Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/rpor

Original research article

Acute toxicity and quality of life in high risk prostate cancer patients: Updated results of randomized hypofractionation trial

Agata Karklelyte, Konstantinas Povilas Valuckas, Romas Griskevicius, Ernestas Janulionis, Eduardas Aleknavicius*

National Cancer Institute, Radiotherapy, Santariskiu 1, Vilnius, Lithuania

ARTICLE INFO

Article history:
Received 17 January 2018
Received in revised form
25 April 2018
Accepted 23 June 2018
Available online 26 July 2018

Keywords:
Prostate cancer
Hypofractionation
Acute toxicity
Radiotherapy
Quality of life

ABSTRACT

Purpose: The aim of our study was to perform the final analysis of acute toxicity and quality of life data obtained from 221 consecutive patients who suffered from intermediate-to-high risk prostate cancer.

Methods: In this trial, 221 patients were randomized to receive either hypofractionated (63 Gy in 20 fractions, 4 fractions/week) or conventionally fractionated (76 Gy in 38 fractions, 5 fractions/week) radiotherapy to the prostate and seminal vesicles. Elective pelvic lymph node irradiation with 46 Gy in 23 fractions sequentially and 44 Gy in 20 fractions simultaneously was also applied.

Results: There was no statistically significant difference in acute GU and GI toxicity in men treated with hypofractionated (SIB) (Arm 2) in comparison with patients who had conventional fractionation (Arm 1) radiation therapy. Multivariate analysis using logistic regression showed statistical significant association between acute GU ≥ 1 and PTV(LN) ($p = 0.008$) only. We found out that clinically relevant decrease (CRD) was significantly higher only in the urinary domain of Arm 1 at month 3 ($p = 0.02$).

Conclusion: Our study demonstrated that hypofractionated radiotherapy was associated with a small but insignificant increase of acute toxicity. The reduction of overall treatment time has no significant influence on patients' QOL in any domain.

1. Introduction

During the last decade, improved physical sparing of the normal tissues with the most recent technologies and a better understanding of prostate cancer radiobiology has prompted a number of moderate as well as extreme hypofractionation trials using different treatment schedules with the aim of exploring the outcome and toxicity of shorter regimes. The better physical sparing of normal tissues using intensity modulated radiation (IMRT) techniques has resulted in a re-evaluation of the use of a few large dose fractions with shorter

* *Corresponding author.*
E-mail address: agata.karklelyte@gmail.com (A. Karklelyte).
https://doi.org/10.1016/j.rpor.2018.06.008

treatment duration.[1–5] The treatment goal is to obtain a high rate of tumour control with low toxicity, while taking into consideration convenience and costs for the patient and to the health care system.

The data of 124 participants were analysed and reported previously; the aim of current report is to provide confirmation of previous conclusions concerning acute toxicity and QOL of the patients, as the larger number of patients surveyed exhibits same statistical importance trends.

2. Methods and materials

2.1. Study design and radiation technique

The patients population and methods have been previously described.[6] From 2010 to May 2014, a total of 221 consecutive patients we enrolled in this study. Patients were randomized to receive either hypofractionated (63 Gy in 20 fractions, 4 fractions/week) or conventionally fractionated (76 Gy in 38 fractions, 5 fractions/week) to the prostate and seminal vesicles. Elective pelvic lymph node irradiation with 46 Gy in 23 fractions sequentially and 44 Gy in 20 fractions simultaneously was also applied. Whole pelvis radiotherapy was applied to all patients in Arm 1 and Arm 2. This study was designed to test the hypothesis that a high-dose hypofractionation regimen is equivalent to a conventional fractionation scheme in terms of acute GI and GU toxicity. The radiation techniques and dosimetric constraints have been previously described.[6] The prostate clinical target volume was contoured as the CTVp. The entire seminal vesicles were contoured as the CTVsv. Pelvic lymph nodes were contoured as the CTVln following RTOG consensus guidelines.[7] The planned target volume PTV for the prostate PTVp was generated as a 10 mm expansion around the respective CTV, except for posterior part at the prostate-rectum interface where the expansion was 7 mm. PTVsv was generated as a 10 mm in all directions. The nodal PTVln was generated by a 5 mm expansion of the CTVln nodes. PTVp and PTVsv were merged into PTV1, PTVln – into PTV2. PTV1 and PTV2 received between 95% and 108% of the prescription dose. In Arm 1 treatment was prescribed to PTV1 76 Gy in 23 fractions (2 Gy/fraction) and PTV2 sequentially received 46 Gy in 15 fractions (Gy/fraction). Arm 2 patients were prescribed to PTV1 63 Gy in 20 fractions (3.15 Gy/fraction) and PTV2 simultaneously received 44 Gy (2.2 Gy/fraction). Daily images guidance was performed. Patients were selected according to National Comprehensive Cancer Network (NCCN) criteria: stage T3a–T3b, biopsy Gleason score (GS) of 8–10; pretreatment PSA level (iPSA) >20 ng/mL, or the presence of at least two of the following clinical characteristics: iPSA of 11–20 ng/mL, T ≥ 2c, GS = 7. Elective pelvic nodal treatment was administered according to a proposed ≥15% risk of occult pelvic lymph node involvement as calculated using the Roach formula.[8] Patients characteristics are detailed in Tables 1 and 2. The simulation and treatment procedures used have been extensively reported in a previous article.[6] All patients received ADT (LHRH agonist only) which typically started 3–4 months before RT and continued for a total duration of ≥6 months. All patients received ADT concurrent with pelvic RT. The statistical analysis have been described in a previously published article.[6]

