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Modelling late stool frequency and rectal pain after radical radiotherapy in prostate cancer patients: Results from a large pooled population

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ABSTRACT

Aim: To investigate late gastrointestinal toxicity in a large pooled population of prostate cancer patients treated with radical radiotherapy. Normal tissue complication probability models were developed for late stool frequency and late rectal pain.

Methods and materials: Population included 1336 patients, 3-year minimum follow-up, treated with 66–80 Gy. Toxicity was scored with LENT-SOMA-scale. Two toxicity endpoints were considered: grade $\geqslant$2 rectal pain and mean grade (average score during follow-up) in stool frequency >1.

DVHs of anorectum were reduced to equivalent uniform dose (EUD). The best-value of the volume parameter n was determined through numerical optimization. Association between EUD/clinical factors and the endpoints was investigated by logistic analyses. Likelihood, Brier-score and calibration were used to evaluate models.

External calibration was also carried out.

Results: 4% of patients (45/1122) reported mean stool frequency grade >1; grade $\geqslant$2 rectal pain was present in the TROG 03.04 RADAR population only (21/677, 3.1%): for this endpoint, the analysis was limited to this population.

Analysis of DVHs highlighted the importance of mid-range doses (30–50 Gy) for both endpoints.

EUDs calculated with n = 1 (OR = 1.04) and n = 0.35 (OR = 1.06) were the most suitable dosimetric descriptors for stool frequency and rectal pain respectively.

The final models included EUD and cardiovascular diseases (OR = 1.78) for stool frequency and EUD and presence of acute gastrointestinal toxicity (OR = 4.2) for rectal pain.

Conclusion: Best predictors of stool frequency and rectal pain are consistent with findings previously reported for late faecal incontinence, indicating an important role in optimization of mid-range dose region to minimize these symptoms highly impacting the quality-of-life of long surviving patients.

1. Introduction

The majority of studies devoted to gastrointestinal side effects after radiotherapy for prostate cancer are focused on rectal bleeding, faecal incontinence and overall acute gastrointestinal toxicity. These studies often resulted in the quantification of dose-volume effects for organs-at-risk (primary the rectum) and led to the development of predictive models for radiotherapy-induced toxicity, which sometimes include clinical risk factors [1–3].

Nevertheless, chronic radioinduced rectal syndrome includes other symptoms [4], such as urgency, increased stool frequency and rectal pain. There is insufficient knowledge on the incidence

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of these morbidities and on their relationship with the dose distribution in the rectum and in the anal canal. This is mainly due to their being relatively rare effects; there is difficulty in identifying radiation as the cause of these impairments in an ageing population together with the lack of controlled questionnaire-based prospective scoring describing the pre-radiotherapy baseline situation.

Nevertheless, these symptoms may clearly have a non-negligible impact on the quality of life (QoL) of long-surviving patients [5] and consequently deserve attention.

The availability of a large dataset consisting of a pooled population from two large prospective trials [6,7] that represents more than one thousand patients with a minimum of 3 years of follow-up allowed us to focus on these often neglected gastrointestinal side effects: stool frequency and rectal pain.

The two cohorts were treated at different hospitals, with different dose levels, with different radiotherapy techniques, in different countries and in different time frames. As a consequence, current pooled population presented with a wide variety of dosimetric and clinical parameters, with the potential to reach sufficient statistical power to assess main associations between the selected rare side effects and clinical/dosimetric features. The aim of current study was to develop multivariable logistic (MVL) regression models for both the above mentioned toxicity endpoints.

2. Materials and methods

2.1. Patient population

A pooled population from two high quality multicentre prospective trials on radiotherapy for prostate cancer was created.

a. Airopros 0102: a prospective multicentre observational trial specifically designed to evaluate dosimetric/clinical factors associated with acute and late rectal syndrome symptoms after radical radiotherapy for prostate cancer (details can be found in [6,8–10]).
b. TROG03.04 RADAR: a prospective multicentre randomized trial designed to determine whether adjuvant androgen suppression, bisphosphonates and radiation dose escalation might improve oncologic outcomes in localized prostate cancer (details in [7,11–15]). In this trial, toxicity was prospectively scored as a secondary endpoint.

