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ASSESSMENT OF EFFICACY AND TOXICITY OF THE FRACTIONATED RADIOTHERAPY WITH STEREOTACTIC BODY RADIOSURGERY BOOST IN PROSTATE CANCER PATIENTS: PILOT CLINICAL STUDY RESULTS.

Oncology

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ABSTRACT

Background: Prostate cancer (PC) represents one of the most common malignancies in men. Radiotherapy (RT) has been used more often therapy. Stereotactic body radiosurgery (SBRS) has become used, as monotherapy. The effects of SBRS boost, added to RT have not been extensively studied.

Purpose: to prospectively assess efficacy and toxicity of the hypofractionated SBRS boost in RT, in prostate cancer patients.

Methods and Materials: RT of the prostate up to 50 Gy, with additional hypofractionated SBRS, with fractionated dose of 7 Gy, twice were used. 22 patients, age 45 to 80 years with localized prostate adenocarcinoma were included. The median observation time was 60 months (23 - 66).

Results: No patient in this study had PC recurrence. There was no unacceptable toxicity.

Conclusions: Conventional radiotherapy, combined with SBRS boost, appears to be safe and efficient in patients with localized prostate cancer. These results justify initiation of the randomized trial.

KEYWORDS

prostate, radiotherapy, radiosurgery

INTRODUCTION

Prostate cancer (PC) represents one of the most common malignancies in men, and its morbidity and mortality have been growing steadily. The incidence of PC increases with advanced age, and therefore, due to aging of the male population, this disease has become a growing epidemiological concern. Currently, in Poland, over 8000 of new PC cases per year has been reported, with a tendency to rise. Recently, an introduction to a routine diagnostic work-up, of the serum prostate specific antigen (PSA) test has resulted in earlier detection of majority of the localized PC cases. [1,2]

Aaccording to the „Consensus Development Conference on the Management of Clinically Localized Prostate Cancer", [3] radiotherapy (RT) has been used more often, as the main treatment method for PC since 1987.

According to different authors, during a three-year period, following the radical prostatectomy, 14-27% of patients had experienced a disease recurrence. Over the past several years, due to immense technological advances in radiotherapy, the dose escalation for localized PC resulted in improvement of progression-free survival. This was made possible, mostly due to reduction of the irradiation field. However, it should also be noted that the dose escalation can lead to an increased risk of late toxicity (rectal and urinary). A tolerable dose for the bladder and rectum has been estimated as 60 Gy (for rectum - with irradiation of 100 cm3 , and for bladder - with irradiation of total volume - TD5/5 = 60 Gy; also , it should be noted that TD50/5 = 80 Gy - means a 5 % risk of toxicity for the dose of 60 Gy, and a 50 % risk for the dose of 80 Gy). With the RT dose escalation to 70 Gy and above, it is impossible to avoid toxicity in the area of surrounding critical organs, including bladder and rectum. In turn, a reduction of the margin between prostate gland, and the planning target volume (PTV) can cause an increased risk of "geographical" errors, related to both inadequacy of target planning, and the prostate movement during the fractionated irradiation. Based on our prior research experience, the prostate movement is mostly related to its anterior-posterior axis. For instance, in 21 of 40 analyzed patients (52.5%), the prostate motion exceeded 1 cm (according to our study findings, described elsewhere). [4] These preliminary results have revealed that there is a correlation between the prostate's mobility range and treatment effects of RT.

Unfortunately, an attempt to increase the target volume of irradiated tissues occurs at the expense of an increased risk of late intestinal/rectal and urinary toxicity. One of the ways to reduce late bladder and rectal toxicity, while keeping the escalated RT dose, is to utilize Image - Guided Radiation Therapy (IGRT).

Hypofractionated radiation with the IGRT can substantially increase efficacy, with each administered fraction. Also, a larger radiation dose per fraction, delivered in a smaller number of fractions can be more effective.

Several studies have been conducted on combined application of the hypofractionated radiation and IGRT. In a large Scandinavian randomized study, a dose of 7 x 6,1 Gy was used in the treatment arm. [5] This was compared to the dose of 39 x 2 Gy, in the control arm. In the Madsen's study, the dose of 6,7 Gy, administered 5 times per week was used. [5] The authors did not report any significant increase of urinary or rectal toxicity

In radical treatment of patients with early stages, organ confined prostate cancer, in our Oncology Center (Gliwice, Poland), we are presently using a total dose of 76 Gy, conventionally fractionated, with the fraction dose of 2 Gy, administered 5 times per week.

However, to our knowledge, the effects of stereotactic body radiosurgery (SBRS) boost, added to the conventional RT have not been extensively studied.

