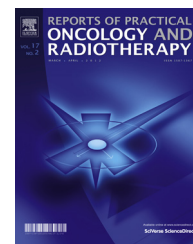




ELSEVIER

Available online at www.sciencedirect.com

SciVerse ScienceDirect

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

Original research article

Late rectal and bladder toxicity following radiation therapy for prostate cancer: Predictive factors and treatment results



Rafael Fuentes-Raspall^{a,b,*}, José Maria Inoriza^c, Alvaro Rosello-Serrano^{a,b},
Carmen Auñón-Sanz^{a,b}, Pilar Garcia-Martin^c, Gemma Oliu-Isern^c

^a Catalan Institute of Oncology, Hospital Universitari "Josep Trueta" Girona, Spain

^b Institut de Recerca Biomèdica de Girona, IDIBGi, Spain

^c Unit of Hyperbaric Medicine, Hospital de Palamós, Girona, Spain

ARTICLE INFO

Article history:

Received 14 February 2013

Received in revised form

25 April 2013

Accepted 25 May 2013

Keywords:

Rectal toxicity

Bladder toxicity

Radiotherapy

Predictive factors

Treatment

Hyperbaric oxygen

ABSTRACT

Aim: This study aimed at investigating factors associated to late rectal and bladder toxicity following radiation therapy and the effectiveness of Hyperbaric Oxygen Therapy (HBOT) when toxicity is grade ≥ 2 .

Background: Radiation is frequently used for prostate cancer, but a 5–20% incidence of late radiation proctitis and cystitis exists. Some clinical and dosimetric factors have been defined without a full agreement. For patients diagnosed of late chronic proctitis and/or cystitis grade ≥ 2 treatment is not well defined. Hyperbaric Oxygen Therapy (HBOT) has been used, but its effectiveness is not well known.

Materials and methods: 257 patients were treated with radiation therapy for prostate cancer. Clinical, pharmacological and dosimetric parameters were collected. Patients having a grade ≥ 2 toxicity were treated with HBOT. Results of the intervention were measured by monitoring toxicity by Common Toxicity Criteria v3 (CTCv3).

Results: Late rectal toxicity was related to the volume irradiated, i.e. $V50 > 53.64$ ($p = 0.013$); $V60 > 38.59\%$ ($p = 0.005$); $V65 > 31.09\%$ ($p = 0.002$) and $V70 > 22.81\%$ ($p = 0.012$). We could not correlate the volume for bladder. A total of 24 (9.3%) patients experienced a grade ≥ 2 . Only the use of dicumarinic treatment was significant for late rectal toxicity ($p = 0.014$). A total of 14 patients needed HBOT. Final percentage of patients with a persistent toxicity grade ≥ 2 was 4.5%.

Conclusion: Rectal volume irradiated and dicumarinic treatment were associated to late rectal/bladder toxicity. When toxicity grade ≥ 2 is diagnosed, HBOT significantly ameliorate symptoms.

© 2013 Greater Poland Cancer Centre. Published by Elsevier Urban & Partner Sp. z o.o. All rights reserved.

* Corresponding author at: Catalan Institute of Oncology, Hospital Universitari "Josep Trueta" Girona, Spain. Tel.: +34 609721315; fax: +34 972217344.

E-mail address: rfuentes@iconcologia.net (R. Fuentes-Raspall).

1507-1367/\$ – see front matter © 2013 Greater Poland Cancer Centre. Published by Elsevier Urban & Partner Sp. z o.o. All rights reserved. <http://dx.doi.org/10.1016/j.rpor.2013.05.006>

1. Background

Radiation therapy is a well established treatment for prostate cancer in organ-confined disease, including early and locally advanced cases and post-operatively when appropriate.^{1,2} During recent decades, doses delivered to the prostate gland and seminal vesicles have been increased due to studies demonstrating that better disease control can be obtained through radiation dose escalation. Although present delivering techniques using three dimensional conformal radiotherapy (3CRT) or intensity modulated radiotherapy (IMRT) have significantly reduced doses to surrounding normal tissues, concern still exists regarding late toxic effects on the bladder and rectum.^{3–6} Previously published reports on late toxicity in relation to 3D-CRT for prostate cancer show an incidence of between 5% and 20% of patients.^{7,8}

Some factors have been previously described in relation to late rectal and/or bladder toxicity, including clinical, pharmacological and dosimetric factors. However, a general consensus does not exist among the various reports.^{9–12}

