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Quality of life in prostate cancer

Multi-variable models of large International Prostate Symptom Score worsening at the end of therapy in prostate cancer radiotherapy

Federica Palorini [a,*], Tiziana Rancati [b], Cesare Cozzarini [c], Ilaria Improta [a], Viviana Carillo [a,1], Barbara Avuzzi [d], Valeria Casanova Borca [e], Andrea Botti [f], Claudio Degli Esposti [g], Pierfrancesco Franco [h], Elisabetta Garibaldi [i], Giuseppe Girelli [j,2], Cinzia Iotti [k], Angelo Maggio [l], Marcella Palombarini [m], Alessio Pierelli [n], Emanuele Pignoli [o], Vittorio Vavassori [p], Riccardo Valdagni [b,d], Claudio Fiorino [a]

[a] *Medical Physics, San Raffaele Scientific Institute;* [b] *Prostate Cancer Program, Fondazione IRCCS Istituto Nazionale dei Tumori;* [c] *Radiotherapy, San Raffaele Scientific Institute;* [d] *Radiation Oncology 1, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano;* [e] *Medical Physics, Ospedale ASL9, Ivrea;* [f] *Medical Physics, Arcispedale S.M. Nuova – IRCCS, Reggio Emilia;* [g] *Radiotherapy, Ospedale Bellaria, Bologna;* [h] *Radiotherapy, Ospedale Regionale U. Parini-AUSL Valle d'Aosta, Aosta;* [i] *Radiotherapy, Istituto di Candiolo – Fondazione del Piemonte per l'Oncologia IRCCS, Candiolo;* [j] *Radiotherapy, Ospedale ASL9, Ivrea;* [k] *Radiotherapy, Arcispedale S. M. Nuova – IRCCS, Reggio Emilia;* [l] *Medical Physics, Istituto di Candiolo – Fondazione del Piemonte per l'Oncologia IRCCS, Candiolo;* [m] *Medical Physics, Ospedale Bellaria, Bologna;* [n] *Medical Physics, Cliniche Gavazzeni-Humanitas, Bergamo;* [o] *Medical Physics, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano; and* [p] *Radiotherapy, Cliniche Gavazzeni-Humanitas, Bergamo, Italy*

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ABSTRACT

Purpose/objective: Prospectively assessing clinical/dosimetry factors affecting the acute worsening of urinary functionality after radiotherapy for prostate cancer.

Material/methods: DUE01 population was considered, including patients treated with conventional or moderate hypo-fractionation (2.2–2.7 Gy/fr). Relevant clinical factors were collected, urinary symptoms were self-reported through the International Prostate Symptom Score (IPSS) before and at the end of radiotherapy; while absolute weekly dose–surface histograms (DSH_w) were chosen as dosimetry descriptors.

An IPSS increase of at least 10 and 15 points ($\Delta IPSS \geqslant 10$ and $\Delta IPSS \geqslant 15$) were chosen as endpoints. Patients with baseline IPSS > 20 were excluded. Relevant factors were chosen through a bootstrap-based in silico methodology.

Results: Complete information was available for 380 patients: 77/380 (20%) and 28/380 (7%) with $\Delta IPSS \geqslant 10$ and $\Delta IPSS \geqslant 15$, respectively.

Neoadjuvant hormone was protective (OR = 0.49 and 0.69). DSH_w at 8.5 Gy/week and 12 Gy/week were risk factors, with additional risk for patients who use cardiovascular drugs and anti-hypercholesterolemia drugs.

In the hypo-fractionated subgroup ($n = 209$) the role of cardiovascular drugs (OR = 2.16) for $\Delta IPSS \geqslant 10$ and anti-hypercholesterolemia drugs (OR = 2.80) for $\Delta IPSS \geqslant 15$, together with DSH_w (10 Gy/week and 12.5 Gy/week, respectively), was confirmed.

Conclusion: Current study shows a dose–surface/volume effect for acute large worsening of urinary functionality; several clinical variables largely impact the risk and especially all the factors related with vascular diseases.

Urinary toxicity is an important side effect for patients treated with radical radiotherapy (RT) for prostate cancer, but the impact of dosimetry and clinical factors on the urinary sequelae is not clear so far.

A few evidences exist that the dose in the urethra/bladder neck is predictive of severe toxicity [1–5] while recent studies suggested that the bladder trigone might correspond to a particularly radiosensitive region [6–7]. Nevertheless, the possible correlation between the dose–volume histograms (DVHs) and the onset of toxicities remains unclear. This might be due to the difficulties in the prospective assessment of urinary symptoms and their proper scoring as well as to the fact that bladder is a hollow and flexible structure, so that other dose descriptors, like the dose–surface

* Corresponding author.
E-mail address: palorini.federica@hsr.it (F. Palorini).
[1] Currently at Radiotherapy, Centro AKTIS Diagnostica e Terapia SpA, Marano di Napoli, Italy.
[2] Currently at Nuovo Ospedale, ASL Biella, Biella, Italy.

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histograms (DSH), should be used in order to represent the dose received by the bladder wall [8].

With respect to clinical predictors, published data are also controversial and not easily comparable, as they often differ in endpoint definitions, in data collection modalities, patient selection and treatment. However, pre-treatment urinary symptoms, prior transurethral resection of the prostate (TURP) and smoke are often reported to have an impact on the risk of acute and late toxicities [3,9,10].