Therefore, we designed and conducted a pilot study, in order to explore this treatment modality.

PURPOSE OF THE STUDY

The aim of our study was to prospectively assess toxicity and efficacy of the SBRS boost in radiotherapy, in patients with early stages of prostate cancer (PC).

Specific goals of our study included:
1. Examination of the risk of acute and late toxicity, in prostate cancer patients treated with conventional RT, with hypofractionated SBRS boost,

2. Evaluation of efficacy of the conventional RT with hypofractionated SBRS boost, among PC patients.

MATERIALS AND METHODS

Study group.

Between August 2007 and October 2008, 22 patients, age 45-80 years (mean age 67,5 years; standard deviation SD 7,35), with localized (favorable and intermediate risk group) prostate adenocarcinoma, biopsy-proven (stage T1cN0M0-T2bN0M0, Gleason score ≤ 7, and mean initial PSA level < 20 ng/ml) were included into the study, conducted at Oncology Centre in Gliwice, Poland.

In all of the patients, prior to their enrollment into the study, the following tests were performed:

Medical history and physical examination, with digital rectal exam (DRE),

Transrectal ultrasound (TRUS),
Pelvic Nuclear Magnetic Resonance (NMR),
Complete blood count (CBC) and current PSA level,
Chest radiogram (CXR),
Bone scan .

In all the participants: metastatic disease was excluded, estimated survival time was > 5 years, and their general condition was assessed, according to WHO scale. The study was approved by Bioethics Commission. All the patients signed their voluntary informed consent to participating in the study. In addition, the following excluding criteria were used: current or previous diagnosis of the second malignancy (except from the skin cancer), and uncompensated heart failure or respiratory insufficiency.

Treatment.

In this study, radiation therapy of the prostate was used, with tissue margin of 1-1,5 cm, up to the dose of 50 Gy (We had not possibility to do IGRT during every day irradiation in 2007 year). This treatment was combined with hypofractionated SBRS, with fraction dose of 7 Gy, applied twice, at the beginning, and at the end of the treatment.

Due to such a design and methodology, the treatment could have been performed with 3 mm tissue margin.

An equivalent target dose for the prostate was calculated as follows:
For SBRS boost:

D(2) : D(7) = {□/□ + d(7)} : {□/□ + d(2)}
with assumption that □/□ = 1,5: D(2) = 14 x {1,5 + 7) : (1,5 + 2) = 34
with assumption that □/□ = 3: D(2) = 14 x {3 + 7) : (3 + 2) = 28
A total dose: 84 Gy (assuming □/□ = 1,5)
78 Gy (assuming □/□ = 3)
An equivalent dose for the rectal part (isodose) was calculated as follows:

For SBRS boost:
D(2) : D(7) = {□/□ + d(7)} : {□/□ + d(2)}
with assumption that □/□ = 4: D(2) = 14 x {4 + 7) : (4 + 2) = 25,6
with assumption that □/□ = 7: D(2) = 14 x {7 + 7) : (7 + 2) = 21,8
D(7) – total dose for the fractionated dose 7 Gy
d(2) –fractionated dose 2 Gy
d(7) – fractionated dose 7 Gy

Therefore, the total dose, depending on the accepted □/□ ratio was for the prostate 78-84 Gy, whereas the dose for rectum (isodose) was 21,8-25,6 Gy.

Dose escalation in the prostate area, compared to the one, previously used for conventional RT (76 Gy) was 2-7 Gy, with simultaneous reduction or maintenance of the dose in rectal area (0,4-4,2 Gy). A simultaneous application of SBRS allowed to reduce the rectal volume, irradiated with the dose above 50 Gy.

In addition, the treatment time was reduced to 5 weeks, compared with 7,5-8 weeks of standard RT.

Radiotherapy was planned in three-dimensional fashion, as conformal 3DRT, or - with the use of intensity-modulated radiotherapy (IMRT), combined with conventional RT, and SBRS boost.

The following treatment schedule was conducted:
Conventional RT– prostate area with 0.7-1.5 cm margin:
Total dose – 50 Gy,
Fractionated dose– 2 Gy,
Fraction number – 25,
Treatment time – 25 days of therapy during 5 weeks,
Radiotherapy days – Monday – Friday,
Total Volumes irradiated :
GTV (gross tumor volume) – prostate tumor (specified only for T2a-T2b),
CTV – prostate gland,

PTV (planning treatment volume) – prostate gland with margin (1 cm anteriorly and laterally, 0.7-1.0 cm rectally , and 1.5 cm above and below of the prostate).

