Original Article

Factors Predicting Late Rectal Disorders after Radiation Therapy for Prostate Cancer

Toshiya Maebayashi[1], Naoya Ishibashi[1], Takuya Aizawa[1], Masakuni Sakaguchi[1], Hideki Sato[2], Katsuhiko Sato[3], Tsuyoshi Matsui[3], Kenya Yamaguchi[3], Satoru Takahashi[3]

[1]Department of Radiology, Nihon University School of Medicine, Tokyo 173-8610, Japan
[2]Department of Gastroenterology and Hepatology, Nihon University School of Medicine, Tokyo 173-8610, Japan
[3]Department of Urology, Nihon University School of Medicine, Tokyo 173-8610, Japan

Abstract

Background: Although various studies have been conducted on the effects of radiation therapy for prostate cancer, rectal toxicity after radiation therapy for prostate cancer, which is an important late adverse event associated with radiation therapy, has not been sufficiently examined. This study aimed to assess the associations of late rectal disorder (LRD) with dosimetric, anatomic, and clinical factors in patients with prostate cancer who underwent three-dimensional conformal radiation therapy (3D-CRT).
Methods: We retrospectively analyzed 104 patients undergoing 3D-CRT between January 2009 and October 2011. Thirty patients were administered anticoagulation/antiplatelet (AC/AP) agents. The standard dose was 74 Gy. Uni- and multi-variate analyses were performed to identify factors predictive of LRD after 3D-CRT.
Results: The median follow-up period was 66 (range: 14–87) months. LRD occurred in 10.6% (11/104) of patients. The median time from RT to LRD was 15 months (range: 7–41 months). Sixty-four percent of those with LRD (7/11 patients) had been given AC/AP agents. Fifty-five (6/11) patients had severe internal iliac artery calcification. By univariate analysis, significant predictors of LRD were internal iliac artery calcification, administration of AC/AP agents, and age. Being very elderly was the significant predictor identified by multivariate analysis ($P = 0.0276$). For patients receiving AC/AP agents and those with severe internal iliac artery calcification, the LRD incidences were 23.3% (7/30 patients) and 23.1% (6/26 patients), respectively, and being 75 years of age or older was a significant predictor in these subsets.
Conclusions: Our results suggest advanced age, administration of AC/AP agents, and severe internal iliac artery calcification to be risk factors for LRD in patients undergoing standard RT. Therefore, it is necessary to administer radiation with particular caution in the very elderly, especially those receiving AC/AP agents and/or with severe internal iliac artery calcification.

Key words: Anticoagulation/Antiplatelet Agents; Late Rectal Disorder; Prostate Cancer; Radiation Therapy; Severe Internal Iliac Artery Calcification

Introduction

Primary treatment options for prostate cancer include radiation therapy (RT) and radical prostatectomy. In the recent years, irradiation and surgery have been regarded as achieving equivalent cancer control. There are many reports on the therapeutic efficacy of these procedures, whereas reports on adverse events are limited.[1-23]

Late rectal disorder (LRD) after RT for prostate cancer, an important delayed adverse event, develops long after the completion of treatment. Although there are reports on treatment-related factors[16-22] and on patient-related factors[2-7,12-14] associated with LRD, comprehensive assessments have not as yet been performed. Few prospective studies have addressed the incidence and severity of posttreatment LRD.[19] To identify risk factors for LRD,

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.216406

Address for correspondence: Dr. Toshiya Maebayashi, Department of Radiology, Nihon University School of Medicine, 30-1 Oyaguchi Kami-cho, Itabashi-ku, Tokyo 173-8610, Japan
E-Mail: maebayashi.toshiya@nihon-u.ac.jp

Received: 29-08-2017 **Edited by:** Ning-Ning Wang
How to cite this article: Maebayashi T, Ishibashi N, Aizawa T, Sakaguchi M, Sato H, Sato K, Matsui T, Yamaguchi K, Takahashi S. Factors Predicting Late Rectal Disorders after Radiation Therapy for Prostate Cancer. Chin Med J 2017;130:2441-6.

we evaluated age, complications, background factors, and irradiation doses. We evaluated these factors in detail, focusing particularly on patients receiving oral anticoagulant and antiplatelet (AC/AC) agents, those with severe internal iliac artery calcification and very elderly patients.

