Conformal radiotherapy (3D CRT) for non-metastatic androgen-independent prostate cancer: costly and sophisticated but ineffective treatment?

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Piotr MARTENKA[1] , Piotr MILECKI[1], Małgorzata ŻMIJEWSKA-TOMCZAK[1], Zbigniew KWIAS[2]

[1] Department of Radiotherapy, Greatpoland Cancer Centre, ul. Garbary 15, 61-866 Poznań, Poland,
[2] Chair of Urology, University School of Medical Sciences, ul. Kurlandzka 1, 61-650 Poznań, Poland

Address for correspondence:
Piotr Milecki
Radiotherapy Department of the Greatpoland Cancer Centre
ul. Garbary 15,
w61-049 Poznań, Poland
e-mail: piotr.milecki@wco.pl

ABSTRACT

Purpose: Patients with diagnosis of hormone-refractory prostate cancers (HRPC) present a very heterogeneous population, and therefore it has been proposed to sub-categorize them into two subgroups depending on presence or absence of distant metastases. While the former subgroup has been typically treated with palliative intention, for the latter apparently there is no standard approach. The role of three-dimensional conformal radiotherapy (3D-CRT) for this subgroup has not been well documented in the literature. Thus, the purpose of this work is to analyze the results of treatment of non-metastatic androgen-refractory prostate cancer (ARPC) with 3D-CRT and to investigate the potential prognostic factors which influenced the results.

MATERIAL AND METHODS: Of 424 patients with diagnosis of localized and locally advanced prostate cancer who were treated between 1999 and 2004 in our centre, forty-three (n=43) patients were classified as non-metastatic ARPC. Distant metastases were excluded by negative bone scan, negative chest X-ray and negative pelvic CT for lymph node metastases. The median pre-hormone therapy PSA (pre-HT PSA) level for this group was 24 ng/ml (range 1 to 120) and 5.7 ng/ml (range 0.06 to 27) at the beginning of radiotherapy (pre-RT PSA). Clinical T stage distribution, defined according to the 2002 AJCC, was as follows: T1c = 12, T2 = 23, and T3 = 8 patients, respectively. Of 44 patients, 39 had a Gleason score of 2-7 and 4 had a Gleason score of 8 -10. All patients with diagnosis of non-metastatic ARPC were treated with 3D-CRT with the daily fraction dose of 2 Gy to a median total dose of 68 Gy (range from 60 to 74 Gy). The median duration of androgen ablation therapy before RT was 26 months (range from 7 to 96). The median time of follow-up after 3D-CRT was 27 months (range from 13 to 62) and from the beginning of androgen ablation was 53 months (range from 20 to 158). The following prognostic factors were evaluated in univariate and multivariate analysis: age, pre-HT PSA, pre-RT PSA, Gleason score, total dose, PSA doubling time (PSADT< 6 months vs. PSADT > 6 months).

RESULTS: The 5-year actuarial overall survival was 82% and 5-year clinical relapse free-survival rate was 49%. During the follow-up 14 patients developed disease progression (locoregional and/or distant and/or biochemical) and two patients died of prostate cancer. The univariate analysis indicated that pre-HT PSA > 20 ng/ml, pre-RT PSA > 4ng/ml, and the high-risk group defined according to NCCN criteria (PSA >20 ng/ml and Gleason score >7) were statistically significant factors for the risk of disease progression.

CONCLUSIONS: Three-dimensional conformal radiotherapy for patients with non-metastatic ARPC is a valuable method of treatment for the subgroup of patients with pre-HT PSA<20 ng/ml and Gleason score < 8. For patients classified as the high-risk group according to NCCN criteria 3D-CRT seems to be an ineffective treatment due to the observed high incidence of distant failure, and should be viewed as costly and sophisticated yet ineffective intervention. For this subgroup a systemic modality of treatment such as chemotherapy or biological manipulation should be considered.

