# HORMONAL THERAPY AND 3D CONFORMAL RADIOTHERAPY IN PROSTATE CANCER: EARLY TOXICITY OF COMBINED TREATMENT

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## SUMMARY

**Purpose:** to evaluate acute toxicity of combined treatment (androgen ablation and high-dose 3D conformal radiotherapy [3D-CRT]) in patients with a localized cancer of prostate.
**Materials and methods:** Between April 1999 and March 2000, at the Greatpoland Cancer Centre in Poznań, 22 patients with prostate cancer (T1-T3 N0 M0) were treated with 3 D conformal radiation therapy and hormonal therapy. Patients represented a localized disease (T1 = 4 patients, T2 = 11 patients), and locally disease (T3 = 7 patients). No patients had clinically detectable distant metastases. Neoadjuvant androgen ablation therapy (bilateral orchiectomy or LH-RH agonists and flutamide) was administered to all patients. Radiotherapy was performed using 15 MV photons in the daily fraction of 1.8 Gy to the total median dose of 70.2 Gy (range, 67.8 to 72 Gy). Acute toxicities were evaluated according to the Radiation Therapy Oncology Group morbidity scoring scale.
**Results**: All patients completed the entire course of radiotherapy and were assessable for evaluation of acute toxicities. The most common side effects of androgen ablation were "hot flushes" and gynecomastia, although these were mild. The main problems during irradiation and a few weeks after the completion of radiotherapy were related to:
- the genitourinary tract (urgency, nocturia, dysuria) with toxicities of grade 0 and 1 (80% of patients) and grade 2 (20% of patients),
- the gastrointestinal tract (rectal discomfort and mild diarrhea) with toxicities grade 0 and 1 (75% of patients) and grade 2 (25% of patients).

**Conclusions:** Preliminary results of combined treatment (androgen ablation and 3 D-CRT) have suggested that such modality is well tolerated with only modest acute toxicities of the gastrointestinal and genitourinary tracts.

**Key words:** prostate cancer, 3D radiotherapy, hormonal therapy, acute morbidity.

## INTRODUCTION

The number of diagnosed cases of prostate cancer is on the increase in Poland (the incidence rate for 1993 was 13.7 per 100.000 males and the mortality was 10.3 per 100.000) [1]. The five-year survival patients with prostate cancer stands now at 37% and is among the lowest in European countries, where the average 5-year overall survival is 55% [2].

The role of radiotherapy in the treatment of localized prostate cancer is well established, although there are still many controversies concerning its efficancy [3]. Three-dimensional conformal radiotherapy (3D-CRT) may lead to more favorable outcome in a localized stage of the cancer. For example, Hanks and al. [4] reported improvement of treatment outcomes from 48% to 79% based on the PSA as an indicator of biochemical relapse. Zelefsky et al. [5] with the increase in dose to 81 Gy, 18 months after the completion of radiotherapy achived normalisation of PSA in 99% of cases in T1/T2b stage, in 90% of cases in T2c stage and in 81% of cases

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in T3 stage. Since the 5-year, biochemical disease-free survival rate for 3D-CRT is similar to that for radical prostatectomy, early and late morbidities have become increasingly important in making decision concerning the treatment procedure.

Recently high-dose 3D conformal radiotherapy in conjunction with androgen depletion has been introduced at our department in an attempt to improve the results of treatment. The data from literature have shown that the outcome in patients treated with hormonal therapy and radiotherapy (combined treatment) were significantly better than radiotherapy treatment alone [6,7].

## PURPOSE

The aim of this study was to evaluate early toxicity of combined treatment: androgen ablation therapy (neoadjuvant, during irradiation and follow-up) and three-dimensional conformal radiotherapy (3D-CRT) in patients with prostate cancer.

