ARTICLE Libri Oncol., Vol. 34 (2006), N^{o} 1-3, 13 – 18

THE FIRST EXPERIENCE WITH THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY FOR PROSTATE CANCER IN THE UNIVERSITY HOSPITAL FOR TUMORS IN ZAGREB

MLADEN SOLARIĆ and MIRKO ŠAMIJA

Department of Radiation Therapy, University Hospital for Tumors, Zagreb, Croatia

Summary

Three-dimensional (3D) conformal radiation therapy is a standard of care in prostate cancer patients. It is delivered in either adjuvant or salvage setting, and only occasionally as palliative treatment. The University Hospital for Tumors in Zagreb, Croatia introduced the technique in November 2005.

During the introductory period of six months, 3D-conformal radiotherapy was given to 86 prostate cancer patients, the majority of them with primary prostate cancer (60.47%). Only 4 patients received palliative treatment, and the remaining 30 were administered post-surgical (adjuvant or salvage) radiotherapy. The paper presents characteristics of patients and their treatment. The median duration of irradiation planning was 17.5, 15 and 13 days for primary, adjuvant and salvage radiotherapy, respectively. A radiation dose exceeding 70 Gy was delivered to 48 (92.31%) of primary irradiated patients with the median dose of 76 Gy. The median dose in both adjuvant and salvage irradiated patients was 10 Gy lower. The standard box technique was applied in 98.91% of patients. Treatment took longer than anticipated for the median of 10 days at primary and adjuvant radiotherapy, and for 15 days at salvage radiotherapy. Acute urinary and rectal side effects of radiation were reported in 22.54% and 23.94% of patients, respectively.

The first experiences show the feasibility of 3D-conformal radiation therapy for prostate cancer patients at the University Hospital for Tumors. The complexity of the procedure, non-existence of a unique algorithm, and also heavy linac workload are the reasons for the relatively long irradiation planning. Longer treatment is less a result of side effects than of occasional problems with linear accelerators. The low rate of early side effects primarily results from a retrospective study and incomplete records of radiotherapy side effects.

KEY WORDS: *prostate cancer, 3D-conformal radiotherapy, dose escalation, toxicity*

PRVA ISKUSTVA S TRODIMENZIJSKOM KONFORMALNOM RADIOTERAPIJOM U LIJEČENJU RAKA PROSTATE U KLINICI ZA TUMORE U ZAGREBU

Sažetak

Trodimenzijska konformalna radioterapija predstavlja standard u primarnom liječenju bolesnika s rakom prostate. Primjenjuje se i pri adjuvantnoj i tzv. radioterapiji 'spasa' (engl. salvage), a u palijativnom zračenju tek sporadično. U Klinici za tumore u Zagrebu ova je tehnika uvedena u studenom 2005. godine.

Tijekom prvog šestomjesečnog razdoblja trodimenzijska konformalna radioterapija započela je u 86 bolesnika s rakom prostate. Većinom se radilo o primarnom liječenju raka prostate (60,47%). Tek je u 4 bolesnika provedeno palijativno liječenje, dok je u ostalih 30 bolesnika provedena poslijeoperacijska radioterapija (adjuvantna ili terapija 'spasa'). Prikazane su osobine bolesnika i provedenog liječenja. Medijan trajanja pripreme zračenja iznosio je 17,5 dana pri primarnoj, 15 dana pri adjuvantnoj te 13 dana pri radioterapiji 'spasa'. Dozu zračenja veću od 70 Gy primilo je 48 (92,31%) primarno zračenih bolesnika uz medijan doze od 76 Gy. Medijan doze adjuvantno zračenih bolesnika i onih koji su primali radioterapiju 'spasa' bio je za 10 Gy niži. Standardna «box» tehnika zračenja primijenjena je u 98,91% bolesnika. Liječenje je trajalo duže od predviđenog za medijan 10 dana pri primarnoj i adjuvantnoj te 15 dana pri radioterapiji 'spasa'. Akutne urinarne nuspojave zračenja zabilježene su u 22,54%, a od strane rektuma u 23,94% bolesnika.