KEY WORDS: non-metastatic hormone-refractory prostate cancer, three-dimensional conformal radiotherapy, prognostic factors

INTRODUCTION

Optimal treatment of prostate cancer is a field of debate as a result of lack of outcomes of randomized clinical trials which would compare the efficacy of main treatment modalities such as radical prostatectomy, radiotherapy (external beam therapy, brachytherapy), and hormonal therapy (HT) [1]. Hormonal therapy, the third main method of treatment, is used for prostate cancer treatment throughout a wide range of disease presentations because of the dependence of prostate cancer on testosterone [2]. In Poland, many patients are diagnosed in an advanced stage of disease, and thus androgen deprivation therapy (ADT) has frequently been used as the first line of treatment by urologists [3]. Beside that, in some cases of localized stage of disease, treatment is started with ADT as well. The main indication for HT in the latter group of patients is lack of the patient's agreement for active methods of treatment such as surgery or radiotherapy. During hormonal treatment increase of serum PSA level only and/or local progression without clinical evidence of distant progression in many cases changes the patient's decision and gives permission to move on to more radical treatment such as radiotherapy. Generally, for patients classified as nonmetastatic androgen-independent prostate cancer (ARPC) prognosis is poor, with a median survival of approximately 20 months [4]. However, if in this group of patients we could distinguish two main subgroups - the first with occult distant metastases and/or local failure, and the second with local failure alone which is represented by biochemical relapse too - then for the latter group an efficient local therapy might have been strongly indicated and effective. Therefore, selecting the subgroup of patients for whom radiotherapy could be beneficial is a crucial point of treatment of patients classified as ARPC. The role of radiotherapy in the treatment of prostate cancer is well established, although the role of this method of treatment for patients with non-metastatic ARPC is not well documented [5]. To date, only a few studies have described the outcome of radiotherapy in hormone-refractory prostate cancer [6–8]. Moreover, in the aforementioned studies important differences in patient selection and dose fractionation existed.

The aim of this study was to analyze the results of treatment of non-metastatic ARPC with conventionally fractionated 3D CRT and to investigate the potential prognostic factors which influenced the results.

MATERIAL AND METHODS

Patient characteristics

Between May 1999 and December 2004, at the Great Poland Cancer Centre in Poznañ, 424 patients with diagnosis of prostate cancer (T1-T3N0M0) were treated with three-dimensional conformal radiotherapy (3D CRT) with curative intent. In the present study from this cohort only forty-three patients 43 (n=43) were included due to fulfilment of the criteria for non-metastatic ARPC .

The median age of patients was 71 years (range 55–79 years). Distribution of T stage was as follows: (T1c = 12, T2 = 23 patients, T3a = 8 patients). All patients had a pathologically confirmed diagnosis of adenocarcinoma, which was classified according to the Gleason scoring system. The average level of PSA before the beginning of HT (pre-HT PSA) was 25 ng/ml (range 1 to 120 ng/ml) and the average PSA prior to RT (pre-RT PSA) was 5.7 ng/ml (range 0.06 to 27 ng/ml).

Before starting HT the following initial evaluation of disease was performed: digital rectal examination (DRE), transrectal ultrasonography (TRUS), bone scan, pelvis CT, chest X-ray. During hormonal therapy at 3-month intervals DRE was performed and serum PSA level measured.

All patients referred for RT were restaged using the following examinations: physical examination with DRE, bone scan/skeletal X-ray, chest X-ray, PSA serum level. In addition all patients had pelvic lymph nodes evaluated by computer tomography (CT) or magnetic resonance imaging (MRI) or ultrasound (US). None of the patients had diagnostic lymphadenectomy of the pelvic lymph nodes performed. Additionally all patients prior to HT and then before RT had a complete blood count, biochemistry including serum BUN, creatinine, and liver enzymes.

