BULETINUL INSTITUTULUI POLITEHNIC DIN IAŞI
Publicat de
Universitatea Tehnică „Gheorghe Asachi” din Iaşi
Volumul 63 (67), Numărul 4, 2017
Secţia
MATEMATICĂ. MECANICĂ TEORETICĂ. FIZICĂ

THE EFFECT OF DOSE ESCALATION AND OF THE SIZE OF THE TARGET VOLUME ON LATE RECTAL TOXICITY RISK IN ADVANCED LOCALIZED PROSTATE CANCER

BY

ALINA ROGOJANU[1], ALEXANDRU ZARA[1], CAMIL CIPRIAN MIREȘTEAN[1], CĂLIN GHEORGHE BUZEA[1,*] and DRAGOȘ TEODOR IANCU[1,2]

[1]Regional Institute of Oncology, Iași
[2]“Grigore T. Popa” University of Medicine and Pharmacy, Iaşi

Received: October 23, 2017
Accepted for publication: December 22, 2017

Abstract. Radical prostatectomy or high-dose (definitive) radiotherapy are different options of curative treatment in patients with locally advanced prostate cancer. With the help of the Van Herk formula, one can define for each radiotherapy department CTV to PTV margin, taking into account the systematic and random errors occurred during the treatment implementation. These uncertainties setup margin calculated with this method guarantee that there is a 90% probability that 99% of the CTV is covered correctly. The CTV-PTV margins are recommended by the guidelines for every tumor localization but this margin may be reduced or increased depending on the possibilities of ensuring the reproducibility of the treatment in each radiotherapy department. The purpose of this study was to evaluate the effect on OAR of dose escalation up to 80Gy on the target prostate volume and the expansion of the prostate’s PTV by 1, 2 and 3 mm. The potential risk of toxicity, particularly late rectal toxicity, has been evaluated.

Keywords: radical prostatectomy; dose escalation; prostate volume expansion; late rectal toxicity; radiotherapy.

[*]Corresponding author; *e-mail*: calinb2003@yahoo.com

1. Introduction

Radical prostatectomy or high-dose (definitive) radiotherapy (RT) are 2 options of curative treatment in patients with locally advanced prostate cancer.

The use of a more accurate tumor localization by including advanced imaging methods in the radiotherapy treatment plans and also the use of image guided radiation therapy IGRT for position reproducibility during the treatment have led to improved radiotherapy quality. Greater treatment precision would allow a reduction in CTV-PTV margins and the conforming of the planning target volume (PTV) more closely to the clinical target volume (CTV), in order to reduce the volume of healthy unnecessarily irradiated tissue. As a result, doses can be escalated without increasing the risk of toxicity, with local control and survival improvement clinically proven (Zietman *et al*., 2005).

2. Materials and Methods

Each patient underwent CT simulation in supine position. Target volume and organs at risk (bladder, rectum, femoral heads) were delineated on 3mm slices CT simulation. The planning target volume include the prostate + seminal vesicles, with a 10 mm additional margin in each direction, except posteriorly where the margin was 5 mm in order to reduce rectum dose. According to the GETUG recommendations IGRT was associated with IMRT treatment. The total dose delivered to the prostate was 74Gy, respectively 56Gy and 46Gy for seminal vesicular and pelvic lymph nodes in standard fractionation.

Five patients with locally advanced prostate cancer were selected for this planning study. Patients were placed in a supine position and they were asked to keep their rectum empty. A protocol to fill the bladder with 500 mL of water before simulating after pre-emptying the bladder at the time of simulation and during treatment has also been used to control the filling of the bladder.

The recommendation of International Commission on Radiation Units and Measurements (ICRU 50 Report) were followed for delineation of the OAR and target volumes.

All plans were generated using 6 MV photons with five coplanar fields. A dosimetric guideline from the Royal Marsden NHS Trust allowed to receive 65Gy, 70Gy, and 75Gy for 30%, 15%, and 3%, respectively of entire rectum volumes (Clark *et al*., 2002; Odrazka *et al*., 2005).

Daily kV imaging for position verification and correction were performed prior to each treatment session.