Methods

Ethical approval

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 *Helsinki declaration* and its later amendments or comparable ethical standards. This study was approved by the institutional review board of Nihon University School of Medicine, and patient informed consent was obtained (Trial registration number: Nihon University Itabashi Hospital Clinical Research Center RK-170214-10).

Patient characteristics

This retrospective study included 104 patients who underwent conformal RT for prostate cancer between January 2009 and October 2011. Their ages ranged from 54 to 85 years (median, 72 years). The follow-up periods ranged from 14 to 87 months (median, 66 months). Patient characteristics including cancer status are summarized in Table 1. Thirty patients were administered oral AC/AP agents, 26 had severe internal iliac artery calcification, 61 had hypertension, and 18 had diabetes mellitus, with some overlap among these classifications.

Treatments consisted of standard three-dimensional conformal RT (3D-CRT) for the prostate in 74 patients, whole-pelvis RT (WP-RT) followed by 3D conformal prostate boost in seven, and salvage/adjuvant 3D-CRT for the postsurgical site after radical prostatectomy in 23 patients. The median total dose was 74 Gy (range, 60–74 Gy). The standard 3D-CRT dose was 74 Gy, WP-RT plus prostate boost was 50 Gy plus 20–24 Gy, and salvage/adjuvant RT was 64 Gy. Patients with intermediate risk underwent concomitant hormone deprivation therapy for 6 months and those with high risk received this treatment for 3 years. According to the treatment strategies for LRD at our hospital, patients with Grade Ia lesions by the Sherman *et al*'s. classification[24] received prednisolone suppositories. Based on the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) morbidity scores, the patients with Ia lesions were classified as having Grade 2 morbidity. Patients with Grade Ib by the Sherman *et al*'s. classification[24] underwent endoscopic coagulation with argon plasma. Based on the RTOG/EORTC morbidity scores, these cases were classified as having Grade 3 morbidity. For this study, we defined patients whose calcification occupied more than half of the arterial lumen as having severe medial internal iliac artery calcification.

Table 1: Characteristics of patients who underwent conformal RT for prostate cancer (n = 104)

Characteristics	Value
Follow-up (months), median (range)	66 (14–87)
Age (years), median (range)	72 (54–85)
Stage (UICC 7th), *n* (%)	
I	27 (27)
II	18 (17)
III	48 (46)
IV	11 (11)
NCCN risk group, *n* (%)	
Low	7 (7)
Intermediate	24 (23)
High	73 (70)
Initial PSA (ng/ml), median (range)	20.57 (4.05–914.00)
Gleason score, *n* (%)	
≤6	17 (16)
7	32 (31)
8	16 (15)
9	22 (21)
10	6 (6)
Unknown	1 (1)

PSA: Prostate-specific antigen; UICC: Unio Internationalis Contra Cancrum; NCCN: National Comprehensive Cancer Network; RT: Radiation therapy.

Statistical analysis

LRD-free survival was calculated using the Kaplan-Meier method, and differences were expressed at a 5% significance level with a two-tailed log-rank test. Uni- and multi-variate analyses were performed to identify factors predicting LRD after 3D-CRT. In accordance with the reported possible risk factors,[1-23] we analyzed age applying a threshold of 75 years, AC/AP agents, severe internal iliac artery calcification, diabetes mellitus, chronic renal failure, and hypertension as categorical variables, while radiation field and total radiation dose were analyzed as continuous variables.

Multivariate analyses of the data were performed using the Cox proportional hazards model. The SPSS 21.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for all calculations and survival displays. Late complications were graded according to the National Cancer Institute-Common Terminology Criteria, Version 4.0.[25] The statistical significance level was set at $P < 0.05$.