Hormonal therapy

In the analyzed group of patients, the decision concerning HT was made before consultation

with a radiotherapist, which is unfortunately common in our community and therefore has not always been based on strict criteria derived from evidence-based medicine. For these patients treatment was started with antiandrogen (flutamide) for a minimum of 2 weeks and then LHRH agonists were introduced. After a few weeks of therapy, the LHRH agonists alone were continued. In cases where the PSA level increased in 3 consecutive evaluations with 2-week intervals between measurements, the patient was classified as having androgen-refractory prostate cancer (ARPC). In such a clinical scenario the patient was referred for radiotherapy. All patients during and after the end of the radiotherapy course were treated with LHRH. During the follow-up additional hormonal manipulation was performed with the maximal androgen blockade (MAB) when antiandrogen was added. No other forms of second lines of ARPC were performed in the analyzed group. For all patients hormonal therapy was continued to the end of life.

Radiotherapy technique

Simulation and treatment were performed in a supine position with "comfortable" full bladder. All patients had CT scanning of the pelvis in the treatment position (supine position) at 5 mm increments across the treatment field. Radiotherapy was administered using 20 MV photons in a daily fraction of 1.8 Gy – 2.0 Gy to a total median dose of 70.4 Gy (range 60 Gy to 74 Gy). The planning target volume (PTV) was defined as the clinical target volume (CTV) which encompassed the prostate with the base of the seminal vesicles and ± the seminal vesicles with margins in all directions about 1.0 cm around the prostate gland ± seminal vesicles. In each case the following organs at risk (OAR) were outlined: the bladder, rectum, colon, and femoral heads.

Elective treatment of pelvic lymph nodes was included when the risk of involvement was higher than 15% calculated according to the formula proposed by Roach et al. [9] The elective irradiation of pelvic lymph nodes was based on the four-field technique (the box technique) to a median total dose of 46 Gy, and then a boost to the seminal vesicles and prostate gland was implemented.

In each case the set-up and dose distributions were checked by electronic portal imaging device (EPID) and dosimetry in vivo performed at the start of the treatment and then in each week and/or in the case of change of the treatment plan.

Acute side effects including those arising during the irradiation course and within the first 90 days after the completion of treatment were evaluated using the European Organization for Research and Treatment of Cancer / Radiation Therapy Oncology Group (EORTC/RTOG) morbidity scoring scale. The median time of follow-up after the treatment was 26 months (range from 7 to 62 months). During the follow-up patients were followed by a radiation oncologist and urologist at three-month intervals. No patients were lost to follow-up.

Statistical analysis

The Kaplan-Meier method was used to estimate survival curves. Comparison between analyzed groups was performed with the log-rank test. In all tests a significance level of 0.05 was used. The time from the end of RT to the death or the last follow-up date was defined as the survival time. In overall survival (OS) analysis all causes of death were taken into account. In cases where the cause of death was unclear, the presence of clinically evident prostate cancer at the time of death was considered death due to prostate cancer. For analysis of cancer, progression-free survival (PFS), deaths due to prostate cancer, and regional, distant or local relapse of prostate cancer and/or biochemical relapse defined according to the American Society for Therapeutic Radiology and Oncology (ASTRO) definition were considered.

Follow-up

For each patient the follow-up consisted of a medical history, digital-rectal examination, and PSA level (obtained prior to examination). The interval between control visits was 3 months. During visits acute or late side effects were evaluated according the EORTC/RTOG morbidity scale.

RESULTS

Overall survival and progression-free survival

The 5-year actuarial overall survival was 82% and 5-year progression-free survival rate was 49% (Figs. 1, 2). During the follow-up 15 pa-

tients developed disease progression (locoregional and/or distant and/or biochemical), two patients died of prostate cancer, and 5 patients died due to concurrent illness. The univariate analysis indicated that pre-HT PSA serum level > 20 ng/ml (test log rank, p= 0.03), and the high-risk group defined according to NCCN criteria (PSA >20 ng/ml and Gleason score >7) (test log-rank p= 0.01) were statistically significant factors for the risk of disease progression (Figs. 3,4,5). Other analyzed factors such as age, T-stage, and PSA DT were not indicated as prognostic factors for results of radiotherapy.