The study of Ye and collaborators proves that by using of kV imaging and prostate fiducial markers to reproduce the position mean shifts in the inferior and superior directions were significantly greater, whereas AP and left-

right shifts did not differ as compared to the positioning with the aid of kV using bony landmarks. CBCT (cone-beam CT) positioning brings theoretical benefits through the ability to better locate of soft tissue landmarks but the is potentially more important when patient's bladder and rectum size vary significantly during the treatment (Ye *et al*., 2015).

Barney *et al.* evaluated CBCT-guided IGRT, comparing it to kV portal image-guided fiducial alignment. And find that 60% of shift differences between the two positioning methods were greater than 3.0 mm, the authors endorsed fiducial alignment based on CBCT-related increases in treatment time because of repositioning by the physician based on soft tissue alignment. The time of CBCT images acquisition is not without consequences, studies proving the need to increase CTV-PTV margins by prolonging intrafractional treatment time (Barney *et al*., 2011).

For 333 patients treated with external beam radiotherapy, 285 patients treated with radical radiotherapy and 48 patients postoperative radio-treated, rectal toxicity was related to the mean rectal dose and with anticoagulant/antiplatelet therapy with no differences in toxicity profile (Martinez-Arribas *et al.*, 2017).

In a retrospective study including 277 treated with 70Gy (10.8%), 74Gy (63.9%) and 80Gy (25.3%) using IMRT without pelvic irradiation rectal toxicity according to CTCA (Common Terminology Criteria for Adverse Events) version 4.0 was analyzed. The radiation doses of 80Gy is associated with a greater long-term grade ≥ 2 rectal toxicity but grade 3 toxicities were low for IMRT radiotherapy (6.2%) (Jolnerovski *et al*., 2017).

3. Results

For the IMRT prostate plans with prescribed dose of 74Gy only 12 of the 20 proposed plans met the condition V65 < 17% and only 8, 5 and 4 plans for 76Gy, 78Gy and 80Gy respectively. Only for 4 IMRT treatment plans V40 was < 35%. For the 74Gy prescription for which optimized plans were made for each target volume, prostate PTV expansion by 1mm increased average V65 by 7.32% V40 by 3.17% relative to the reference plane. Expansion of 2 mm and 3 mm increased average V65 by 7.04% and 8.25% respectively and V40 by 3.06% and 5.33% respectively. Dose escalation at 76Gy 78Gy and 80Gy plan optimizations led to an increased average V65 with 7.52%, 7.87% and 8.07% and an increased average V40 with 4.3%, 4.37% and 4.73% for the plan with prostate PTV expanded by 1mm. For PTV + 2mm, V65 values were increased by 7.69%, 8.12% and 8.39% and V40 values increased by 4.26%, 5.54% and 4.82%. If the planning was performed on a 3 mm expanded prostate PTV, V65 increased by 8.65%, 9.1% and 9.46% and V40 increased by 5.14%, 5.44% and 5.74% (Figs. 1 and 2).

For the rectum, Dmax was obtained with a maximum increase of 8.38% and Dmean with a maximum of 10.04% higher by combining the escalation of the dose and prostate PTV expansion. For the other OARs (bladder, femoral heads), isotropic expansion of PTV and dose escalation leads in most of the proposed treatment plans to an increase of Dmax and Dmean, proportional to the PTV volume and to the escalated prescribed dose. The effect is visible for optimized plans with isotropic expansion of the target volume for which in isolated cases lower values were obtained after replanning and for non-optimized plans by simply escalating the prescribed dose (Figs. 3-10).