Table 1 – Patients characteristics.*

	Arm 1	Arm 2
N	106	115
Gleason score		
≤7	90 (85%)	107 (93%)
>7	16 (15%)	8 (7%)
cT-stage		
≤T2c	20 (19%)	17 (15%)
>T2c	86 (81%)	98 (85%)
iPSA		
≤20 ng/mL	76 (72%)	92 (80%)
>20 ng/mL	30 (28%)	23 (20%)

Abbreviations: Arm 1 = conventional fractionation; Arm 2 = hypofractionation.
* $p < 0.05$ between groups two-sample t-test.

2.2. Follow-up schedule and toxicity assessment

Patients were evaluated weekly during 12 weeks starting from the beginning of irradiation. Toxicity was assessed according to the Radiation Therapy Oncology Group (RTOG) acute urinary and rectal toxicity scale.[9] Patients reported outcomes were measured using the Expanded Prostate Cancer Index Composite (EPIC).[10] The EPIC was measured at baseline and then monthly during acute period of treatment.

3. Results

Of all 221 patients, 106 were assigned to conventional fractionation Arm 1 and 115 to hypofractionation Arm 2. No patients were lost to follow-up. The characteristics are shown in Tables 1 and 2. No treatment interruptions occurred. We found statistically higher volume percentages of the rectum and bladder treated with the high ($V_{100\%}$) and low ($V_{52.6\%}$, $V_{65.8\%}$) dose cut-points in Arm 2, as compared with Arm 1. The bladder total volume and PTV (LN) was higher in Arm 1, and the rectum total volume in Arm 2.

3.1. Acute toxicity

The data of acute toxicity for all patients are presented in Table 3. There was no Grade 4 acute GU or GI toxicity. As well, there was no statistically significant differences in acute GU and GI toxicity in men treated with hypofractionated radiation therapy in comparison with those who had conventional fractionation. The incidence of GU 2 toxicity was slightly higher in Arm 1 than in Arm 2. However, the results for GU 3 were higher in Arm 2, and 6% of patients experienced GU 3 acute toxicity. Concerning bowel function, the patients in Arm 2 experienced higher GI 2 and GI 3 toxicity in comparison with Arm 1, but the differences were not statistically significant.

The weekly maximum of acute GU and GI toxicity (mean values) are shown in Figs. 1 and 2. The evaluation of the association between acute GU and GI toxicity, bladder and rectum volume, PTV (P), PTV (SV), PTV (LN) volume, when receiving specific doses, was performed by means of multivariate analysis using logistic regression. The only statistically significant association was found out between GU > 1 and PTV (LN) ($p = 0.008$).

Table 2 – Patients characteristics and dosimetric parameters.