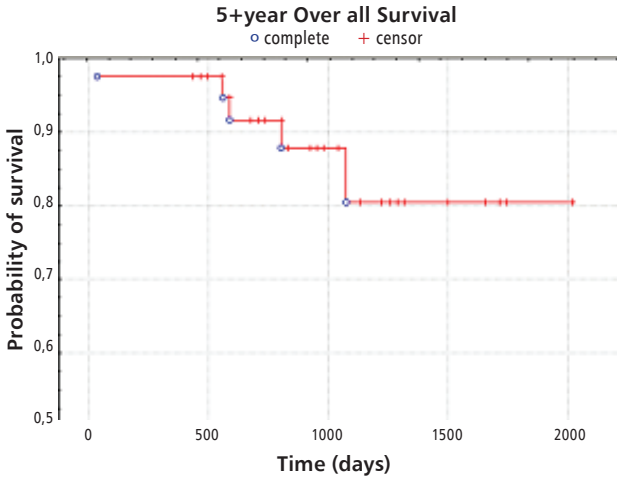

Fig. 1. 5-year overall survival

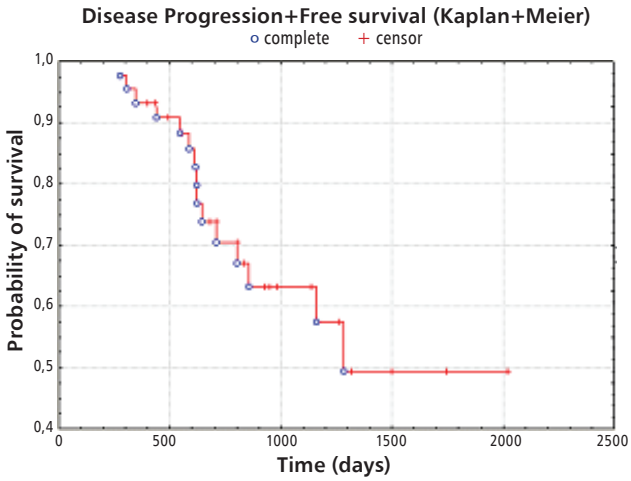

Fig. 2. Disease progression-free survival for all patients (Kaplan-Meier method).

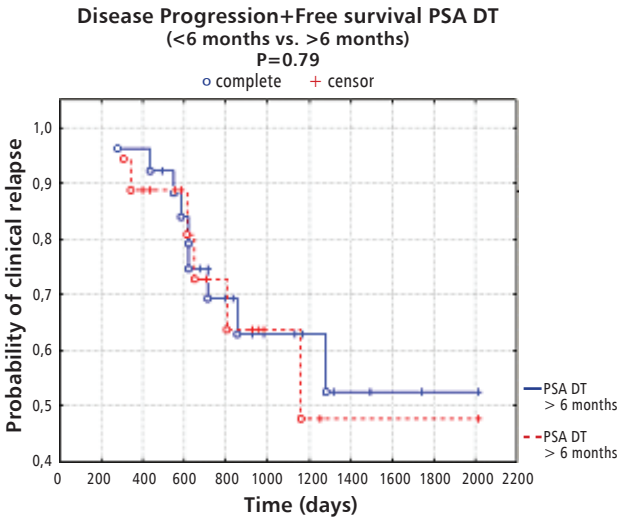

Fig. 3. Progression-free survival according to PSA DT

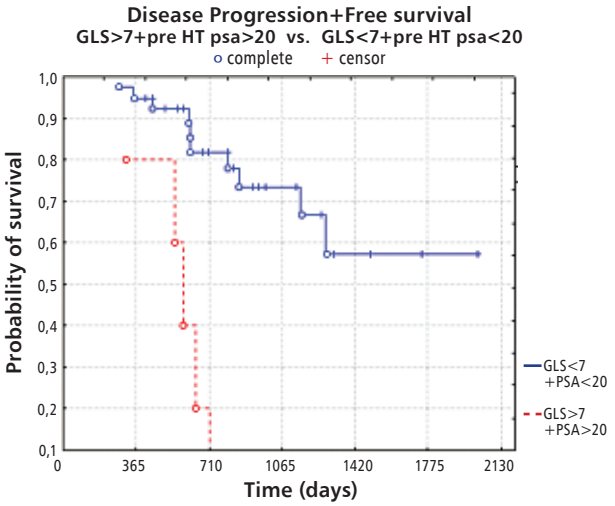

Fig. 4. Progression-free survival according to combined risk factors (GLS and pre-HT PSA)

