VIA MEDICA

Artykuł oryginalny

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2020, tom 5, nr 2, 64–70

ISSN 2543–5248
www.nowotwory.edu.pl

Testicular dose contributed by X-ray volume image--(XVI)-guided intensity-modulated radiotherapy (IMRT) in prostate cancer patients

Dominika Hempel[1, 2], Robert Chrenowicz[3, 4], Tomasz Filipowski[2], Marek Z. Wojtukiewicz[1], Ewa Sierko[1, 2]

[1]*Department of Oncology, Medical University of Bialystok*
[2]*Department of Radiotherapy, Comprehensive Cancer Center in Bialystok*
[3]*Department of Physics, Comprehensive Cancer Center in Bialystok*
[4]*Department of Physics, University of Bialystok*

Introduction: To assess the dose received by testes during XVI-guided IMRT in prostate cancer patients (PCPs).
Material and methods: Testes dose was calculated in 56 PCPs who underwent definitive IMRT using 6 MV or 15 MV photon energies. The dose was measured by thermoluminescent dosimeters (TLDs) MTS-N attached to the scrotum during the first three fractions of IMRT. Testicular concomitant exposure from XVI was measured using a PTW DIADOS E diagnostic dosimeter in ten randomly chosen patients.
Results: The mean and standard deviation values of the average calculated testes dose was 123 ± 117 cGy comprising 1.6% of the prescribed total irradiation dose (Dt). A testicular dose measured by TLDs was 303 ± 110.5 cGy (4% of Dt) and depended on the distance from isocenter to testes (r = –0.8). From one XVI scan, the detected testicular mean dose was 4.3 mGy. Mean XVI scan numbers for all patients was 10.4 so mean concomitant dose in testes was 44.7 mGy (0.06% of Dt).
Conclusions: Testicular dose may be significant in the aspect of fertility during IMRT in PCPs. Kilovoltage XVI-contributed dose to testes seems to be clinically negligible.

Biuletyn PTO NOWOTWORY 2020; 5, 2: 64–70

Key words: prostate cancer, testes doses, XVI, IMRT

Introduction

Prostate cancer (PC) is the second most common cancer and the third most common cause of cancer-related death among men in Poland [1]. It is diagnosed mainly in the age group 65–79 years. Prostate-specific antigen (PSA) measurement was introduced to the diagnosis of PC in 1970 resulting in a growing number of younger patients (aged 45–64) suffering from this disease [2]. Radiotherapy (external beam radiotherapy, EBRT or/plus brachytherapy) is a standard treatment modality in localized PC patients (PCPs) [2–4]. As far as EBRT is concerned, it is preferable to use more sophisticated techniques (e.g. intensity-modulated radiation therapy, IMRT) [5, 6]. Epidemiological changes in the PC incidence pattern are enforcing alterations in the approach taken by physicians. It seems that the sexual area and even fertility aspects cannot be neglected in some subset of PCPs. During EBRT delivered to the prostate, the testes, which are in close proximity

How to cite:
Hempel D, Chrenowicz R, Filipowski T, Wojtukiewicz MZ, Sierko E. *Testicular dose contributed by X-ray volume image-(XVI)-guided intensity-modulated radiotherapy (IMRT) in prostate cancer patients.* *NOWOTWORY J Oncol* 2020; 70: 47–53.

to this organ, are unshielded. The specific structure (seminiferous tubules are composed of germinal, Sertoli and Leydig cells) and functions of the testes (both reproductive and endocrine) determine their radiobiological response. Germinal cells divide and differentiate to produce spermatocytes, spermatids and eventually spermatozoa or sperm cells. In humans, the transition time from stem cells to spermatozoa is about 74 days. Leydig cells produce the male hormone testosterone. A mean testicular dose as low as 100 cGy leads to a temporary reduction in the number of spermatozoa while 150 cGy may cause temporary sterility. Azoospermia lasting several years occurs after 2 Gy and permanent azoospermia occurs after a dose of about 6 to 8 Gy in 2-Gy fractions [7, 8]. In turn, even much higher doses have little effect on the Leydig cells in the adult so whereas irradiation of the testes can lead to sterility, it has little or no effect on the libido [7, 9]. What is of paramount importance is the fact that fractionated radiotherapy or even low-doses of scattered radiation reaching the testes during pelvic area irradiation are more harmful to germinal cells than single high-dose exposure. This results from the fact that some proportion of the stem cells move from a radioresistant phase of the cell cycle into more radiosensitive phases in the course of definitive fractionated irradiation [8]. Animal studies have revealed that low-dose radiotherapy would result in persistent double-strand breaks in the spermatogonial stem cells [10], injury to the blood-testis barrier [11] and temporarily observed testosterone abnormal function [12].

