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Original article

Results of combined radiotherapy and hormonal treatment of prostate cancer patients with initial PSA value >40 ng/ml

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ABSTRACT

Aim: To evaluate the outcome of prostate cancer patients with initial PSA value >40 ng/ml.
Background: The outcome of prostate cancer patients with very high initial PSA value is not known and patients are frequently treated with palliative intent. We analyzed the outcome of radical combined hormonal treatment and radiotherapy in prostate cancer patients with initial PSA value >40 ng/ml.
Methods: Between January 2003 and December 2007 we treated, with curative intent, 56 patients with non-metastatic prostate cancer and initial PSA value >40 ng/ml. The treatment consisted of two months of neoadjuvant hormonal treatment (LHRH analog), radical radiotherapy (68–78 Gy, conformal technique) and an optional two-year adjuvant hormonal treatment.
Results: The median time of follow up was 61 months. 5-Year overall survival was 90%. 5-Year biochemical disease free survival was 62%. T stage, Gleason score, PSA value, and radiotherapy dose did not significantly influence the outcome. Late genitourinal and gastrointestinal toxicity was acceptable.
Conclusion: Radical treatment in combination with hormonal treatment and radiotherapy can be recommended for this subgroup of prostate cancer patients with good performance status and life expectancy.

Background

The prostate specific antigen (PSA) is the main factor in defining the extent and prognosis of disease in patients with prostate cancer. The risk of locally advanced disease,[1] lymph node metastasis and distant bone metastasis[2] increase with rising PSA value. The prediction value of nomograms for disease extent prediction decreases with increasing PSA value.[3] High initial PSA value can occur in the absence of metastatic

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disease induced, for example, by inflammation of the prostate, but values are usually not very high.[4] A more accurate diagnosis is, in such cases, difficult and potentially useful methods may be natrium-fluorid PET scanning for the detection of bone metastasis[5,6] or a PET scan with ^{11}C-cholin.[7,8] These examinations are not standard today, however.

Patients with an extremely high PSA value are often treated with palliative intent. The main risk of this approach is the progression of localized disease and side-effects accompanying permanent hormonal blockade. On the other hand, a radical approach with radical radiotherapy carries the risk of overtreatment, early progression outside the treatment volume, and side-effects of radical radiotherapy. The addition of radiotherapy to the permanent hormonal treatment increased overall survival of patients with locally advanced prostate cancer[9] and the addition of hormonal therapy to radiotherapy increased overall survival of high risk prostate patients.[10,11] The question remains, if the radical treatment approach is also suitable for patients with extremely high initial PSA value.

Aim

The aim of this work is to evaluate treatment results in a group of prostate cancer patients with initial PSA value >40 ng/ml.

Materials and methods

Between January 2003 and December 2007 we treated, with curative intent, 56 patients with non-metastatic prostate cancer and an initial PSA value >40 ng/ml. Staging investigations included PSA, biopsy, CT or MRI scan of pelvis, and bone scan. The main characteristics of the patient group are outlined in Table 1. The treatment consisted of neoadjuvant hormonal treatment (2 months, LHRH analog), radiotherapy and optional adjuvant hormonal treatment (antiandrogen 2 years). The main characteristics of the treatment are outlined in Table 2. The treatment was performed on linear accelerators with a nominal photon beam energy of 6 MeV, using a conformal 3D technique. Clinical target volume for the initial phase of treatment included the pelvic region with boost to the prostate/seminal vesicles during the second phase or prostate gland/seminal vesicles only, dependent on the decision of the physician. The dose was 44–50 Gy/22–25 fractions for the pelvic region and 24–28 Gy/12–14 fractions for the prostate ± seminal vesicles. The total dose was 68–78 Gy/7–8 weeks. The dose was normalized to the maximum in PTV and the dose was prescribed to the reference isodose (usually 93%). Acute and late toxicity was evaluated according to the RTOG scale. The follow-up investigations were performed at 3–6 months intervals with PSA examination, physical examination, and control CT/MRI of pelvis, and bone scan in the case of PSA elevation. PSA relapse was assessed according to the Phoenix criteria.