## MATERIAL AND METHODS

Between April 1999 and March 2000, at the Greatpoland Cancer Centre in Poznań, 22 patients with prostate cancer (T1-T3N0M0) were treated with hormonal therapy and high-dose 3 D-CRT. The median age of patients was 68 years (range: 55-75 years). All patients had a histological diagnosis of prostate adenocarcinoma, but only some of patients were classified according to the Gleason scoring system. The average level of PSA before radiotherapy was 15 ng/ml (range, 4 to 60 ng/ml). No patients had clinically detectable distant metastases (negative bone scan, chest X-ray – without change). All of them suffered from a localized organ limited disease (T1 = 4 patients, T2 = 11 patients), and locally disease (T3 = 7 patients) and had their lymph nodes evaluated by computer tomography and ultrasonography. Only patients without any pathology in these examinations were treated with 3 D-CRT. We did not perform diagnostic lymphadenectomy of the pelvic lymph nodes. When a high risk of lymph nodes metastases was suspected a large pelvic fields encompassing regional nodes were included in treatment planning. Neoadjuvant androgen ablation therapy (orchiectomy or LH-RH agonists and flutamide) was administered to all patients. Orchiectomy was performed in 5 out of 22 patients. During and after completion of radiotherapy all patients received androgen depletion treatment (gosereline: 3.6mg/ 4 weeks). An average time of androgen ablation was 6 months (range: 3 to 12 months).

Simulation and treatment were performed in a supine position with a ”comfortable” full bladder. All patients had CT scanning of the pelvis in the treatment position. Images were obtained at 5 mm increments accross the treatment field. Patients were immobilized during simulation and irradiation with the individually immobilization cast. Radiotherapy was administered using 15 MV photons in a daily fraction of 1.8 Gy to the total median dose of 70.2 Gy (range: 67.8 to 72 Gy) prescribed at the isocenter (ICRU point). The planning target volume (PTV) was defined as the gross target volume and clinical target volume (GTV + CTV): the prostate and the seminal vesicles with 10 mm margins around the prostate except for the posterior margin (prostate - rectum interface) where a margin about 5 mm was used to decrease the risk of rectum morbidity. All plans consisted of anterior and two lateral fields. In case of T3 stage or PSA level higher than 20 ng/ml or Gleason score above 7, the elective irradiation of pelvic lymph nodes to the total dose of 45 Gy was introduced. In such cases in first phase of treatment four fields (box-technique) were used. We have checked the geometry of the irradiated fields by electronic portal imaging performed at the start of the treatment and than in 10 -day intervals. Examples of dose volume histograms (DVHs) of treatment plans for the prostate plus seminal vesicles are shown *in Figure 1*, and the prostate with seminal vesicles and elective pelvic irradiation is represented *in Figure 2*. In vivo dosimetry was performed for each patient at the beginning and the mid- of treatment. We did not observe any significant deviation between the planned and measured doses.