Radiation treatment planning and delivery - with empty bladder and rectum
Hypofractionated SBRS irradiation:
Total dose – 14 Gy,
Fractionated dose – 7 Gy,
Fraction number – 2.
Treatment time – 2 days of therapy during 5 weeks,

Radiotherapy days – Saturdays, the first fraction before, and the last one after completion of the conventional RT.

Total Volumes irradiated :
GTV – prostate tumor (specified only for T2a-T2b),
CTV – prostate gland,
PTV – prostate gland, with margin of 3 mm.

Radiation treatment planning and delivery with empty bladder and rectum During irradiation using IGRT, verification of the prostate location in real time, was performed on the Clinac 2300 CBCT apparatus.

Follow-up examinations
Follow-up examinations were conducted every week, during the treatment period. They included physical exam and evaluation of acute toxicity.

These post-treatment examinations were conducted after 1 month, and after 3 months from the time of RT completion, and then, every 3 months, for 2 years. Subsequently, they were done every 6 months, after completion of the two-year observation period (or more often, depending on the patient's needs). These follow-up exams included:

1. Medical history and physical examination,
2. PSA serum level,
3. Evaluation of acute and late toxicity,
4. Urinalysis,
5. Rectal endoscopy - as needed,
6. CXR - as needed,
7. Abdominal and pelvic USG or TRUS - as needed

The median observation time was 48 months (23 - 60). Two patients were lost to follow-up, after 23, and 25-months; death of the second patient (77 years old) was confirmed as unrelated to cancer, and it was not possible to retrieve any follow-up information about the first patient.

Statistical analyses.

The following criteria were used in the study assessment:
Total survival,
Asymptomatic (progression –free) survival,
Percentage of biochemical failure (recurrence),
Percentage of clinical recurrence,
Evaluation of acute toxicity, according to EORTC/RTOG,
Evaluation of late toxicity, according to EORTC/RTOG,
Diagnostic criteria of treatment failure,

Biochemical failure (recurrence), according to ASTRO f criteria from 2005 (three-fold increase of serum PSA level),
Clinical diagnosis of local recurrence,
Clinical diagnosis of metastases.

Kołmogorow-Smirnow-Lillieforse's test was used to verify distribution of the 3 measured variables (mean age, mean initial PSA level, and Gleason score) . It was determined that the age had the normal distribution in all of the study groups. In contrast, the mean initial PSA level, and Gleason's score did not have normal distribution, in patients' groups with or without occurrence of urinary toxicity. In groups with or without intestinal/rectal toxicity, the distribution of these 3 measured variables was normal. Thus, the mean initial PSA, and Gleason's score in the patient groups (created according to the presence vs. absence of urinary or intestinal/rectal toxicity), were compared by using a non-parametric U-Mann-Whitney's test, and the remaining variables were compared by using the parametric Student's t - test. Statistical significance was set at the 0.05 level (p value). All the statistical analyses were conducted in Statistica computer program.

RESULTS

We did not observe any cancer depended death in analyzed group during all follow-up period. No case of the disease recurrence (clinical or biochemical) was found in any of the study participants.

A total of 22 patients, aged from 45 to 80 years (mean age 67,5 years; SD 7,35), participated in the study, and the median observation time was 60 months (23 - 66). Two patients were lost from our observation, after 23, and 25 months (from the termination time of their treatment). In case of the second patient, information about death, unrelated to oncological causes was confirmed, at the age of 77 years. There was no retrievable follow-up data, related to the first patient.

The study patients were analysed in groups, according to the toxicity (urinary and intestinal/rectal) that they experienced:

1. There was no occurrence of the urinary toxicity in13 patients, compared to the group of 9 patients, who experienced the urinary toxicity at least once (one patient - toxicity grade II - on two consecutive observations, during therapy and one month after irradiation, one patient – toxicity grade I - on four follow-ups, one patient – toxicity grade I - on two follow-ups, and six patients –toxicity grade I , observed only once).

2. There was no occurrence of the rectal toxicity in 16 patients, compared to the group of 6 patients, who experienced the intestinal toxicity at least once (one patient –toxicity grade I - 4 times , one patient –toxicity grade I -3 times, and four patients – toxicity grade I - one time).

In patients, who had a sporadic incidence of the urinary toxicity (n=9) or intestinal toxicity (n=11), there was no difference with regard to the age, mean initial PSA level, and Gleason's score , as compared to those, who did not experience this kind of toxicity (n=13, and n=11, respectively).