Results

Radiation therapy

The Xio (version 4.4.0–4.6.0; Elekta CMS Software, St. Louis, MO, USA) therapy planning device was used to administer RT, and doses were calculated using the Clarkson method. The RT procedures were as follows. In cases receiving standard conformal RT, the clinical target volume (CTV) consisted of the entire prostate gland and the seminal vesicle base, and the planning target volume (PTV) was set as the CTV with 8-mm margins to establish the recommended radiation field. However, when a radiation field was set on the rectal surface, PTV was modified to consist of the CTV with approximately 5-mm margins. The basic dose was 2 Gy per fraction for a total dose of 74 Gy.

When the cumulative dose exceeded 50 Gy, we excluded the seminal vesicle base from the radiation field. According to RTOG 0126,[26] the rectum was defined as a contoured, solid structure from the anus (at the level of the ischial tuberosities) to the rectosigmoid flexure. If the patient had pelvic lymph node metastasis, irradiation up to 50 Gy was applied to the lesser pelvis, followed by conformal RT applied to the prostate gland for a total dose within 70 to 72 Gy. In cases receiving salvage RT, the CTV consisted of the site after prostatectomy, and the PTV was set as the CTV with 8-mm margins. The basic dose was 2 Gy per fraction for a total dose of 64 Gy.

Adverse events

LRD was observed in 11 of the 104 (10.6%) patients [Figure 1]. In all the 11 patients, LRD was confirmed endoscopically. According to the Sherman *et al.*'s classification,[24] LRD was classified as Grade Ia in eight patients and Ib in three; endoscopic coagulation was performed in three of these 11 patients. The times from RT until the onset of LRD ranged from 7 to 41 months (median, 15 months) and were within 2 years in all but one of the 11 patients. The latter patient suffered a myocardial infarction and started taking AC/AP therapy 3 years after RT.

Seven of the 11 patients with LRD were taking oral AC/AP agents and one had hepatic cirrhosis. Six of the 11 patients with LRD had severe internal iliac artery calcification. The significant predictors by univariate analysis included the use of oral AC/AP agents, age, and severe internal iliac artery calcification [Figures 2–4]. The multivariate analysis confirmed age to be a significant predictor of LRD [Table 2]. When we analyzed patients receiving oral AC/AP agents, the proportion with LRD was 23.3% (7/30 patients) and age was a significant predictor in this subset [Figure 5]. When we analyzed patients with severe internal iliac artery calcification, the proportion with LRD was 23.1% (6 of 26 patients) and age was again a significant predictor in this subset [Figure 6]. LRD occurred in 20.0% (3 of 15) of the patients with severe calcification and taking oral AC/AP agents. LRD occurred in 27.2% (3 of 11) of the patients with severe calcification not taking oral AC/AP agents. One patient with neither oral AC/AP agent treatment nor calcification had uncontrolled hypertension and diabetes.

All patients with a total dose of 70 Gy or more delivered to at least 7% of the rectal volume had LRD. In addition, LRD was observed in three of the four patients receiving a total dose of 65 Gy or more to at least 16% of the rectal volume. Out of the seven patients given RT covering the lesser pelvis, one presented with LRD and this patient had been taking oral AC/AP agents. No LRD occurred in any of the patients receiving irradiation to the postoperative site.

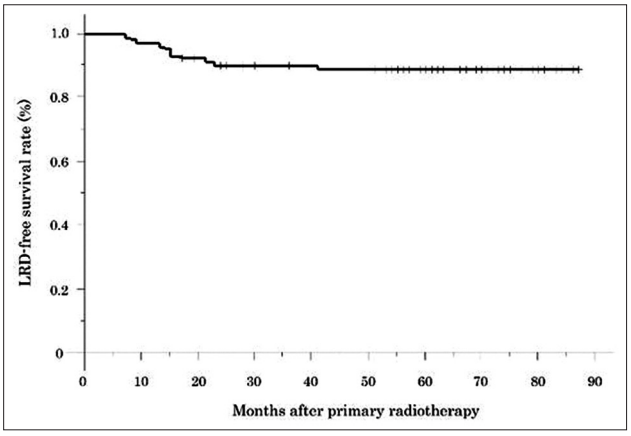

Figure 1: Rate of late rectal disorder-free survival in all patients ($n = 104$).