Side effects of therapy

Acute genitourinary (GU) symptoms included increased urgency, nocturia and dysuria. GU toxicities grade 0 and/or 1 were noted for 80% of patients and grade 2 in 20% of patients. The urinary symptoms typically appeared during the third week of radiotherapy treatment and resolved within a few weeks after the end of radiotherapy. Mild relief medication (anti-inflammatory) was required in 15% of patients. Only 10 patients were administered an alpha-1 adrenoreceptor-blocking agent for acute uri-

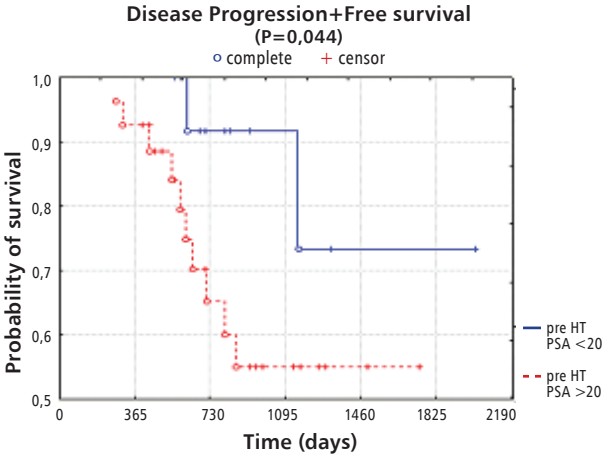

Fig. 5. Disease progression-free survival according to pre-HT PSA

nary symptoms, and this treatment was very effective and resulted in significant resolution of symptoms in 90% of cases.

The most significant acute adverse effects observed in the gastrointestinal tract (GI) were rectal discomfort, nausea, and mild diarrhoea. Generally, these side effects were mild to moderate (grade 1 or 2). The most commonly prescribed drugs for lowering the intensity of GI morbidities were loperamide and nonsteroidal anti-inflammatory drugs such as ibuprofen and diclofenac. Only a few patients required about two weeks' medication (loperamide) for diarrhoea. Acute rectal side effects were observed at the end of treatment (usually after the 4th week of irradiation moderate loose-stools/diarrhoea). In general, GI toxicity grades 0 and 1 were observed in 75% of patients and grade 2 in 25% of patients.

No acute or late GU or GI toxicities graded as 3 or 4 according to the RTOG/EPRTC scale were observed in the analyzed group of patients. The most frequent side effect observed from GU during the follow-up was microscopic haematuria and urgency.

The most common side effects of androgen ablation were "hot flushes", gynecomastia, and loss of potency and libido, although these side effects were mild and not classified in the RTOG/EORTC morbidity scale.

DISCUSSION

Prostate cancer is one of the most important health problems in industrialized countries and the leading cause of cancer-related death. For the early stage of disease patients may be treated with surgery or radiotherapy, whose efficacy is regarded as equivalent. The third method of treatment is hormonal therapy, which represents the standard treatment for locally advanced or metastatic prostate cancer [10]. In earlier clinical stages hormonal therapy is advocated based on individual preferences of patients.

