Conformal Radiotherapy for Prostate Cancer

Longer Duration of Acute Genitourinary Toxicity in Patients with Prior History of Invasive Urological Procedure

Karel Odrážka, Jaroslav Vaňásek, Miloslava Vaculíková, Jiří Petera, Milan Zouhar, Zdeněk Zoul, Jan Stejskal, Zuzana Škrabková and David Kadečka

From the Departments of Oncology and Radiotherapy (K. Odrážka, M. Vaculíková, J. Petera, M. Zouhar, Z. Zoul, D. Kadečka) and Biophysics (Z. Škrabková), Charles University Hospital, Hradec Králové, Department of Radiotherapy, Regional Hospital, Pardubice (J. Vaňásek), Department of Radiotherapy, Regional Hospital, Jihlava (J. Stejskal), Czech Republic

Correspondence to: Karel Odrážka, MD, Department of Oncology and Radiotherapy, Charles University Hospital, 500 05 Hradec Králové, Czech Republic. Tel: +420 49 583 3175. Fax: +420 49 583 2081. E-mail: odrazka@fnhk.cz

Acta Oncologica Vol. 40, No. 7, pp. 810–815, 2001

The incidence and predictors of acute toxicity were evaluated in patients treated with three-dimensional conformal radiotherapy (3D-CRT) for localized prostate cancer. Between December 1997 and November 1999, 116 patients with T1-T3 prostatic carcinoma were enrolled in the study. Ninety patients were treated with 70 Gy and 26 patients with T3 tumors received 74 Gy. Of the 116 patients 42 (36.2%) had a prior history of invasive urological procedure (IUP) (transurethral resection of the prostate or transvesical prostatectomy for benign prostatic hyperplasia). Acute gastrointestinal (GI) and genitourinary (GU) symptoms were graded according to the EORTC/RTOG scoring system. Toxicity duration after the completion of 3D-CRT was recorded. The majority of patients experienced only mild or no (Grade 1) acute toxicities. Medications for GI and GU symptoms (Grade 2) were required by 28.4% and 12.9% of patients, respectively. Only one case of Grade 3 GI toxicity (0.9%) was observed. Seven patients (6.1%) experienced severe GU toxicity (Grade 3 or 4). No correlation was found between acute toxicity and age, stage, dose (70 Gy vs. 74 Gy), IUP and pelvic lymphadenectomy. A significant relationship was observed between the duration of acute GU toxicity and prior IUP. Symptoms persisted for more than 4 weeks in 51.9% and 26.0% of patients with and without a prior history of IUP, respectively ($p = 0.02$). The incidence of acute complications, associated with 3D-CRT for prostate cancer, was acceptable in our cohort of patients. A prior history of IUP resulted in a significantly longer duration of acute GU toxicity.

Received 30 November 2000
Accepted 16 August 2001

Three-dimensional conformal radiotherapy (3D-CRT) of prostate cancer has allowed us to deliver high doses of radiation to the target volume while sparing more of the surrounding healthy tissues. The 'high-dose volume' of critical structures (rectum and bladder), covered by 90% isodose, can be reduced by more than 40% in comparison with conventional techniques (1). Several retrospective studies showed, that the dosimetric advantages of 3D-CRT were associated with acute morbidity reduction (2–4).

However, the results of three randomized studies assessing acute toxicity are not consistent (5–7). Pollack et al. (6) compared treatment toxicity after 78 Gy using 3D-CRT with that after 70 Gy using conventional radiotherapy. There were no differences between the two treatment arms in terms of Grade ≥ 2 acute toxicity. In the Royal Marsden study (7) comprising 266 patients with pelvic malignancies (52% with prostate cancer), acute symptoms were assessed according to a patient questionnaire. Despite a 13% reduction in high-dose volume of normal tissues ($p = 0.02$), the acute symptoms were almost identical in both arms. In a recent randomized study conducted by Koper et al. (5), 266 patients with T1-4 prostate carcinoma were included. All patients were treated with 66 Gy using a three-field technique. A significant reduction in acute Grade 2 GI toxicity (19% vs. 32%) was observed with the conformal technique in comparison with the conventional technique ($p = 0.02$). In contrast, no difference in the incidence of acute GU toxicity was found.