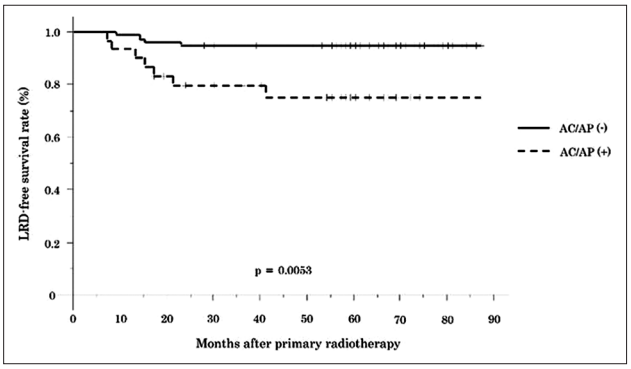

Figure 2: Late rectal disorder-free survival and anticoagulation/antiplatelet agent use. *P* values were calculated by the stratified log-rank test. Anticoagulation/antiplatelet (+), patients using anticoagulant/antiplatelet agents ($n = 30$); anticoagulation/antiplatelet (−), patients not using these agents ($n = 74$).

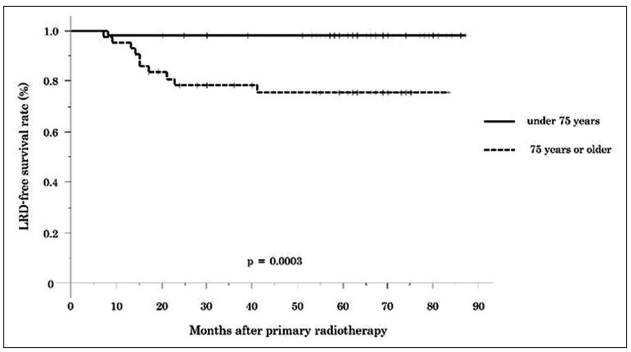

Figure 3: Late rectal disorder-free survival and age. *P* values were calculated using the stratified log-rank test. Under 75 years ($n = 61$); 75 years or older ($n = 43$).

Discussion

We usually consult with several specialists in the fields of gastroenterology, urology, and radiology, during LRD conferences held at our institute. LRD is not a major concern for gastroenterologists, in part due to the lack of an established strategy for managing LRD, and few have experienced cases actually requiring endoscopic treatment. Urologists advocated avoiding adverse events associated with radical therapies whenever possible because patients with prostate cancer can generally expect considerably longer survival than those with other urological malignancies.

Table 2: Uni- and multi-variate analyses of risk factors predicting late rectal disorders after RT for prostate cancer (n = 104)

Factor	Univariate		Multivariate	
	RR (95% *CI*)	*P*	*RR* (95% *CI*)	*P*
Age	0.062 (0.008–0.482)	0.0003	0.095 (0.012–0.771)	0.0276
Calcification	3.871 (1.180–12.700)	0.0160	1.438 (0.354–5.847)	0.6118
AC and AP agents	4.850 (1.147–16.596)	0.0053	2.784 (0.650–11.925)	0.1676
DM	3.012 (0.881–10.301)	0.0643	1.687 (0.417–6.833)	0.4634
CRF	3.081 (0.393–24.169)	0.2588	1.584 (0.159–15.788)	0.6950
HT	3.400 (0.734–15.746)	0.0957	1.568 (0.307–8.000)	0.5885
Total RT dose	0.442 (0.117–1.667)	0.2150	0.570 (0.141–2.306)	0.4304

RR: Relative risk; *CI*: Confidence interval; AC: Anticoagulant; AP: Antiplatelet; DM: Diabetes mellitus; CRF: Chronic renal failure; HT: Hypertension; RT: Radiation therapy.