Variable	Arm 1		Arm 2		*p*-Value
	Median	Avg ± stdev	Median	Avg ± stdev	
Age	66	65 ± 7	66	65 ± 6	0.753
Gleason score	7	7 ± 1	6	7 ± 1	0.274
iPSA	11.1	18 ± 17	10	15 ± 16	0.054
PTV volume					
PTV (P)	109.4	119 ± 35	112.8	120 ± 34	0.855
PTV (SV)	89.4	92 ± 21	86.2	89 ± 18	0.197
PTV (LN)	632	641 ± 106	622.4	629 ± 99	0.384
Bladder					
Total volume ± SE (cc)	114	153 ± 102	108	131 ± 76	0.085
V52.6% ± SE (cc)	81	77 ± 16	92	89 ± 11	<.001
V65.8% ± SE (cc)	56.5	56 ± 17	61	63 ± 17	0.005
V78.9% ± SE (cc)	38	39 ± 15	39	40 ± 14	0.537
V92% ± SE (cc)	23	25 ± 12	27	27 ± 11	0.268
V100% ± SE (cc)	10	12 ± 9	13	15 ± 8	0.050
Rectum					
Total volume ± SE (cc)	65	68 ± 15	67	70 ± 19	0.476
V52.6% ± SE (cc)*	68	66 ± 16	83	81 ± 12	<.001
V65.8% ± SE (cc)*	47	46 ± 14	53	54 ± 13	<.001
V78.9% ± SE (cc)*	31.5	31 ± 10	34	34 ± 10	0.062
V92% ± SE (cc)*	18	19 ± 8	21	20 ± 7	0.468
V100% ± SE (cc)*	5	6 ± 6	9	9 ± 5	0.003

Abbreviations: Arm 1 = conventional fractionation; Arm 2 = hypofractionation.
* $p < 0.05$ between groups two-sample *t*-test.

Table 3 – Maximum and week 12 GU and GI toxicity.

Group	Max GU toxicity				Max GI toxicity			
Grade	0	1	2	3	0	1	2	3
Arm 1	11 (10%)	61 (58%)	30 (28%)	4 (4%)	30 (28%)	36 (34%)	40 (38%)	0 (0%)
Arm 2	8 (7%)	69 (60%)	31 (27%)	7 (6%)	20 (17%)	37 (32%)	55 (48%)	3 (3%)
p-Value	0.473	0.785	0.881	0.542	0.053	0.778	0.130	0.248
Group	GU toxicity at week 12				GI toxicity at week 12			
Grade	0	1	2	3	0	1	2	3
Arm 1	65 (66%)	29 (29%)	5 (5%)	0 (0%)	78 (79%)	13 (13%)	8 (8%)	0 (0%)
Arm 2	78 (77%)	22 (22%)	1 (1%)	0 (0%)	87 (86%)	9 (9%)	5 (5%)	0 (0%)
p-Value	0.070	0.223	0.117	–	0.171	0.340	0.369	–

Abbreviations: Arm 1 = conventional fractionation; Arm 2 = hypofractionation; NS = difference not significant ($p < 0.05$).

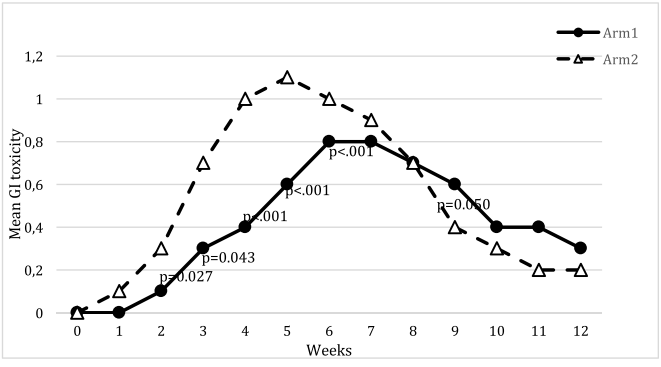

Fig. 1 – Weekly changes in the mean GI toxicity.

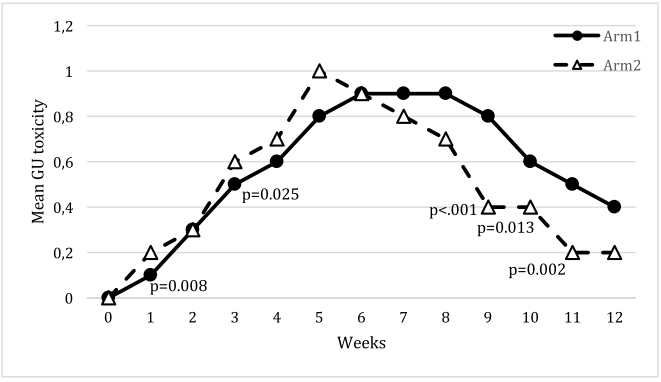

Fig. 2 – Weekly changes in the mean GU toxicity.

Table 4 – EPIC score (±SE) at each time point.