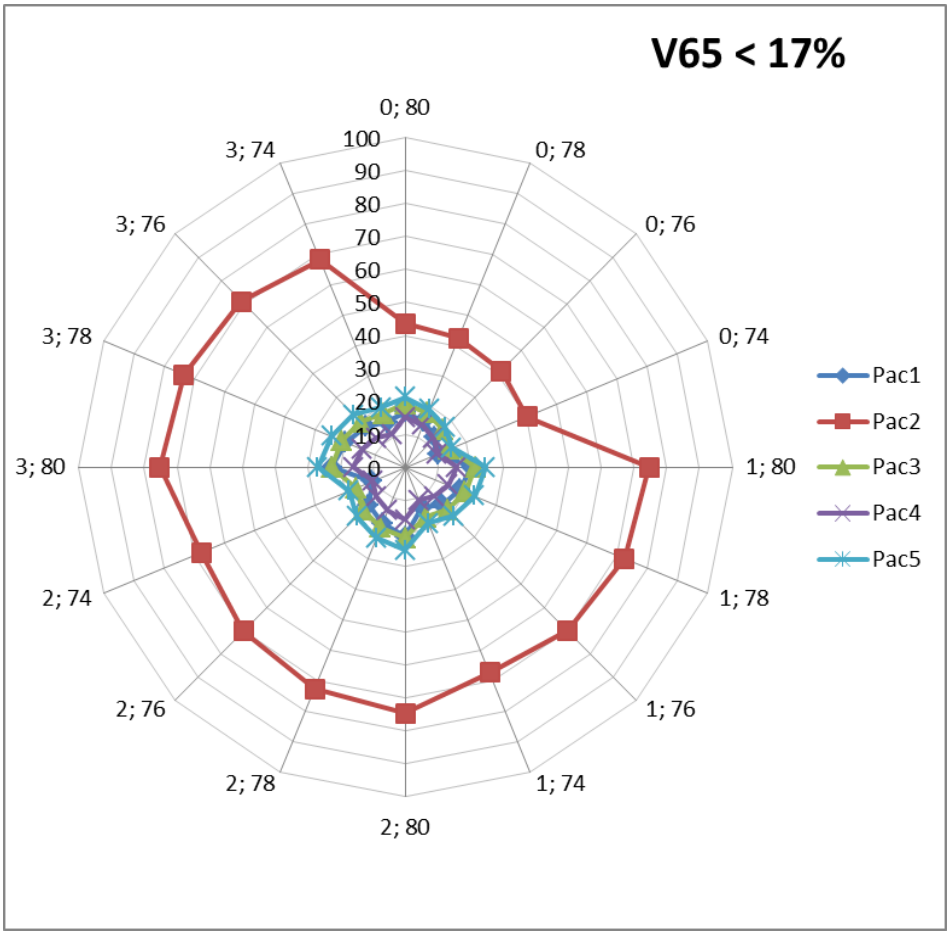

Fig. 1 – V65 chart for isotropic expansion of PTV and dose escalation. Note the labels of the rays mean (PTV expansion; dose escalation value).