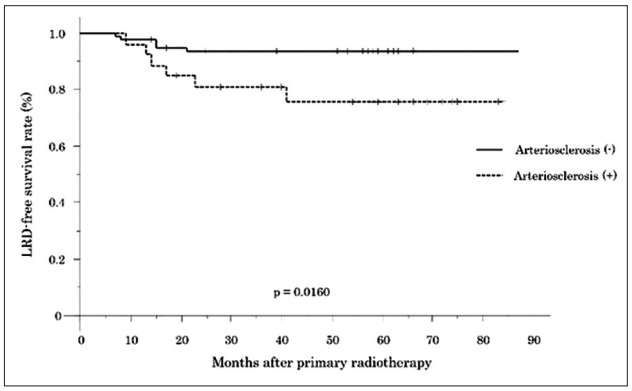

Figure 4: Late rectal disorder-free survival in patients with severe arteriosclerosis. *P* values were calculated using the stratified log-rank test. Arteriosclerosis (+), patients with arteriosclerosis (n = 26); arteriosclerosis (−), patients without arteriosclerosis (n = 78).

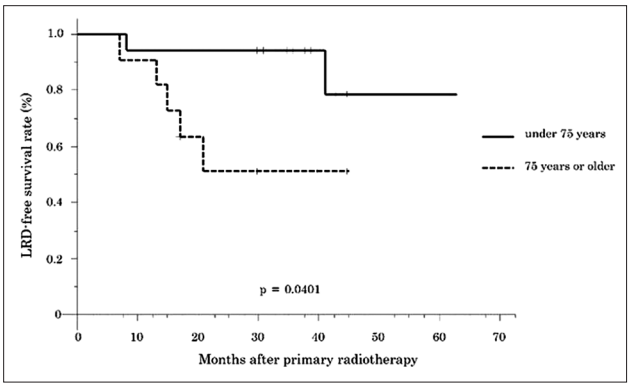

Figure 5: Late rectal disorder-free survival in patients taking anticoagulation/antiplatelet agents by age (n = 30). *P* values were calculated using the stratified log-rank test. Under 75 years (n = 13); 75 years or older (n = 17).

The present results suggest advanced age, the use of oral AC/AP agents, and severe internal iliac artery calcification to be risk factors for LRD following RT for prostate cancer. Comprehensive assessment of LRD after RT has not yet been achieved. Advanced age,[1,5-7] other complications,[15,18] diabetes mellitus,[5,12-15] hormone therapy,[5,15] and the use of oral AC/AP agents[2-5] have been identified as patient-related risk factors, though few multicenter clinical studies have addressed these issues in detail.[19]

Among the various oral drugs administered for concomitant diseases, we analyzed only oral AC/AP agents in this study. The proportion of patients with LRD in this population was 23.3% (7/30 patients). In addition, the analysis of patients receiving oral AC/AP agents revealed a significant difference in age. This suggested that these two factors might additively increase the risk for LRD.

In addition, we identified the causes of LRD in 76 patients without apparent dose- or drug-related risk factors. Among these 76 cases, there were 11 with severe arteriosclerosis. Thus, we speculated that this patient-related factor, which has not previously been a research focus, might contribute to postirradiation LRD. Among the patients with LRD, four (4/11 patients) were not receiving oral AC/AP therapy. Of these four patients, three had severe arteriosclerosis. Vascular insufficiency due to arteriosclerosis may also be a causative factor for LRD, as suggested by Takeda *et al*.[3]

Moreover, among the thirty patients receiving oral AC/AP therapy, there were 15 with severe arteriosclerosis. LRD occurred in seven and three, respectively, of these 30 and 15 patients. Though the univariable analysis identified each of these as risks for LRD, we found no synergistic effect between these two factors. Circulatory disturbance has been regarded as one of the causes of LRD after RT. Since the study results suggested that severe arteriosclerosis might be a risk factor for LRD, we hypothesized that anticoagulant therapy might reduce the risk of LRD in patients with severe arteriosclerosis. However, no synergistic effects were observed. The main limitation of the present study is its small sample size, and it is thus necessary to conduct a large-scale clinical investigation in the future.

