3D conformal Radiotherapy in Prostate Cancer Treatment: Preliminary Results

Eduardas Aleknavičius,
Birutė Aleknavičienė,
Feliksas Jankevičius,
Mindaugas Grybauskas

Vilnius University Oncology Institute,
Conservative Cancer Treatment Clinic,
Santariškių 1,
LT-2600 Vilnius, Lithuania
E-mail: e.aleknavicius@loc.lt

The purpose of our work was to analyse the effect of conformal (3D) radiotherapy on local prostate cancer control and disease-free survival.

We analysed 36 patients aged from 45 to 86 years with T2 prostate tumours. Hormonal therapy was started before conformal radiotherapy using a SATURN-43 linear accelerator and the TARGET planning system. Irradiation was administered with 2 Gy per day to a total dose of 63–74 Gy to the prostate.

The early treatment results are available. In 35 (93%) patients a decrease in prostate volume was observed. Also, a significant prostate-specific antigen (PSA) decrease was confirmed. In general, metastases in the study group were determined in 6 pts and local progression in 2 pts.

Acute 1–2 grade radiotherapy reactions were observed in 23 pts (58%). The most frequent acute reactions were cystitis, disuria, diarrhoea. Cystitis was reliably more frequent when the total dose was ≥66 Gy ($p = 0.03$).

Late (grade 3–4) complications (radiation ulcer of urinary bladder and rectum) were observed in 6 pts (16%). In 3 of 21 patients (14%) late complications were detected when the total dose was ≤65 Gy and in 3 of 12 patients (20%) when the total dose was ≥66 Gy. Disease-free survival was 17 months, time to progression was 18.2 ± 1.9 months.

Our data confirm a significant decrease of PSA and prostate volume after 3D conformal radiotherapy treatment. The small number of patients and short follow-up period are insufficient to determine the effects of therapy in local prostate tumour.

Key words: prostate cancer, 3D conformal radiotherapy, radiation toxicity

INTRODUCTION

Prostate cancer is one of the most frequent cancers in men. Over the last years the incidence of prostate cancer in Lithuania has rapidly increased from 565 to 963 cases (1).

The main treatment methods still are prostatectomy and radical radiotherapy. The standard radiotherapy method such as ^{60}Co and 2D planning gives no desirable results. Results are better when combined methods – hormonal therapy and modern 3D conformal radiotherapy – are employed (2, 3).

Cancer of the prostate is a hormone-dependent cancer in the treatment of which the role of hormone therapy has recently been recognized. There are some data that neoadjuvant hormonal therapy as the initial treatment procedure in localy advanced prostate cancer influences the prognosis of patients managed by radical radiotherapy for prostate carcinoma (4).

Resent clinical trials have shown that external irradiation combined with an LH-RH analogue, with or without an antiandrogen, used 2–4 months before irradiation or from the first day of irradiation, improved either disease-free survival, local recurrence-free survival, metastatic-free survival or overall survival ($p < 0.001$) in patients with poorly differentiated tumour (5).

The main purpose of radiotherapy is to reduce tumor volume, improve local control, reduce local recurrence, local morbidity and metastases. This strategy has the advantage of not requiring radiation dose escalation with the attendant risk of morbidity (6).

Eradicating the local disease in prostate cancer through the use of irradiation can be maximized by careful targeting and by application of the largest safety tolerable dose. Both of these goals are facilitated by 3-dimensional treatment planning which allows accurate targeting of radiation and allows complex field configuration and block designs (7).

Over the past 3 years we have been treating our patients with a 3D conformal technique, conforming the high dose volume more closely to the shape of the target tissue. The goal of the treatment technique is adequate target coverage with maximal sparing of critical normal structures.

The ongoing work is the first attempt in Lithuania to estimate the results of three-dimensional (3D) conformal radiotherapy. This paper discusses our preliminary results in local control and adverse effects of radiotherapy in patients with adenocarcinoma of the prostate.

MATERIALS AND METHODS

The cases of the first 36 patients treated with a linear accelerator from November 1999 to December 2001, with the diagnosis of adenocarcinoma of the prostate, without evidence of dissemination have been analysed. According to UICC-TNM Classification of Malignant Tumours, in all 36 patients were established $T_2N_0M_0$ (II stage) prostate tumours.