Androgen withdrawal in groups of patients with prostate cancer produce subjective and/or objective response rates in approximately 80% of patients, but after some time the response to androgen deprivation is diminished [11]. In that case the patient is classified as androgen independent and many different terms have been used to describe cancers that relapse after initial hormonal ablation therapy, including HRPC, androgen-independent cancers and hormone-independent cancers [12]. True HRPC is commonly defined as at least two serial rises in serum PSA obtained at least 2 weeks apart despite castrate levels of serum testosterone. In order to fulfil the criteria for true HRPC, additional conditions such as either antiandrogen withdrawal or one secondary hormonal manipulation should have been met. In the present work patients fulfil only the first part of the definition of HRPC and thus the evaluated group should be considered as androgen-independent with possible hormone-sensitive prostate cancer (AIPC). Using this definition a growing population of asymptomatic patients with a rise of PSA serum level but with negative re-staging for distant metastases can be selected. Thus, androgen-independent prostate cancer is a very heterogeneous disease including a variety of different patient cohorts with significant different median survival times. Although the re-staging is negative for distant metastases we can expect some proportion of patients for whom micrometastases exist. In this group of patients an impact of radical radiotherapy on survival would not be expected, but for other cases when cancer disease is limited to a local or regional stage radiotherapy may change the results.

It is worth adding that the subgroup of non-metastatic HRPC patients is growing due to strict PSA-based evaluation of hormonal ther-

apy and other forms such as radical prostatectomy or radiotherapy. Nevertheless, for the non-metastatic group there is no standard approach. Treatment of non-metastatic hormone refractory prostate cancer is a challenge for both the urologist and radiation oncologist. According to our current understanding of HRPC there is no general agreement whether to continue testicular androgen suppression or not. Sustained hormonal ablation should still affect the population of cancer cells that are not hormone-resistant. On the other hand, an androgen withdrawal effect has been well documented showing a biochemical response after stopping hormone ablation in some patients.

The role of other methods of treatment are being investigated [1]. The role of radiotherapy for patients with non-metastatic hormone-refractory prostate cancer has not been well documented. The most important factor is to distinguish patients who are truly free from distant metastases from those with distant micrometastases. For the latter group loco-regional therapy such as radiotherapy would be completely ineffective. According to many investigators, important parameters which may help to differentiate between local and distant relapse include: timing of PSA increase after surgery, PSA velocity, PSA doubling time (PSADT), pathological stage, and Gleason score of specimen. PSA elevations developing within the treatment are associated with distant recurrences [13]. It was shown that a median PSADT of 4.3 months is associated with distant relapse, whereas a median PSADT of 11.7 months tends to predict local failure [14]. For patients with asymptomatic PSA-only progression, according to Lange et al. biochemical failure precedes clinical disease progression from 6 to 48 months [15].

Thus we could expect that a group of patients exists without distant or even regional metastases, i.e. truly free of micrometastases, that are classified as non-metastatic HRPC, and such patients are good candidates for local therapy such as radiotherapy. The dilemma in considering a treatment strategy is that there are very scarce data concerning outcomes of radiotherapy in this subset of patients. Moreover, median doses of radiotherapy reported for such patients are lower than those typically used in prostate cancer treatment (>70Gy), not mentioning the recently reported possible advantage of using even higher doses such as 78Gy. This probably reflects the fact that for these localized but highly advanced and hormone-resistant prostate cancer patients there is general agreement on lower doses to avoid unnecessary complications in the light of poor prognosis and more palliative-like treatment. It is well known that doses higher than 70Gy are likely to result in increased rectal wall toxicity. In our subset of patients the median dose was 70.4Gy, although there were a few patients treated with 60Gy for the reason given in the latter sentences.

According to Lankford et al. [6], who treated 29 patients with a median dose of 66 Gy, radiotherapy is highly effective in terms of local control (61% at 4 years); however, 80% of patients failed with distant metastases within 4 years. This poor outcome probably reflects the fact that 79% of the patients in that study had disease spread to lymph nodes, which confers high risk of distant spread. Therefore conformal high-dose treatment in that subset of patients should be viewed as solely palliative intervention. In contrast, in our study patients with lymph node involvement were excluded and this approach resulted in relatively good outcome of 5-year PFS and OS at the level of 49% and 82%, respectively. Comparable results were recently published by Akimoto et al., with 5-year clinical relapse-free and overall survival of 56% and 87%, respectively [7]. They also referred to their study only patients who had no signs of lymph node metastases as evaluated by CT. However, in their study a hypofractionated regimen with fraction dose of 3 Gy given three times weekly was implemented. Therefore, having in mind the disputable value of ?/ß ratio in adenocarcinoma of the prostate, it is difficult to directly compare these studies [16].