IMRT allows the delivery of a higher total dose than 3-D conventional radiotherapy (CRT) to the target volume without exceeding the tolerance dose to the organs at risk (OARs) such as the rectum or the bladder, by careful modulation of photon fluence within a subset of the beams [5, 6, 13, 14]. On the other hand, a considerable increase in the number of beams and monitor units (MUs) for IMRT produces a risk of the delivery of a higher equivalent dose in the OARs located outside the target volume (secondary scattered radiation from the patient) [15]. In addition, tissues outside the primary beam trajectory may be also exposed to low doses of scattered and leakage radiation attributable to imperfections in the radiation delivery devices – secondary scattering from the machine head or the floor and walls of the room [15, 16]. Furthermore, during the course of IMRT, the patient is subjected to an additional dose called "concomitant exposure" from image-guided localization and verification procedures (IGRT), e.g. kilovoltage X-ray volume imaging (kV XVI) [17–20].

Although the dose received by the testes during CRT on the pelvic area guided by portal films has been widely investigated [2, 21–24], little is known about the testes-dose contributed by IMRT (MV energy) and XVI (kV energy) in PCPs. The aim of the present study was to assess the quantity of undesired testicular doses during XVI-guided IMRT for localized PCPs.

Material and methods

The calculations were performed in 56 localized PCPs (Tab. I) who underwent small field step-and-shoot IMRT with curative intent. The work was carried out in accordance with The Code of Ethics of the World Medical Association (the Declaration of Helsinki) for experiments involving humans. Approval for this study was obtained from the Human Care Committee of the Medical University in Bialystok, Poland. Informed written consent was obtained from the patients.

Table I. Characteristics of the studied group – prostate cancer patients (n = 56) treated with definitive small field step-and-shoot intensity-modulated radiation therapy (IMRT)

Characteristics	Value
Age (year), mean min–max	70 54–83
TNM* (n†): T1N0M0 T2N0M0 T3N0M0 T4N0M0	 13 39 2 2
PSA [ng/ml], mean	28.5
Gleason score, mean	6.9
Fraction dose [Gy]	2
Total dose [Gy], mean	74
Total dose [Gy], min–max	66–76
Photon beam energy – X [MV]: 6 15	 29 27

TNM*: T – tumour, N – lymph node, M – metastase; n† – number of patients

Radiotherapy planning and treatment

The IMRTs were planned in accordance with the protocol applied for PCPs in Comprehensive Cancer Center in Bialystok, Poland. Patients were immobilized in the supine position on styrofoam with individually selected accessories such as a kneefix or feetfix. Next, computed tomography (CT) scans of the pelvic area and testes were performed for patients immobilized in the treatment position, which provided the basis for target and OAR delineation. The clinical target volume (CTV) comprised the prostate and the base of the seminal vesicles (SV). An 8–10 mm margin encompassing the CTV was added to create a planning target volume (PTV). The delineation was comprised of the following OARs: the bladder, the rectum, the heads of the femoral bones and additionally to standard protocol – the testes. Inverse planning Oncentra MasterPlan V 3.3 SP3 (Nucletron, Veenendaal, The Netherlands) with a collapsed cone algorithm (Elekta Corporation, Atlanta, GA) was used to create IMRT plans. Measurements in homogeneous and inhomogeneous phantoms (Alderson Radiation Therapy Phantom, ART) were performed (data not provided) to validate the dose calculation accuracy of the Oncentra Masterplan TPS. In this study, we did not specifically separate the dose from head leakage or collimator scatter which have been measured to comprise 0.5% of the fractionated dose (corresponding

therefore to 0.38 Gy for a radiotherapy treatment delivering 76 Gy). IMRT plans were created with a configuration of 7–9 coplanar beams, generated individually for each patient using a 1 cm – multileaf collimater (MLC). All the IMRT plans created by the Oncentra Masterplan TPS were verified using ion chamber arrays including PTW729 and IBA Matrixx systems before treatment. Photon 6 MV or 15 MV beams generated by an Elekta (Elekta, Stockholm, Sweden) linear accelerator using the XVI technique (Elekta, XVI R4.5) as IGRT were used for the treatment process (Tab. I).

Testicular dose calculated in the treatment planning system (TPS)

Based on the CT datasets of the 56 PCPs, the testes dose was calculated in the TPS. The 3D dose distributions, mean, median, maximum and minimum doses regarding testes were analyzed for a total dose of 76 Gy delivered to the prostate in 38 fractions. The correlation between CTV, PTV volume and testes dose was analyzed.