An invasive urological procedure (IUP), usually transurethral resection of the prostate (TURP) or transvesical prostatectomy for benign prostatic hyperplasia (TVPE), performed prior to radical irradiation may have an impact on treatment morbidity. There are insufficient data regarding the influence of TURP/TVPE on acute

 ISSN 0284-186X

toxicity associated with 3D-CRT. Chou et al. (8) assessed the tolerance of 3D-CRT in 52 patients who were eligible for interstitial implant monotherapy, but they did not demonstrate any relationship between prior TURP and the incidence of acute GU toxicity.

In this study, we examined the incidence, severity, and duration of acute toxicity in patients treated for localized prostate cancer using 3D-CRT. The patient-related and treatment-related predictors of toxicity were evaluated. Particular attention was focused on the relationship between prior IUP and acute GU toxicity. Although less important than late effects, acute toxicity has been used as an endpoint, because lower GI and GU symptoms are troublesome in a substantial proportion of patients, and because the potential predictive value of acute reactions for the development of late toxicity should be elucidated.

MATERIAL AND METHODS

Patient characteristics

Between December 1997 and November 1999, a total of 116 patients with prostate cancer were treated with 3D-CRT at the Department of Oncology and Radiotherapy, Charles University Hospital in Hradec Králové. Patients with the following characteristics were included in the study: localized prostatic disease, no clinical or surgical signs of nodal involvement, no clinical evidence of distant metastases—1992 American Joint Committee on Cancer clinical stage T1-3 NX (N0) M0.

The baseline and treatment characteristics are summarized in Table 1. The median follow-up time was 16 months, ranging from 5 to 29 months. A history of IUP performed before 3D-CRT was recorded in 42/116 (36.2%) patients. The median interval between TURP/TVPE and the start of radiotherapy was 20.5 weeks (range 5–750 weeks). The treatment was initiated earlier than 10 weeks after IUP in only one patient. Neoadjuvant androgen deprivation (luteinizing hormone-releasing hormone analogue and antiandrogen) was initiated 2–3 months prior to 3D-CRT and continued during the course of radiotherapy in patients with bulky tumors. Stage T3 patients received hormonal therapy in 26/32 (81.3%) of cases.

Table 1

Patient and treatment characteristics (n = 116)

Age (mean, SD)	69 years (6)
Stage	
T1	24/116 (20.7%)
T2	60/116 (51.7%)
T3	32/116 (27.6%)
Initial PSA (median, range)	12.1 (0.1-150.0)
Invasive urological procedure	
TURP	29/116 (25.0%)
TVPE	13/116 (11.2%)
Pelvic lymphadenectomy	29/116 (25.0%)
Neoadjuvant androgen deprivation	48/116 (41.4%)
Dose	
70 Gy	90/116 (77.6%)
74 Gy	26/116 (22.4%)

Radiotherapy

Patients were simulated and treated in supine position and they were asked to have a full bladder at the time of simulation and during treatment. A standard vacuum cushion (Vac-Lok, MED-TEC) was used for immobilization of the legs, from the upper thigh cranially to the ankles caudally. The planning CT scans were taken 5 mm apart at a 5-mm thickness.

A 3D treatment planning system (Cadplan 2.7.9, Varian) was used for all treatment plans. Standard recommendations as published by the International Commission on Radiation Units and Measurements (ICRU 50 Report) were followed (9). The structures of interest were contoured on consecutive CT slices: gross tumor volume (GTV), rectum, urinary bladder, and femoral heads. The GTV included the entire prostate and the base of seminal vesicles in T1 and T2 tumors, and the entire prostate and seminal vesicles in T3 tumors. The clinical target volume (CTV) accounting for possible microscopic spread corresponded to the GTV. A non-uniform margin was added to the CTV (10 mm anteriorly, posteriorly and laterally, and 15 mm superiorly and inferiorly) using an automated volume expansion to create the planning target volume (PTV). Greater margins in vertical dimensions (15 mm) were implemented because the definition of the prostate apex on CT scans shows a certain degree of inaccuracy (10, 11). The organs at risk (rectum, urinary bladder, femoral heads) were contoured on the slices crossing the PTV and up to 1 cm above/below the PTV according to the ICRU 50 Report.