The pre-treatment work-up included history, physical examination, evaluation of serum prostatic acid phosphatase, chest X-ray, prostate and pelvic computed tomography (CT) and ultrasound (US) examination, complete blood count with serum aspartate transaminase and alanine transaminase (Table 1).

Lymph node evaluation was carried out by ultrasound and computed tomography. Ten patients with obstructive urinary symptoms underwent transurethral resection (TURP) of the prostate.

The histological confirmation was obtained in all cases. The initial diagnosis of prostate cancer had been established by a needle biopsy alone in 26 patients (72%), in another 10 patients (28%) a TURP was performed before treatment.

Histologic grade G1 was established in 8 patients, G2 in 17 patients and G3 in 11 patients.

The distribution of patients by PSA level and histologic grade (G) is shown in Table 2. There was a significant correlation between PSA level and poorly differentiated histology. In 35 patients the Gleason score was established. For 19 patients the 2–6 Gleason score, for 16 patients the 7–10 Gleason score were established.

For all patients hormonal therapy was administered without any clinical evidence of distant metastases. The main hormonal therapy regime was Triptorelini with Bicalutamidi. (Table 3). Hormonal therapy was started prior to initiation of radiotherapy and was continued throughout the irradiation. After completion of radiotherapy all patients received androgen depletion treatment. The average time of androgen ablation was 8 months (range, 4–15 months).

All patients were irradiated with high energy photons (15–25 MV) produced by a SATURN-43 linear accelerator with the distance of 100 cm from the source to the axis of treatment. Radiotherapy was planned on simulator. All patients had split-course radiotherapy with four-field (box) technique. As a

Table 1. **Carcinoma of prostate: pre-treatment investigation**

Investigation	Patients	%
Chest XR	34	97
Bone scan	20	57
Cystoscopy	5	15
Pelvis CT	36	100
Ultrasound	36	100
Alkaline phosphatase	27	77
Acid phosphatase	27	77
TURP	10	27

Table 2. **Distribution of patients according to PSA level and grade**

PSA ng/ml	G1 pts.	G2 pts.	G3 pts.
≤ 4	–	2	–
> 4 ≤ 10	2	7	3
> 10 ≤ 20	5	2	–
> 20	1	6	8
Total	8	17	11
%	22	47	31

Table 3. **Distribution of patients according to hormonotherapy**

LH-RH analogue	Antiestrogen	Number of patients
Goserelini	Biculatomidi	5
Triptorelini	Biculatomidi	16
Triptorelini	Ciproteroni	7
Goserelini	Ciproteroni	1
Triptorelini	–	–
Goserelini	–	1
Orchiectomy	Ciproteroni	6
Total		36

Table 4. **Distribution of patients according to total doses**

Number of patients	Dose on prostate(Gy)	Dose on seminal vesicle (Gy)
13	63	60
3	65	62
5	67	64
13	69	66
1	72	68
1	74	70

rule, treatment was interrupted for 2–3 weeks after 36–40 Gy.

Before irradiation, a CT scan was performed on a flat couch with the patient in the treatment position from the level of L5-S1 to ischial tuberosities. The 1.0 cm cuts were made. Skin marks were placed on the patient to guide placement during simulation and CT.

The planned total dose delivered to the prostate was 63–74 Gy in daily increments of 2 Gy, five times per week. Fifteen (42%) patients received doses to the prostate in the range of 69–74 Gy, and 21 (58%) patients were treated with lower doses (63–67 Gy) (Table 4). Generally, the reasons for lower doses of radiation were acute complications.

The planned target volume was defined as prostate and the seminal vesicle (Fig. 1 a, b, c, d). In the case when PSA level was higher than 20 ng/ml or the Gleason score above 7, the elective irradiation of pelvic lymph nodes to the total dose of 40–45 Gy was introduced. Treatment volume during the course of irradiation was reduced. After 40–45 Gy lymph nodes were excluded from irradiation fields, followed by a boost to the prostate only to 20–28 Gy in 10–14 fractions.

The boost included the entire prostate and seminal vesicles plus 1 cm margin, except at the prostate–rectum interface where a 0.5–0.8 cm margin was used to decrease the risk of rectal toxicity (8, 9).

