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ORIGINAL ARTICLE

Neoadjuvant hormonal therapy in prostate cancer – impact of PSA level before radiotherapy

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Summary

Purpose: *To retrospectively investigate the impact of prostate specific antigen (PSA) level after neoadjuvant androgen-deprivation therapy (ADT) on biochemical relapse-free survival in patients with prostate cancer who received radical radiotherapy (RT).*

Methods: *Between March 2003 and March 2008, 128 men with localized prostate cancer underwent neoadjuvant ADT for 4-6 months followed by radical RT. Biochemical relapse-free survival was compared between patients with pre-RT PSA ≤ 0.1 vs > 0.1 ng/mL.*

Results: *At a median follow up of 47.3 months, biochemical relapse-free survival was significantly higher in patients with a pre-RT PSA ≤ 0.1 ng/mL compared with pre-RT PSA > 0.1 ng/mL (85.6 vs 63.2%, p = 0.0025).*

Conclusion: *The current analysis demonstrating better treatment outcome in patients with excellent biochemical response to neoadjuvant ADT, supports an individualized treatment strategy.*

Key words: *androgen-deprivation therapy, neoadjuvant hormonotherapy, prostate cancer, PSA, radiotherapy*

Introduction

External beam radiotherapy (EBRT) represents a curative treatment option for patients with prostate cancer. There is now growing evidence supporting a benefit for combining hormonal therapy with radiotherapy [1-5]. Combined modality approach with ADT and radical RT has become the standard of care for men with clinically localized, high-risk adenocarcinoma of the prostate. According to recent studies patients with intermediate risk features may also derive benefit. The role of neoadjuvant ADT before RT in the management of prostate cancer is a topic of active investigation in recent years, but there is currently no consensus regarding the optimal duration of neoadjuvant ADT. Recently, 4 randomized controlled trials have confirmed improved biochemical control outcomes using hormonal therapy [6-10]. A number of ADT schedules of different duration are used, ranging from 2 to 10 months of neoadjuvant and/or concurrent ADT before RT. Unfortunately no randomized trial could demonstrate benefit of any schedule examined [11-13].

Optimal duration of neoadjuvant ADT may vary, depending on the tumor burden and hormonal responsiveness. Hormone therapy tailored to the biochemical response of the individual patient may be a more appropriate approach, minimizing the side effects and maximizing the therapeutic benefit.

This study aimed to evaluate the impact of PSA levels after ADT on biochemical relapse-free survival in patients with prostate cancer treated with neoadjuvant ADT and radical RT.

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Methods

Between March 2003 and March 2008, a total of 128 patients with histologically verified localized prostate cancer were primarily treated with neoadjuvant hormonal therapy and curative RT at the Department of Oncology and Radiotherapy, Charles University Hospital in Hradec Kralove. Pretreatment diagnostic evaluation consisted of physical examination, PSA, Gleason score, computed tomography of pelvis, radionuclide bone scan and transrectal ultrasonography of the prostate. Patients were distributed into 3 recurrence risk groups according to the National Comprehensive Cancer Network guidelines. Intensity modulated radiotherapy (IMRT) to a dose 78 Gy was used in 71 patients and 57 men received simultaneous integrated boost to deliver 82 Gy to the prostate and 73.8 Gy to the seminal vesicles.

The RT technique used was described earlier [14-16]. Briefly, patients were planned and treated in a supine position and were advised to have a comfortably full bladder. A vacuum cushion or knee and feet support (VacLok/Dual Leg Positioner Cushion, MED-TEC) have been used for immobilization. Patients were treated with 5 coplanar fields (angles 45, 100, 180, 260, 315), and intensity-modulated beams were delivered with a dynamic multileaf collimator, using the sliding window technique.

The inverse planning system (CadPlan R.6.3.6. with Helios module/Eclipse 7.3, Varian) was used to generate all treatment plans. Clinical target volume (CTV) included the entire prostate and the base of the seminal vesicles (with the exception of cases with seminal vesicles invasion, where prostate and the whole seminal vesicles were covered). The planning target volume (PTV) was created by adding a 10 mm margin to the CTV. Rectum and bladder were delineated in CT slices 10 mm superior and inferior of the slices containing the PTV. The prescribed dose was 78 Gy in daily fractions of 2 Gy.