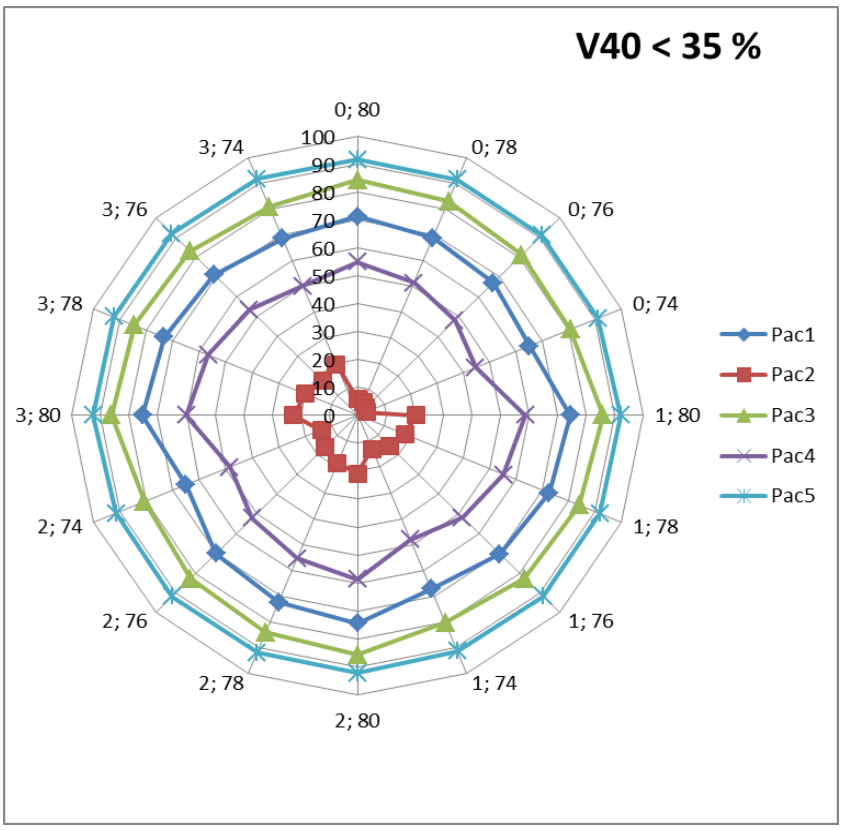

Fig. 2 – V40 chart for isotropic expansion of PTV and dose escalation. Note the labels of the rays mean (PTV expansion; dose escalation value).

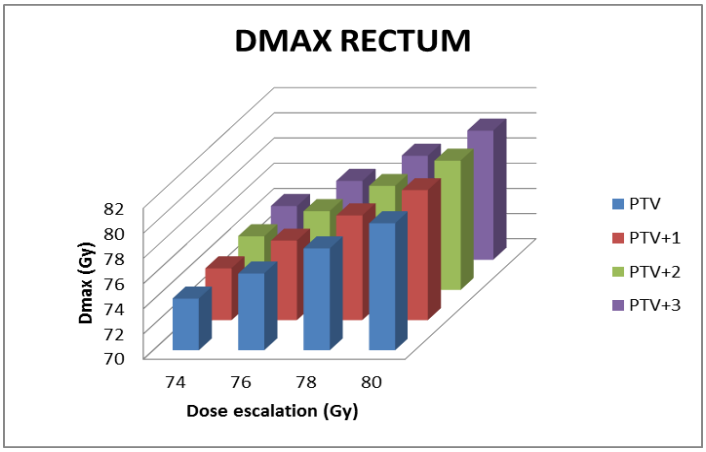

Fig. 3 – Dmax variation for isotropic expansion of PTV and dose escalation in rectum.

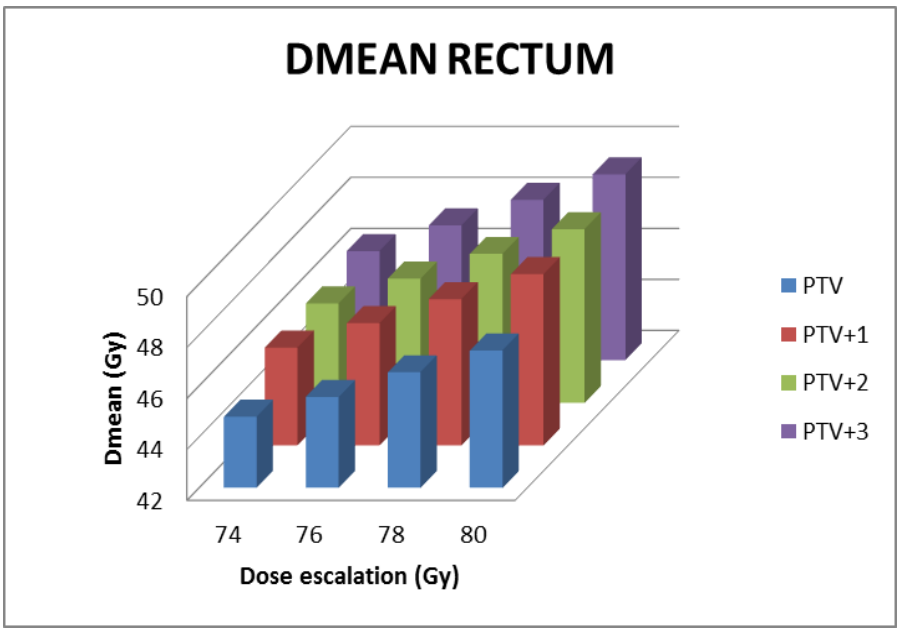

Fig. 4 – Dmean variation for isotropic expansion of PTV and dose escalation in rectum.