The parameters for optimization included a specified dose to the planned target volume (PTV) and critical structures. The dose distribution closely conformed to the shape of prostate and created a rapid dose fall-off through the bladder and rectum (Fig. 2 a, b, c). For our patients the parameters to desired dose distribution included dose uniformity 95% to the PTV and limits of 70–80% to the rectal and bladder wall, respectively.

Using the Beams Eye View (Fig. 3) display, the four-field pelvis blocks are designed to encompass the prostate, seminal vesicles (Fig. 4 a, b).

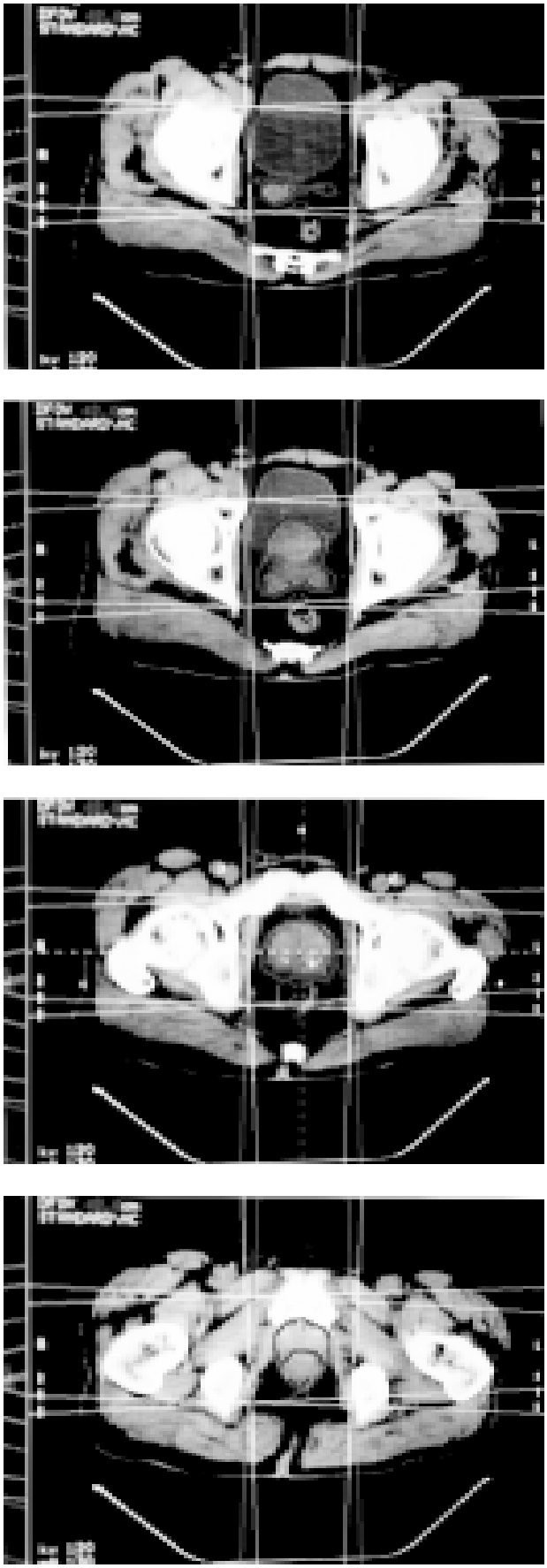

Fig. 1. Typical target volume delineation in four-field treatment technique

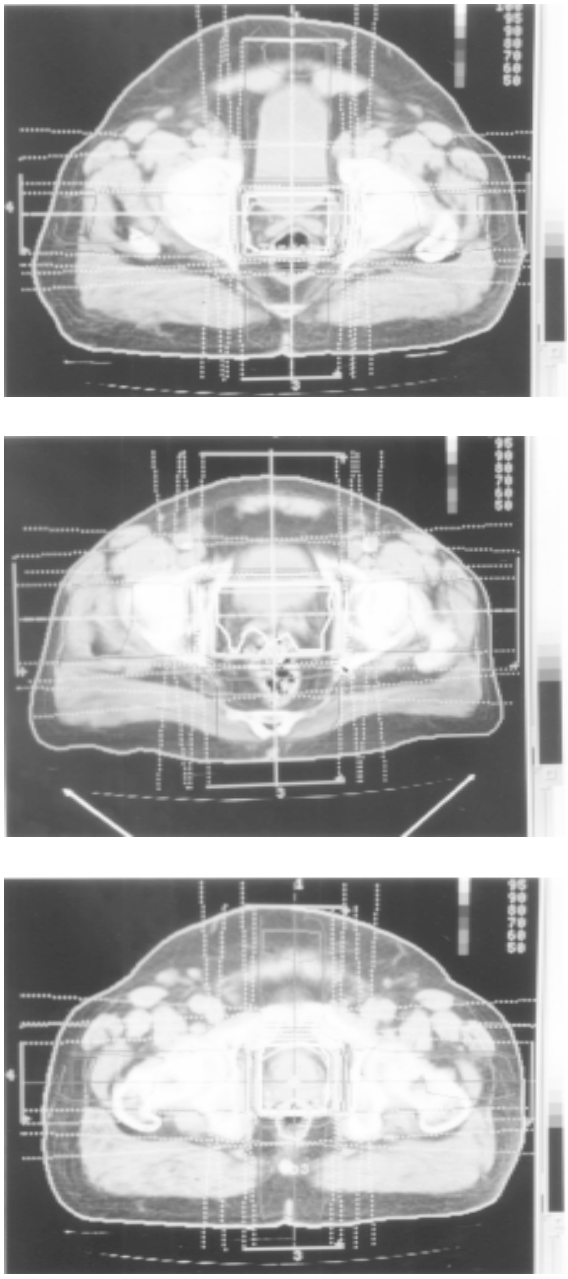

Fig. 2. Three-dimentional dose distribution for the standard four-field technique in the treatment of prostate cancer

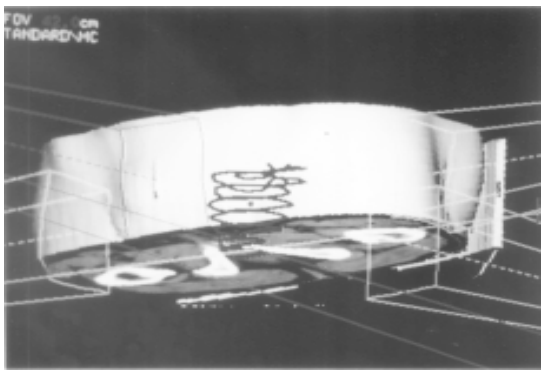

Fig. 3. Standard three-dimensional beams-eye view of representing structures and fields of irradiation