Testicular dose measured by thermoluminescent dosimeters (TLD)

Thermoluminescent dosimeters (TLDs) MTS-N (Radcard, Krakow, Poland) were attached to the scrotum in close proximity to the testes for each of ten randomly chosen patients during the first three fractions of definitive IMRT (6 MV). Dose measurements were obtained using lithium-fluorine round chips with a diameter of 4.5 mm and a thickness of 0.9 mm. All TLDs were previously prepared in a MagmaTherm laboratory furnace and calibrated. Annealing was started by dosimeters heating to a temperature of 400 ± 5°C for 1 h and this was followed by a cooling down to 80°C for 17 h. Calibration was performed in an X-ray beam of narrow spectrum N-80, N-l00, N-l20, N-150. A Mikrolab RA'04 device (Mikrolab, Krakow, Poland) was used to readout the dose as measured. Final calculations were obtained using calibration factors. The total doses to the testes of each patient were calculated from the mean dose of the three TLD measurements and extrapolated for a treatment course of 38 fractions. The mean distance from isocenter to detector was 12.2 cm. The overall number of TLD measurements was 30. The accuracy of in vivo TLD measurements was verified using an anthropomorphic phantom and multidetector matrix PTW 729 with PMMA phantom.

kV XVI-contributed testes dose measurements

Concomitant testicular dose was measured in 10 randomly chosen patients included in the study. A PTW DIADOS E diagnostic dosimeter with semiconductor detector of the T60004 type (PTW, Freiburg, Germany), previously calibrated in the Central Laboratory for Radiological Protection in Warsaw, was used to measure testes dose contributed by kV XVI. Calibration was performed using an X-ray beam of narrow spectrum N-80, N-l00, N-l20, N-150. The dosimeter was placed in the area of the testes. An M15F1 (M15: medium collimater, size 15 cm; F1: bow-tie filter; 120 kVp, 64 mA, acquisition angle range –180; 180, acquisition time 120s) was used in procedures.

In accordance with protocol, XVI was performed before the 1st, 2nd, 3rd and every 7th fraction as well as in each case of more than 5mm displacement in pelvic area. The number of XVI procedures performed for each patient was counted so that the total testes dose contributed by XVI over the full course of treatment could be calculated.

QA procedures were performed in line with the instructions covered in "Customer Acceptance Tests" as well as "Instructions For Use" in the XVI 4.5 manuals.

The data was statistically analyzed using the computer software Microsoft Excel and Statistica ver.10. Spearman's test ranks were chosen for verification of the hypotheses. A confidence level of 0.05 was accepted. A correlation test of Spearman's ranks was used for correlation analysis, which is a nonparametric measure of statistical dependence between random variables.

Results

MV-testicular dose calculations

The mean and standard deviation (mean ± SD) value of the average testes dose was 123 ± 117 cGy comprising 1.6% of the prescribed treatment dose (76 Gy). The mean values of minimum and maximum doses were 53 and 370 cGy, respectively. The smallest calculated dose in the testes was 0 Gy, the highest – 35.19 Gy (Tab. II).

A trend for increased testes dose in patients irradiated with higher energy was observed. However, dosimetric comparisons between IMRTs using 6 MV and 15 MV photon energies were not significantly different – mean testes doses were 100 *vs* 130 cGy, respectively ($p > 0.05$).

Table II. Testes doses calculated for prostate cancer patients who underwent definitive small field IMRT (n = 56, prescribed treatment dose 76 Gy, daily dose 2 Gy, SD – standard deviation)

Value	Calculated testes dose			
	Mean dose [cGy]	Median dose [cGy]	Minimum dose [cGy]	Maximum dose [cGy]
Mean ± SD	123 ± 117	122 ± 70	53 ± 42	370 ± 69
Median (25–75%)	98 (56–150)	97 (60–150)	55 (19–78)	102 (160–317)
Min–Max	9–73	9–234	0–166	15–3519

Mean volume of CTV, PTV and testes was 87.5, 264.5 and 57.4 cm^3, respectively. There was no correlation between CTV (r = 0.2) or PTV volume (r = 0.3) and mean testicular dose.

MV-testicular dose measurements

The secondary testes dose was measured for ten PCPs during the first three fractions of definitive IMRT (total dose 76 Gy, 38 fractions, 6 MV photon energy). A mean testicular dose of 7.97 ± 2.9 cGy (min-max 5.17–11.62 cGy) was delivered during one fraction of IMRT (with the mean value taken from 3 measurements for 10 patients). The total testes dose after 38 fractions for these patients was calculated to be 303 ± 110.5 cGy (min–max 196.5–441.6 cGy) and correlated with the distance from the isocenter to the testes (r = –0.84) (Tab. III).