To analyze categorical variable, which did not have normal distribution, the entire group of study patients was divided into 2 groups, based on their initial PSA level (<10 vs. >10 ng/ml). To establish a relation between the occurrence of urinary and intestinal toxicity, and the categorical variables, □2 test , or □2 with Yates' correction, or the Fisher's exact test were used.

No correlation was found between the occurrence of urinary toxicity (p=0,1099), and intestinal toxicity (p=0,2291), and the PSA level in two groups (PSA < 10 vs.> 10 ng/ml). In addition, no correlation was found between the occurrence of urinary (p=0,5000), and rectal (p=0,3176) toxicity, and the T clinical, and T MRI (for bladder - p=0,1631, for intestines -p=0,4710).

DISCUSSION

The combination of Image Guided Radio surgery Boost with Conformal Radiotherapy is our originally idea. Our study revealed that conventional radiotherapy, combined with radiosurgical boost, appears to be safe and efficient therapeutic method in patients with localized prostate cancer. The most important observation is that there was 100% cancer-related survival. Also, no disease recurrence (clinical or biochemical) was found. We report that in our study group, the level of urinary and intestinal/rectal toxicity was fully acceptable. This is the first study showed radiosurgical boost combined with conformal radiotherapy. There are a lot of studies showed hypofractionated radiosurgery and few studies showed brachytherapy boost combined with conformal external beam irradiation but there were not study like this one before.

This way of therapy could be useful in oncology centers treated large number of patients. Treatment time is shorter about two and half weeks and patients are irradiated using standard regime for linear accelerator. Of course it could told that our group is not very large but this is pilot study and because of it this number of patients fully acceptable. IGRT has become standard method for prostate cancer patients but there are still many centers, especially in Eastern Europe, with too small number of accelerators you can easy check prostate position before each fraction and too large number of patients to have to treat. Combine quickly every day irradiation not very high dose and very precisely IGRT boost irradiation could be possible, using our method.

It is very difficult to compare our results with the other. We must strongly establish, that there are not published studies about the same regime of treatment. Of course there are a lot of studies about radiosurgery but none combined radiosurgery with standard irradiation earlier. So we can only discuss radiobiology aspects of study and compare our results with radiosurgery alone.

According to some recently published studies, it can be concluded that the radiobiological □/□ ratio (in the range of 1 – 3.1) for prostate cancer (PC) is lower than for cancers of other organs as well as for majority of healthy tissues, including intestines and rectum . [6, 7, 8, 9,10,11]. The value of □/□ ratio for rectum, as one of the most important critical organs, affected by late toxicity , during conventional radiotherapy for PC, has been estimated to be in the range of 4 – 7.7 [12, 13, 14]. Maciejewski et al. [15] revealed the existence of so called 'plateau effect' that occurs after exceeding a total dose of 70 Gy, during conventional RT of the PC. On the other hand, Suwiński [16] in his debate with Maciejewski indicates a possibility of the 'quasi-plateau' effect, caused by occurrence of distant metastases. Also, Suwiński points out to some difficulties, related to implementation of the hypofractionated RT into clinical oncology practice.

In attempt to compare our study results with the ones published by other authors it should be emphasized that the concept of combining conventionally fractionated radiotherapy with the stereotactic boost represents an original idea of the authors, and was never used, in any oncology center worldwide.

Therefore, our study findings can only be compared to the results obtained with the hypofractionated RT. Similarly to already mentioned Widmark's work [5], we did not observe the increased percentage of urinary or intestinal/rectal toxicity, among our study patients.

Although, new findings continue to appear on this subject, and some of them have been presented at scientific meetings, there is only a limited number of research articles on this topic. In addition, Cyber Knife has been used more often, as illustrated by studies of Freeman's et al., in which a dose of 35 Gy was administered in 7 fractions [17, 18]. There was one study published in 2012 about stereotactic body radiotherapy post external beam irradiation but median follow-up of this study is 18.3 months (range, 12.6–43.5), so authors can not write about late effects [19].

The results obtained by our team, and also by some other authors appear promising, especially in light of ASTRO 2010 recommendations, according to which, conducting randomized clinical trials should be a priority in the area of SBRS for PC. [20].
We have started randomized trial comparing this regime with standard prostate cancer irradiation.

CONCLUSIONS

Conventional radiotherapy, combined with radiosurgical boost, appears to be safe and efficient therapeutic method in patients with localized prostate cancer. We report that in our study group, the level of urinary and intestinal/rectal toxicity was fully acceptable. Also, no disease recurrence (clinical or biochemical) was found. The obtained preliminary results (of this pilot study) justify initiation of the longer term randomized trial, which is warranted to evaluate the efficacy and toxicity in patients with early stage prostate cancer.

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