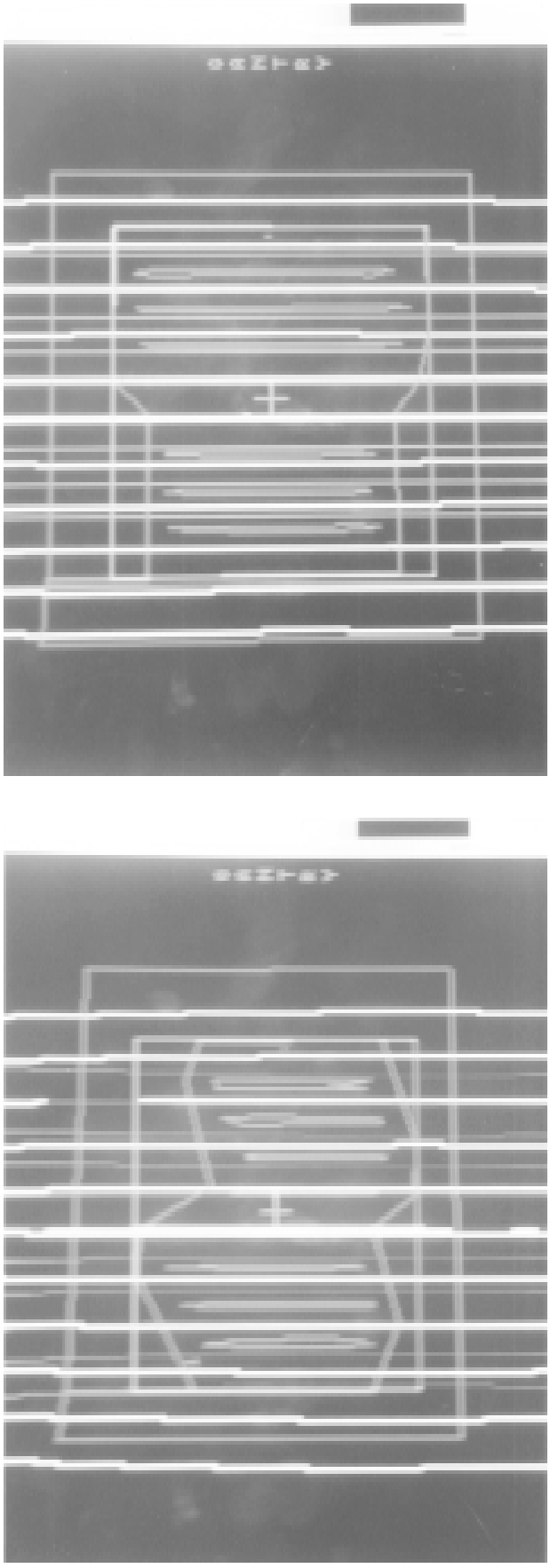

Fig. 4. Digitally reconstructed anterior-posterior and lateral treatment fields for prostate patients

RESULTS

Short-term results of 36 patients are available. All patients completed neoadjuvant hormonal therapy as planned. The average duration of neoadjuvant hormone therapy was 8 months. Treatment was not interrupted for hormone toxicity. However, at the end of radiotherapy 8 patients refused hormone, for the reason of adverse effects. The common manifestations were hot flushes, gynecomastia and liver disfunction.

After radiotherapy the prostate volume was measured repeatedly. Prostate volume measured by ultrasound or CT decreased in 35 patients, on average by 30% (from 74.7 ± 6.5 to 52 ± 3.9 ml). These values are statistically reliable ($p = 0.012$).

Serum PSA concentration decreased in all patients (from 28.8 ± 5.3 ng/ml to 6.9 ± 4.3 ng/ml). Data on the time to PSA progression were available for all patients. Progression was observed in 8 patients from 36 (22%). The mean time to PSA progression was 17 months.

Acute 1–2 grade radiotherapy reactions were observed in 23 pts (64%). No patients were observed to have acute grade 3–4 toxicity from radiotherapy. Most frequent acute 1–2 grade reactions were cystitis, dysuria, diarrhoea (Table 5).

In the follow-up period late complications (hydronephrosis, radiation ulcer of urinary bladder or rectum) were observed in 6 pts (16%). Grade 3–4 late reactions were observed in 3 from 21 pts (14%) when the total dose was ≤65 Gy and in 3 from 12 pts (20%) when the total dose was ≥66 Gy. Ulcer cystitis was reliably more frequent when the total dose was ≥66 Gy ($p = 0.03$) (Table 6).

Table 5. **Acute adverse effects developed after radiotherapy**

Doses, Gy	Acute reactions				
	Cistitis (pts)	Rectitis (pts)	Both (pts)	Total (pts)	%
≤ 65	8	1	2	11	52
≥ 66	8	–	4	12	80
Total	16	1	6	23	

Table 6. **Late complications developed after radiotherapy**

Doses, Gy	Late complications			%
	Ulcerus v. urinariae	Ulcerus rectum	Total	
≤ 65	2	1	3	14
≥ 66	2	1	3	20
Total	4	2	6	

Local tumour control was achieved in all (100%) patients. In the follow-up period metastases were determined in 6 pts and local progression in 2 pts. Time to progression was 18 ± 1.9 months ($p = 0.0015$).

Follow-up

Patients were seen every 3 months for the first year and later after 4–6 months. At each visit the patients had a history and physical examination which included routine blood work, a rectal digital examination as well as prior estimation for the PSA.

X-rays and bone scans were done as indicated symptomatically. Routine prostate biopsies were not done. The median follow-up was 14 months with the range 6 to 26 month.

Relapse was defined as a clinical or radiological evidence of progressive disease. Elevated levels of PSA were also taken as an evidence of local or distant relapse. Local failure was defined as a clinical evidence of progressive disease in the prostate or pelvic nodes more than 6 months after radiotherapy. Distant relapse was determined by clinical or radiographic evidence of haematogenous metastases.