Prva iskustva upućuju na provedivost trodimenzijske konformalne radioterapije u bolesnika s rakom prostate u Klinici za tumore. Složenost postupka, nepostojanje jedinstvenog algoritma, no i opterećenost uređaja za zračenje razlozi su relativno dugog trajanja pripreme za zračenje. Duže trajanje liječenja od predviđenog manje je posljedica nuspojava nego povremenih kvarova linearnih akceleratora. Zabilježena mala pojavnost ranih nuspojava temeljno je posljedica retrospektivne studije i nepotpunog bilježenja nuspojava u kartone zračenja.

KLJUČNE RIJEČI: *rak prostate, 3D-konformalna radioterapija, pojačavanje doze, toksičnost*

INTRODUCTION

Three-dimensional radiation therapy is an irradiation technique with the profile of photon beams conforming exactly to the shape of the target volume, and thus achieving better protection of surrounding tissues. Therefore, the technique enables the delivery of either the same irradiation dose as with conventional radiotherapy but causing fewer side effects, or a higher irradiation dose that cannot be delivered with conventional radiotherapy.

Since starting some 15 years ago, three-dimensional radiation therapy has been administered to patients with prostate cancer. Experiences are numerous, and this indication region has been considered the most explored with regard to this technique. The literature reports a few randomized studies investigating early (acute) and late radiation side effects and the efficacy of radiation therapy for disease control. Two randomized studies showed the same irradiation dose delivered with the 3D-conformal technique produced less early (acute) rectal side effects compared to conventional radiotherapy (1, 2). Raising the dose to the prostate from 68 Gy to 78 Gy using 3D-conformal radiotherapy did not result in higher incidence of early side effects (3). Deanaley et al. showed that the same dose of conformal radiation was associated with lower incidence of late rectal side effects compared to the conventional technique (3). Raising the radiation dose, however, was accompanied with a higher incidence of late side effects in spite of better preservation of the surrounding tissue. A number of phase II studies showed the validity of raising the dose related to the treatment efficacy. Two randomized studies justified raising the radiation dose to 78 Gy, or 79.2 Gy with a higher survival rate without signs of the disease (4, 5). The above was the reason for accepting 3D-conformal radiotherapy with radiation doses over 72 Gy as standard in primary radiotherapy for prostate cancer (6).

In 2005, the University Hospital for Tumors in Zagreb, Croatia acquired the equipment to perform 3D-conformal radiotherapy. Irradiation of prostate cancer patients showed to be an adequate model for introducing new irradiation techniques. The reason for it has been a vast experience and rationale for implementing 3D-confromal radiation therapy for prostate cancer, and also an increased number of prostate cancer patients referred for radiation treatment to the University Hospital. The number of patients with prostate cancer referred for radiation treatment increased six-fold during the last 10 years. The increase is primarily based on a 10-fold increased number of patients referred for primary radiotherapy (Graph 2).

This paper shows our first experiences with three-dimensional conformal radiation therapy for patients with prostate cancer.

MATERIAL AND METHODS

A retrospective study was done on prostate cancer patients who were referred for radiotherapy to the University Hospital over a six-month period and received 3D-conformal radiotherapy for their disease.

Data about patients and treatment procedure were collected from their radiotherapy records. Radiotherapy records of prostate cancer patients who previously did not receive radiation therapy and were referred for radiotherapy planning in the period from November 1, 2005 to April 30, 2006 were singled out. The study shows prostate cancer patients receiving 3D-conformal radiotherapy. The first such treated patient started radiation therapy on November 8, 2005, and was also the first patient in the Republic of

Croatia treated with the three-dimensional conformal technique.