Acute reactions included those arising during the irradiation and others within

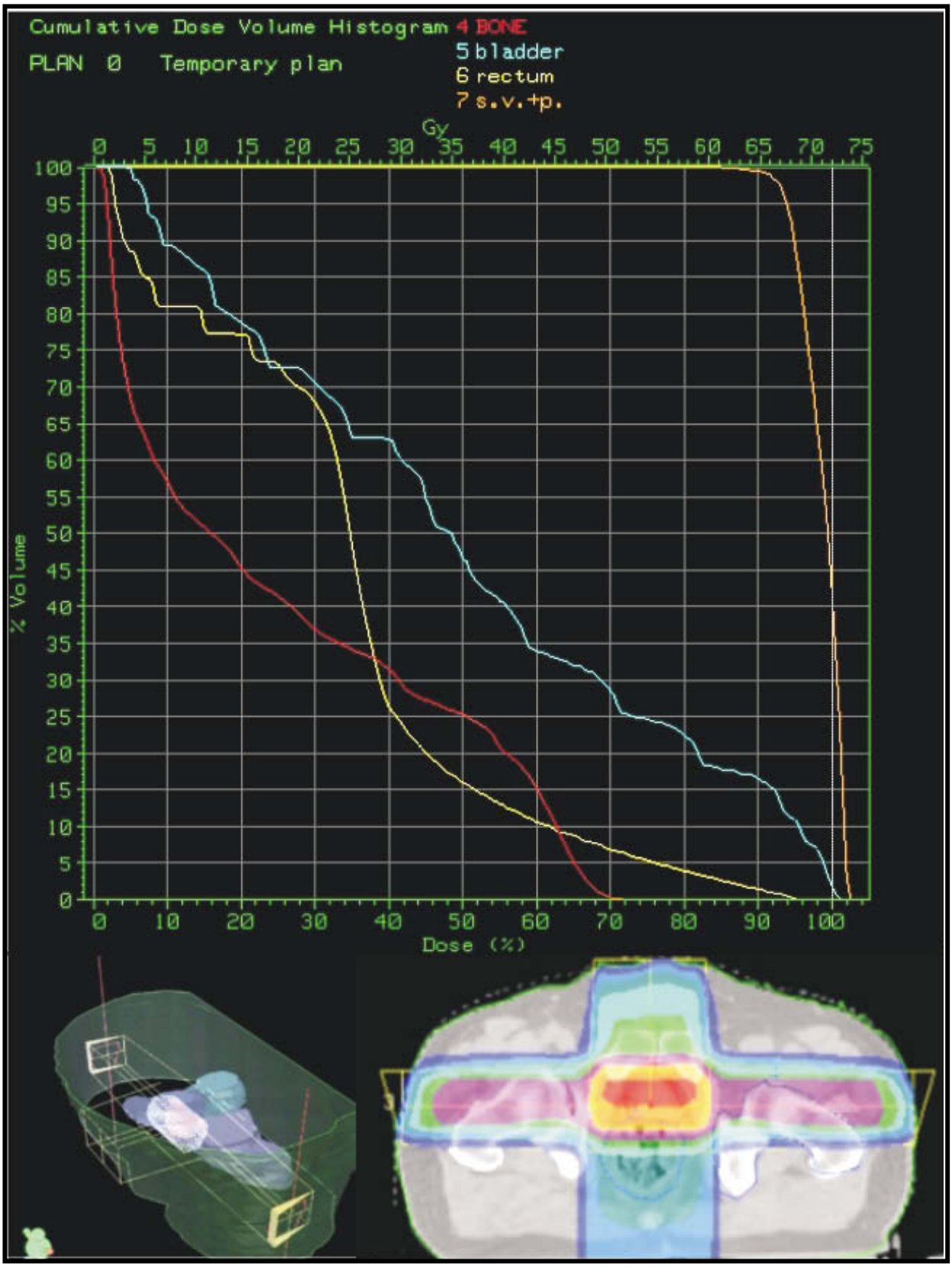


Fig. 1. Dose Volume Histograms for the three field technique which encompassed only the prostate and seminal vesicles to the total dose of 72 Gy.