Time points	Baseline	1 month		2 months		3 months		p-Value (ANOVA)
Arm	1/2	1	2	1	2	1	2	
N	219	102	115	102	105	99	102	
Urinary domain	93.1	84.1 (1.4)	82 (1.6)	81.9 (1.5)	83 (1.6)	87.4 (1.4)	92.3 (1.2)	0.4933
Function	98.1	92.4 (1.2)	92.3 (1.2)	92.3 (1.1)	91.4 (1.3)	95.3 (1)	95.6 (1)	0.8087
Bother	89.5	78.1 (1.8)	74.7 (2.1)	74.5 (2)	77 (2.1)	81.8 (1.9)	89.9 (1.5)	0.3297
Incontinence	97.4	94.4 (1.1)	93.5 (1.4)	93.3 (1.3)	92.6 (1.6)	95.6 (1.2)	96 (1.2)	0.8303
Irritative/obstructive	91.1	79.1 (1.8)	76.9 (1.9)	76.8 (1.9)	78.7 (1.9)	83.5 (1.7)	90.3 (1.4)	0.3821
Bowel domain	96	84 (1.8)	79.5 (2)	84.5 (1.7)	80.7 (2.1)	91.3 (1.5)	93.3 (1.2)	0.6152
Function	95.9	83 (1.8)	76.5 (2.1)	83.5 (1.7)	78.5 (2.1)	90.4 (1.5)	91.9 (1.3)	0.3882
Bother	96	84 (1.8)	79.5 (2)	84.5 (1.7)	80.7 (2.1)	91.3 (1.5)	93.3 (1.2)	0.6152
N	216	100	114	101	104	98	101	
Sexual domain	27.8	22.1 (1.4)	25.1 (1.6)	24.2 (1.5)	26.4 (1.6)	24 (1.7)	25.5 (1.6)	0.2156
Function	12.4	5.7 (1.3)	8 (1.5)	7.4 (1.5)	7.5 (1.7)	7.7 (1.7)	8 (1.6)	0.6128
Bother	62.4	59.1 (4)	63.5 (4)	62.2 (3.9)	69.1 (3.8)	60.7 (4)	64.9 (4.1)	0.2877
N	219	101	115	102	105	99	102	
Hormonal domain	86.1	84.7 (1.5)	85.5 (1.4)	85.8 (1.4)	84.5 (1.5)	84.7 (1.5)	87.8 (1.4)	0.8126
Function	79.1	78.1 (2)	79.3 (1.7)	79.2 (1.9)	76.8 (2.1)	78 (2.1)	82.6 (1.9)	0.8556
Bother	91.9	90.3 (1.3)	90.7 (1.3)	91.2 (1.2)	90.9 (1.3)	90.3 (1.3)	92.2 (1.3)	0.8048

Abbreviations: Arm 1 = conventional fractionation; Arm 2 = hypofractionation; N = number of patients.

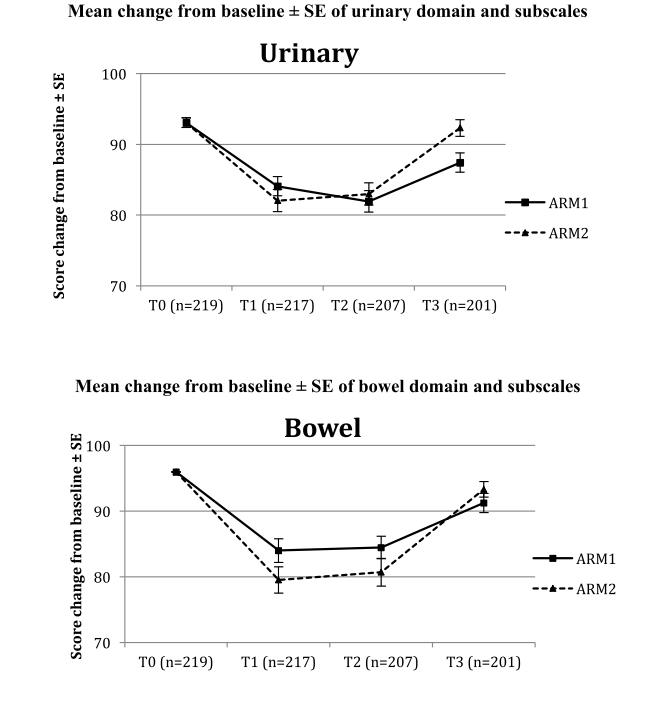

Fig. 3 – Mean change from baseline ± SE of urinary and bowel domains.

