholds for having '*a little*' *up to* '*very much*' *problems*. In the EORTC questionnaires, *problems* were defined as symptom scale scores 1–100, and functioning scale scores or general health status scores 0–99. For the GISEQ, *problems* were defined as scale scores 1–10.

Radiation technique and potential risk factors for persistent gastrointestinal symptoms were used as covariates in statistical analyses [10–13]. Potential risk factors were current smoker (yes/no), age ($\geqslant$70 years/<70 years), presence of diabetes (yes/no), pre-treatment gastrointestinal symptoms (score $\geqslant$33 on at least one single EORTC item/score <33 on all six items), and acute gastrointestinal symptoms at 8 weeks following radiotherapy onset (score $\geqslant$67 on at least one single EORTC item/score <67 on all six items). Differences between the IG and the SCG were tested using Chi-square statistics.

Generalized estimating equations (GEE) were used to model the effect of dietary intervention as a function of time by including dichotomized data from pre-treatment (i.e., baseline) and 12–24 months post-radiotherapy. The models were adjusted for