Concomitant kV-testicular dose measurements

In all 10 patients the detector was located outside the XVI verification field. A single XVI procedure delivered a mean dose of 4.3 ± 2.0 mGy (min-max: 2.1–9.1 mGy) to the testes. The mean number of XVI verifications performed during radiotherapy was 10.4 (min-max: 7–16) so that the total mean dose from XVI procedures was 46.3 mGy (min–max: 24.5–136.5 mGy) (Tab. IV).

Conclusions

Testicular dose contributed by megavoltage IMRT, as well as concomitant dose added by the kV XVI procedure were analyzed in the current study. According to the data indicated in the literature, the testes dose originating from neutrons generated at high energies is very small (0.04% of the treatment dose) and has not been taken into consideration in this analysis [25, 26]. Unfortunately, the minimum dose which affects testes function in irradiated PCPs has not been precisely determined. Based on patient studies of testicular injury following conventionally fractionated irradiation, it seems that doses smaller than 20–50 cGy should not cause hormonal impairment [22, 24] while doses ranged 100–350 cGy are sufficient to impair germinal cells [7, 24, 27–32]. The standard total dose applied for PCPs treated with definitive IMRT in the present study was 76 Gy (38 fractions). The dose constraints were not specified for the testes to determine the dose distribution in a standard situation where testes are not contoured as critical structures. We found that for these patients the mean doses to the testes were 123 cGy (calculated by TPS) or 303 cGy (measured by TLDs), comprising 1.6 or 4.0% of the total treatment dose. The difference between the calculated and measured doses may result from the fact that TLDs detected only a superficial dose in one point of the scrotum while TPS assessed the dose distribution throughout the whole organs. Moreover, it is well known that TPS may undercalculate the peripheral dose in irradiated patients [33].

Importantly, the doses detected by both methods indicate that IMRT may be associated with testes function impairment if no constraints are determined during the planning process. If the testes are not imaged and delineated, the treatment planning system does not regard them as "worth-protection", resulting in beam fluence through the genitalia. Additionally, a high number of MUs delivered during IMRT may increase internal scattering leading ultimately to a clinically significant testicular dose. Intensity modulation techniques require the accelerator to be energized 3–4 times longer than that for 3D-CRT methods, thus increasing linear accelerator head leakage and the overall exposure of the patient to secondary radiation [15, 23, 34–37]. The equivalent doses for the whole body produced by IMRT are greater than those seen when using conventional radiation [38, 39]. On the other hand, due to multileaf collimater (MLC) movements, the effective field size in IMRT is smaller than in 3-D CRT which may help reduce the dose received by nearby out-of-field organs, such as the gonads in PCPs [15, 34, 39]. The results of other studies have shown that the testes, despite the increased number of MUs for IMRT, receive as much as a 2.5 times lower dose during IMRT than 3-D CRT when regarded as critical structures [34, 40]. Data presented by Deng et al. [41] and Martin et al. [42] showed that, during definitive IMRT, testes doses contributed by photon scattering may be as low as 0.7–1.4 cGy per fraction (in our study – 3.2 cGy). Basing on the available literature, mean testicular doses from CRT calculated to 76 Gy ranged from 206.9 to 234 cGy comprising 2.72–3.08% of the prescribed

Table IV. Assumed XVI-contributed testes dose for whole course of treatment (10.4 scans)

Testes dose per scan [mGy]		Testes dose (10.4 scans) [mGy]	
Mean ± SD	Min–Max	Mean	Min–Max
4.3 ± 1.99	2.1–9.1	44.7	21.84–94.64

Table III. Testes dose measured for prostate cancer patients who underwent definitive 6 MV small field IMRT (n = 10, prescribed treatment dose 76 Gy, daily dose 2 Gy)

Value	Measured testes dose		Distance isocenter-detector [cm]
	One fraction – 2 Gy [cGy]	38 fractions – 76 Gy [cGy]	
Mean ± SD	7.97 ± 2.9	303 ± 110.5	12.2 ± 1.35
Median (range 25–75%)	6.74 (5.8–10.5)	256.1 (220.8–399.8)	12 (11.6–13.5)
Min–Max	5.17–11.62	196.5–441.6	9–14.5

dose, thus being higher than the doses presented for IMRT [2, 21, 31]. This is why dynamic techniques are the method of choice in PCPs with plans for a family, providing the testes are given high priority as an avoidance structure in order to minimize beam fluence through the genitalia.