Patients were treated with four coplanar wedged fields (two lateral fields 90°, 270°, and two anterior oblique fields 30°, 330°). The structures of interest were displayed using beam's eye view (BEV) mode and the individual beams were shaped with a multileaf collimator (MLC). Another margin of 10 mm was left between the PTV and the leaves of the MLC, accounting for beam penumbra. The prescribed dose was specified to the ICRU point (isocenter) and normalized to 100%. Dose-volume histograms (DVH) were created for the treatment plan optimization procedure. Dose inhomogeneity ranging from 92 to 107% in the PTV was accepted, although the recommended 95–107% variation was fulfilled in the majority of patients. No more than 35% of the rectal volume and 45% of the bladder volume were allowed to receive the prescribed dose.

A 6 MV linear accelerator (Clinac 600 C, Varian) was used to deliver radiation. The prescribed dose was 70 Gy over 7 weeks in daily fractions of 2 Gy for 90/116 (77.6%) patients. The remaining 26/116 (22.4%) patients (all of them with T3 tumors) were treated with 74 Gy over 7.5 weeks. Our treatment policy has changed over time: while

Table 2

EORTC/RTOG acute radiation toxicity scoring criteria

Grade	Lower GI symptoms
1	Increased frequency or change in bowel habits not requiring medication; rectal discomfort not requiring medication
2	Diarrhea requiring parasympatholytic drugs; mucous discharge not requiring pads; rectal or abdominal pain requiring analgesics
3	Diarrhea requiring parenteral support; severe mucous or blood discharge requiring pads; abdominal distention
4	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion
	GU symptoms
1	Urinary frequency or nocturia twice pretreatment habit; dysuria, urgency not requiring medication
2	Urinary frequency or nocturia less than every hour; dysuria, urgency, bladder spasm requiring local anesthetic
3	Urinary frequency and nocturia hourly or more frequently; dysuria, pelvis pain, or bladder spasm requiring regular frequent narcotics; gross hematuria with/without clot passage
4	Hematuria requiring transfusion; acute bladder obstruction not secondary to clot passage, ulceration or necrosis

a uniform dose of 70 Gy was initially given to all patients, since April 1998, patients with T1 and T2 tumors received 70 Gy, and those with T3 tumors were given 74 Gy.

Treatment verification was required weekly using an electronic portal imaging device (PortalVision 3.8, Varian). Portal images in 10 randomly selected patients were analyzed to assess the set-up reproducibility. For the three axes, the systematic and random errors of the mean isocenter displacement were 1.6–2.3 mm (1 SD) and 1.3–1.4 mm (1 SD), respectively (unpublished data). The reproducibility of the PTV, rectum, and bladder localization has not been verified.

Acute toxicity evaluation

Acute lower gastrointestinal (GI) and genitourinary (GU) symptoms were graded according to the EORTC/RTOG scoring system (Table 2) (6, 12). All patients were seen at least weekly during the course of radiotherapy. The first follow-up visit was scheduled to take place 4 weeks after the completion of treatment and the second 8 weeks thereafter. Patients were then seen every 3 months. Symptoms occurring in the course of radiotherapy and up to 90 days from the end of treatment were considered for the acute toxicity evaluation. The medication for relief of symptoms was prescribed—if needed—by the attending radiation oncologist. The duration of symptoms after the completion of treatment (less than 4 weeks, 4 to 12 weeks, more than 12 weeks) was also recorded.