Disease-free survival was calculated with respect to presence or absence of abnormal PSA levels.

DISCUSSION

This report is the first in Lithuania and demonstrates the clinical implementation of 3D-conformal radiotherapy in a small group of patients with localized prostate cancer. The patients enrolled in our study had local carcinoma of the prostate and were treated with curative intent.

Now this treatment method replaces conventional radiotherapy. The main advantages of such a treatment in prostate cancer are the better delineation of target volume and organs at risk. In this way radiation dose conforms better to the tumour and it is possible to increase the dose to the tumour (10).

The use of 3D conformal radiotherapy with neoadjuvant hormonal therapy was motivated by the hope that hormonal therapy could “de-bulk” the tumor volume (11, 12).

In our group, early and late side effects of treatment were evaluated. The toxicity was evaluated according to the RTOG morbidity scale. The average total dose prescribed to the target volume was 66 Gy. In each case we kept the total dose below 60 Gy to 35% of the rectum volume.

Generally, we used fields that encompassed the prostate and seminal vesicles and pelvis lymph nodes. Only 12 of 36 patients were irradiated without

pelvic elective fields in the first part of treatment. Probably the application of large fields is one of the most important factors responsible for the fact that we observed more side effects (64%) of our treatment. The most pronounced side effects were dysuria, increased frequency of urination, diarrhoea, ulcerus.

Doses above 70 Gy significantly increased local tumor control. A relationship has been shown between control of the tumor in the prostate by radiotherapy and decreased risk of metastases (13). In our cases 15 patients received total doses over 68 Gy (69–74 Gy), 21 patients received doses of 63–67 Gy.

It may be desirable to escalate the radiation dose to 70 Gy and beyond, but the price for such an increased dose is an increased number of complications. The blader and the rectum are the two dose-limiting structures that abut the prostate. Delivering doses beyond 70 Gy doubled the rate of serious complications from slightly over 6% (14).

For rectal complications, the RTOG has noted a strong dose dependence. Rectal injury revealed a dose-related 60% 2-year incidence of moderate or severe proctitis among patients treated beyond 75 Gy. Thus, most clinicians are fearful of exposing the prostate to beyond 70 Gy and many limit their dose to 65 Gy to avoid serious morbidity (15). In our analysis we determined late complications in 6 patients (16%).

Such a high rate of complications could be provoked by an increased dose to urinary bladder and rectum caused by using comparable large boost fields, in which seminal vesicles and lymph nodes were included (16).

CONCLUSIONS

In this work we discuss only early treatment results and observed side effects during the course of radiotherapy. In conclusion, the only clear consensus about the effect of 3D conformal radiotherapy in our study are the commonly observed reduction of prostate volume and a high rate of late complications with increasing the total doses.

Because there is a strong relation among tumor volume, seminal vesicle invasion and metastases, it might be that the benefit of combined treatment, if any, lies in decreasing the prostate volume and a more precise dosage of radiotherapy, resulting in better local control and possibly also in a shorter time to progression and survival.

The follow-up is still too short to allow a definitive conclusion about 3D conformal radiotherapy with respect to biochemical progression, disease-free and overall survival. Further studies are necessary to define the exact positive role of hormonal therapy with 3D conformal radiotherapy. With increasing numbers of patients we will be able to evaluate the real significance of neoadjuvant hormonal therapy.