3.2. *Quality of life*

All patients completed the initial EPIC questionnaire prior to treatment. For subsequent time points, the number of patients that completed this questionnaire varied. The mean change in EPIC scores over time for each domain (bowel, urinary, hormonal, sexual) for all patients is given in Table 4. Graphically, change in QOL is shown in Fig. 3. For urinary and bowel QOL, decline was most notable in months 1 and 2, which mostly recovered in month 3 in Arm 2. After transient decline in months 1 and 2, the bowel and urinary QOL following hypofractionated radiotherapy, recovered back to baseline levels and had no significant influence on patients' QOL in any domain and subscales.

Table 5 – Clinically relevant decrease (CRD) in EPIC urinary domain.

	Urinary domain		
Months	Month 1	Month 2	Month 3
Arm 1	53%	70%	55%
Arm 2	70%	68%	42%
t-Test	NS	NS	0.02

Abbreviations: Arm 1 = conventional fractionation; Arm 2 = hypofractionation; NS = difference not significant ($p < 0.05$).

The proportion of patients with CRD of EPIC scores in the urinary domain are summarized in Table 5. The CRD in Arm 1 was significantly higher, in comparison with Arm 2, only in urinary domain at month 3 ($p = 0.02$).

4. Discussion

Acute toxicity during or after radiotherapy is an important item and may affect the patients' quality of life. The schedules of radiotherapy ranging from moderate to ultra-high dose per fraction are reported in different clinical studies regarding hypofractionation. The comparison of results obtained in our study with the results of other studies are rather difficult, as the treatment time schedules, doses per fraction, treatment volumes, total doses and hormonotherapy are all different. Furthermore, the questionnaires for acute toxicity assessment used are different. In order to compare our results with the results from other studies, we excluded the studies where a combination of EBRT and brachytherapy, extreme hypo fractions (5–10 Gy per fraction) were used.

An evidence base of moderate hypofractionation (2.5–4 Gy per fraction) has been reported in six randomized controlled trials that have been published to date. Some of the randomized trials that compared conventional fractionation and hypofractionation regimens were limited because of the use of a conventional treatment dose was too low or was not biologically equivalent to the hypofractionation arm. In most of the hypofractionation studies, the radiation dose was delivered using IMRT with image guidance. Although, in several former studies three-dimensional conformal RT was applied. Therefore, the interpretation of the results of the latter studies becomes difficult. Arcangeli et al. conducted a randomized trial comparing conventional fractionation (80 Gy/2 Gy/8 weeks) to hypofractionation (62 Gy/3.1 Gy/5 weeks) in high-risk prostate cancer patients. Acute GU ≥2 toxicity developed in 34 (40%) of 85 and 39 (47%) of 83 patients ($p = 0.45$) in the conventional and hypofractionation arms, respectively. Only 1 patient in each group developed Grade 3 toxicity. Acute GI Grade 2 toxicity was detected in 18 (21%) of 85 and 29 (35%) of 83 patients ($p = 0.07$) in the conventional and hypofractionation arms, respectively. A higher toxicity grade was not detected in this study.[11–18]

The dose of radiation administered to the prostate per fraction in our study was similar to that delivered in the aforementioned trial. However, the treatment volume and radiation therapy technique were different. In our study, elective pelvic lymph node irradiation possibly had an impact on the acute GI toxicity rate.