Statistics

The relationship between critical organs exposure and acute toxicity was assessed using the DVH analysis. The DVH for the PTV, rectum, and urinary bladder were routinely performed. The mean, minimal, and maximal doses in the rectum and bladder were recorded. Furthermore, the volumes of the organs at risk (% and ccm) exposed to a defined dose of radiation (60 Gy, 65 Gy, 70 Gy, and 74 Gy) were registered. Apart from the DVH analysis, the incidence of acute toxicity was studied regarding tumor stage (T1 and T2 vs. T3), prescribed dose (70 Gy vs. 74 Gy), age, neoadjuvant hormonal treatment, prior IUP, and pelvic lymphadenectomy (PLA). A biostatistic computer program (NCSS 6.0.21) was used for univariate analysis. A statistical correlation between continuous variables (DVH parameters, age) and acute toxicity was determined using a non-parametric Mann-Whitney test. The discrete variables (stage, dose, hormonal treatment, IUP, PLA) were evaluated by the contingency-table statistics (χ^2 test, Fisher's exact test).

RESULTS

Conformal radiotherapy was well tolerated: 82/116 (70.7%) of patients experienced either mild or no acute GI toxicity (Fig. 1). Medication for relief of symptoms was necessary in 33/116 (28.4%) of patients. Only one case (0.9%) of Grade 3 toxicity was recorded. Clinical stage, dose, hormonal treatment, IUP, PLA, and age had no impact on the incidence and duration of GI symptoms.

Overall, 94/116 (81.0%) of patients experienced Grade 1 or less acute GU toxicity (Fig. 2). Only 15/116 (12.9%) of patients required medication for bladder symptoms. Severe acute morbidity (Grade 3 or 4) developed in 7/116 (6.1%) of patients. Urinary frequency hourly or more often was observed in 3 patients, while a temporary catheter had to be inserted in 4 patients because of bladder obstruction. The urinary catheter was removed 3 months after the end

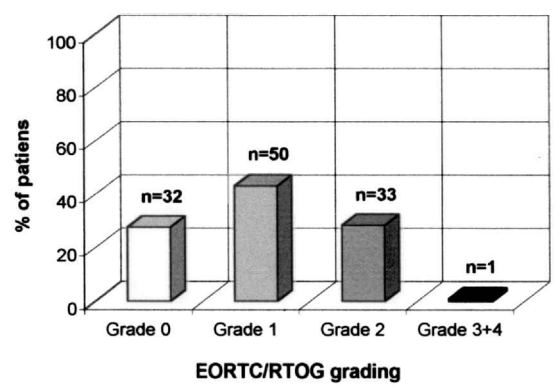

Fig. 1. Incidence of acute GI toxicity.

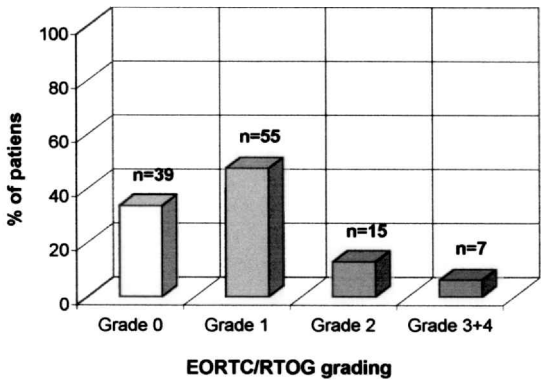

Fig. 2. Incidence of acute GU toxicity.

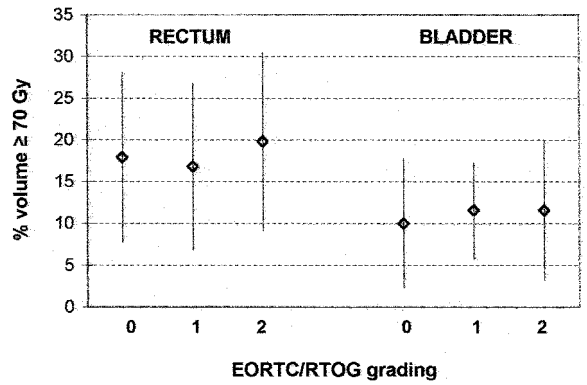

Fig. 4. Acute toxicity in relation to the mean percentage of critical organs ($\pm$ 1 SD) exposed to a dose of 70 Gy.

of treatment at the latest in 3 out of 4 patients. Clinical stage, dose, hormonal treatment, IUP, PLA, and age had no impact on the incidence of GU symptoms. A trend suggesting increased rates of Grade 3 and 4 GU toxicity in patients with prior IUP was observed ($p = 0.097$).