All patients were treated with radical three-dimensional conformal radiotherapy (3DCRT) in the period 2002–2004 and 2004–2007 for Airopros 0102 and TROG03.04 RADAR, respectively. The prescribed dose was between 66 and 80 Gy (median 73.2 Gy, interquartile range 70–75 Gy, 1.8–2 Gy/day in all cases).

Co-morbidities (diabetes, hypertension, cardiovascular diseases, and the presence of haemorrhoids), previous abdominal/pelvic surgery, use of drugs and previous/concomitant loco-regional diseases were evaluated with a specifically designed questionnaire administered prior to radiotherapy. Information on the quality and duration of the hormonal therapy was also recorded when prescribed to the patient. These clinical information was collected from both trials in a similar way.

Other information concerning the volume definition, planning and treatment modalities as well as the distribution of the main clinical parameters of the two populations have previously been reported in detail [6–8,11]. Of particular importance is the delineation of the anorectum: an anatomically based definition (from the anus to the point where the rectum turns into the sigmoid) was used by the participating centres in both trials. This definition was previously found to be sufficiently robust for the aims of dose-volume studies. The dose-volume histogram (DVH) of the solid rectum was here considered. Details on reported rectal volumes are given in the Supplementary Material.

2.2. Toxicity assessment and endpoint definition

Patients were assessed at the start and the end of radiotherapy and every 6 months thereafter for at least 3 years of follow-up.

Gastrointestinal symptoms were determined according to the LENT/SOMA (Late Effects of Normal Tissue/Subjective, Objective, Management and Analytic) scoring system for late radiation morbidity.

Late rectal pain and stool frequency were analysed in the current study.

Rectal pain was considered as a peak toxicity and grade $\geqslant 2$ (i.e., intermittent & tolerable OR persistent & intense pain) was scored as a toxicity event. We defined a late event if it occurred in the time frame 6–36 months after the end of 3DCRT. For stool frequency, we chose a longitudinal definition; mean stool frequency was defined as the average score during the 3-year period after RT. Patients with at least three out of six follow-up points were included in this analysis. A stool frequency average grade >1 was arbitrarily considered as the endpoint as it selects those patients with persistent symptoms (i.e., patients who on average evacuated $\geqslant 3$ times/day), more likely to be those whose symptoms are actually due to radiotherapy.

Longitudinal definitions of toxicity were already considered for faecal incontinence by Gulliford et al. [16] and Fiorino et al. [17], which suggested that the longitudinal approach is more appropriate in describing both the severity and persistence of moderate symptoms that are very important for QoL and the social activities of patients.

The baseline questionnaire was used to exclude patients with symptoms that were already present before radiotherapy, while the end of treatment evaluation was defined acute gastrointestinal toxicity following the RTOG/EORTC definition.

2.3. Development of multivariable logistic models

Univariable logistic regression was used to determine the association between toxicity and clinical/dosimetric/treatment related factors.

The rectal dose-volume histogram (DVH) was reduced to the Equivalent Uniform Dose (EUD).

The value of the rectum volume parameter n for the two considered toxicity endpoints was determined through a numerical optimization: a set of EUDs were computed for a set of n-values ranging from 0 to 1 in 0.05 steps. These EUDs were inserted in univariable logistic models and n-value maximizing log likelihood (LLH) was chosen as the most suitable.

The MVL analysis was performed to include all covariates that were associated with the endpoint in the univariable analysis (covariates with $p < 0.15$). The odds ratio (OR) was used to express the strength of association of a parameter with the considered symptom.

The goodness-of-fit was determined through the Hosmer-Lemeshow (HL) test and the calibration plot (slope coefficient and R^2). The gap between predicted probabilities and observed toxicity rates was evaluated through Brier score.

Internal validation was assessed through 10,000 bootstrap resamplings from the original population, while external independent validation was carried out on a more recent Italian population treated with Intensity Modulate Radiation Therapy (IMRT) in 2010–2014. Prescribed dose was between 68 and 80 Gy. Follow-

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