In addition, our findings suggest that lower MV-energy is associated with reduced testicular dose. These results are in agreement with other studies which have shown a weak dependence of photon dose outside the treatment field on beam energy [16, 43]. According to King et al. [44] the photon scattered dose in the testes is about 1.3 times higher with 15 MV beams compared with 6 MV beams. The dependence of testicular dose on CTV/PTV volume was also described [44–46]. In our study, where all patients were irradiated on small fields, a correlation between CTV, PTV volume and mean testicular dose was not observed.

It would be impossible to determine on the basis of this study what the exact components of the measured dose are. According to van der Giessen [43], the major contributors of dose to tissues in close proximity to the field edge are collimator scatter and patient scatter. As the distance increases from the field edge collimator scatter decreases, and patient scatter, as well as head leakage, becomes more dominant [15, 47, 48].

In the current study, the testicular dose decreased with increasing distance from the isocenter to the testes. Many studies have shown such an association and out-of-field dose data are often presented as a function of distance from the field edge or central axis relative to the tumor target in the patient [15, 19, 47, 49, 50].

Concomitant exposure – XVI

It is assumed that the additional imaging dose should be lower than 2% of the therapy dose variation in order to comply with the ALARA convention rule [51]. In the present study we found that kV XVI increased the total testicular dose by 4.3 mGy per fraction (max 9.1 mGy). There are very few studies in the literature exploring the impact of CBCT-based prcoedures (XVI Elekta, Varian OBI system) on the testes dose in PCPs [35, 50]. Both Hyer et al. [52] and Deng et al. [41] determined the mean testicular dose from one procedure of CBCT as 29 mGy. Most importantly, the results from the Deng study comprise mean testes doses for different OBI field spans. The testes dose for a 30 cm-field produced 57 mGy while for 10 cm-field – only 2 mGy (this calculation is similar to ours, received for a 15 cm XVI field from the measured method). In Hyer's investigation [52], the detector was placed in some cases within the XVI field which also increased the testes doses and may explain the differences with the present study where the detector was never located in the field. The testes concomitant dose deserves additional investigation on a large group of patients with different XVI settings.

The results of the current study indicate that the dose in the testes may be significant from a fertility perspective during IMRT in PCPs. It seems that the IMRT protocol for PCPs who have not completed family planning should involve the determination of the testes as an avoidance structure to keep the dose as low as reasonably achievable during the optimization process. The kilovoltage XVI-contributed dose to the testes seems to be clinically negligible, especially if verifications are performed once or twice a week using a small field span. To minimize the testicular dose in PCPs with plans for a family, the establishment of a specific quality assurance protocol for XVI-guided IMRT is warranted.

Conflict of interest: none declared

Ewa Sierko
Medical University of Bialystok
Department of Oncology
ul. Ogrodowa 12
15-027 Białystok, Poland
e-mail ewa.sierko@iq.pl

Received: 17 Nov 2019
Accepted: 10 March 2020

Acknowledgments

The authors gratefully acknowledge the physicians of the Department of Radiotherapy in the Comprehensive Cancer Center in Bialystok, Poland for delineation of the testes in the studied patients.

References

1. National Cancer Registry (2014). http://onkologia.org.pl.
2. Boehmer D, Badakhshi H, Kuschke W, et al. Testicular Dose in Prostate Cancer Radiotherapy. Strahlenther Onkol. 2005; 181(3): 179–184, doi: 10.1007/s00066-005-1282-1.
3. Candela-Juan C, Perez-Calatayud J, Ballester F, et al. Calculated organ doses using Monte Carlo simulations in a reference male phantom undergoing HDR brachytherapy applied to localized prostate carcinoma. Med Phys. 2013; 40(3): 033901, doi: 10.1118/1.4791647, indexed in Pubmed: 23464344.
4. Wallis CJD, Mahar AL, Choo R, et al. Second malignancies after radiotherapy for prostate cancer: systematic review and meta-analysis. BMJ. 2016; 352: i851, doi: 10.1136/bmj.i851, indexed in Pubmed: 26936410.
5. Vora S, Wong W, Schild S, et al. Outcome and Toxicity for Patients Treated with Intensity Modulated Radiation Therapy for Localized Prostate Cancer. J Urol. 2013; 190(2): 521–526, doi: 10.1016/j.juro.2013.02.012.
6. Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol. 2017; 71(4): 618–629, doi: 10.1016/j.eururo.2016.08.003, indexed in Pubmed: 27568654.
7. Shalet SM. Effect of irradiation treatment on gonadal function in men treated for germ cell cancer. Eur Urol. 1993; 23(1): 148–151; discussion 152, doi: 10.1159/000474584, indexed in Pubmed: 8386642.
8. Lee SH, Shin CHo. Reduced male fertility in childhood cancer survivors. Ann Pediatr Endocrinol Metab. 2013; 18(4): 168–172, doi: 10.6065/apem.2013.18.4.168, indexed in Pubmed: 24904872.
9. Vassilakopoulou M, Boostandoost E, Papaxoinis G, et al. Anticancer treatment and fertility: Effect of therapeutic modalities on reproductive system and functions. Crit Rev Oncol Hematol. 2016; 97: 328–334, doi: 10.1016/j.critrevonc.2015.08.002, indexed in Pubmed: 26481950.
10. Grewenig A, Schuler N, Rübe CE. Persistent DNA Damage in Spermatogonial Stem Cells After Fractionated Low-Dose Irradiation of Testicular Tissue. Int J Radiat Oncol Biol Phys. 2015; 92(5): 1123–1131, doi: 10.1016/j.ijrobp.2015.04.033, indexed in Pubmed: 26059351.
11. Son Y, Heo K, Bae MJ, et al. Injury to the blood-testis barrier after low--dose-rate chronic radiation exposure in mice. Radiat Prot Dosimetry.