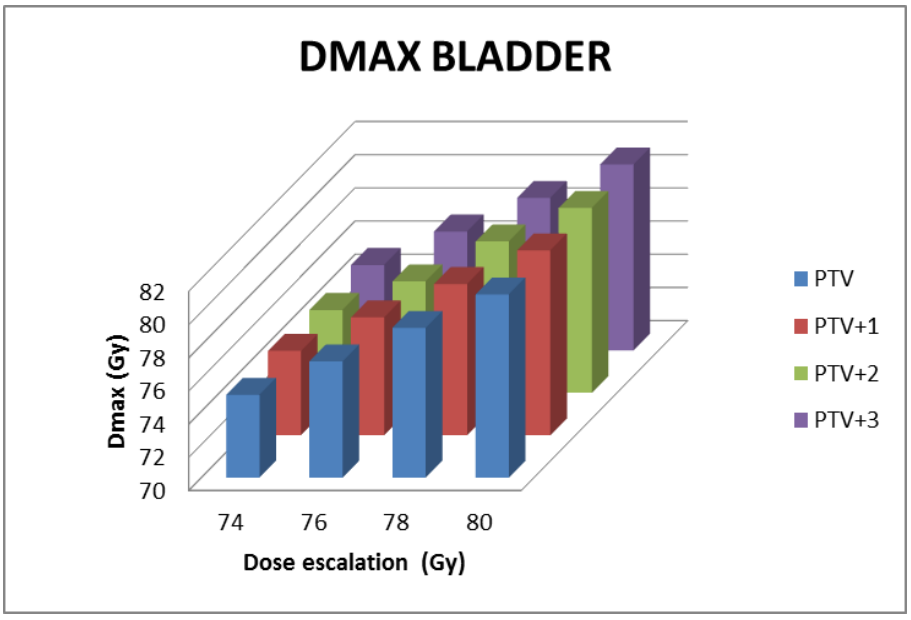

Fig. 5 – Dmax variation for isotropic expansion of PTV and dose escalation in bladder.

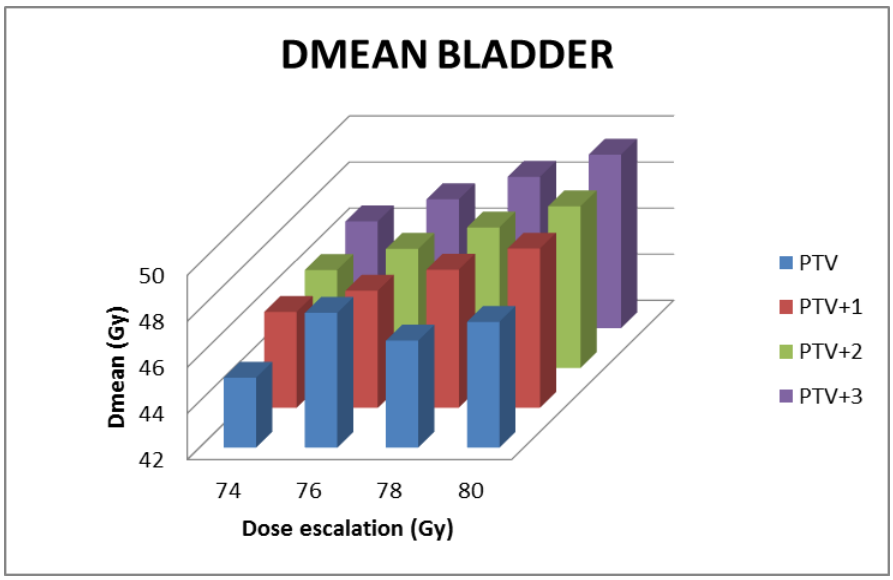

Fig. 6 – Dmean variation for isotropic expansion of PTV and dose escalation in bladder.