Signs of GU toxicity lasted more than 4 weeks after the completion of 3D-CRT in 27/77 (35.1%) of patients who experienced at least Grade 1 GU symptoms during treatment. Interestingly, a positive history of IUP was a significant predictor of acute toxicity duration (Fig. 3). Four weeks after the end of radiotherapy, the GU symptoms persisted in 14/27 (51.9%) patients with a positive history of IUP compared with 13/50 (26.0%) of those with a negative history of IUP ($p = 0.02$). Only 7/77 (9.1%) patients were symptomatic 12 weeks after treatment: 5/50 (10.0%) of the patients in the group without prior IUP and 2/27 (7.4%) of those with a history of IUP. The interval between TURP/TVPE and the start of 3D-CRT (≤ 20 weeks vs. > 20 weeks) had no impact on toxicity duration, as 5/12 (41.7%) patients with a shorter interval suffered from protracted GU symptoms, compared to 9/15 (60.0%) of those with a longer interval ($p = 0.34$). Moreover, toxicity duration did not depend on the type of invasive procedure (TURP vs. TVPE, $p = 0.88$).

Dose-volume histogram analysis failed to reveal a statistically significant correlation between exposed volume of critical organs and acute toxicity grade (Fig. 4). A large volume of bladder (ccm) receiving 74 Gy or more was associated with a higher incidence of severe acute GU morbidity (Grade 3 or 4). Nevertheless, this correlation did not reach a statistically significant level ($p = 0.11$); moreover, a small number of patients with severe toxicity ($n = 7$) should be considered.

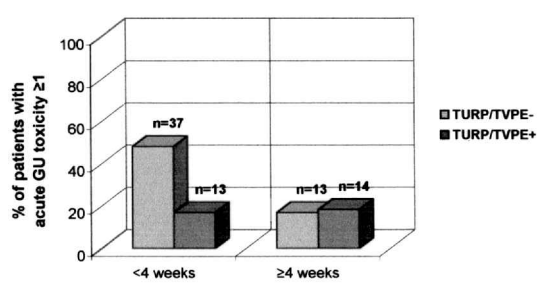

Fig. 3. Impact of prior TURP/TVPE on the duration of acute GU toxicity.

DISCUSSION

Acute GU morbidity associated with 3D-CRT is acceptable even with doses exceeding 70 Gy (3, 5, 6, 8, 13–16) (Table 3). In our group of patients, the incidence of Grade 2 GU toxicity was particularly low. On the other hand, severe urinary toxicity was slightly more pronounced. 7/116 (6.0%) patients experienced Grade 3 or 4 bladder symptoms. What is noteworthy is that in 5 of these 7 patients the 3D-CRT was preceded by TURP/TVPE.

Out of 116 patients, 42 (36.2%) had a previous history of IUP. In this patient population, the rate of IUP is two to three times higher than that in comparable published reports (3, 8). A considerable incidence of IUP suggests that many patients had suffered from obstructive symptoms before the diagnosis of cancer was made. Surprisingly, an almost identical incidence of TURP/TVPE was observed among patients with T1, T2 tumors—30/84 (35.7%)—compared with those with T3 tumors—12/32 (37.5%).