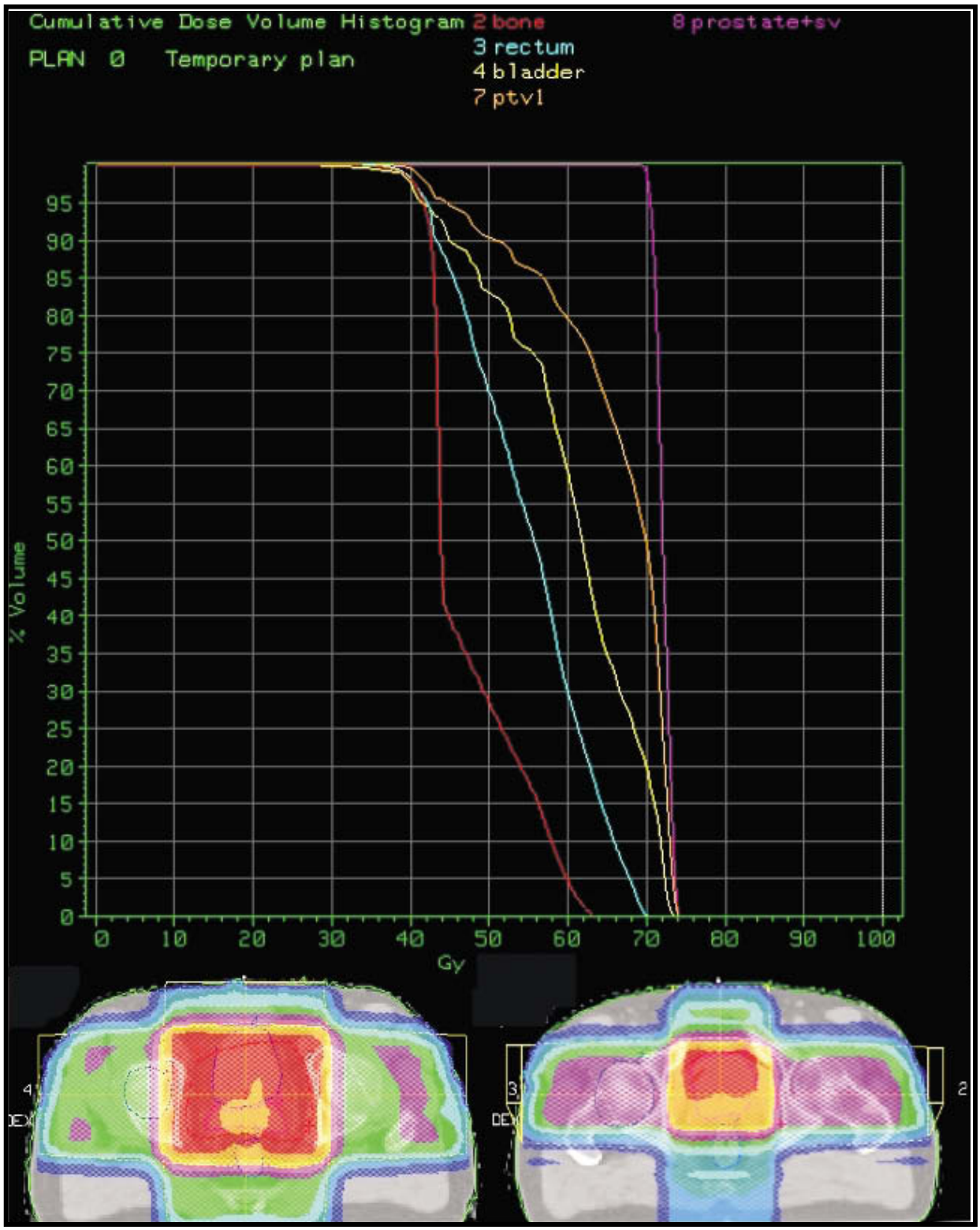


Fig. 2. Dose Volume Histograms for II phases of treatment (box technigue = 45 Gy and than three fields which encompassed the prostate and seminal vesicles to total dose of 72 Gy).

the first 90 days after the completion of treatment. Acute toxicities were evaluated using the Radiation Therapy Oncology Group (RTOG) morbidity scoring scale at weekly evaluations. The median follow-up was 11 months (range: 6 to 15 months). During the follow-up patients were followed by a radiation oncologist and urologist at one month intervals.

## RESULTS

All our patients completed the entire course of radiotherapy and were assessable for evaluation for acute toxicities and early biochemical outcome (PSA). The most common side effects of androgen ablation were „hot flushes", gynecomastia, although these were mild. No gaps during irradiation were introduced caused by acute side effects of the treatment.