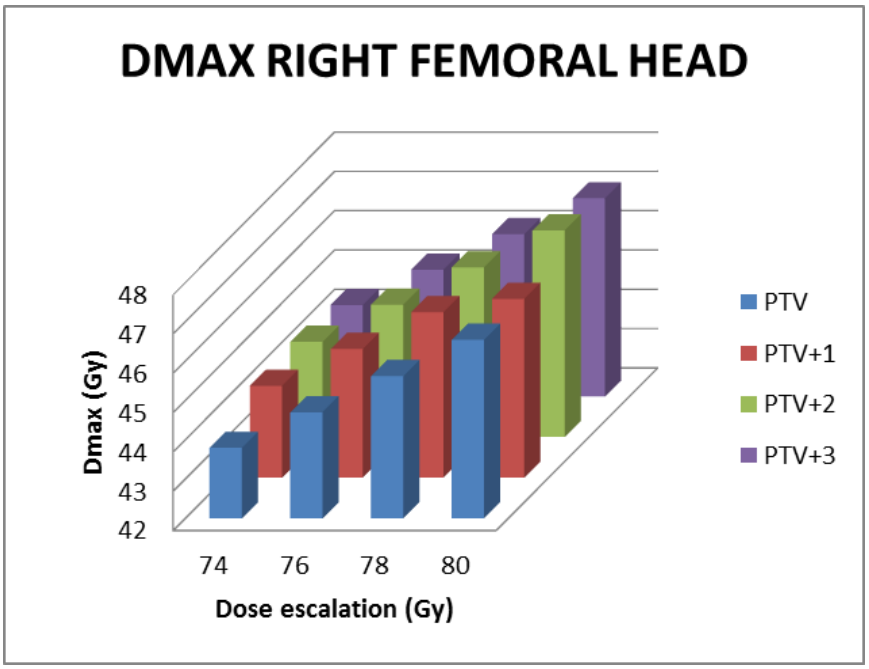

Fig. 7 – Dmax variation for isotropic expansion of PTV and dose escalation in right femoral head.

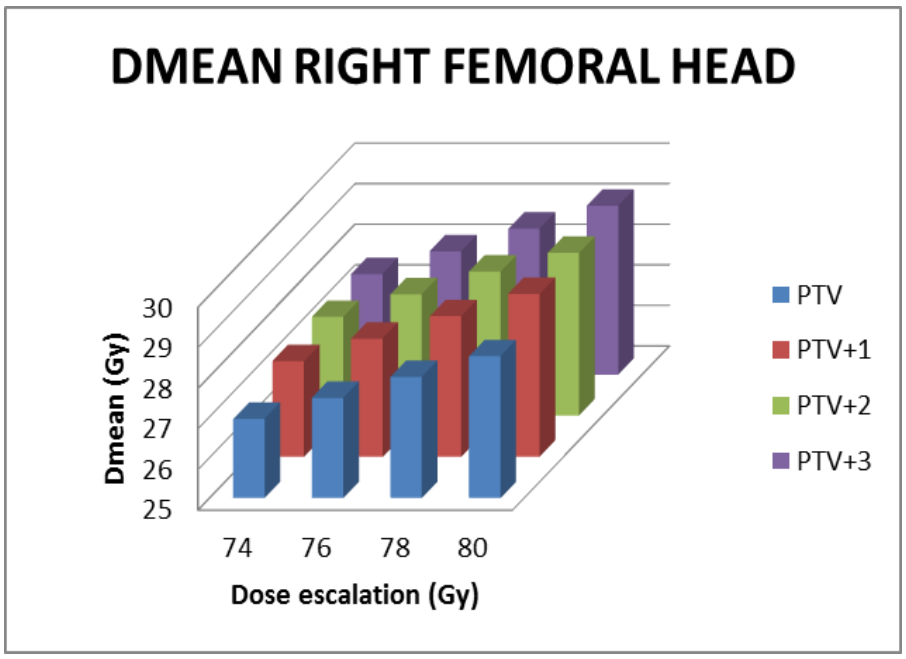

Fig. 8 – Dmean variation for isotropic expansion of PTV and dose escalation in right femoral head.