The aim of this work was to assess the best clinical and dose factors affecting large worsening of urinary symptoms, as described by the International Prostate Symptom Score (IPSS), in patients treated with radical RT for prostate cancer.

We considered, here, the final dataset of the DUE01 study (539 patients) and the worsening of symptoms was evaluated through the difference between IPSS at RT end and IPSS before RT. This analysis differs from the previous preliminary study on 247 patients [11], where the presence of acute urinary symptoms at the end of RT was evaluated (primary endpoint was absolute-IPSS $\geqslant 15$ at the end of treatment) instead of the change in the IPSS scoring examined in this work. Furthermore, we here considered more details about the effect of comorbidities, previous surgeries and use of drugs, and improved the procedure for selecting the best predictors. The choice of relevant factors and the determination of the variable odds ratios were carried out through an in silico methodology that combined more advanced techniques of data mining, which included bootstrap resamplings, plus a backward feature selection based on minimization of residuals and a basket and network analysis of the bootstrapped datasets.

Materials and methods

The DUE01 study

DUE01 is a prospective multicenter study aimed at developing predictive models of urinary toxicity and erectile dysfunction after radical high-dose RT for prostate cancer.

Patients were enrolled between April 2010 and December 2014, after the approval of Ethics Committees of all the participating Institutes.

Details of the study may be found elsewhere [11,12]. In summary, relevant clinical and planning data were prospectively collected for each patient. The continuous clinical parameters included patient age and body mass index (BMI) (kg/m^2); while the categorical clinical parameters (yes/no) detailed the comorbidities, the use of drugs, previous abdominal surgeries, a previous transurethral resection of the prostate (TURP), smoke, alcohol and the neo-adjuvant hormone therapies (HT). Planning dose data included the clinical target volume (CTV) and planning target volume (PTV) in cc, the PTV prescription dose (continuous, Gy) and whether pelvic lymph nodes or seminal vesicles were irradiated (categorical, yes/no).

Full planning data were uploaded on dedicated software (VODCA, MSS Medical Software Solutions, Hagendorn, Switzerland).

The bladder dose–surface histograms (DSH) were chosen as dose descriptors, since they were found good surrogates of the dose to the bladder wall in a previous work [13] and, in particular, their absolute weekly values (DSH_w) were considered as different fractionation schemes were allowed [11]. The absolute weekly dose–volume histograms (DVH_w) were also examined since easily related to clinical practice.

In the current analysis, urinary symptoms were described by the IPSS questionnaire, filled in by the patients before and after RT. It takes into account seven urinary symptoms (incomplete emptying, frequency, intermittency, urgency, weak stream, straining, nocturia) scored from 0 (absence of the symptom) to 5 (symptom almost always present). The IPSS sum, therefore, ranges from 0 to 35.

Late IPSS worsening (till 5-year follow-up), in addition to incontinence, hematuria and urethral stenosis, are also prospectively scored but they were not considered in the current investigation.

End-points for worsening of urinary symptoms

The worsening of urinary symptoms was evaluated by two distinct endpoints: 1) IPSS increase of at least 10 points after RT ($\Delta IPSS \geqslant 10$) and 2) $\Delta IPSS \geqslant 15$, for the evaluation of a more severe detriment.

The analysis was focused on the subgroup of patients with baseline IPSS $\leqslant 20$, since they had the possibility of satisfying both the endpoints. This group will be thereafter identified as "whole population". The analyses were repeated on a smaller subgroup of patients treated with hypo-fractionated radiotherapy (HYPO: 2.2–2.7 Gy/fraction).

Preliminary assessment of clinical and dose predictors

All the collected clinical and dose parameters were included in the analysis, with some restrictions. Due to the strong correlation between DSH_w (DVH_w) values, a linear correlation filter with $r < 0.85$ was used to select representative independent dose predictors. Categorical clinical parameters <25 positive cases (7%) were excluded.

Absolute average DSH_w (DVH_w) of patients with/without $\Delta IPSS \geqslant 10$ (or $\Delta IPSS \geqslant 15$) was compared through two-sided t-tests. The selection of the best clinical and dose predictors to be included in the multi-variable models was performed with an in silico simulation, as described in the following section.

Statistical analysis: assessing the best predictors and developing multivariable models

A method based on in silico experimentation and aimed at identifying the best predictors of a binary endpoint was used, with the purpose of detecting the leading robust variables and minimizing the noise due to the particular dataset, thus trying to avoid both under- and over-fitting.

It followed, with adjustments, a procedure firstly introduced by El Naqa [14]: the treatment response curve was approximated by the logistic function, while the bootstrap resamplings were performed to explore the recurrence of the selected variables in order to check their stability. A further bootstrap resampling was introduced here for the evaluation of the odds ratios of the selected variables.

The in silico experiment was implemented using the KNIME software (KNIME GmbH, Germany) and consisted in the following processing steps:

1) 1000 bootstrap samplings of the original dataset were created, as suggested in[14];
2) backward feature selection based on minimization of residuals was performed on each bootstrap sample;
3) the rate of occurrences and the placement of each variable (selected by the backward feature selection) in the 1000 bootstrapped datasets were used to classify the most robust predictors. A synthetic index, called normalized area (NArea, a rigorous definition of this index in given in the Supplementary material), was defined for ranking each predictor: it corresponds to the area under the histogram representing the number of occurrences of each variable (x-axis) at a given importance level in each re-sampled dataset (an example in Fig. S3);