The process of radiotherapy planning started with simulation on a simulator-based CT system, specifically modified for planning of radiotherapy treatment, which in the University Hospital for Tumors is SOMATOM Sensation Open (Siemens). During simulation, a silicon catheter was inserted into the patient's rectum, contrast urethrogram was made and for the spatial reference point position three skin marks were used. CT images were transferred to the computer system to perform contouring of target volumes and risk organs: FocalSim (CMS) and Coherence Dosimetrist (Siemens). Using one of these two softwares, the physician contoured prostate, seminal vesicles and, if applicable, pelvic lymph nodes, urinary bladder, and rectum. In patients undergoing primary radiotherapy, the clinical target volume (CTV) complied with the prostate with or without seminal vesicles and pelvic lymph nodes. In prostatectomized patients, CTV contours were based on their earlier position of the prostate and seminal vesicles. The planning target volume (PTV) was obtained using three-dimensional enlargement of CTV for 0.8 – 1.2 cm margin. The isodose plan was made using the computer software for 3-dimensional planning XiO (CMS). The majority of patients received irradiation treatment with 4 coplanar, perpendicular photon beams, X15MV or X18MV, using the box technique. CTV encompassed the 95% isodose line, ant the maximum dose to CTV was up to 107% compared to the prescribed dose. Based on the isodose plan, the spatial isocenter position and its position in relation to the reference point were defined. The isocenter position was marked with three skin marks using movable laser systems. Radiation treatment was delivered by linear accelerators Mevatron (Siemens) and Primus (Siemens) using a multi-leaf collimator.

The patients were divided in 4 groups related to the modality of radiation treatment applied: primary (radical), adjuvant, salvage and palliative radiotherapy. Pretherapy parameters included: patient age, time period between diagnosis or prostatectomy and initiation of radiotherapy, PSA levels, Gleason score, and stage of the disease. In patients receiving primary and palliative radiation treatment, PSA levels were recorded before the start of therapy (including hormone therapy), while in patients receiving radiotherapy after prostatectomy, PSA levels were recorded before the start of radiotherapy. In patients receiving primary and palliative radiation treatment, the stage of the disease was assessed at digital rectal examination (DRE) and/or transrectal ultrasound of the prostate, computerized tomography of the pelvis and bone scintigraphy for patients with PSA levels exceeding 10 ng/ml. In patients receiving radiation therapy after prostatectomy, the stage of the disease was assessed upon their pathological finding. The therapy procedure was outlined using target volume analysis, irradiation dose, irradiation technique, duration of irradiation planning, use of hormone therapy, and early (acute) side effects using the RTOG scoring system (7).

Numerical data were reported as a percent share or median value (range).

RESULTS

In the six-month period, the planning of 3D-conformal radiotherapy was initiated in 86 patients with prostate cancer. The planning for primary, adjuvant, salvage and palliative radiation treatment was done for 52 (60.47%), 13, 17 and 4 patients, respectively. In view of their small number, the study excluded patients un-

Table 1.

BASELINE AND TREATMENT CHARACTERISTICS

	Primary radiotherapy	Adjuvant radiotherapy	Salvage radiotherapy
Patient age (range)	73 years (57 – 79)	64 years (56 – 74)	67 years (50 – 75)
PSA (range)	10.96 ng/ml* (3,2 – 427,47)	0.03 ng/ml (0 – 0,22)	1 ng/ml (0 – 9.58)
Gleason score (range)	7 (3 – 9)	7 (5 – 9)	7 (3 – 10)
Median duration of radiotherapy planning (range)	17.5 days (1 - 52)	15 days (0 - 48)	13 days (4 - 51)
Median departure from planned treatment duration (range)	10 days (-4 – 29)	10 days (1 – 23)	15 days (0 – 39)
Radiation dose (range)	76 Gy (68 – 78)	66 Gy (64 – 70)	66 Gy (66 – 74)