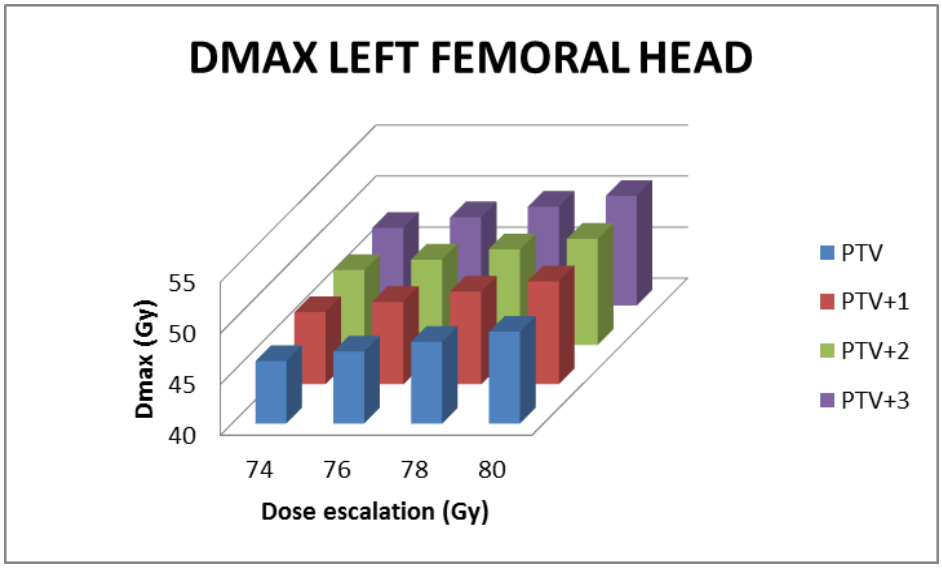

Fig. 9 – Dmax variation for isotropic expansion of PTV and dose escalation in left femoral head.

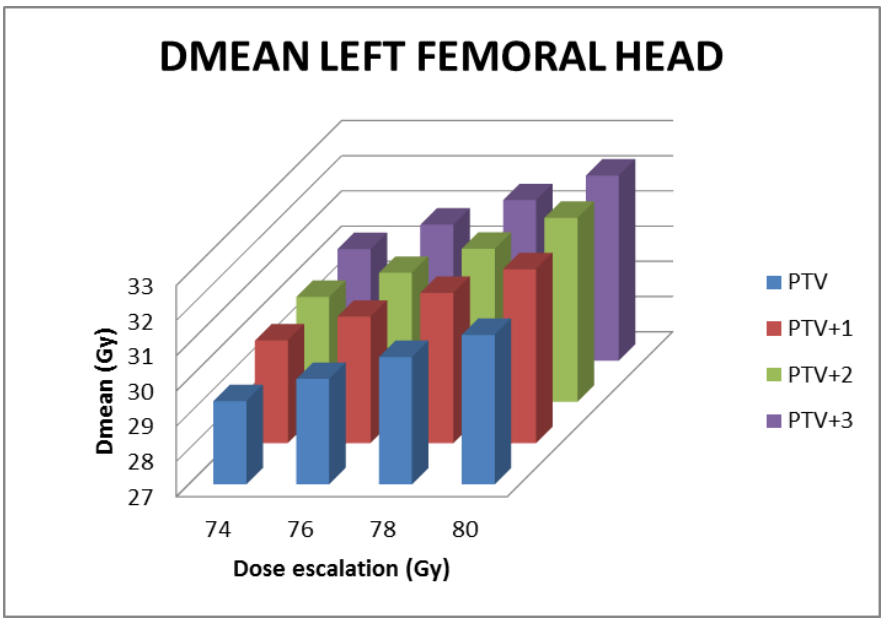

Fig. 10 – Dmean variation for isotropic expansion of PTV and dose escalation in left femoral head.