It is rare for severe late rectal and/or bladder toxicity following radiation to be diagnosed, whereas toxicities higher than grade >2 (CTCv3) are more frequently observed due to their being very detrimental to daily activities and quality of life. Various different interventions have been tested to determine whether they improve or ameliorate symptoms deriving from chronic proctitis, particularly rectal bleeding, including corticosteroids or sucralfate topic applications and cauterization or argon therapy, but with unclear benefits.^{13,14}

For years, Hyperbaric Oxygen Therapy (HBOT) has been described as an effective option for late rectal and bladder toxicity, but most reports are retrospective and indicated for patients failing in other interventions. Another limitation of these studies is that they have analyzed heterogeneous groups with a wide range of primary tumors and radiation techniques.^{15–18} To the best of our knowledge, only one multicentre randomized trial has been published comparing HBOT with placebo for chronic and refractory radiation proctitis. In said study, however, most patients were treated for gynecological tumors, including external radiotherapy and some forms of brachytherapy.¹⁴ A study reporting a significant improvement in symptom control and quality of life has been recently reported.¹⁸

In order to provide further insight into factors influencing late pelvic toxicity following radiation i.e. proctitis and/or cystitis, we conducted a study on a cohort of consecutive patients treated uniformly with conformal radiation therapy (3D-CRT) for prostate cancer. Our aims were to describe the influence of clinical and dosimetric factors as predictors for late pelvic toxicity of patients treated with 3DCRT for prostate cancer. We also report the incidence of toxicities and final results after treating with HBOT patients having a grade >2.

1.1. Aim of the study

The aim of the study is to find clinical and dosimetric predictive factors for late rectal/bladder toxicity for prostate cancer

patients treated using three dimensional conformal radiotherapy and to measure the final toxicity reduction after using hyperbaric oxygen therapy on patients experiencing a toxicity grade ≥ 2 .

2. Materials and methods

We included patients treated radically or post-operatively at the Catalan Institute of Oncology's Radiation Oncology Service in Girona (ICO-Gi) with 3D-CRT for prostate cancer.

Inclusion criteria were: histological diagnosis of prostate cancer, clinical stage from T1 to T4, radical radiation therapy and post-operative or adjuvant therapy using 3D-CRT. A minimum follow-up of 6 months was required.

Late radiation proctitis or cystitis was classified according to CTCv3 and was considered only when started 6 months or later after the completion of 3D-CRT.¹³

Radiation therapy was administered at a single institution (ICO-Gi) using 3D-CRT with 18Mv photon equipment (CLINAC 2100-Varian®). Typical dose prescription was 50 Gy to 95% of the Planned Target Volume (PTV1) encompassing the prostate gland and seminal vesicles with a 7–10 mm margin. When clinically admissible, posterior margin was limited to 5 mm. A boost of 26 Gy was delivered after excluding seminal vesicles (PTV11) from the PTV1. In cases of seminal vesicle involvement, demonstrated either by MRI or surgery (T3b/pT3b), PTVs were designed accordingly in order to provide sufficient coverage of the disease.

Patients treated post-operatively received a dose of 70–72 Gy to 95% of PTV1 and treatment volumes according to international guidelines.^{1,20}

Normal tissue constraints for rectum were V50 < 65% and V70 < 20%; and for bladder V60 < 40%. Doses to femoral heads were limited to 50 Gy whenever possible. Dose distribution, doses to rectum and bladder and Dose Volume Histograms (DVH) were calculated using the Eclipse software v 7.5 (Varian®).

Baseline study protocol included the following factors regarding clinical, surgical and pharmacological history: cTNM and pTNM when appropriate, Gleason score, diagnostic PSA level (ng/mL). Co-morbid conditions, i.e., diabetes, hypertension, collagen diseases, abdominal surgery, arteriopathy, inflammatory bowel disease, benign anal pathology, smoking habit, anticoagulants, antiaggregants, androgen deprivation and chemotherapy treatments.

Dosimetric parameters recorded for rectum were: maximum doses (D_{max}); V50, V60, V65 and V70; for bladder: D_{max} , V40, V50 and V60.