Grade 1 toxicities involved minimum symptoms and required no medication. Grade 2 toxicities were slightly more severe and required medication. Loperamide was the most commonly prescribed drug and nonsteroidal antiflammatory drugs such as ibuprofen, diclofenac that were used to control GU symptoms. The most significant acute adverse effects noted in the gastrointestinal tract (GI) were nausea, rectal discomfort and mild diarrhea (grade 1 or 2). Diarrhea occured when the elective pelvic lymph nodes were irradiated. Acute rectal side effects were observed at the end of treatment. Usually after the $4^{th}$ week of irradiation moderate loose-stools/diarrhea occurred and, only few patients required short-time (two weeks) medication (loperamide). The GI toxicity grade 0 and 1 were observed in 75% of patients and grade 2 in 25% of patients.

Acute genitourinary (GU) symptoms included increased urgency, nocturia and dysuria. The GU toxicities were grade 0 and 1 (80% of patients) and grade 2 (20% of patients). The urinary symptoms typically appeared during the third week of treatment and resolved within a few weeks later.

No grade 3 or 4 GI and GU toxicities were observed. Generally mild relief medication (antyinflammatory) was required in 25% of patients. We noted that some symptoms of early reaction to irradiation may have overlapped with some symptoms, which occured before treatment.

## DISCUSSION

At present three-dimensional treatment planning and conformal irradiation (3DCRT) reaplaces 2 dimensional (2D) techniques in the treatment of many cancers, especially that of the prostate cancer [8]. The main advantages of such a treatment planning in prostate cancer are: use of CT images for better delineation of the target and sourrounding organs at risk (rectum, bladder, femoral head), and more precise information for the more sophisticated computer calculating systems. In this way radiation dose conforms better to the tumour, and that is why, the dose to the adjuncet tissue decreases, which make it possible to increase the dose to the tumour. On the other hand, a normal tissue toxicity is on the same level or is even decreased [9, 10, 11].

In our paper, early side effects of a combined treatment (androgen ablation therapy and 3D radiotherapy) patients with prostate cancer (stage T1-T3 N0M0) were evaluated. The data from literature indicate that a combined treatment may lead to better results [12]. Example of combined treatment was the trial study conducted by RTOG (RTOG 9202): neoadjuvant androgen ablation was introduced 2 months prior to irradiation and then was continued during radiotherapy and for 2 years after termination of irradiation. In a group of patients treated with hormonal therapy and radiotherapy the 5-year overall survival rate was 80% vs. 69% in patients without additional hormonotherapy [7]. Another well documented trial that shown a therapeutic benefit was study carried out by Bolla et al. [6]. In this study two modalities of treatment were compared: radiotherapy alone versus radiotherapy plus long-term adjuvant hormonotherapy (3 years). This study confirmed that combined treatment resulted in an increase of 5 years survival from 62% to 79% ($p = 0.001$). The question whether it represents sensitization of the tumor to radiation due

to androgen deprivation or constitute an additive therapeutic effect, remain unresolved. Many studies demonstrated statistically significant reductions in the volume of the irradiated tissue because neoadjuvant androgen supression reduced the volume of prostate cancer and the volume of the enlarged prostate gland [13]. The tumour volume reduction may also result in the improvement of the blood flow and decrease in the tumour cell hypoxia. According to Zelefsky et al. [5] neoadjuvant androgen deprivation seemed to have a significant impact on local control, and reduced the recurrence rate, but did not influence the overall survival. These data also indicate that the combined treatment is associated with a higher incidence of treatment induced impotence. Among the 159 patients who were potent (able to maintain a functional erection) before treatment, the 2-year actuarial incidence of impotence was 43%, compared with 27% for 385 patients who received radiation alone ($p<0,001$).

Generally, the combined treatment is a promising option of treatment because offers better results without overlapping toxicities [16].

