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Inclusion of clinical risk factors into NTCP modelling of late rectal toxicity after high dose radiotherapy for prostate cancer

Tiziana Rancati [a], Claudio Fiorino [b,*], Gianni Fellin [c], Vittorio Vavassori [d], Emanuela Cagna [e], Valeria Casanova Borca [f], Giuseppe Girelli [g], Loris Menegotti [h], Angelo Filippo Monti [i], Francesca Tortoreto [j], Stefania Delle Canne [k], Riccardo Valdagni [a,l]

[a] *Prostate Program, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy;* [b] *Medical Physics, San Raffaele Scientific Institute, Milano, Italy;* [c] *Radiotherapy, Ospedale Santa Chiara, Trento, Italy;* [d] *Radiotherapy, Cliniche Humanitas Gavazzeni, Bergamo, Italy;* [e] *Department of Radiotherapy, Ospedale Sant'Anna, Como, Italy;* [f] *Medical Physics; and* [g] *Radiotherapy, Ospedale di Ivrea, Italy;* [h] *Medical Physics, Ospedale Santa Chiara, Trento, Italy;* [i] *Medical Physics, Ospedale Sant'Anna, Como, Italy;* [j] *Radiotherapy; and* [k] *Medical Physics, Ospedale Fatebenefratelli, Roma, Italy;* [l] *Radiotherapy, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy*

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ABSTRACT

Background and purpose: To fit an NTCP model including clinical risk factors to late rectal toxicities after radiotherapy for prostate cancer.
Methods and materials: Data of 669 patients were considered. The probability of late toxicity within 36 months (bleeding and incontinence) was fitted with the original and a modified Logit-EUD model, including clinical factors by fitting a subset specific TD_{50}s: the ratio of TD_{50}s with and without including the clinical variable was the dose-modifying factor (D_{mod}).
Results: Abdominal surgery (surg) was a risk factor for G2–G3 bleeding, reflecting in a TD_{50} = 82.7 Gy and 88.4 Gy for patients with and without surg (D_{mod} = 0.94; 0.90 for G3 bleeding); acute toxicity was also an important risk factor for G2–G3 bleeding (D_{mod} = 0.93). Concerning incontinence, surg and previous diseases of the colon were the clinical co-factors. D_{mod}(surg) and D_{mod}(colon) were 0.50 and 0.42, respectively for chronic incontinence and 0.73 and 0.64, respectively for mean incontinence score $\geqslant$1. Best-fit *n* values were 0.03–0.05 and 1 for bleeding and incontinence, respectively. The inclusion of clinical factors always improved the predictive value of the models.
Conclusions: The inclusion of predisposing clinical factors improves NTCP estimation; the assessment of other clinical and genetic factors will be useful to reduce parameter uncertainties.
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During the last decades, the availability of individually assessed dose–volume information permitted the development of a large number of dose–volume analysis [1], as recently summarized in the Quantec report [2], and a still more rapid improvement is expected in the next years.

The development of normal tissue complication (NTCP) models is an important step of this process; the basic idea was to pragmatically "reduce" the dose–volume histogram (DVH) of an organ at risk to a number expressing the risk of toxicity, through a simple mathematical model [3].

Rectal toxicity in the treatment of prostate cancer has historically been one of the most investigated issues, primarily due to the large number of patients treated, in a quite similar way in terms of dose–volume, to the robust scoring definition (at least for bleeding) and to the easy way of defining the rectum [4,5].

Large prospective trials deeply investigated this issue [6–11] and suggested DVH constraints to limit the risk of bleeding and, in a minor extent, of other symptoms, as recently summarized in a few reviews [12–14]. In particular, the limited risk of bleeding in modern conformal (3DCRT) and Intensity Modulated Radiotherapy (IMRT) is also due to our improved knowledge of the rectal dose–volume effect [12].

A few investigators were also able to assess best parameters of NTCP models of rectal bleeding [15–18] and of other endpoints like incontinence and loose stool [16].

There is a substantial agreement around the prevalent serial behaviour of the rectum when considering late bleeding [14]. On the other hand, the NTCP modelling of late incontinence is less precisely defined [16].

A few investigations supported the existence of clinical [6–9] and genetic [19–21] factors that may play an independent role in predicting rectal toxicity. This point reflects the more and more efficient delivery of well tailored dose distributions, with the consequent decrease of the relative impact of the "dose" compared to other factors associated to a higher individual radio-sensitivity

* Corresponding author. Address: Medical Physics Department, San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milano, Italy.
E-mail address: fiorino.claudio@hsr.it (C. Fiorino).

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and/or a reduced repair capacity; abdominal surgery, acute toxicity, previous bowel diseases were all reported to influence the risk of rectal toxicity [6–9]; however, only one study considered the inclusion of clinical co-factors in NTCP models of rectal side-effects [16].

In the current work, we fit the data of the AIROPROS0102 trial (669 patients) with the NTCP logistic EUD-based model (Logit-EUD [22,23]), including the clinical variables which were previously found significantly associated to an increased risk of late bleeding and incontinence [6,7,24–26].

Materials and methods

The AIROPROS0102 trial

Patients (1132) were initially enrolled in the AIROPROS0102 prospective multicentre trial.

The main aim of the study was to prospectively assess clinical and dosimetric predictors of late rectal toxicity after 3DCRT for prostate cancer.

