JBUON 2013; 18(3): 669-674
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Treatment of high risk prostate cancer with combined radiotherapy and hormonal treatment– results and identification of factors influencing outcome

J. Kubes[1], K. Dedeckova[1], J. Cvek[2], V. Vondráček[1], J. Dvořák[1], S. Argalacsová[1], M. Navrátil[1], J. Buril[1]

[1]*Institute of Radiation Oncology, Faculty Hospital Na Bulovce and 1st Faculty of Medicine, Charles University, Prague;* [2]*Oncological Clinic, Faculty Hospital Ostrava, Ostrava, Czech Republic*

Summary

Purpose: *The aim of this work was to prospectively analyze the outcome of combined hormonal treatment and radical radiotherapy in high risk non metastatic prostate cancer patients (T1-4, N0-1, M0).*

Methods: *Between April 2003 and December 2007 196 patients with high risk prostate cancer were treated with curative intent. The treatment consisted of 2-month neoadjuvant hormonal treatment (LHRH analog), radical radiotherapy (68-78 Gy, conformal technique) and an optional 2-year adjuvant hormonal treatment.*

Results: *The median follow up time was 59 months. Five-year overall survival was 86% and 5-year biochemical disease free survival (DFS) 70%. Factors found to be statistically significant relative to outcomes were Gleason score (p=0.017), initial PSA value (p=0.039) and adjuvant hormonal treatment (p=0.035). There was no significant association between radiotherapy dose or volume and biochemical DFS (bDFS). Late genitourinary and gastrointestinal toxicity was acceptable.*

Conclusion: *Treatment combining hormonal therapy and radical radiotherapy can be recommended for this subgroup of prostate cancer patients. Adjuvant hormonal treatment should also be used.*

Key words: *high risk, hormonal therapy, prostate cancer, PSA, radiotherapy*

Introduction

Treatment results for patients with high risk prostate cancer are still unsatisfactory. Five-year bDFS is around 60% and treatment of relapses is a serious problem. A published series reported 5-year bDFS from 44% in the older trials [1] i.e. radiotherapy alone, to an excellent 93% for a combination of external radiotherapy and high dose rate interstitial brachytherapy [2]. A large subgroup of patients with disease relapse still exists. Treatment results can be improved with radiotherapy dose escalation or by combining radiotherapy with hormonal treatment. There are a lot of uncertainties regarding the dose, the radiotherapy target volume and combinations with neoadjuvant or adjuvant hormonal treatments. We combined hormonal treatment with radiotherapy in patients with high risk prostate cancer starting in 2003 and the aim of this work was to analyze results of this therapeutic approach as well as to identify factors influencing biochemical relapse.

Methods

We identified 197 patients with high risk prostate cancer treated at our institution with combined therapy between April 2003 and December 2007. The initial examination included PSA, transrectal ultrasound, bone scan when PSA > 20 ng/ml, and MRI or CT of the pelvis in the presence Gleason score 8–10 or T3a and higher on ultrasound. Stratification of patients into the high risk group was performed according to D'Amico system [3]. The main patient characteristics are outlined in Table 1.

Correspondence to: Jiri Kubes, MD, PhD. Budínova 2, Prague 8, 18000, Czech Republic. Tel: +42 0777661574, Fax: +42 0283840873, E-mail: jiri.kubes@fnb.cz
Received: 09/01/2013; Accepted: 25/01/2013

Table 1. Patient characteristics

Characteristics	*N (%)*
Age (years), median (range)	69 (38–81)
T stage	
T1	27 (13.71)
T2	84 (42.63)
T3a	38 (19.28)
T3b	27 (13.7)
T4	17 (8.62)
Tx	4 (2.03)
N stage	
N0	193 (97.97)
N1	4 (2.03)
Gleason score	
2-6	91 (46.19)
7	42 (21.32)
8-10	56 (28.43)
x	8 (4.06)
PSA (ng/ml), median (range)	25 (3.4–276)

Table 2. Treatment modalities used in this study

Treatment modalities	*N (%)*
Neoadjuvant hormonal treatment	
Yes	173 (87.82)
No	24 (12.18)
Adjuvant hormonal treatment	
Yes	124 (62.94)
No	73 (37.06)
Radiotherapy-volume	
Pelvis	116 (62.94)
Prostate	81 (37.06)
Radiotherapy-dose (Gy)	
Mean	74
Median (range)	78 (64-78)

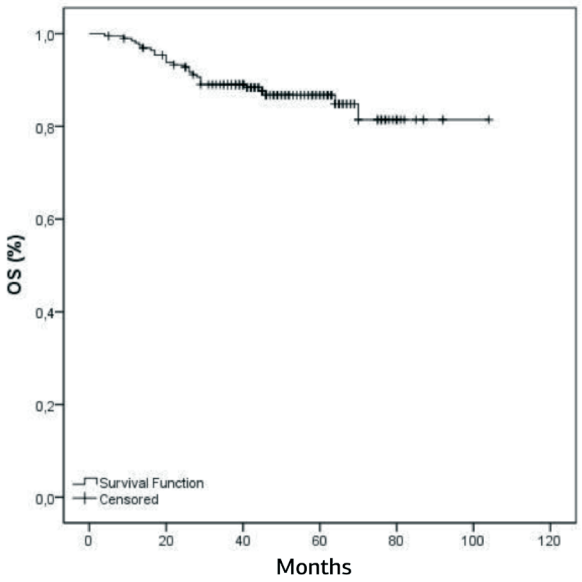

Figure 1. Overall survival.