* PSA level before potential hormone therapy

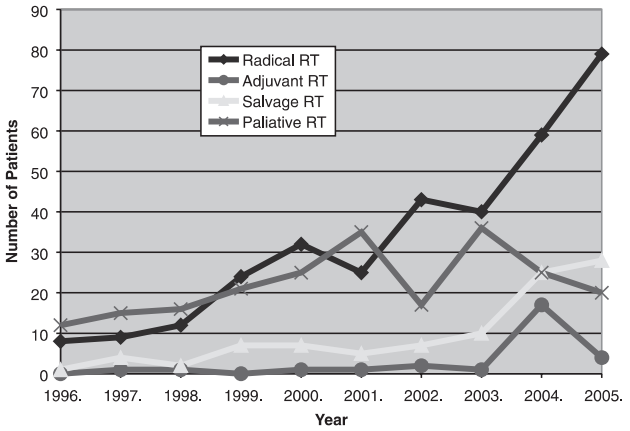

Figure 1. Prostate cancer patients undergoing radiation treatment at the University Hospital for Tumors in Zagreb, Croatia in the ten-year period

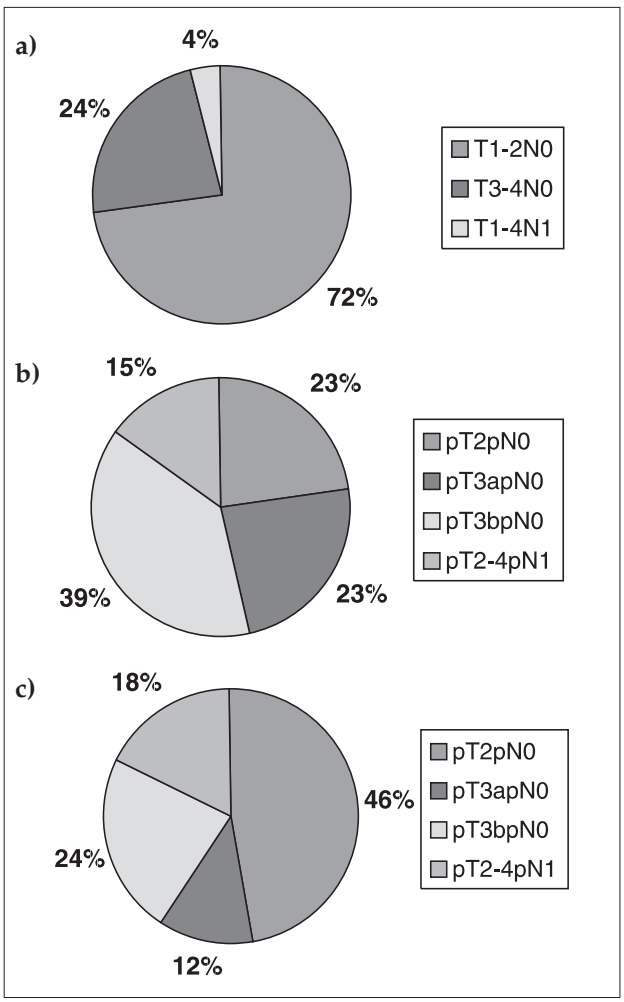

Figure 2. TNM stage distribution in patients receiving primary (a), adjuvant (b) and salvage (c) radiation therapy

dergoing palliative treatment. By July 1, 2006, 71 patients (82.56%) completed their radiotherapy treatment.

Patient age, PSA levels and Gleason score are shown in Table 1. Graph 2 shows the distribution of patients with regard to the stage of the disease. Hormone therapy before the start of radiation treatment was administered to 33 (63.46%) patients receiving primary radiotherapy, 4 (30.77%) patients undergoing adjuvant and 4 (23.53%) patients receiving salvage radiation therapy. All of these patients continued with hormone therapy, consisting of orchidectomy or use of LH-RH agonists and/or antiandrogens, during their course of radiotherapy. Tumor-positive resection margin was reported in 11 (84.62%) and 4 (23.53%) patients undergoing adjuvant and salvage radiation treatment, respectively. Nadir PSA levels over 0.3 ng/ml were reported after prostatectomy (residual disease) in 4 (23.53%) patients receiving salvage radiation treatment. The median interval between prostate biopsy and the onset of primary radiotherapy was 111 days (range 40-1,547 days). In adjuvantly irradiated patients, the median interval between prostatectomy and the onset of radiation treatment was 117 days (range 81-203 days). In 2 (15.38%) patients, adjuvant radiotherapy started more than 6 months after prostatectomy. The median interval between prostatectomy and the onset of radiotherapy in patients receiving salvage treatment was 669 days (range 85-1,394 days).