Received 10 April 2002
Accepted 30 May 2002

References

1. Kurtinaitis J, Aleknavičienė B, Tamašauskienė J. Pagrindiniai onkologinės pagalbos rezultatai Lietuvoje. 2001: 1–39.
2. J. A. del Regato et al. Twenty-year follow-up of patients with inoperable cancer of the prostate (stage C) treated by radiotherapy: report of a national cooperative study. Inter J Rad Oncol Biol Phys 1993; 23(2): 197–210.
3. Clinical experience with intensity-modulated radiation therapy (IMRT) in prostate cancer. Radiat Oncol 2000; 55(3): 241–9.
4. Vaillancourt L, Tetu B, Fradet Y et al. Effects of neoadjuvant randomise therapy combined androgen blockade on normal prostate and prostatic carcinoma. Am J Surg Pathol 1996; 20: 86–93.
5. Prezioso D et al. Role of neoadjuvant treatment in clinically confined prostate cancer. Eur Urol 1999; 35: 17–22.
6. Pilepich MV et al. A derivation with radiation therapy alone for locally advanced prostatic cancinoma: a randomised comparative trial of the radiation therapy oncology group. Urology 1995; 45: 616–23.
7. Holtzman M, Carlton CE, Scardino PT. The frequency and morbidity of local recurrence after definitive radiotherapy for stage T3 prostate cancer. J Urol 1991; 146: 1578–82.
8. Kiricuta IC et al. Target volume definition in radiation oncology 2001: 143–82.
9. Perez CA. Principles and Practice of Radiation Oncology. 3rd ed. 1998: 1617.
10. Zelefsky MJ, Leibel SA, Kucther GJ, Fuks Z. Three-dimensional conformal radiotherapy and dose escalation: where do we stand? Semin Radiat Oncol 1998; 8: 107–14.
11. Zelefsky MJ, Leibel SA, Gaudin PB et al. Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. Int J Radiat Oncol Biol Phys 1998; 41: 491–50.
12. Pollack A, Zagars GK, Rosen II. Prostate cancer treatment with radiotherapy: maturing methods that minimize morbidity. Semin Oncol 1999; 26: 150–61.
13. Labrie F, Dupont A, Cussan L et al. Downstaging of localized prostate cancer by neoadjuvant therapy with flutamide and Lupron: the first controlled and randomized trial. Clin Invest Med 1994; 16: 499–509.
14. Van Poppel H, de Ridder D, Elgamal AA et al. Neoadjuvant hormonal therapy before radical prostatectomy decreases the number of positive surgical margins in stage T2 prostate cancer: interim results of a prospective randomized trial: the Belgium Uro-Oncological Study Group. J Urol 1995; 154: 429–34.

15. Perez CA, Pilepch MV, Garcia D et al. Definitive radiation therapy in carcinoma of prostate: experience at Mallinckrodt Institute of Radiology. NCI Monogr 1988; 7: 85–94.
16. Hanks GE, Martz KL, Diamond JJ. The effect of dose on local control of prostate cancer. Int J Radiat Oncol Biol Phys 1988; 15: 1299–306.

E. Aleknavičius, B. Aleknavičienė, F. Jankevičius, M. Grybauskas

YPATINGAI TIKSLI PROSTATOS VĖŽIO SPINDULINĖ TERAPIJA PANAUDOJANT TRIMATĮ (3D) PLANAVIMĄ: PRELIMINARŪS REZULTATAI

S a n t r a u k a

Prostatos vėžio atvejų pastaraisiais metais Lietuvoje sparčiai daugėja. Pagrindiniu prostatos vėžio gydymo metodu lieka radikali spindulinė terapija. Šiuo metu plačiai naudojamos standartinės spindulinės terapijos metodikos turi nemažai trūkumų, kurie nebeleidžia toliau gerinti tiesioginius ir atokius prostatos vėžio spindulinio gydymo rezultatus.

Tolimesnis progresas galimas tik panaudojus naujausias ligonių paruošimo švitinimui ir švitinimo technologijas. Šio tyrimo tikslas buvo įvertinti naujas spindulinės terapijos galimybes panaudojant gydymui šiuolaikinę trimatę spindulinės terapijos sistemą bei linijinį greitintuvą.

Naujas spindulinės terapijos metodas leidžia daug tiksliau apibrėžti planuojamus apšvitinti audinių tūrius, padidinti švitinimo dozes, apsaugoti sveikus aplinkinius audinius. Tai pirmas bandymas Lietuvoje pritaikyti prostatos vėžio gydymui šiuolaikines švitinimo technologijas ir atlikti preliminarų gydymo rezultatų įvertinimą.

Neblogi tiesioginiai gydymo rezultatai teikia daug vilčių, tačiau palyginti nedidelis ligonių skaičius ir trumpas stebėjimo laikas neleidžia įvertinti gydymo efektyvumo. Būtinas tolimesnis ligonių stebėjimas ir atokių gydymo rezultatų įvertinimas.

Raktažodžiai: prostatos vėžys, spindulinė terapija, spindulinės reakcijos