2015; 167(1-3): 316–320, doi: 10.1093/rpd/ncv270, indexed in Pubmed: 25948832.
12. Demir A, Karadag MA, Cecen K, et al. Effects of testosterone treatment on recovery of rat spermatogenesis after irradiation. J Pak Med Assoc. 2015; 65(3): 300–305, indexed in Pubmed: 25933566.
13. Sujenthiran A, Nossiter J, Charman SC, et al. National Population-Based Study Comparing Treatment-Related Toxicity in Men Who Received Intensity Modulated Versus 3-Dimensional Conformal Radical Radiation Therapy for Prostate Cancer. Int J Radiat Oncol Biol Phys. 2017; 99(5): 1253–1260, doi: 10.1016/j.ijrobp.2017.07.040, indexed in Pubmed: 28974414.
14. Pollack A, Abramowitz MC. Weighing the Addition of Androgen Suppression Therapy to Radiotherapy Dose Escalation for Intermediate-Risk Prostate Cancer. J Clin Oncol. 2016; 34(15): 1715–1717, doi: 10.1200/JCO.2015.66.2320, indexed in Pubmed: 26976421.
15. Xu XG, Bednarz B, Paganetti H. A review of dosimetry studies on external-beam radiation treatment with respect to second cancer induction. Phys Med Biol. 2008; 53(13): R193–R241, doi: 10.1088/0031-9155/53/13/R01, indexed in Pubmed: 18540047.
16. Singhal MK, Kapoor A, Singh D, et al. Scattered radiation to gonads: role of testicular shielding for para-aortic and homolateral illiac nodal radiotherapy. J Egypt Natl Canc Inst. 2014; 26(2): 99–101, doi: 10.1016/j.jnci.2014.03.002, indexed in Pubmed: 24841161.
17. Halg RA, Besserer J, Schneider U. Systematic measurements of whole--body imaging dose distributions in image-guided radiation therapy. Med Phys. 2012; 39(12): 7650–7661, doi: 10.1118/1.4758065, indexed in Pubmed: 23231313.
18. Hess CB, Thompson HM, Benedict SH, et al. Exposure Risks Among Children Undergoing Radiation Therapy: Considerations in the Era of Image Guided Radiation Therapy. Int J Radiat Oncol Biol Phys. 2016; 94(5): 978–992, doi: 10.1016/j.ijrobp.2015.12.372, indexed in Pubmed: 27026304.
19. Fricker K, Thompson C, Meyer J. Assessment of concomitant testicular dose with radiochromic film. Australas Phys Eng Sci Med. 2013; 36(3): 269–277, doi: 10.1007/s13246-013-0208-y, indexed in Pubmed: 23794085.
20. Loutfi-Krauss B, Köhn J, Blümer N, et al. Effect of dose reduction on image registration and image quality for cone-beam CT in radiotherapy. Strahlenther Onkol. 2015; 191(2): 192–200, doi: 10.1007/s00066-014-0750-x, indexed in Pubmed: 25238990.
21. Amies CJ, Mameghan H, Rose A, et al. Testicular doses in definitive radiation therapy for localized prostate cancer. Int J Radiat Oncol Biol Phys. 1995; 32(3): 839–846, doi: 10.1016/0360-3016(95)00524-3, indexed in Pubmed: 7790272.
22. Fraass BA, Kinsella TJ, Harrington FS, et al. Peripheral dose to the testes: the design and clinical use of a practical and effective gonadal shield. Int J Radiat Oncol Biol Phys. 1985; 11(3): 609–615, doi: 10.1016/0360-3016(85)90196-8, indexed in Pubmed: 3972670.
23. Koshy M, Paulino AC, Marcus RB, et al. Extra-target doses in children receiving multileaf collimator (MLC) based intensity modulated radiation therapy (IMRT). Pediatr Blood Cancer. 2004; 42(7): 626–630, doi: 10.1002/pbc.20030, indexed in Pubmed: 15127418.
24. Kinsella TJ, Trivette G, Rowland J, et al. Long-term follow-up of testicular function following radiation therapy for early-stage Hodgkin's disease. J Clin Oncol. 1989; 7(6): 718–724, doi: 10.1200/JCO.1989.7.6.718, indexed in Pubmed: 2497228.
25. Tosi G, Torresin A, Agosteo S, et al. Neutron measurements around medical electron accelerators by active and passive detection techniques. Med Phys. 1991; 18(1): 54–60, doi: 10.1118/1.596751, indexed in Pubmed: 2008172.
26. Kry SF, Salehpour M, Titt U, et al. Monte Carlo study shows no significant difference in second cancer risk between 6- and 18-MV intensity-modulated radiation therapy. Radiother Oncol. 2009; 91(1): 132–137, doi: 10.1016/j.radonc.2008.11.020, indexed in Pubmed: 19147246.
27. Izard MA. Leydig cell function and radiation: a review of the literature. Radiother Oncol. 1995; 34(1): 1–8, doi: 10.1016/0167-8140(94)01501-s, indexed in Pubmed: 7792393.
28. Daniell HW, Clark JC, Pereira SE, et al. Hypogonadism following prostate-bed radiation therapy for prostate carcinoma. Cancer. 2001; 91(10): 1889–1895, doi: 10.1002/1097-0142(20010515)91:10<1889::aid--cncr1211>3.0.co;2-u, indexed in Pubmed: 11346871.
29. Daniell HW, Tam EW. Testicular atrophy in therapeutic orchiectomy specimens from men with prostate carcinoma: association with prior prostate bed radiation and older age. Cancer. 1998; 83(6): 1174–1179, doi: 10.1002/(sici)1097-0142(19980915)83:6<1174::aid-cncr17>3.0.co;2-2, indexed in Pubmed: 9740083.