To our knowledge, no significant reduction in acute GU toxicity has been reported so far in randomized trials comparing conformal and conventional radiotherapy for localized prostate cancer (5–7). It has been suggested that urinary symptoms are predominantly caused by mucositis and edema in the prostatic part of the urethra. This assumption is supported by the nature of the symptoms (urinary frequency, urgency) as well as the particularly low incidence of acute GU toxicity in patients treated with 3D-CRT after radical prostatectomy (17). 3D-CRT has the potential for sparing more of the bladder volume as compared with conventional radiotherapy but the prostatic urethra region is always exposed to a prescribed dose.

Table 3

Acute GU toxicities during 3D-CRT reported in the literature

Reference	No. of patients	Total dose (Gy)	Prior TURP (%)	Acute GU toxicity (%)	
				Grade 2	Grade 3+4
Chou et al. (8)	52	66.6–79.2	10	33	0
Koper et al. (5)	129	66	NS	16	2
Michalski et al. (13)	288	68.4–73.8	NS	25	1.7
Pollack et al. (6)	29	78	NS	28	3.4
Soffen et al. (14)	26	68	NS	15	NS
Wachter et al. (15)	291	66	NS	23	0
Zelefsky et al. (3)	743	64.8–81.0	12	37	0.7
Zelefsky et al. (16) [1]	23	75.6	NS	48	8.7

[1] 3D-CRT combined with neoadjuvant and concomitant chemotherapy (estramustine phosphate and vinblastine).

Consequently, a significant reduction in acute urinary symptoms cannot be expected, even with advanced 3D techniques.

In our study we found that the IUP was a strong predictor of acute GU toxicity duration. Four weeks after the end of treatment, significantly more patients were symptomatic in the group with prior IUP compared with those who did not have a history of IUP ($p = 0.02$). Note, however, that the protracted acute GU toxicity mostly resolved with time. Only 9.1% of the initially symptomatic patients had signs of toxicity 12 weeks after treatment. Similarly, Soffen et al. (14) reported acute symptoms lasting more than one month in 3/26 (11%) patients treated with 3D-CRT. The authors did not distinguish between GI and GU symptoms. In a recent analysis by Chou et al. (8), 13/52 (25%) patients experienced residual urinary symptoms one month after conformal radiotherapy.

When TURP is required before radiotherapy, the literature suggests that delaying radiation by 6 to 8 weeks from the time of TURP will minimize incontinence and bladder neck contractures to acceptable levels (18, 19). In our group of patients, the interval between TURP/TVPE and 3D-CRT was rather long (median 20.5 weeks) and had no impact on GU toxicity.

A controversy exists regarding an association between the incidence of acute symptoms and the onset of late complications (3, 20, 21). In a report by Zelefsky et al. (3), acute toxicity was a significant predictor of development of late toxicity. Furthermore, a prior TURP was a significant predictor of development of urethral stricture. The 5-year actuarial likelihood was 4% for patients who had a prior TURP, compared with 1% for those who did not undergo an invasive procedure ($p = 0.03$). Conversely, in a randomized study comparing conformal and conventional radiotherapy in 225 men treated with 64 Gy, Dearnaley et al. (20) were unable to demonstrate any relationship between the incidence of acute toxicity and the development of late complications.

In summary, the incidence of acute toxicity, observed in our group of patients treated with 3D-CRT for prostate cancer, did not differ significantly from that found in similar published series. IUP was identified to be a significant predictor of protracted urinary toxicity. However, the acute GU symptoms resolved in the overwhelming majority of patients within 3 months. A longer follow-up is needed to evaluate whether IUP is likely to influence late toxicity.