As for treatment-related factors, LRD occurred when a dose of 70 Gy or more was delivered to at least 7% of the rectal volume (3 of 3 patients). However, in the other four of these seven patients, LRD occurred despite <3% of the rectal volume having received a dose of 70 Gy or more. In fact, LRD occurred when a dose of 65 Gy or more was delivered to more than 16% of the rectal volume (3 of 4 patients). However, in the other three of seven patients with LRD, the LRD occurred despite <4% of the rectal volume having received a dose of

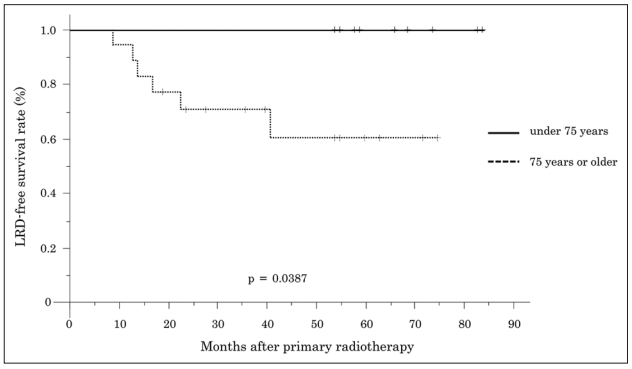

Figure 6: Late rectal disorder-free survival in patients with severe internal iliac artery calcification by age. *P* values were calculated using the stratified log-rank test. Under 75 years ($n = 9$); 75 years or older ($n = 17$).

65 Gy or more. Of course, the incidence of LRD does not depend on doses alone, as reported by Hamstra *et al*.[1]

The time from irradiation until the onset of LRD was <2 years in all but one of the 11 patients. Based on the results, we can reasonably assume that LRD would generally occur <2 years after irradiation unless other factor(s), such as the use of AC/AP agents, which may subsequently cause or contribute to the development of this late complication, is present.[9-11,17-23] Since the mechanisms of action of AC/AP agents vary, an exact cause cannot be specified. However, given the severity of hypertension and diabetes mellitus and the possible involvement of arteriosclerosis in the conditions of our present patients, vascular endothelial dysfunction might be a major factor contributing to LRD.

Since it is anticipated that increasing numbers of very or extremely elderly patients will undergo RT in the future, the possibility of complications developing after irradiation should be considered, even in those without comorbidities. The use of oral AC/AP agents, which is often necessary to prevent the onset of cerebral or myocardial infarction after irradiation, should be taken into consideration as a possible cause of or contributor to postirradiation LRD.[4] Thus, meticulous treatment planning and follow-up are necessary, particularly for very elderly patients. Surgery might also be an option for preventing rectal bleeding after RT. Thus, in all patients undergoing RT, attention should be paid to organs at risk. In addition, doses to the rectum might need to be reduced if feasible, when administering therapies such as intensity-modulated radiation therapy (IMRT).

Currently, our mainstay for external beam irradiation for prostate cancer is IMRT. As a preliminary arrangement for changing equipment from 3D-CRT to IMRT, it was essential to conduct a risk assessment for the development of LRD. Based on the present results, we confirmed the rectal dose limitation in planning of IMRT together with image-guided RT. We are planning to report the results of a toxicity analysis, examining 3D-CRT versus IMRT, based on the data obtained in the present study.

In conclusion, the results suggest the use of oral AC/AP agents, advanced age, and severe internal iliac artery calcification to be risk factors for LRD after RT for prostate cancer. In clinical practice, it appears to be important to treat very elderly patients cautiously, especially those administered oral AC/AP agents, as well as to reduce doses to the rectum whenever feasible.