Initially, hypofractionated radiotherapy was performed to irradiate the prostate only. With the wider spread of 3D-conformal radiation therapy technique, as well as IMRT, a more sophisticated dose delivery to the prostate/prostate bed with a simultaneous radiation of pelvic lymph nodes has been integrated in recent trials for patients with high risk for lymph node metastases. In order to make an accurate conclusion, we tried to compare our results with the results obtained in trials with a similar irradiated volume. The data concerning acute toxicity are very scarce in reported randomized trials, comparing elective pelvic radiotherapy with prostate-only radiotherapy in clinically node-negative, intermediate-to-high risk prostate cancer patients. The data concerning acute toxicity are not present in all reports of trials with pelvic lymph nodes irradiation. In RTOG 94–13, there was a trend for higher acute Grade 3 GI toxicity associated with WPRT + NCHT, but it was not statistically significant as in our study.[19] In the GETUG-01 trial, a small but insignificant acute GI toxicity with pelvic irradiation was observed; GU acute Grade ≥2 toxicity was similar in both arms.[20] The acute toxicity, while using pelvic radiotherapy, results were mostly published in the retrospective trials and some increase in acute side-effects was reported, principally gastrointestinal rather than genitourinary. Mantini et al. obtained data similar to ours and reported no Grade 4 acute toxicity. Statistically insignificant Grade 3 acute toxicity in GI and GU (2.4% and 3.5%, respectively) was also reported. The overall incidence of GI and GU acute Grade 2 was similar in patients treated with PORT or WPRT (GI, 10.2 vs. 9.9%, p = NS; GU, 15.2% vs. 11.6%, p = NS).[21] Adkison et al. reported data of dose-escalated treatment of the pelvic lymph nodes with 56 Gy in 2 Gy fractions with concomitant treatment of the prostate to 70 Gy in 28 fractions of 2.5 Gy. They reported only Grade 2 acute toxicity in GU and GI (38% and 32%, respectively).[22] We found out that the incidence of GI 2 and GI 3 toxicity was higher in Arm 2 possibly because the total prescribed dose was administrated not only to the prostate but also to the seminal vesicles or it could be influenced by a sufficiently larger posterior margin (7 mm) between PTV and the rectum. Inter-fractional or intra-fractional prostate motion and a lack of oral contrast at simulation to distinguish large and small bowel can be a possible predictor of GI acute toxicity.

Urinary symptoms are the most common acute toxicities associated with external beam radiation therapy of prostate cancer. Most patients' symptoms are mild; however, reported rates of Grade ≥3 acute urinary toxicity range from 0 to 15%.[23–25]

The comparison of QOL in intermediate and high-risk prostate cancer patients who had undergone radical treatment using two different fractionation regimes was also performed in our study. We assessed the impact of our Arm 1 and Arm 2 regimens on the urinary, rectal, sexual, and hormonal QOL. The QOL compared with the baseline changed for each EPIC domain at months 1, 2 and 3. However, these changes were not statistically significant. The biggest difference of QOL between the arms were observed in gastrointestinal domain. CRD was statistically significantly higher only in the urinary domain in Arm 1 at month 3 when compared with Arm 2.

The assessment of QOL endpoints during acute toxicity period in studies of hypofractionated therapy is uncommon. These studies are mostly retrospective and the number of prospective studies is limited. Another difficulty for comparison of the data obtained in different studies includes the usage of various QOL questionnaires and treatment methods. A lot of studies perform assessment of treatment impact on patients suffering from prostate cancer, while comparing radical prostatectomy with external beam therapy, or brachytherapy and external beam therapy. However, the studies comparing results of different external beam fractionation regimens are very rare. From this point of view, our findings could be compared with QOL results reported by Pinkawa et al. These results demonstrated differences in QOL between PORT and WPRT. It was found out that external beam therapy was associated with greatest negative impact on urinary and bowel QOL during the acute phase at the end of the treatment. However, while comparing WPRT and PORT only differences in the bowel domain were demonstrated. No differences in urinary, sexual, and hormonal domains were revealed.[26]

This study was a single-institution one and included a relatively small number of participants; therefore, this may be a possible drawback. However, we hope that the results of this study will be helpful in assessment of the impact of acute toxicity on patients' QOL while implementing different fractionation regimens.

5. Conclusions

Our study demonstrated that hypofractionated radiotherapy was associated with a small but insignificant increase of acute toxicity. The reduction of overall treatment time has no significant influence on patients' QOL in any domain.

Conflict of interest

None declared.

Financial disclosure

None declared.