Table 1 – Patient characteristics.

Age (years)	Median 68 (52–81)
T stage	
T1	7 (12.5%)
T2	28 (50%)
T3a	9 (16%)
T3b	7 (12.5%)
T4	4 (7%)
Tx	1 (2%)
N0	56 (100%)
Gleason score 2–6	25 (45%)
Gleason score 7	15 (27%)
Gleason score 8–10	14 (25%)
Gleason score x	2 (3%)
PSA (ng/ml)	Median 68 ng/ml (42–276)

Table 2 – Proportion of treatment modalities.

Neoadjuvant hormonal treatment	Yes 55 (98%), No 1 (2%)
Adjuvant hormonal treatment	Yes 37 (66%), No 19 (34%)
Radiotherapy—volume	Pelvis 48 (86%), prostate 8 (14%)
Radiotherapy—dose (Gy)	Median 74 Gy (68–78 Gy)

Statistics

Overall survival (OS) and biochemical disease free survival (bDFS) were calculated using the Kaplan–Meier method. Univariate analysis of predictive factors was undertaken using the Mantel-Cox test. The log-rank test provided a statistical comparison of two groups. A p-value <0.05 was considered to be significant.

Results

The median follow up time during the evaluation period (March 2011) was 61 months. 52 patients were alive, three patients died due to tumor progression, and one died without tumor. 5-Year overall survival was 90% and 5-year biochemical disease free survival (bDFS) was 62%. Kaplan–Meier survival curves for overall and biochemical-disease free survival are shown in Fig. 1. We also analyzed the influence of T stage, Gleason score, PSA level (with median cut-off), radiotherapy target volume (prostate only versus whole pelvis), radiotherapy dose (with 74 Gy cut-off), and adjuvant hormonal treatment to the biochemical relapse-free survival. None of these factors significantly influenced bDFS. There was a strong trend for better results in the group with PSA values below the median (67.5 ng/ml, $p = 0.075$). 20 (37.5%) treatment failures were observed during the time of evaluation. PSA relapse alone was detected in 10 (17.8%) patients, eight (14.3%) patients had PSA relapse followed by bone dissemination, one (1.8%) patient had PSA relapse, local relapse, and bone dissemination and one (1.8%) patient had PSA relapse and paraaortal lymph node dissemination. Acute and late toxicity were evaluated according to the RTOG scale. Therapy of the rectal bleeding with Argon-laser was considered as grade III toxicity. The data for acute and late gastrointestinal (GI) and genitourinal (GU) toxicity can be found in Table 3. No toxicity ≥ 2 for other organs was observed.

Table 3 – Acute and late GI and GU toxicity.

RTOG scale	Gr.0	Gr.1	Gr.2	Gr.3	Gr.4
Acute GI	30%	29%	41%	0%	0%
Acute GU	16%	53.4%	27%	1.8%	1.8%
Late GI	41.1%	19.6%	33.9%	5.4%[a]	0%
Late GU	87.5%	1.8%	10.7%	0%	0%

[a] Argon-laser coagulation was considered as gr.3 late rectal toxicity.