Acknowledgment

The authors thank Bierta Barfod for her contribution to language editing of this manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Hamstra DA, Stenmark MH, Ritter T, Litzenberg D, Jackson W, Johnson S, *et al.* Age and comorbid illness are associated with late rectal toxicity following dose-escalated radiation therapy for prostate cancer. Int J Radiat Oncol Biol Phys 2013;85:1246-53. doi: 10.1016/j.ijrobp.2012.10.042.
2. Ishikawa H, Tsuji H, Kamada T, Hirasawa N, Yanagi T, Mizoe JE, *et al.* Risk factors of late rectal bleeding after carbon ion therapy for prostate cancer. Int J Radiat Oncol Biol Phys 2006;66:1084-91. doi: 10.1016/j.ijrobp.2006.06.056.
3. Takeda K, Ogawa Y, Ariga H, Koto M, Sakayauchi T, Fujimoto K, *et al*. Clinical correlations between treatment with anticoagulation/antiplatelet and late rectal toxicity after radiotherapy for prostate cancer. Anticancer Res 2009;29:1831-4.
4. Choe KS, Jani AB, Liauw SL. External beam radiotherapy for prostate cancer patients on anticoagulation therapy: How significant is the bleeding toxicity? Int J Radiat Oncol Biol Phys 2010;76:755-60. doi: 10.1016/j.ijrobp.2009.02.026.
5. Vavassori V, Fiorino C, Rancati T, Magli A, Fellin G, Baccolini M, *et al.* Predictors for rectal and intestinal acute toxicities during prostate cancer high-dose 3D-CRT: Results of a prospective multicenter study. Int J Radiat Oncol Biol Phys 2007;67:1401-10. doi: 10.1016/j.ijrobp.2006.10.040.
6. Fiorino C, Fellin G, Rancati T, Vavassori V, Bianchi C, Borca VC, *et al.* Clinical and dosimetric predictors of late rectal syndrome after 3D-CRT for localized prostate cancer: Preliminary results of a multicenter prospective study. Int J Radiat Oncol Biol Phys 2008;70:1130-7. doi: 10.1016/j.ijrobp.2007.07.2354.
7. Britton KR, Takai Y, Mitsuya M, Nemoto K, Ogawa Y, Yamada S. Evaluation of inter- and intrafraction organ motion during intensity modulated radiation therapy (IMRT) for localized prostate cancer measured by a newly developed on-board image-guided system. Radiat Med 2005;23:14-24.
8. Skwarchuk MW, Jackson A, Zelefsky MJ, Venkatraman ES, Cowen DM, Levegrün S, *et al.* Late rectal toxicity after conformal radiotherapy of prostate cancer (I): Multivariate analysis and dose-response. Int J Radiat Oncol Biol Phys 2000;47:103-13. doi: 10.1016/S0360-3016(99)00560-X.
9. Schultheiss TE, Lee WR, Hunt MA, Hanlon AL, Peter RS, Hanks GE. Late GI and GU complications in the treatment of prostate cancer. Int J Radiat Oncol Biol Phys 1997;37:3-11.
10. Lawton CA, Bae K, Pilepich M, Hanks G, Shipley W. Long-term treatment sequelae after external beam irradiation with or without hormonal manipulation for adenocarcinoma of the prostate: Analysis of radiation therapy oncology group studies 85-31, 86-10, and 92-02. Int J Radiat Oncol Biol Phys 2008;70:437-41. doi: 10.1016/j.ijrobp.2007.06.050.
11. Liu M, Pickles T, Agranovich A, Berthelet E, Duncan G, Keyes M, *et al*. Impact of neoadjuvant androgen ablation and other factors on late toxicity after external beam prostate radiotherapy. Int J Radiat Oncol Biol Phys 2004;58:59-67.