30. Grigsby PW, Perez CA. The effects of external beam radiotherapy on endocrine function in patients with carcinoma of the prostate. J Urol. 1986; 135(4): 726–727, doi: 10.1016/s0022-5347(17)45831-9, indexed in Pubmed: 3083117.
31. Zagars GK, Pollack A. Serum testosterone levels after external beam radiation for clinically localized prostate cancer. Int J Radiat Oncol Biol Phys. 1997; 39(1): 85–89, doi: 10.1016/s0360-3016(97)00311-8, indexed in Pubmed: 9300743.
32. King CR, Lo A, Kapp DS. Testicular dose from prostate cyberknife: a cautionary note. Int J Radiat Oncol Biol Phys. 2009; 73(2): 636–637; author reply 637, doi: 10.1016/j.ijrobp.2008.09.004, indexed in Pubmed: 19147028.
33. Joosten A, Bochud F, Baechler S, et al. Variability of a peripheral dose among various linac geometries for second cancer risk assessment. Phys Med Biol. 2011; 56(16): 5131–5151, doi: 10.1088/0031-9155/56/16/004, indexed in Pubmed: 21775792.
34. Howell RM, Hertel NE, Wang Z, et al. Calculation of effective dose from measurements of secondary neutron spectra and scattered photon dose from dynamic MLC IMRT for 6 MV, 15 MV, and 18 MV beam energies. Med Phys. 2006; 33(2): 360–368, doi: 10.1118/1.2140119, indexed in Pubmed: 16532941.
35. Klein EE, Maserang B, Wood R, et al. Peripheral doses from pediatric IMRT. Med Phys. 2006; 33(7): 2525–2531, doi: 10.1118/1.2207252, indexed in Pubmed: 16898456.
36. Mansur DB, Klein EE, Maserang BP. Measured peripheral dose in pediatric radiation therapy: a comparison of intensity-modulated and conformal techniques. Radiother Oncol. 2007; 82(2): 179–184, doi: 10.1016/j.radonc.2007.01.002, indexed in Pubmed: 17257700.
37. Intensity Modulated Radiation Therapy Collaborative Working Group. Intensity-modulated radiotherapy: current status and issues of interest. Int J Radiat Oncol Biol Phys. 2001; 51(4): 880–914, doi: 10.1016/s0360-3016(01)01749-7, indexed in Pubmed: 11704310.
38. Followill D, Geis P, Boyer A. Estimates of whole-body dose equivalent produced by beam intensity modulated conformal therapy. Int J Radiat Oncol Biol Phys. 1997; 38(3): 667–672, doi: 10.1016/s0360-3016(97)00012-6, indexed in Pubmed: 9231693.
39. Verellen D, Vanhavere F. Risk assessment of radiation-induced malignancies based on whole-body equivalent dose estimates for IMRT treatment in the head and neck region. Radiother Oncol. 1999; 53(3): 199–203, doi: 10.1016/s0167-8140(99)00079-1, indexed in Pubmed: 10660198.
40. Wang B, Xu XG. Measurements of non-target organ doses using MOSFET dosemeters for selected IMRT and 3D CRT radiation treatment procedures. Radiat Prot Dosimetry. 2008; 128(3): 336–342, doi: 10.1093/rpd/ncm363, indexed in Pubmed: 17627959.
41. Deng J, Chen Z, Yu JB, et al. Testicular doses in image-guided radiotherapy of prostate cancer. Int J Radiat Oncol Biol Phys. 2012; 82(1): e39–e47, doi: 10.1016/j.ijrobp.2011.01.071, indexed in Pubmed: 21489702.
42. Martin JM, Handorf EA, Price RA, et al. Comparison of testicular dose delivered by intensity-modulated radiation therapy (IMRT) and volumetric-modulated arc therapy (VMAT) in patients with prostate cancer. Med Dosim. 2015; 40(3): 186–189, doi: 10.1016/j.meddos.2014.11.003, indexed in Pubmed: 25595491.
43. van der Giessen PH. Calculation and measurement of the dose at points outside the primary beam for photon energies of 6, 10, and 23 MV. Int J Radiat Oncol Biol Phys. 1994; 30(5): 1239–1246, doi: 10.1016/0360-3016(94)90335-2, indexed in Pubmed: 7961034.
44. King CR, Maxim PG, Hsu A, et al. Incidental testicular irradiation from prostate IMRT: it all adds up. Int J Radiat Oncol Biol Phys. 2010; 77(2): 484–489, doi: 10.1016/j.ijrobp.2009.04.083, indexed in Pubmed: 19733013.
45. King CR, Kapp DS. To treat pelvic nodes or not: could the greater testicular scatter dose from whole pelvic fields confound results of prostate cancer trials? J Clin Oncol. 2009; 27(36): 6076–6078, doi: 10.1200/JCO.2009.24.3808, indexed in Pubmed: 19858377.
46. Buchli C, Al Abani M, Ahlberg M, et al. Assessment of testicular dose during preoperative radiotherapy for rectal cancer. Acta Oncol. 2016; 55(4): 496–501, doi: 10.3109/0284186X.2015.1073349, indexed in Pubmed: 26362484.
47. Kase K, Svensson G, Wolbarst A, et al. Measurements of dose from secondary radiation outside a treatment field. Int J Radiat Oncol Biol Phys. 1983; 9(8): 1177–1183, doi: 10.1016/0360-3016(83)90177-3.
48. Bednarz B, Hancox C, Xu XG. Calculated organ doses from selected prostate treatment plans using Monte Carlo simulations and an anatomically realistic computational phantom. Phys Med Biol. 2009;