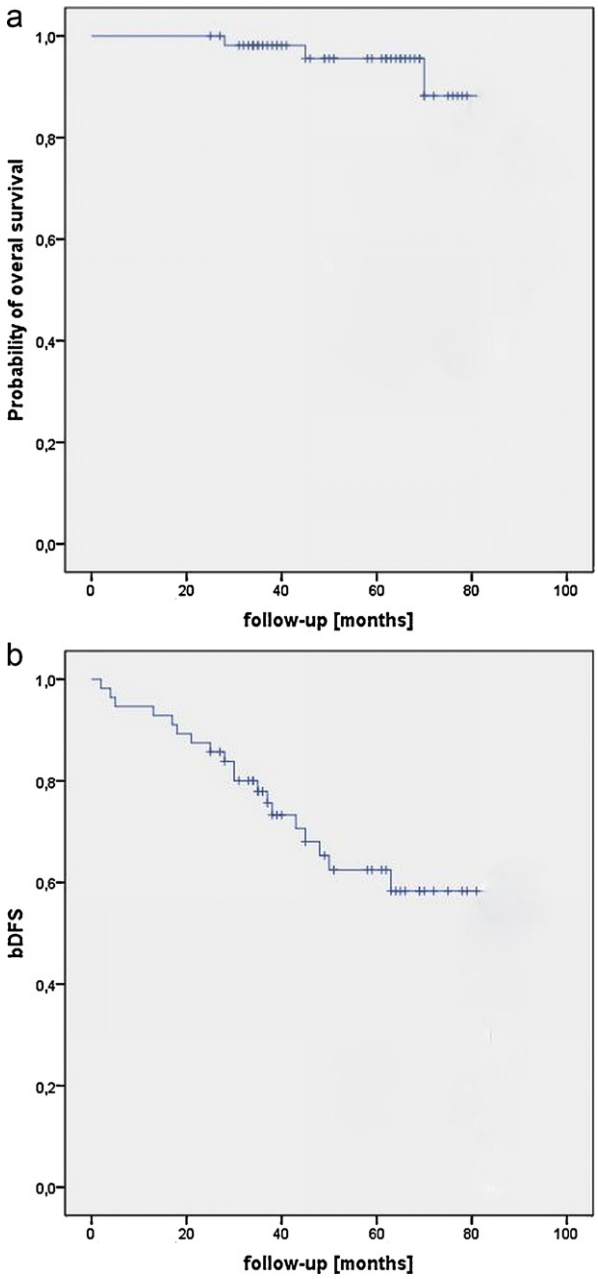

Fig. 1 – Overall survival (a) and biochemical-disease free survival (bDFS) (b).

Discussion

An initial PSA value higher than 40 ng/ml is considered as a very poor prognostic factor and physicians often offer less radical or only palliative treatment for this subgroup of patients. The value of the PSA which excludes patients from radical treatment is not known. Some studies used PSA > 150 ng/ml as an exclusion criterion. The main problem in the treatment of this subgroup of prostate cancer patients is the risk of local overtreatment with possible late effects of radiotherapy in the radical approach. On the other hand, there is a high risk of progression of localized disease in combination with side-effects of the whole-life hormonal treatment in the palliative approach. Treatment should be sufficiently effective in the disease control with an acceptable frequency of side effects. The main question is how many patients are without tumor progression upon the completion of treatment and if the treatment toxicity is acceptable.

A possible solution is a better selection of patients for radical treatment. Some proportion of patients had disseminated disease at the time of diagnosis, but a significant proportion of patients with high initial PSA had tumor limited to the prostate, without extra prostatic extension or seminal vesicle invasion.[12] Current methods often cannot discriminate disseminated disease. Bone scans with ^{99}Tc is a standard examination in prostate cancer patients with PSA > 20 ng/ml. The probability of bone metastasis in this group is higher than 20% and the risk increases with rising values.[13] Natrium fluoride PET may offer higher sensitivity but reports about this method are controversial. Markers of bone metabolism, like bone formation markers (bone specific alkaline phosphatase, propeptides of type I collagen), bone resorption markers (bone sialoprotein), and osteoclastogenesis markers (osteoprotegerin) are other possibilities for improving the detection of bone metastasis.[14–16] Distinct suggestions for diagnosing skeletal lesions for patients with extremely high PSA levels do not exist. Second most probable locations of dissemination are pelvic or paraaortal lymph nodes. The standard investigation is a CT scan. Magnetic resonance imaging does not have a better sensitivity than a CT for detecting lymph node metastasis.[17] Metastases to other organs are extremely rare and it is not necessary to deal with them. Cholin-PET is a promising method with sensitivity of 55–100% and specificity of 77–86% for the detection of primary tumors.[7,18–20] Sensitivity and specificity of 18F-fluorocholin for the detection of lymph-node metastasis in men with intermediate or high risk tumors were 45% and 96%, respectively.[21] Others investigated the value of this examination in the detection of bone metastasis and specified values of sensitivity at 79% and specificity at 97%.[22]

Our strategy of radical treatment includes neoadjuvant hormonal treatment, radical radiotherapy (with dose escalation in significant proportion of men), and optionally adjuvant hormonal therapy.