We have defined acute toxicity as side effects of treatment which occured during the course of irradiation and also 90 days after the termination of radiotherapy. This definition is generally accepted by radiation oncologistes, but the time factor used as the criterion which distinguishes acute and late morbidities may reflect the lack of knowledge about the real nature of response to irradiation in health tissue. In our study, the acute toxicity was evaluated according to the RTOG morbidity scale. The average total dose prescribed to the target was 70.2 Gy and this dose level in the treatment of patients with prostate cancer lies in the middle range of dose escalation [17,18]. In each case, we kept the total dose below 70 Gy to 30% of the rectum volume. Another fact is worth to stressing is that the volume of the irradiated rectum received only a small fraction of the total dose even in case the of elective irradiation of the pelvic lymph nodes.

Each patient received androgen depletion treatment with LH-RH (goserelin) or bilateral orchiectomy plus flutamide. During irradiation and follow-up we did not observe any additional side effect except „hot flushes" and gynecomastia, which are typical to hormonal therapy. We have also attempted to introduce a questionnaire in which we asked each patient about the potency defined as a possibility of sexual activity. The questionnaire was filled up at the beginning the radiotherapy, during radiotherapy and during the follow-up. Only 10 patients out of 22 were evaluable for this questionnaire (11 patients refused), and no patients did not observe any decrease of potency during course of irradiation and follow-up. This evaluation has not been complete due to a very short time of the follow up. It is known, that progression of the impotence caused by irradiation is very slow and even takes years.

We have generally, used only small fields which encompassed the prostate and seminal vesicles leaving out pelvis lymph nodes. Only 7 out of 22 patients were irradiated using pelvic elective fields in first phase of treatment. There is still no agreement whether yes or not administer elective irradiation of the pelvic lymph nodes. According to data from literature, introduction an elective irradiation of pelvic lymph nodes does not change the overall survival rate in patients with a localized stage of disease but the toxicity of treatment seems to be higher [19,20]. Probably the application of the small fields is one of the most important factors which was responsible for the fact that we did not observe more severe GI side effects of our treatment. The levels of toxicities from gastrointestinal tract (GI) observed in our group of patients were in the same range as those reported by other authors [21]. Six of 22 patients experienced acute grade 1 GI morbidity. Only 25% of them had grade 2 acute toxicity from GI and no patient required a intensive medical treatment. No patients experienced grade 3 or 4 morbidity.

The more pronounced side effects from the genitourinary tract (GU) were: nocturia, dysuria, increased frequency of urination. Only 5 out of 22 patients had grade 1 GU toxicity and also 5 out of 22 patients had grade 2 GU morbidity. We did not note any

GU toxicities higher than grade 2. The same observations were made by Pilepich et al. [22] and by Soffen et al. [23]. These investigators applied a higher total dose, even up to 78 Gy or 81 Gy. We have to emphasize that in the majority of our patients we used small fields which covered the prostate and seminal vesicles and it could have led to an decrease in the volume of the irradiated tissue. We did not observe more pronunced acute side effects because these are more volume-dependent than dose-dependent [24].

We did not try to evaluate early biochemical response (PSA) due to small number of patients and short time of the follow-up [25,26].

In this work, we have only evaluated early side effects of the combined treatment during the course of radiotherapy, and time of 3 months after completion of treatment. The resolvment of side effects releated to the radiotherapy and the hormonal therapy were done at about 3 months of the follow-up.

In our opinion, the quality of patient's life even during such a short time in relation to overall survival time after treatment is important and may influence the decision making about treatment.

## CONCLUSIONS

Major problems in the use of EBRT concerns the risk of developing of radiation proctitis and rectal bleeding. The preliminary results of treatment with a high-dose 3 D-CRT suggest that such a modality is well tolerated with only modest acute toxicites of GI and GU without severe toxicities. Neo-adjuvant therapy does not exacerbate radiation included toxicity. A longer follow-up is needed to evaluate the longer-term tolerance of treatment which could seem more important both from the patient's point of view and from that of the outcome of treatment.

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