12. Kalakota K, Liauw SL. Toxicity after external beam radiotherapy for prostate cancer: An analysis of late morbidity in men with diabetes mellitus. Urology 2013;81:1196-201. doi: 10.1016/S0360-3016(03)00777-6.
13. Herold DM, Hanlon AL, Hanks GE. Diabetes mellitus: A predictor for late radiation morbidity. Int J Radiat Oncol Biol Phys 1999;43:475-9.
14. Akimoto T, Muramatsu H, Takahashi M, Saito J, Kitamoto Y, Harashima K, *et al.* Rectal bleeding after hypofractionated radiotherapy for prostate cancer: Correlation between clinical and dosimetric parameters and the incidence of grade 2 or worse rectal bleeding. Int J Radiat Oncol Biol Phys 2004;60:1033-9. doi: 10.1016/j.ijrobp.2004.07.695.
15. Giordano SH, Lee A, Kuo YF, Freeman J, Goodwin JS. Late gastrointestinal toxicity after radiation for prostate cancer. Cancer 2006;107:423-32. doi: 10.1002/cncr.21999.
16. Pederson AW, Fricano J, Correa D, Pelizzari CA, Liauw SL. Late toxicity after intensity-modulated radiation therapy for localized prostate cancer: An exploration of dose-volume histogram parameters to limit genitourinary and gastrointestinal toxicity. Int J Radiat Oncol Biol Phys 2012;82:235-41. doi: 10.1016/j.ijrobp.2010.09.058.
17. Huang EH, Pollack A, Levy L, Starkschall G, Dong L, Rosen I, *et al.* Late rectal toxicity: Dose-volume effects of conformal radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2002;54:1314-21. doi: 10.1016/S0360-3016(02)03742-2.
18. Fellin G, Fiorino C, Rancati T, Vavassori V, Baccolini M, Bianchi C, *et al.* Clinical and dosimetric predictors of late rectal toxicity after conformal radiation for localized prostate cancer: Results of a large multicenter observational study. Radiother Oncol 2009;93:197-202. doi: 10.1016/j.radonc.2009.09.004.
19. Hoffman KE, Voong KR, Pugh TJ, Skinner H, Levy LB, Takiar V, *et al.* Risk of late toxicity in men receiving dose-escalated hypofractionated intensity modulated prostate radiation therapy: Results from a randomized trial. Int J Radiat Oncol Biol Phys 2014;88:1074-84. doi: 10.1016/j.ijrobp.2014.01.015.
20. Peeters ST, Heemsbergen WD, van Putten WL, Slot A, Tabak H, Mens JW, *et al.* Acute and late complications after radiotherapy for prostate cancer: Results of a multicenter randomized trial comparing 68 Gy to 78 Gy. Int J Radiat Oncol Biol Phys 2005;61:1019-34. doi: 10.1016/j.ijrobp.2004.07.715.
21. Kuban DA, Tucker SL, Dong L, Starkschall G, Huang EH, Cheung MR, *et al.* Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phys 2008;70:67-74. doi: 10.1016/j.ijrobp.2007.06.054.
22. Storey MR, Pollack A, Zagars G, Smith L, Antolak J, Rosen I. Complications from radiotherapy dose escalation in prostate cancer: Preliminary results of a randomized trial. Int J Radiat Oncol Biol Phys 2000;48:635-42. doi: 10.1016/j.ijrobp.2007.06.054.
23. Michalski JM, Winter K, Purdy JA, Parliament M, Wong H, Perez CA, *et al.* Toxicity after three-dimensional radiotherapy for prostate cancer on RTOG 9406 dose Level V. Int J Radiat Oncol Biol Phys 2005;62:706-13. doi: 10.1016/j.ijrobp.2007.06.054.
24. Sherman LF, Prem KA, Mensheha NM. Factitial proctitis: A restudy at the University of Minnesota. Dis Colon Rectum 1971;14:281-5.
25. NCI. CTCAE. Available from: http://www.evs.nci.nih.gov/ftp1/CTCAE/About.html. [Last accessed on 2017 Jan 05].
26. Bruner DW, Hunt D, Michalski JM, Bosch WR, Galvin JM, Amin M, *et al.* Preliminary patient-reported outcomes analysis of 3-dimensional radiation therapy versus intensity-modulated radiation therapy on the high-dose arm of the Radiation Therapy Oncology Group (RTOG) 0126 prostate cancer trial. Cancer 2015;121:2422-30. doi: 10.1002/cncr.29362.