Follow-up was based on regular visits every 3 months during the first 2 years, every 6 months until 5 complete years and annually thereafter. Toxicities for proctitis and cystitis according to CTCv3 were recorded at every visit.¹³

In patients diagnosed of proctitis and/or cystitis grade ≥ 2 , a colonoscopy, cystoscopy or both were performed to confirm diagnoses and exclude other etiologies. Finally, patients considered to be candidates, were referred to the Unit of Hyperbaric Medicine at Palamós Hospital, Girona (Spain) for Hyperbaric Oxygen Therapy (HBOT).

2.1. Statistical analysis

For the statistical analysis, the groups of variables defined as tumor characteristics, co-morbid conditions and pharmacological history were treated as categorical (usually dichotomy: yes/no). Age and radiation doses were analyzed as continuous.

Radiation toxicity according to the CTCv3 grading system was re-codified as a dichotomous scale (yes/no), code “yes” included grades 1–4.

In order to study a possible correlation between toxicity and categorical variables, a bi-variant descriptive model using contingency tables was used. We applied Chi-square tests and exact Fischer's statistics. Where there was a statistically significant association, we calculated the odds ratio.

All statistical calculations were done using the SPSS software version 18.

3. Results

From 1st June 2007 to 30th June 2010, a total of 278 patients were treated with radiation therapy for prostate cancer, 257 of them met the inclusion criteria, 21 were excluded because they received a combination of external radiotherapy and high dose rate brachytherapy or were missed of follow-up.

Age was 70 ± 6.14 years (range 52–82 years).

Tumor characteristics are shown in Table 1. In short, most frequent T stage was T2a/b (25%), Gleason 7 was assigned to almost half of the patients (48.2%) and pre-treatment PSA <10 ng/mL was the most frequent, measured in 45.5% of cases.

Radiation therapy was prescribed as radical treatment in 216 (84%) cases and post-operatively in 41 (16%).

Doses to the rectum for the whole group were: D_{max} : 76.02 ± 1.99 Gy (range 77.95–71.40 Gy), V50 Gy(%): 53.47 ± 12.72 (range 79.86–33) and V70 Gy(%): 21.82 ± 10.42 (range 43–4).

Doses to the bladder were: D_{max} 75.88 ± 1.97 Gy (range 78.27–71.4 Gy), V60 Gy(%): 42.57 ± 17.69 (range 68–12).

Follow-up time calculated from the end of radiotherapy to the last visit was 38.9 ± 9.6 months (range 9.50–58.6 months; median 39.6 months). During the follow-up, 15 patients died

and 5 were lost. However, all but one who died 9 months after treatment was followed for a minimum time of 12 months.

Incidence of rectal toxicity according to CTCv3 was: no toxicity, 203 (78.99%); Grade 1, 30 (11.7%); Grade 2, 24 (9.3%). Incidence of bladder toxicity was: no toxicity, 206 (80.15%); Grade 1, 31 (12.1%); Grade 2, 20 (7.8%). Only 7 (2.7%) had toxicity Grade 2 in both locations.

After treating the group of patients presenting late rectal or bladder bleeding with HBOT, overall grade 2 toxicity was reduced to 4.5%.

3.1. Clinical/dosimetric factors and late toxicities

Univariate analyses showed that factors associated with late rectal toxicity were older age, comparing <65 years vs. 65–74 years vs. >74 years ($p=0.042$), treatment with acenocumarol ($p=0.014$) and radical radiotherapy vs. post-operative/adjutant ($p=0.018$). In the case of bladder toxicity, none of the analyzed factors showed statistical significance. After analyzing statistically significant factors in a multivariate model, none of them retained statistical significance (Table 2).

Average doses as measured on dose–volume histograms (D_{max} , V50, V60, V65 and V70) for rectal toxicity were significantly higher in patients experiencing toxicity ($p<0.05$), but this significance was not observed for the maximum dose (D_{max}). For bladder toxicity, we could not demonstrate any statistical significance between D_{max} , V40, V50 and V60 and late toxicity (Table 3).

During the follow-up, 15 (5.8%) patients had a biochemical relapse, 5 (1.94%) had a loco-regional failure, 8 (3.11%) had distant metastasis and 15 (5.8%) died; 5 (1.94%) were lost. However, all patients were followed for at least 12 months.