The selection criteria were: (a) histologically confirmed prostate adenocarcinoma, and (b) participating centres using 3DCRT with prescription doses $\geqslant$ 70 Gy, at 1.8–2.0 Gy/fr.

All patients received 3DCRT with prescription doses $\geqslant$ 70 Gy, 1.8–2.0 Gy/fr. A more detailed description of protocol aim, selection criteria, and technical/dosimetric issues have been previously reported [6,7,24].

Information regarding co-morbidity (diabetes, hypertension, previous disease of the colon, presence of haemorrhoids), previous abdominal surgery (rectum-sigma resection, kidney resection, cholecystectomy, appendectomy), TURP or TURV, and use of drugs (hormonal therapy, antihypertensives, anticoagulants) was recorded.

Treatment planning was performed on CT scans using a slice interval $\leqslant$5 mm. Patients were scanned with an empty rectum to enhance the reliability of the rectal DVH [27]: an anatomy-based definition of the rectum was followed [6,7,24]: the rectum (considered as a solid organ) was drawn on CT slices starting just above the anal verge and continuing until it turns into the sigmoid colon. If rectal volume (including filling) was >100 cm^3, repeat scanning was suggested. A dummy run on rectum contouring variability was performed and this definition was found to be sufficiently robust [4,5].

Rectal DVHs of the entire treatment were recorded for all patients.

Late rectal toxicity scoring and endpoint definition

A self-administered questionnaire [7] scoring rectal and intestinal toxicities was filled in by the patients before the treatment (basal), within 1 month after therapy, and subsequently every 6 months, up to 3 years after therapy.

Late rectal bleeding and faecal incontinence were defined as follows:

(a) G2 bleeding: bleeding >2 times/week.
(b) G3 bleeding: daily bleeding or blood transfusion and/or laser coagulation and/or surgical procedure.
(c) G1 incontinence: unintentional stool/mucous discharge "sometimes" experienced.
(d) G2 incontinence: unintentional stool/mucous discharge "often" experienced or sporadic use of sanitary pads.
(e) G3 incontinence: daily unintentional stool/mucous discharge or sanitary pads >2 times/week.

NTCP models for bleeding included data of all patients with a 36-month complete follow-up and complete dosimetric and clinical records (n = 669).

For faecal incontinence, only patients with at least three filled questionnaires, including the 36 months questionnaire information, were considered (n = 506).

For NTCP modelling four endpoints were considered:

1. G2–3 bleeding: at least one G2–G3 bleeding event at any time 5 months after 3DCRT.
2. G3 bleeding (as above, only G3).
3. Chronic G2–3 late incontinence (Clinc): G2 or G3 incontinence at any time after 5 months after 3DCRT that never completely recovered (i.e., after a G2–G3 event, at least G1 incontinence was recorded till 3 year follow-up).
4. Mean late incontinence (Mlinc): the average score of late incontinence. We choose Mlinc $\geqslant$ 1 as cutoff for NTCP modelling.

Results on the correlation between the above described endpoints and clinical/dosimetric risk factors have been presented in previously published papers [7,24,26] and were used to select the clinical factors.

Determination of NTCP model parameters and uncertainties

The Logit+EUD model [22,23] was fitted the toxicity data: the logit formula, with log-transformation of the dose variable, describes the dose–response relationship through TD_{50} and k (the slope of the curve at TD_{50}):

$$\mathrm{NTCP(D)} = \frac{1}{1 + \left(\frac{TD_{50}}{D}\right)^{k}} \tag{1}$$

Eq. (1) holds for uniform organ irradiation at dose D.

When considering non-uniform dose distributions, the DVH is converted to EUD through:

$$\mathrm{EUD} = \left(\sum_i v_i \cdot D_i^{\frac{1}{n}}\right)^n \tag{2}$$

where D_i and v_i correspond to a point of the differential DVH and n is a non-negative parameter describing the volumetric dependence of the dose–response relationship: when $n \to 0$, EUD tends to the maximum dose, while for n = 1 the EUD is the mean dose.

In order to include predisposing clinical features, the modified NTCP model proposed by Peeters et al. [16] was adopted.

In this model a subset of specific TD_{50}s for patients without and with the clinical risk factor was fitted, while estimating n and k from the entire data set. The dose-modifying factor (D_{mod}) is defined by the ratio of TD_{50}s, and measures the horizontal shift of the dose–response curve when comparing patients without and with the predisposing feature.

The modified NTCP model can include more than one clinical risk factor by introducing different D_{mod} for each clinical factor.

For rectal bleeding TD_{50}s were estimated for patients without and with a history of abdominal surgery and for patients exhibiting and not exhibiting acute GI toxicity ($\geqslant$G1).

For faecal incontinence TD_{50}s were estimated for patients without and with a history of abdominal surgery and for patients with and without previous diseases of the colon.

Best estimates of the model parameters were done by using the Maximum Likelihood method, using the MINUIT software minimization package [CERN, Geneva]; details can be found in [15].

The uncertainties of the parameters were estimated by the 68% confidence interval (CI), by considering the mono-dimensional likelihood profiles and varying one parameter while keeping the others constant at their optimum values. This method takes non-linearity into account and results in non-symmetric confidence intervals. We wish to underline that this method cannot take correlation between parameters into account. In order to consider