The effectiveness of neoadjuvant hormonal treatment was demonstrated in a number of clinical studies. This treatment has a low incidence of side-effects and is indicated for patients with intermediate and high risk prostate cancer.[23,24] We used a short term hormonal treatment, although today a longer neoadjuvant treatment is recommended.[25] PSA decline after neoadjuvant treatment may be used as another prognostic factor for the decision between radical and palliative treatment.[26]

Radiotherapy is the key factor in determining the success of radical treatment and the severity of side effects in comparison with the palliative approach. The effect of radiation depends on dose, target volumes, and radiotherapy technique. The treatment of the pelvic lymphatic region has some advantages in comparison with prostate only radiotherapy in high risk prostate cancer patients. RTOG 9413 trials demonstrated a 13% improvement of progression free survival for pelvic RT versus prostate only RT.[27–29] Our data showed a much better disease free survival for the prostate only radiotherapy group. The limited volume was indicated only for T1 or T2 stage, Gleason score <7 and PSA below median value and, therefore, the number of these patients was small (14%). In spite of this, we hypothesized that this was a selection bias and that whole pelvis radiotherapy was indicated in this extremely high risk group, especially higher T stage or Gleason score. Dose-response characteristics of prostate cancer are well documented.[30,31] Effects of higher dosage were not demonstrated in our group. There is some trend for better results with higher doses. We hypothesized that this might be due to the short time of follow up. The next issue is the frequency of late effects of the radiotherapy. We used a 3D conformal technique. IMRT technique significantly reduces the number of side effects, as was demonstrated,[32] and may be used for additional dose escalation.[33,34] The majority of late effects were in our rectal bleeding group. 5.4% of our patients needed treatment with laser coagulation and none of them required surgery. We did not observe urogenital late effects worse than grade 2. Our conclusion from toxicity data is that benefits of adding radiotherapy are much higher than disadvantages. The frequency of late site effects was similar as in published reports for the 3D CRT.[35] Moreover, we hypothesize, that by using IMRT and optimization of treatment position the frequency of side effects may be significantly diminished.[36,37]

Adjuvant hormonal therapy is a standard option in the high risk prostate cancer group and improves overall survival of high risk group by 16%.[38] However, long-term adjuvant treatment has many side effects, including cardiovascular disorders and a higher incidence of diabetes,[39,40] although recent reports dispute the risk of cardiovascular effects.[41] We did not observed statistically significant difference between adjuvant treatment and no adjuvant treatment. We indicate AHB especially in patients with high Gleason score (8–10) or stage T3b or higher. AHB is optional for other patients. Interestingly, we did not observe any differences in bDFS between higher and lower Gleason score groups or higher and lower T stage. We hypothesize that neoadjuvant hormonal treatment in combination with radical radiotherapy may be sufficient in high risk patients with a low Gleason score and low T stage. This assumption needs further evaluation.

Treatment failure, in the majority of patients, consisted of PSA failure followed by bone metastasis. Only one relapse in the radiotherapy treatment volume was observed. Very low frequency of local problems is another benefit of the radical approach. There was a statistically insignificant trend for better results for the subgroup with initial PSA value below median value of 68 ng/ml, as can be expected. 5-Year bDFS for this subgroup is 76% and for patients with higher initial values it is 48%. I can be concluded that, specifically, patients with PSA values of 40–70 ng/ml should be treated with a radical intent.

Data about treatment outcome of patients with very high initial PSA values are not available. Recently, Canadian authors published bDFS and OS at 5 years 39% and 78%, respectively, in 64 patients with initial PSA > 40 ng/ml. Our results are better, possibly due to higher doses and intensive hormonal treatment.[42]

Conclusion

Radical treatment of patients with initial PSA values >40 ng/ml has an excellent 5-year biochemical disease free survival with a low risk of side effects from the treatment. Progression of disease is usually outside the radiotherapy treatment volume with local problems eliminated. We can recommend the radical treatment approach for this subgroup of prostate cancer patients with a good performance status and life expectancy.

Conflict of interest

None declared.

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