The mean age of this sub group was 72 ± 3.38 years (range 65–78 years). Ten out of 24 patients diagnosed with grade ≥ 2 rectal toxicity did not receive HBOT because they did not complain of active rectal bleeding. A total of 20 patients experienced bladder toxicity but only 4 complained of hematuria; all 4 also had rectal bleeding. The final number of patients treated with HBOT was 14. Late rectal and bladder toxicity CTCv3 ≥ 2 for the whole group was 9.3%. After using up-front HBOT on patients experiencing rectal or bladder bleeding 10 patients remained unchanged (non-bleeder group) and only 1 of the 14 patients experiencing bleeding had persistent symptoms, leaving a final 4.28% of patients with any form of late pelvic toxicity.

Table 1 – Tumor characteristics.

	Patients	%
cTNM		
T1-T1c	62	24.1
T2a I b	64	24.9
T2c	54	21.0
T3a	52	20.2
T3b I c	20	7.8
T4	1	0.4
TX	4	1.6
Gleason		
<7	77	30
7	124	48.2
>7	47	18.3
Unknown	9	3.5
PSA (ng/mL)		
<10	117	45.5
10–20	91	35.4
>20	46	17.9
Unknown	3	1.1

4. Discussion

Radiation therapy is one of the most frequently prescribed treatments for localized prostate cancer and, as most patients are cured or have long survival times, late toxicity is an important concern for radiation oncologists.

Previously published reports on late toxicity in relation to 3D-CRT for prostate cancer show an incidence of between 5% and 20%. In our own group of patients, it was 9.3%, which we consider to be within the range of previous papers.⁷

Despite the fact that radiation proctitis and/or cystitis are not very frequent, when they do occur they are very

Table 2 – Co-morbid conditions and concomitant treatments in relation to late rectal and bladder toxicity.

Co-morbid conditions	Patients (%)	Rectal tox. 0 vs. >0.		Bladder tox. 0 vs. >0	
		Chi value	p	Chi value	p
Diabetes	46 (17.9)	0.020	0.886	0.195	0.659
Hypertension	102 (39.7)	0.243	0.622	0.486	0.490
Collagens diseases	3 (1.2)	0.006	0.937	0	0.993
Abdominal surgery ^a	107 (41.6)	2.471	0.480	1.829	0.609
Arteriopathy ^b	33 (12.8)	0.278	0.598	0.027	0.868
Inflammatory bowel disease	2 (0.8)	0.948	0.330	0.507	0.477
Benign anal pathology	21 (8.2)	0.077	0.781	0.445	0.505
Smoking habit					
Active smoking	60 (23.3)	0.054	0.82	0.012	0.913
Pharmacological treatments					
Anticoagulants ^c	19 (7.4)	6.099	0.014	0.123	0.726
Antiaggregants ^d	35 (13.6)	0.049	0.824	0.789	0.374
Androgen deprivation ^e	170 (66.1)	0.235	0.628	1.176	0.278
Chemotherapy	1 (0.4)	0.271	0.603	0.252	0.616

^a Abdominal surgery includes intra and extra-peritoneal surgery.

^b Included ischemic heart disease.

^c Includes acenocumarol treatment.

^d Includes aspirin and clopidogrel.

^e Includes bicalutamide and/or LH-RH analogs.

detrimental to quality of life and normal daily activities. Many different factors have been studied to identify which patients have a higher risk of late radiation proctitis. In our study, we selected those factors we considered most reproducible and measurable, including clinical, pharmacological and dosimetric parameters. Herold et al.,²¹ suggested an increasing incidence of late rectitis in diabetic patients and Fiorino et al.,¹¹ reported that previous abdominal surgery correlates to late rectal syndrome. Other factors, such as age and previous ano-rectal dysfunction, have also been suggested.^{22,23} In our study, we were unable to demonstrate a correlation between co-morbidity and late toxicity; this is most probably due to the small number of patients. However, co-morbid conditions are not uniformly recorded from one study to another; a bias can be suspected in previous published papers and probably our own work too.