In 57 patients the simultaneous integrated boost (SIB) technique was used. CTV1 included the entire prostate only, CTV2 included the seminal vesicles. PTV1 was created by adding a 10 mm margin to the CTV1, PTV2 was generated by a 10 mm expansion of the CTV2. The prescribed dose was 82 Gy (in daily fractions of 2 Gy) for PTV1 and 73.8 Gy (in daily fractions of 1.8 Gy) for PTV2.

All patients were treated with neoadjuvant ADT. This consisted of a combination of luteinizing hormone-releasing hormone (LHRH) plus androgen antagonist (Zoladex + Flutamide) for 4-6 months before and during RT. No patient was treated with adjuvant hormonal therapy (or orchiectomy).

The patients were scheduled to be seen every week during RT, one month after the end of RT, every 3 months for the first 2 years, every 6 months for another 3 years and once a year thereafter. The work-up included a complete history, physical examination and serological determination of PSA at each visit. PSA concentrations were measured in the local lab using commercial kits available at the time. Biochemical relapse was recorded using Phoenix definition [17].

Statistics

Biochemical relapse-free rates were assessed in two groups of patients based on the pre-RT PSA concentration of ≤ 0.1 vs > 0.1 ng/mL. Kaplan-Meier product-limit method was selected to determine the risk of biochemical failure during time. The two groups of patients were compared using log-rank test.

Results

Most of the patients (N=117, 91.4%) were scored as high risk, 2 (1.6%) as low risk and 9 (7%) as intermediate risk. Hormonal treatment in patients with low and intermediate risk was administered due to the large volume of prostate to minimize side effects of RT. Patient distribution according the age, T-stage, Gleason score, risk group, pre-treatment PSA, and RT technique are shown in detail in Table 1.

The median PSA level before starting ADT was 10.3 ng/mL (range 1.3-51.2). With a median follow-up of 47.3 months (range 16 – 106.8) the PSA relapse-free survival rate observed for all the patient population was 78.9 % (Figure 1). Subsequently, the patients were dichotomized into two groups according to the PSA level after neoadju-

Table 1. Patient characteristics

Characteristics	*N (%)*
Age, years, median (range)	71 (51 – 81)
T stage	
T1	4 (3.1)
T2	15 (11.7)
T3	109 (85.2)
Gleason score	
2-6	87 (68)
7	29 (22.6)
8-10	12 (9.4)
Pre-ADT PSA, median (range)	10.3 (1.3 – 51.2)
Risk group	
Low	2 (1.6)
Intermediate	9 (7)
High	117 (91.4)
Radiation technique	
IMRT 78	71 (55.5)
IMRT SIB 82	57 (44.5)
Follow up, months, median (range)	47.3 (16 – 106.8)

ADT: androgen deprivation therapy, IMRT : intensity modulated radiation therapy, SIB : simultaneous integrated boost

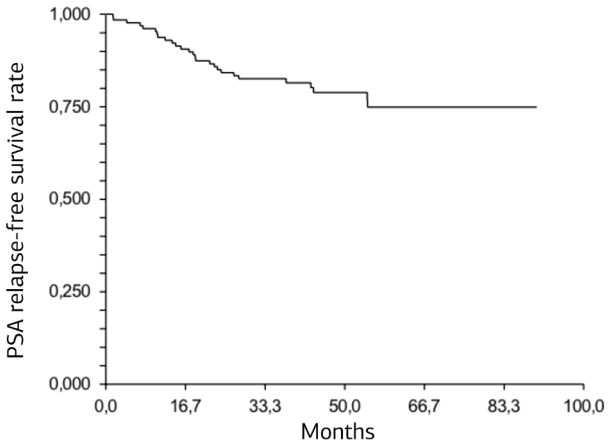

Figure 1. Biochemical relapse-free survival.