Another key issue is the influence of possible radioresistance of prostate cancer cells in the phase of androgen independence. Many studies have focused on the deregulation of apoptosis in the development of androgen-independent disease. High levels of bcl-2 expression are seen with greater frequency as CaP progresses, and a mechanism by which bcl-2 induces its anti-apoptotic effect may be the regulation of microtubule integrity. The fact that the most active chemotherapeutics

in HRPC work by inhibiting microtubule formation suggests that these findings may be clinically relevant. The tumour suppressor gene p53 is more frequently mutated in androgen-independent CaP. Over-expression of bcl-2 and p53 in prostatectomy specimens have been shown to predict an aggressive clinical course.

Our analysis indicated very poor radiotherapy results in the subgroup classified as non-metastatic ARPC patients with high-risk factors (pre-HT PSA >20 ng/ml + Gleason score > 7). On the other hand, radiotherapy could be a valuable method of treatment for patients with lower risk of distant failure classified as pre-HT PSA < 20 ng/ml, Gleason score < 8.

Patients with diagnosis of HRPC present a very heterogeneous population, and therefore it has been proposed to sub-categorize them into two subgroups depending on presence or absence of distant metastases. While the former subgroup has been typically treated with palliative intention, for the latter apparently there is no standard approach.

In the analyzed group of patients only 43 out of 424 patients received ADT as sole treatment. Such a strategy of treatment was advocated by leading urologists, who started hormonal therapy very early after having obtained the diagnosis of prostate cancer (e.g. T3). During the hormonal therapy, biochemical failure occurred. In such cases 80% of patients changed their decision and chose RT. From this group after re-staging distant metastases were indicated in 10% of patients who were not included in radiotherapy radical treatment.

Generally, the data from the literature indicate that combined treatment (hormonal therapy plus radiotherapy) may lead to prolongation of overall survival in a more advanced stage of disease [17 EUA]. An 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 hormone therapy [18]. Another well documented trial study, which showed a therapeutic benefit, was carried out by Bolla et al. [19], who confirmed that combined treatment resulted in an increase of 5-year survival from 62% to 79% (p= 0.001).

In our study combination of androgen deprivation therapy and RT was based on different rules and indication that a typical combined treatment strategy exists. Thus, it is impossible to answer the question of what is the relationship between androgen deprivation therapy and RT.

One of the most important issues of treatment of patients with diagnosis of HRPC apart from prolongation of survival is avoiding significant side effects of therapy which could influence the quality of life of treated patients. From this point of view during the course of radiotherapy and follow-up we did not observe any significant side effects scored as grade III according to the RTOG/EORTC classification.

Treatment of non-metastatic HRPC patients is a challenge for both urologists and radiotherapists. Implementation of radiotherapy in case of distant metastases or in very high risk of distant failure (micrometastases) produces morbidity and is connected with high cost of treatment which is represented by direct and indirect costs. In such cases radiotherapy constitutes a costly form of palliative treatment. Another aspect of strategy of treatment of patients with non-metastatic HRPC concerns the subgroup of patients who are potential candidates for cure or prolongation of survival due to application of radiotherapy but did not receive such treatment. Thus, the key for the group of patients with non-metastatic HRPC is to find the subgroup which will be candidates to obtain therapeutic gain.

The role of three-dimensional conformal radiotherapy (3D-CRT) for this subgroup, which comprises a significant proportion of prostate cancer patients, has not been well documented in the literature.

CONCLUSIONS

Three-dimensional conformal radiotherapy for patients with non-metastatic ARPC is a valuable method of treatment in terms of progression-free survival provided to the subgroup of patients with pre-HT PSA<20 ng/ml and Gleason score < 8. For patients classified as high risk according to NCCN criteria, 3D-CRT seems to be an ineffective treatment due to the observed high incidence of distant failure and should be viewed as a costly and sophisticated

yet ineffective intervention. For this subgroup a systemic modality of treatment such as chemotherapy or biological manipulation should be considered.

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