54(17): 5271–5286, doi: 10.1088/0031-9155/54/17/013, indexed in Pubmed: 19671968.
49. Bakkal BH, Vural T, Elmas O, et al. Effect of treatment position and radiotherapy planning on testicular dose in patients with rectal carcinoma. J Cancer Res Ther. 2014; 10(3): 558–562, doi: 10.4103/0973-1482.137943, indexed in Pubmed: 25313739.
50. Matsumoto Y, Umezu Y, Fujibuchi T, et al. [Verification of the protective effect of a testicular shield in postoperative radiotherapy for seminoma]. Nihon Hoshasen Gijutsu Gakkai Zasshi. 2014; 70(9): 883–887, doi: 10.6009/jjrt.2014_jsrt_70.9.883, indexed in Pubmed: 25242597.
51. Schneider U, Hälg R, Besserer J. Concept for quantifying the dose from image guided radiotherapy. Radiat Oncol. 2015; 10: 188, doi: 10.1186/s13014-015-0492-7, indexed in Pubmed: 26377196.
52. Hyer DE, Serago CF, Kim S, et al. An organ and effective dose study of XVI and OBI cone-beam CT systems. J Appl Clin Med Phys. 2010; 11(2): 3183, doi: 10.1120/jacmp.v11i2.3183, indexed in Pubmed: 20592702.