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Patient-reported outcome

Patient-reported gastrointestinal symptoms among long-term survivors after radiation therapy for prostate cancer

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ABSTRACT

Background and purpose: With modern radiotherapy technology we have the means to substantially reduce late gastrointestinal toxicities after radiation therapy for prostate cancer. However, there is still a lack of knowledge regarding the spectrum of patient-reported gastrointestinal symptoms after such treatment.

Materials and methods: We conducted a cross-sectional study using a study-specific questionnaire to survey gastrointestinal symptoms 2–14 years after prostate cancer radiation therapy. We included 985 men treated between 1994 and 2006 with primary (EBRT) or salvage (POSTOP) external beam radiation therapy or EBRT and high-dose rate brachytherapy (EBRT BT). We also included 350 non-irradiated population-based controls randomly matched 1:3 for age and area of residence.

Results: Survey participation rate was 89% (874/985) for survivors and 73% (243/332) for controls. We found significant increased prevalence ratios for 13/34 symptoms in the primary EBRT group, 10/34 symptoms in the EBRT BT group and 9/34 symptoms in the POSTOP group, several of which have not been described previously. Bother due to these symptoms increased with increasing symptom intensity and was highest for fecal leakage and defecation urgency.

Conclusions: Our results can be used to inform clinical evaluation and future studies of long-term gastrointestinal toxicity after radiotherapy for prostate cancer.

During the past decades, technical developments in radiation therapy have enabled an increased conformal dose distribution around the target with a lower dose to the surrounding healthy tissue with reduced severe radiation-induced toxicities [1]. This has opened up the possibilities for radiation oncologists to take into account a wider spectrum of toxicities, including those previously regarded as "less severe". However, there is a lack of toxicity profiles based on the survivor's own experiences after radiation therapy as well as knowledge how these relate to corresponding symptoms among healthy individuals (background rates).

The current literature on gastrointestinal toxicity mostly concerns physician reported severe symptoms that require outpatient (grade 2) or hospital-based interventions (grade $\geqslant$ 3) [2]. Furthermore, gastrointestinal symptoms after pelvic radiation therapy have been described as substantially more common than generally recognized and frequently poorly managed [3]. These symptoms affect both the survivors' physical and psychosocial functioning and limit the possibilities of leading a normal life [4]. Therefore, it is also important to identify the 'less severe' gastrointestinal symptoms and their background rates in order to better determine which symptoms to address in the clinic and in future studies.

In this paper we report the occurrence of specific patient-reported gastrointestinal symptoms among long-term prostate-cancer survivors, several of which have not been described previously. In 2008, we invited 985 men who had been treated with radiation therapy at the Sahlgrenska University Hospital, Gothenburg, Sweden between 1994 and 2006 to take part in a large cross-sectional study. Those who agreed received a study-specific questionnaire assessing the occurrence of pelvic symptoms after radiotherapy for prostate cancer, including 34 gastrointestinal symptoms. For comparison, we used information from 243 randomly selected non-irradiated population-based controls matched for age and residency from the Swedish Total Population Register.

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Material and methods

Study population

Using information from the Swedish Total Population Register and computerized hospital medical records, we identified 985 eligible prostate cancer survivors, consecutively treated with radiation therapy between 1994 and 2006 at the Sahlgrenska University Hospital, Gothenburg, Sweden. Data from this study have been presented in seven previous publications [5]. Briefly, the men were treated with individually planned three-dimensional conformal external beam radiation therapy either as primary treatment (EBRT), salvage treatment (POSTOP) after radical prostatectomy or in combination with high dose-rate brachytherapy (EBRT BT). At the time of follow-up they were 80 years old or younger, had no diagnosed distant metastases and were resident in Sweden. For comparison, we randomly selected 350 non-irradiated population-based controls from the Swedish Total Population Register to provide information on symptom background rates. For each three survivors we randomly selected one control man matched for age and area of residence. Selection and matching of controls were done before the men were invited to participate. Thereafter, we excluded 28 of the control men due to a history of prostate cancer, resulting in 322 eligible population-based controls. The Ethics Review Board in Gothenburg approved the project.