REFERENCES

1. Ganswindt U, et al. Optimized coverage of high-risk adjuvant lymph node areas in prostate cancer using a sentinel node-based, intensity-modulated radiation therapy technique. *Int J Radiat Oncol Biol Phys* 2007;**67**(2):347–55.
2. Guckenberg M, et al. Does intensity modulated radiation therapy (IMRT) prevent additional toxicity of treating the pelvic lymph nodes compared to treatment of prostate only? *Radiat Oncol* 2008;**3**:3.
3. Sharma NK, et al. Intensity-modulated radiotherapy reduces gastrointestinal toxicity in patients treated with androgen deprivation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2012;**80**(2):437–44.
4. Vora SA, et al. Analysis of biochemical control and prognostic factors in patients treated with either low-dose three-dimensional conformal radiation therapy or high-dose intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2007;**68**(4):1053–8.
5. Eade TN, et al. A comparison of acute and chronic toxicity for men with low-risk prostate cancer treated with intensity-modulated radiation therapy or (125)I permanent implant. *Int J Radiat Oncol Biol Phys* 2008;**71**(2):338–45.
6. Norkus, et al. A randomized hypofractination dose escalation trial for high risk prostate cancer patients: interim analysis of acute toxicity and quality of life in 124 patients. *Radiat Oncol* 2013;**8**:206.
7. Lawton CA, Michalski J, El-Naqa I, et al. RTOG GU radiation oncology specialists reach consensus on pelvic lymph node volumes for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2009;**74**:383–7.
8. Roach 3rd M. Equations for predicting the pathologic stage of men with localized prostate cancer using the preoperative prostate specific antigen (PSA) and Gleason score. *J Urol* 1993;**150**:1923–4.
9. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995;**31**:1341–6.
10. Wei JT, Dunn RL, Litwin MS, et al. Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assesment of health-related quality of life in men with prostate cancer. *Urology* 2000;**56**: 899–905.
11. Arcangeli G, Sarasino B, Gomelini S, et al. A prospective phase III randomized trial of hypofractionation versus conventional fractionation in patients with high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2010;**78**:11–8.
12. Arcangeli S, Strigari L, Gomellini S, et al. Updated results and patterns of failure in a randomized hypofractionation trial for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2012;**84**:11728.
13. Kuban DA, Nogueras-Gonzales GM, Hamblin L, et al. Preliminary report of a randomized dose escalation trial for prostate cancer using hypofractionation. *Int J Radiat Oncol Biol Phys* 2010;**78**:S58–9.
14. Lukka H, Hayter C, Julian JA, et al. Randomized trial comparing two fractionation schedules for patients with localized prostate cancer. *J Clin Oncol* 2005;**23**:6132–8.
15. Pollack A, Walker G, Horwitz EM, et al. Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer. *J Clin Oncol* 2013;**31**:3860–8.
16. Yeoh EE, Botten RJ, Butters J, et al. Hypofractionated versus conventionally fractionated radiotherapy for prostate carcinoma: final results of phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2011;**81**:1271–8.
17. Yeoh EE, Holloway RH, Fraser RJ, et al. Hypofractionated versus conventionally fractionated radiation therapy for prostate carcinoma: updated results of a phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2006;**66**:1072–83.
18. Dearnaley D, Syndikus I, Sumo G, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: preliminary safety results from CHHiP randomized controlled trial. *Lancet Oncol* 2012;**13**:43–54.
19. Lawton CA, DeSilvio M, Roach M, et al. An update of the phase III trial comparing whole-pelvic to prostate-only radiotherapy and neo-adjuvant to adjuvant total androgen suppression: updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions. *Int J Radiat Oncol Biol Phys* 2007;**69**:646–55.
20. Pommier P, Chabaud S, Lagrange JL, et al. Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Preliminary results of GETUG-01. *J Clin Oncol* 2007;**25**:5366–73.
21. Mantini G, Tagliaferri L, Mattiucci GC, et al. Effect of whole pelvic radiotherapy for patients with locally advanced prostate cancer treated with radiotherapy and long-term androgen deprivation therapy. *Int J Radiat Oncol Biol Phys* 2011;**81**:721–6.
22. Adkison JB, McHaffie DR, Bentzen SM, et al. Phase I trial of pelvic nodal dose escalation with hypofractionated IMRT for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2012;**82**:184–90.
23. Al-Mamgani A, Heemsbergen WD, Peeters ST, et al. Role of intensity-modulated radiotherapy in reducing toxicity in dose escalation for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2009;**73**:685–91.
24. Pollack A, Hanlon AL, Horwitz EM, et al. Dosimetry and preliminary acute toxicity in the first 100 men treated for prostate cancer on a randomized hypofractionation dose escalation trial. *Int J Radiat Oncol Biol Phys* 2006;**64**:518–26.
25. Zelefsky MJ, Fuks Z, Happersett L, et al. Clinical experience with intensity modulated radiation therapy (IMRT) in prostate cancer. *Radiother Oncol* 2000;**55**:241–9.
26. Pinkawa M, et al. Quality of life after whole pelvic versus prostate-only external beam radiotherapy for prostate cancer: a matched-pair comparison. *Int J Radiat Oncol Biol Phys* 2011;**81**(1):23–8.