REFERENCES

1. Dearnaley DP. Radiotherapy of prostate cancer: established results and new developments. Semin Surg Oncol 1995; 11: 50–9.
2. Leibel SA, Heimann R, Kutcher GJ, et al. Three-dimensional conformal radiation therapy in locally advanced carcinoma of the prostate: preliminary results of a phase I dose escalation study. Int J Radiat Oncol Biol Phys 1993; 28: 55–65.
3. Zelefsky MJ, Cowen D, Fuks Z, et al. Long-term tolerance of high dose three-dimensional conformal radiotherapy in patients with localized prostate carcinoma. Cancer 1999; 85: 2460–8.
4. Vijayakumar S, Awan A, Karrison T, et al. Acute toxicity during external-beam radiotherapy for localized prostate cancer: comparison of different techniques. Int J Radiat Oncol Biol Phys 1993; 25: 359–71.
5. Koper PCM, Stroom JC, Van Putten WLJ, et al. Acute morbidity reduction using 3DCRT for prostate carcinoma: a randomized study. Int J Radiat Oncol Biol Phys 1999; 43: 727–34.
6. Pollack A, Zagars GK, Starkschall G, et al. Conventional vs. conformal radiotherapy for prostate cancer: preliminary results of dosimetry and acute toxicity. Int J Radiat Oncol Biol Phys 1996; 34: 555–64.
7. Tait DM, Nahum AE, Meyer LC, et al. Acute toxicity in pelvic radiotherapy: a randomised trial of conformal versus conventional treatment. Radiother Oncol 1997; 42: 121–36.
8. Chou RH, Wilder RB, Ji M, et al. Acute toxicity of three-dimensional conformal radiotherapy in prostate cancer patients eligible for implant monotherapy. Int J Radiat Oncol Biol Phys 2000; 47: 115–9.
9. ICRU Report 50. Prescribing, recording and reporting photon beam therapy. Bethesda, MD: International Commission for Radiation Units and Measurements, 1993.

10. Debois M, Oyen R, Maes F, et al. The contribution of magnetic resonance imaging to the three-dimensional treatment planning of localized prostate cancer. Int J Radiat Oncol Biol Phys 1999; 45: 857–65.
11. Sandler HM, Bree RL, McLaughlin PW, Grossman HB, Lichter AS. Localization of the prostatic apex for radiation therapy using implanted markers. Int J Radiat Oncol Biol Phys 1993; 27: 915–9.
12. Lawton CA, Won M, Pilepich MV, et al. Long-term treatment sequelae following external beam irradiation for adenocarcinoma of the prostate: analysis of RTOG studies 7506 and 7706. Int J Radiat Oncol Biol Phys 1991; 21: 935–9.
13. Michalski JM, Purdy JA, Winter K, et al. Preliminary report of toxicity following 3D radiation therapy for prostate cancer on 3DOG/RTOG 9406. Int J Radiat Oncol Biol Phys 2000; 46: 391–402.
14. Soffen EM, Hanks GE, Hunt MA, Epstein BE. Conformal static field radiation therapy treatment of early prostate cancer versus non-conformal techniques: a reduction in acute morbidity. Int J Radiat Oncol Biol Phys 1992; 24: 485–8.
15. Wachter S, Gerstner N, Goldner G, Dieckmann K, Colotto A, Pötter R. Three dimensional conformal photon radiotherapy at a moderate dose level of 66 Gy for prostate carcinoma: early results. Strahlenther Onkol 1999; 175 (Suppl 2): 84–6.
16. Zelefsky MJ, Kelly WK, Scher HI, et al. Results of a phase II study using estramustine phosphate and vinblastine in combination with high-dose three-dimensional conformal radiotherapy for patients with locally advanced prostate cancer. J Clin Oncol 2000; 18: 1936–41.
17. Zelefsky MJ, Aschkenasy E, Kelsen S, Leibel SA. Tolerance and early outcome results of postprostatectomy three-dimensional conformal radiotherapy. Int J Radiat Oncol Biol Phys 1997; 39: 327–33.
18. Mansfield JT, Stephenson RA. Does transurethral resection of the prostate compromise the radical treatment of prostate cancer? Semin Urol Oncol 1996; 14: 174–7.
19. Seymore CH, El-Mahdi AM, Schellhammer PF. The effect of prior transurethral resection of the prostate on post radiation urethral strictures and bladder neck contractures. Int J Radiat Oncol Biol Phys 1986; 12: 1597–600.
20. Dearnaley DP, Khoo VS, Norman AR, et al. Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial. Lancet 1999; 353: 267–72.
21. 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.