External beam radiation therapy

External beam radiation therapy was based on three-dimensional computerized tomography with the patient in supine position. The patient was treated using a conformal three-field technique with one anterior and two lateral wedged fields with 11 MV or 15 MV photon energy. The clinical target volume (CTV) comprised the prostate or the post-operative prostatic region including the seminal vesicles for locally advanced tumors (T3–T4). The planning target volume (PTV) was defined as the CTV with a 20 mm margin except for the rectal margin, which was 15 mm or at most half the cross-sectional rectal area. At least 95% of the prescribed dose covered 99% of the PTV and a maximum of 107% of the prescribed dose was allowed in the PTV. Information on anal-sphincter region and rectum delineation and dose–volume histograms are provided as supplementary materials (Supplementary Figs. 1–3). None of the men received radiotherapy to the lymph nodes.

Brachytherapy

Brachytherapy was planned based on with transrectal ultrasound with the patient in lithotomy position. The planning target volume was defined as the prostate with 2 mm margin except caudally and cranially. The treatment was delivered using a high dose-rate ^{192}Ir source. The dose distribution was optimized by determining the number of needles, needle positions, and dwell times for the source within each needle. Typically, 11–15 needles were manually inserted through a perineum template under rectal ultrasound guidance. The objective was to cover the PTV with the prescribed dose while keeping the absorbed dose to the anterior rectal wall below 6 Gy per fraction.

The questionnaire

The study-specific questionnaire was in Swedish and was designed to survey symptom occurrence after radiation therapy for prostate cancer and has been described in detail previously [5]. It was developed according to the well-founded method established at the Division of Clinical Cancer Epidemiology at the University of Gothenburg in Göteborg and the Karolinska Institutet in Stockholm, Sweden, documented in more than 100 published articles [6–10]. Briefly, symptoms are identified after in-depth interviews with cancer survivors and operationalized into questions that are verified with individuals of the target population to make sure that they are correctly understood (face validity). A preparatory study is then conducted to test the questionnaire for logistics, participation rate and rate of missing values. If necessary, additional adjustments are made before the main study is conducted where the final questionnaire is sent out to the study participants by mail at one occasion (in this study: survivors, between February and June 2008; controls, between September and November 2008). This study design thus results in a cross-sectional study.

The questionnaire contained 165 questions on long-term symptoms after pelvic radiation therapy, demographic data, information concerning comorbid disease and treatment, quality of life and physical health. Of the 42 questions that dealt with gastrointestinal-related issues, we report on the 34 questions that specifically reflected the occurrence of gastrointestinal symptoms and 8 questions on bother, assessed as reduced well-being, associated with symptoms (Supplementary materials).

Statistical analyses

All calculations were made in SAS 9.2 for Windows (SAS Institute Inc., Cary, NC, USA) or Stata/IC 11.2 for Mac (Stata Corp., College Station, TX, USA). Differences in age were assessed with a two-sided t test and differences in T-stage between the three groups were evaluated with a non-parametric Kruskal–Wallis test. Each symptom question was dichotomized according to predefined cutoffs, balanced between clinical relevance and background noise [8,10]. Symptom prevalence was calculated as the percentage of men reporting the symptom within each group. Adjusted prevalence ratios between survivors and control men with corresponding 95% CIs were calculated using a multivariable log-binomial model including the potentially confounding factors such as age, chronic bowel disease, diabetes and smoking as covariates (GENMOD procedure in SAS 9.2 for Windows) [5,11]. Cuzick's test for trend was used to evaluate differences in the prevalence of gastrointestinal symptoms over time (*nptrend* procedure in Stata/IC 11.2 for Mac). We considered a 95% CI not including 1.0 or a two-sided P-value $\leqslant 0.05$ as indicating statistical significance.

Results

Study population and controls

Altogether 874 (89%) of the 985 eligible prostate-cancer survivors and 243 (76%) of the 332 eligible population-based controls returned a filled in questionnaire. Table 1 shows that men in the EBRT group were older ($p < 0.001$) and had a longer follow-up ($p < 0.001$) compared with those in the EBRT BT and POSTOP groups. Most men were treated with 35 fractions at 2 Gy per fraction externally (EBRT and POSTOP) or 25 fractions at 2 Gy per fraction externally combined with 2 fractions of brachytherapy at 10 Gy per fraction (EBRT BT). The men in the POSTOP group had a significantly lower prevalence of chronic bowel disease and diabetes compared with the other groups. Although the survivors and controls were matched for age and residency the distribution of potentially confounding factors: chronic bowel disease, diabetes and smoking status was imbalanced between these groups. Adjusted prevalence ratios are presented in Table 2.