The duration of radiotherapy planning, applied irradiation dose, and departure from planned treatment duration are given in Table 1. The irradiation dose exceeding 70 Gy was delivered to 48 (92.31%) primarily irradiated patients. In 83 patients, radiation treatment was applied using the box technique. In only one patient, the treatment was done using slanted beams to avoid the hip endoprosthesis. In 27 (51.92%) primarily irradiated patients, the target volume included only the prostate, and in other patients, radiation treatment was delivered to the prostate and seminal vesicles. In 12 (23.08%) patients, additional irradiation was applied also to pelvic lymph nodes. The target volume encompassed pelvic lymph nodes in 2 (15.38%) adjuvantly treated patients and in 4 (23.53%) patients receiving salvage radiotherapy. Long-term hormone therapy

after primary radiotherapy was prescribed for 26 (50%) patients. In 4 patients, this therapy was prescribed without previous neoadjuvant hormone therapy and hormone therapy during the course of radiotherapy.

The early side effects of radiotherapy were studied in all patients after the completion of radiotherapy. In 55 (77.46%) patients, no early urinary side effects were reported. Side effects of RTOG grade 2 and 3 were reported in one and two patients, respectively. In these 2 patients, radiotherapy was temporarily discontinued and the patients were hospitalized for the side effects. Other patients developed mild urinary side effects that did not require any treatment. In 54 (76.06%) patients, no rectal reactions were reported. Side effects RTOG grade 1, 2 and 3 were reported in 13 (18.31%), 3 and only 1 patient, respectively.

DISCUSSION

The study results show that the implementation of 3D-conformal radiotherapy at the University Hospital for Tumors in Zagreb started in a heterogenous group of prostate cancer patients. The majority of patients received primary radiotherapy which complies with the reported tendency towards increased incidence of prostate cancer in the last 10 years.

The median age of primarily irradiated patients was for 9 years greater compared to the median age of the adjuvantly irradiated, showing that the indication for primary radiotherapy is made in the older age group compared to prostatectomy patients. The median Gleason sum of 7 was reported in all patient groups. PSA levels before adjuvant and salvage radiation treatment are incomparable with PSA levels before the onset of treatment in primarily irradiated patients, as such levels are a result of previous prostatectomy with or without signs of biochemical recurrence. The median PSA levels at adjuvant and salvage radiotherapy show the adequate patient selection. The majority of primarily irradiated patients had locally restricted disease. However, the majority of patients receiving adjuvant radiation treatment presented with locoregionally advanced disease. In the group receiving salvage radiotherapy, the share of patients with locally restricted and those with locoregionally advanced prostate cancer was about the same. The validity of adjuvant and salvage treatment is questionable in about 15% patients with the involvement of pelvic lymph nodes. The time interval between biopsy and the onset of irradiation was almost 4 months, equaling the time interval between prostatectomy and the onset of adjuvant radiotherapy. Unlike adjuvant and salvage radiotherapy, the majority of primarily irradiated patients were administered neoadjuvant hormone therapy that continued during the course of radiotherapy. The delay of irradiation onset for patients undergoing primary radiotherapy resulted from neoadjuvant hormone therapy, relatively long irradiation planning and limited availability of the radiotherapy device. In 15% of patients receiving adjuvant radiotherapy, the treatment started more than 6 months after prostatectomy, which is considered optimal. In about 85% of the adjuvantly irradiated, the resection margin was positive, which along with the signs of locoregionally advanced disease justify the treatment option. The time interval between prostatectomy and the onset of salvage radiotherapy was less than 2 years, partially due to the fact that about ¼ of the patients were treated for residual disease. In other patients, however, biochemical recurrence after prostatectomy was reported very early, associating them with a very unfavorable prognosis.