Treatment by androgen deprivation has also been studied in relation to late pelvic radiation toxicity, but without homogeneous results. Zelefsky et al. and Takeda et al.^{7,24} failed to find a correlation between androgen deprivation and late pelvic toxicity, which is consistent with our own results. However, other published reports demonstrated an increasing risk of late genito-urinary toxicity in patients on androgen deprivation.^{10,12,25} One possible explanation is that 15–43% of patients were on androgen deprivation in

previous reports,^{7,10} whereas the percentage for our group was 66.1%. The underlying mechanism behind the process remains largely unclear, however, an impairment of the reparative process after radiation injury induced by androgen deprivation has been hypothesized.²⁵

We were only able to demonstrate an association between anticoagulant treatment and late rectal bleeding, which has also been shown by other authors.^{12,25}

Dose/volume histograms provide much better reproducible results for late rectal toxicity. In our study, a clear relationship exists between higher values of V50, V60, V65 and V70 and an increasing rate of rectal late toxicity, demonstrating that irradiated volume of the rectum plays an important role in toxicity, a finding consistent with previous reports.^{9–11} Our measured bladder toxicity did not show any correlation for dose/volume parameters.

HBOT was first described for treating late radiation proctitis in 1991.²⁶ It was later used in the treatment of late pelvic toxicities following radiation and reported to improve clinical symptoms with a grade 3 group. Mayer et al.²⁷ reported a series of 18 patients treated for radiation proctitis and/or cystitis. Most patients in their group had very long-lasting toxicities and despite some very good results, with only 2 patients not responding, they suggested that earlier treatment could provide a better improvement. Similarly, Jones et al.²⁸

Table 3 – Rectal/bladder toxicity according to irradiated volumes.

	CTCv3 rectum = 0	CTCv3 rectum > 0	p	CTCv3 bladder = 0	CTCv3 bladder > 0	p
D _{max}	76.24 ± 2.25	76.59 ± 2.41	0.342	76.26 ± 2.17	76.27 ± 2.41	0.988
V40	–	–	–	46.31 ± 17.31	44.00 ± 16.48	0.380
V50	49.07 ± 13.52	53.64 ± 11.23	0.013	37.48 ± 14.74	35.65 ± 14.07	0.414
V60	34.15 ± 10.52	38.59 ± 8.89	0.005	28.16 ± 12.28	28.16 ± 12.28	0.397
V65	26.66 ± 9.19	31.09 ± 8.88	0.002	–	–	–
V70	19.65 ± 8.42	22.81 ± 7.85	0.012	–	–	–

treated 10 patients experiencing radiation proctitis refractory to medical or laser therapy with 8 responses and 2 failing. Both authors included patients with toxicities graded 3 or 4 and HBOT was offered 20 or more months after the end of radiotherapy. We decided to treat patients with HBOT as soon as toxicity grade 2 (CTCv3) was diagnosed and results are therefore difficult to compare, but we had better response rates to HBOT, with only one patient out of 14 failing.

After using HBOT an important improvement in symptom control and quality of life could be observed, as previously reported.¹⁹

In summary, we demonstrated a correlation between anti-coagulant treatment, rectal dose and late rectal toxicity. When toxicity was grade 2 or more, the use of HBOT led an important final treatment toxicity reduction. Finally, it is worth highlighting that late gastrointestinal complications of pelvic radiotherapy are present in about 5–20% of long term survivors, which leads to gastrointestinal symptoms affecting quality of life. The most appropriate care for these patients is yet to be found, which opens an important field of research.

Conflict of interest

None declared.

Financial disclosure

The study was financed from grant: FIS PI08/90810.