4. Conclusions

The unpredictable dose distribution and the steep dose gradient leads to the idea that the QUANTEC dosimetric recommendations for the rectum (V50 < 50%, V60 < 35%, V65 < 25%, V70 < 20%, V75 < 15%) may not be sufficient in modern inverse planning radiotherapy techniques. Validation of additional constraints in the context of dose escalation for definitive treatment of locally advanced prostate cancers becomes necessary. Expansion of PTV due to increased uncertainty in patient set-up margin CTV-PTV for the prostate target can increase the risk of late rectal toxicity.

REFERENCES

Barney B.M., Lee R.J., Handrahan D., Welsh K.T., Cook J.T., Sause W.T., *Image-Guided Radiotherapy (IGRT) for Prostate Cancer Comparing kV Imaging of Fiducial Markers with Cone Beam Computed Tomography (CBCT)*, Int. J. Radiat. Oncol. Biol. Phys., **80**, 301-305 (2011).

Clark C.H., Mubata C.D., Meehan C.A. *et al*., *IMRT Clinical Implementation: Prostate and Pelvic Irradiation Using Helios and a 120-Leaf Multileaf Collimator*, J. Appl. Clin. Med. Phys., **3**, 273-284 (2002).

Jolnerovski M., Salleron J., Beckendorf V. *et al*., *Intensity-Modulated Radiation Therapy from 70Gy to 80Gy in Prostate Cancer: Six- Year Outcomes and Predictors of Late Toxicity*, Radiat. Oncol., Jun. 16, **12**, *1*, 99 (2017).

Martínez-Arribas C.M., González-San Segundo C., Cuesta-Álvaro P., *Predictors of Urinary and Rectal Toxicity After External Conformed Radiation Therapy in Prostate Cancer: Correlation Between Clinical, Tumour and Dosimetric Parameters and Radical and Postoperative Radiation Therapy*, Actas. Urol. Esp., Jun. 15, pii: S0210-4806(17)30098-0 (2017).

Odrazka K., Zouhar M., Petera J. *et al*., *Comparison of Rectal Dose-Volume Constraints for IMRT Prostate Treatment Planning*, Phys. Med., October-December, **21**, *4*, 129-135 (2005).

Ye J.C., Qureshi M.M., Clancy P. *et al*., *Daily Patient Setup Error in Prostate Image Guided Radiation Therapy with Fiducial-Based Kilovoltage Onboard Imaging and Conebeam Computed Tomography*, Quant. Imaging Med. Surg., Oct., **5**, *5*, 665–672 (2015).

Zietman A.L., DeSilvio M.L., Slater J.D. *et al*., *Comparison of Conventional Dose vs. High-Dose Conformal Radiation Therapy in Clinically Localized Adenocarcinoma of the Prostate: A Randomized Controlled Trial*, JAMA, **294**, 1233-1239 (2005).

EFECTUL ESCALADĂRII DOZEI ŞI A DIMENSIUNII VOLUMULUI ŢINTĂ ASUPRA RISCULUI DE TOXICITATE RECTALĂ TARDIVĂ ÎN RADIOTERAPIA NEOPLASMELOR DE PROSTATĂ LOCAL AVANSATE

(Rezumat)

Prostatectomia radicală sau radioterapia definitivă sunt 2 opțiuni de tratament curativ pentru pacienții cu cancer de prostată local avansat. Cu ajutorul formulei Van Herk's se pot defini pentru fiecare department de radioterapie marginea de la CTV la PTV tinând cont de erorile sistematice și aleatorii apărute pe parcursul implementării tratamentului. Această zonă de incertitudine adaugată izotrop la CTV asigură o probabilitate de 90% ca 99% din CTV să fie iradiat corespunzător. Marginile CTV-PTV recomandate de ghiduri au valoare orientativă, în fiecare departament ele putând fi reduse sau crescute în funcție de posibilitățile de asigurare a reproductibilității tratamentului. Scopul studiului a fost evaluarea efectului asupra OAR, în special asupra riscului toxicității rectale tardive escaladării dozelor până la 80Gy pe volumul țintă al prostatei și al expandării volumului PTV al prostatei cu câte 1 mm. S-a evaluat riscul potențial de toxicitate, în particular toxicitatea rectală tardivă.