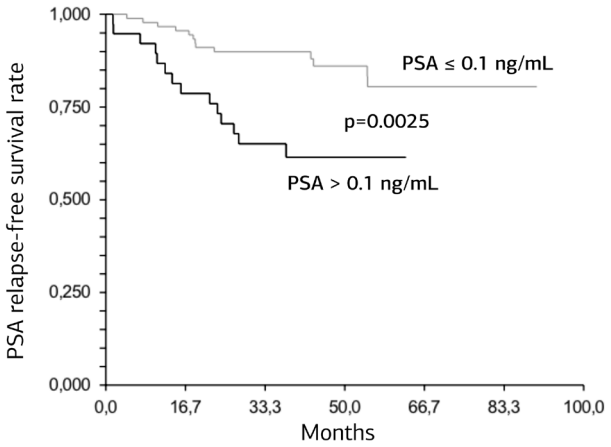

Figure 2. Biochemical relapse-free survival according to pre-radiotherapy PSA ≤ 0.1 or > 0.1 ng/mL.

vant ADT. Ninety patients had PSA concentration ≤ 0. 1 ng/mL and 38 had PSA > 0. 1 ng/mL. The biochemical relapse-free survival was significantly higher in patients with a pre-RT PSA ≤ 0.1 ng/mL compared to patients with pre-RT PSA > 0.1 ng/mL (85.6 vs 63.2 %; p = 0.0025). (Figure 2). The proportion of patients with dose escalated SIB technique was higher in the cohort with PSA > 0.1 ng/mL compared to PSA ≤ 0.1 ng/mL (47.9 vs 38.9 %; p=0.43).

Discussion

The results of the present retrospective study demonstrated significantly better outcome in biochemical relapse-free survival in prostate cancer patients with the PSA level ≤ 0.1 ng/mL after neoadjuvant hormonal treatment. It seems unlikely that the better clinical results in these patients were due to different radiation doses as the proportion of patients with dose escalated SIB technique was higher in the cohort with higher PSA concentration.

The present results are in accordance with a recently published Canadian study that compared two different schedules of neoadjuvant hormonal therapy (3 vs 8 months). While after a median follow up of 6.6 years there was no significant difference between the study arms, in a subsequent analysis patients with PSA ≤ 0.1 ng/mL before RT had better biochemical control irrespective of the treatment arm [18].

Early diagnosis and individually tailored treatment represent the essential factors for cancer cure [19-23]. Both retrospective cohort studies and prospective randomized trials showed improved clinical results with a combination of neoadjuvant and adjuvant hormonal therapy and radical RT in patients with localized prostate cancer. Unfortunately, no randomized trial has been able to demonstrate substantial clinical benefit of one neoadjuvant treatment schedule over another.

Serial measurement of serum PSA concentrations plays an indispensable role in the management of prostate cancer [24]. Present data add to the evidence indicating the significance of determination of biochemical response in the treatment of patients with prostate cancer.

Based on the available data, it appears that biochemical response to neoadjuvant hormonal therapy is more important than the duration of this treatment. It may be hypothesized that patients with suboptimal PSA decline after standard-duration treatment (3-6 months) would require an extension of the duration of neoadjuvant ADT. However, the present retrospective results may be interpreted in an opposite way as suggesting that the PSA concentration after neoadjuvant hormonal treatment may be a prognostic and predictive factor in prostate cancer depending on the individual tumor biology, similarly to the significance of PSA nadir after radical RT alone.

The final decision on whether the PSA concentration after neoadjuvant ADT represents only a prognostic parameter or a biomarker for potential stratification of treatment strategy has to be, hopefully, tested in a prospective randomized study. According to the current recommendations NCCN 2013 it is possible to use hormone treatment (neoadjuvant / concomitant / adjuvant) for 4-6 months in intermediate risk patients undergoing radical RT. Patients with high risk should be treated with combination therapy – RT and long-term hormonal therapy for at least 2-3 years.

The present analysis obviously has some weak points that are due to its retrospective nature or different methods used for PSA determination over time. However, the selected cutoff PSA concentration of 0.1 ng/mL is rather low and it is unlikely that variation of the methods that have been widely discussed could affect the categorical results in this study.

In conclusion, the present analysis demonstrated improved biochemical relapse-free survival in patients with excellent biochemical response to neoadjuvant ADT. Future clinical trials should determine whether prolongation of duration of ADT based on pre-RT PSA level could maximize the effect and minimize the toxicity of treatment.

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