The median duration of radiotherapy planning was 13–17 days depending on the patient group. This can be explained by the complexity of the planning procedure for 3D-conformal radiotherapy. However, a very broad range of radiotherapy planning time of 52 days was recorded. This was due to non-existence of a unique algorithm for radiotherapy planning and the limited linac capacity, therefore a part of the patients had to wait before their onset of treatment. The median dose at primary radiotherapy was for 10 Gy higher compared to adjuvant and salvage radiotherapy. In spite of the relatively broad dose range, 85% of primarily irradiated patients received a higher dose up to 72 Gy. The standardized irradiation technique was used, except in case of inability to perform the procedure. In about 50% of primarily irradiated patients, the target volume encompassed the prostate alone,

while in about 25% of the patients, radiotherapy treatment was delivered also to pelvic lymph nodes. The nodes were, with about equal frequency, encompassed at salvage radiotherapy, and very rarely at adjuvant radiotherapy. The total duration of radiation treatment was longer than initially planned in more than 85% of the patients; in 18.33% of them, the prolongation of radiation treatment time was less than 7 days, which is considered radiobiologically acceptable. The longest median prolongation of radiation treatment was reported for salvage radiotherapy. Except for a few cases of severe acute reactions, the prolongation of treatment time resulted from occasional equipment breakdowns. Due to unfavorable prognostic factors, hormone therapy of up to 2 years after radiotherapy was recommended to 50% of primarily irradiated patients. In 15% of them, hormone therapy started only after the completion of radiotherapy, while others continued to receive the hormone treatment that had been initiated before the onset of radiotherapy. In other groups, the continuation of hormone therapy after the completion of radiotherapy was not recommended.

The acute side effects of radiation treatment were reported in only about 25% of the patients, which is significantly less than 75% reported in the literature (3). Of them 2.38% developed severe urinary side effects that required temporary discontinuation of radiation treatment and hospitalization. The low incidence of acute side effects can be explained by data collection methods and the retrospective nature of this study. As the source of information was radiotherapy records not including all radiotherapy side effects, the data cannot be considered completely reliable.

CONCLUSIONS

The first experiences with 3D-conformal radiotherapy show that the treatment procedure is feasible for prostate cancer patients in the University Hospital for Tumors. The complexity of the procedure, non-existence of a unique algorithm, and also heavy linac workload are the reasons for the relatively long irradiation planning. Longer treatment is less a result of side effects than of occasional problems with linear accelerators. The low incidence rate of early side effects primarily results from a retrospective study and incomplete irradiation side effect records.

REFERENCES

1. Dernaley 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
2. Koper PC, Jansen P, van Putten W, et al. Gastro-intestinal and genito-urinary morbidity after 3D conformal radiotherapy of prostate cancer: observations of a randomized trial. Radither Oncol 2004; 73: 1-9
3. Peeters STH, Heemsbergen WD, van Putten WLJ, et al. Acute and late complications after radiotherapy for prostate cancer: results of a multicenter, randomized trial comparing 68 Gy to 78 Gy. Int J Radiat Oncol Biol Phys 2005; 61: 1019-34
4. Pollack A, Zagars GK, Starkschall G, et al. Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. Int J Radiat Oncol Biopl Phys 2002; 53: 1097-105
5. Zietman AL, DeSilvio ML, Slater JD, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate. JAMA 2005; 294: 1233-9
6. Morris DE, Emami B, Mauch PM, et al. Evidence-based review of three-dimensional conformal radiotherapy for localized prostate cancer: an ASTRO outcome initiative. Int J Radiat Oncol Biol Phys 2005; 62: 3-19
7. Cox JD, Stetz JA, 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

Author's address: Mladen Solarić, MD, Dept. of Radiation Oncology, University Hospital for Tumors, Ilica 197, 10 000 Zagreb, Croatia