REFERENCES

- Thomson Jr IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. *JAMA* 2006;296:2329–35.
- D'Amico AV, Manola J, Loffredo M, et al. 6-Month androgen suppression plus radiation therapy vs. radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. *JAMA* 2004;292(7):821–7.
- Kuban DA, Tucker SL, Dong L, 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.
- Zietman A, DeSilvio ML, Slater JD, et al. Comparison of conventional-dose vs. high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate. A randomized controlled trial. *JAMA* 2005;294:1233–9.
- Dearnaley DP, Sydes MR, Graham JD, et al. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2007;8:475–87.
- Bajon T, Piotrowski T, Andrzej A, Bak B, Blasiak B, Kafmierska J. Comparison of dose volume histograms for supine and prone position in patients irradiated for prostate cancer – a preliminary study. *Rep Pract Oncol Radiother* 2011;16:65–70.
- Zelefsky MJ, Levin EJ, Hunt M, Yamada Y, Shippy AM, Jackson A, et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;70(4):1124–9.
- Heemsbergen WD, Peeters STH, Koper PCM, Hoogeman MS, Lebesque J. Acute and late gastrointestinal toxicity after radiotherapy in prostate cancer patients: consequential late damage. *Int J radiat Oncol Biol Phys* 2006;66(1):3–10.
- 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 large multicenter observational study. *Radiother Oncol* 2009;93:197–202.
- Feng M, Hanlon AL, Pisansky TM, Kuban D, Catton CN, Michalsky JM, et al. Predictive factors for late genitourinary and gastrointestinal toxicity in patients with prostate cancer treated with adjuvant or salvage radiotherapy. *Int J Radiat Oncol Biol Phys* 2007;68(5):1417–23.
- Fiorino C, Fellin G, Rancati T, Vavassori V, Bianchi C, Casanoca Borca V, 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(4):1130–7.
- Valdagni R, Rancati T, Fiorino C, Feelin G, Magli A, Baccolini M, et al. Development of a set of nomograms to predict acute lower gastrointestinal toxicity for prostate cancer 3D-CRT. *Int J Radiat Oncol Biol Phys* 2008;71(4):1065–73.
- http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae3.pdf
- Clarke RE, Tenorio LMC, Hussey JR, Toklu AS, Cone DL, Hinojosa JG, et al. Hyperbaric oxygen treatment of chronic refractory radiation proctitis: a randomized and controlled double-blind crossover trial with long-term follow up. *Int J Radiat Oncol Biol Phys* 2008;72:134–43.
- Jones K, Evans AW, Bristow RG, et al. Treatment of radiation proctitis with hyperbaric oxygen. *Radiother Oncol* 2006;78:91–4.
- Annane D, Depondt J, Aubert P, Villart M, Gehanno P, Gajdos P, et al. Hyperbaric oxygen therapy for radionecrosis of the jaw: a randomized placebo-controlled, double-blind trial from the ORN96 study group. *J Clin Oncol* 2004;22:4893–900.
- Feldmeier JJ, Hampton NB. A systematic review of the literature reporting the application of hyperbaric oxygen prevention and treatment of delayed radiation injuries: an evidence based approach. *Undersea Hyperb Med* 2002;29:4–30.
- Bennett MH, Feldmeier J, Hampton N, et al. Hyperbaric oxygen therapy for late radiation tissue injury (protocol). *Cochrane Database Syst Rev* 2005;3, in review.
- Fuentes-Raspall R, Inoriza JM, Marti-Utset MJ, Auñón-Sanz C, Garcia-Martin P, Oliu-Isern G. Hyperbaric oxygen therapy for late rectal and bladder toxicity after radiation in prostate cancer patients. A symptom control and quality-of-life study. *Clin Oncol (R Coll Radiol)* 2012;24(8):e126.
- Poortmans P, Bossi A, Vandeputte K, Bosset M, Miralbell R, Maingon P, et al. Guidelines for target volume definition in post-operative radiotherapy for prostate cancer, on behalf of the EORTC Radiation Oncology Group. *Radiother Oncol* 2007;84:121–7.
- Herold DM, Hanlon AL, Hanks GE. Diabetes mellitus: a predictor for late radiation radiation morbidity. *Int J Radiat Oncol Biol Phys* 1999;43:475–9.
- O'Brien PC. Radiation injury of the rectum. *Radiother Oncol* 2001;60:1–14.
- Skwarchuk MW, Jackson A, Zelefsky MJ, Venkatraman ES, Cowen DM, Levegrun 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.
- Takeda K, Ogawa Y, Ariga H, Koto M, et al. Clinical correlations between treatment with anticoagulants/antiaggregants and late toxicity after radiotherapy for prostate cancer. *Anticancer Res* 2009;29:1831–4.

-
25. Sanguineti G, Agostinelli S, Foppiano S, Franzone P, et al. Adjuvant androgen deprivation impacts late rectal toxicity after conformal radiotherapy of prostate carcinoma. *Br J Cancer* 2002;**86**:1743–7.
 26. Charneau J, Bouachour G, Person B. Severe hemorrhagic radiation proctitis advancing to gradual cessation with hyperbaric oxygen. *Digest Dis Sci* 1991;**36**:373–5.
 27. Mayer R, Klemen H, Quehenberger F, et al. Hyperbaric oxygen – an effective tool to treat radiation morbidity in prostate cancer. *Radiother Oncol* 2001;**61**:151–6.
 28. Jones K, Evans AW, Bristow RG, Levin W. Treatment of radiation proctitis with hyperbaric oxygen. *Radiother Oncol* 2006;**78**:91–4.