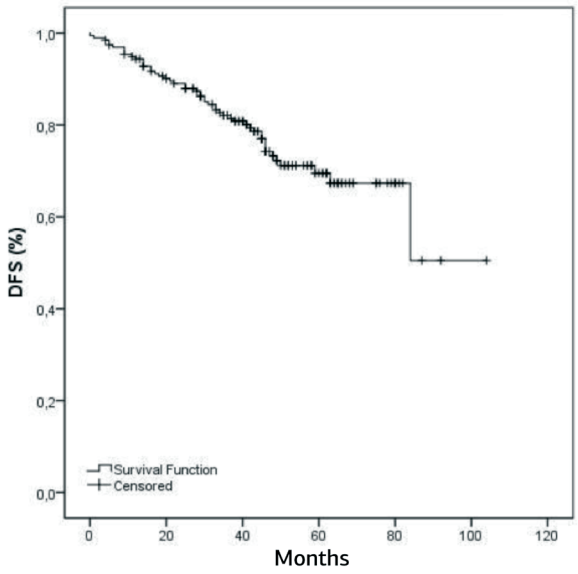

Figure 2. Biochemical disease-free survival.

Treatment

Treatment consisted of neoadjuvant hormonal administration (2 months, LHRH analog/Zoladex 10.8 mg two months before starting radiotherapy), radiotherapy and optional adjuvant hormonal treatment (bicalutamide/Casodex 150 mg/daily for 2 years). Adjuvant hormonal treatment was obligatory for patients with Gleason score 8-10 or T3b stage and optional for other patients. Radiotherapy was performed using linear accelerator with nominal photon beam energy of 18 MeV, using conformal 3D technique. Clinical target volume (CTV) for the initial phase of treatment included the pelvic region with a boost for the prostate/seminal vesicles during the second phase or prostate gland/seminal vesicles alone, depending on the decision of the treating doctor. The prescribed total dose was 70 or 78 Gy and the dose to the pelvic region was 44–50 Gy/22–25 fractions. We used normalization to the Dmax and prescription to the reference isodose (usually 93%). This means that the mean dose in planning target volume (PTV) was approximately 5% higher than the prescribed dose and dose levels were higher than with ICRU planning. Whole pelvic radiotherapy was indicated in cases with higher than 15% risk of pelvic node metastasis based on the Roach's equation [4] or Partin tables [5]. The main characteristics of treatment are outlined in Table 2.

Follow up

Follow up consisted of regular check-ups at 3–6 month intervals which included digital rectal examination and PSA measurement. PSA relapse was assessed according to the Phoenix criteria (nadir + 2 ng/ml). Acute and late toxicity were evaluated according to the RTOG scale.

Statistics

Follow up started at the end of radiotherapy. Overall survival (OS) and bDFS were evaluated using the Kaplan-Meier method and log rank test. Predictive factors (Gleason score, PSA, treated volume i.e. whole pelvis vs prostate only, radiotherapy dose and adjuvant hormonal treatment) were rated using multivariate Cox regression analysis. A p-value < 0.05 was considered significant.

Results

Median follow-up time was 59 months (range 4–96) at the time of evaluation. Alive were 171 (86.8%) patients, 10 (5.1%) patients died due to prostate cancer, 15 (7.6%) died due to other causes with complete disease remission and one (0.5%) patient had a PSA relapse, but died from an unrelated reason. Five-year OS was 86% (Figure 1a) and bDFS 70% (Figure 1b). We analyzed the influence of T stage, Gleason score, initial PSA value, radiotherapy dose, treated volume and adjuvant hormonal treatment on bDFS. bDFS was significantly influenced by the Gleason score (p=0.017, CI 95% 1.149-4.145), initial PSA value (p=0.039; CI 95% 1-1.013) and adjuvant hormonal treatment (p=0.035; CI 95% 0.241-0.949). There was no significant association between radiotherapy dose or volume and bDFS (Table 3).

PSA relapse was assessed at the time of evaluation in 50 (25.4%) patients. The course of disease after PSA relapse was: skeletal metastasis in 15 (7.6%) patients, local relapse in 2 (1%), and lymph node metastasis alone or in combination with parenchymal organ metastasis (lung, liver, pleural cavity) in 3 (1.5%) patients. PSA relapse without metastasis was noticed in 28 (14.2%) patients.

Gastrointestinal and urogenital toxicity is outlined in Table 4. The most common acute toxicity was diarrhea, which was manageable with pharmacological treatment. Acute grade 4 genitourinary toxicity was an acute urinary obstruction in all cases. Late rectal bleeding was usually manageable with local pharmacologic care, treatment with laser coagulation was performed in 10 (5.2%) patients and surgery was necessary in 2 (1.1%) patients. Late genitourinary side effects were rare and mild bladder bleeding was seen in 12 (6.1%) patients. Hormonal treatment was well tolerated and none of the patients required discontinuation. The most frequent side effect of hormonal treatment was gynecomastia (almost 80% of the patients).

Table 3. Multivariate analysis of factors influencing bDFS

Factors	*Sig.*	*Exp(B)*	*95.0% CI for Exp(B)*	
			Lower	*Upper*
Gleason score	0.017	2.183	1.149	4.145
Treated volume	0.418	1.331	0.666	2.659
Adjuvant hormonal treatment	0.035	0.479	0.241	0.949
Initial PSA value	0.039	1.007	1.000	1.013
Radiotherapy dose	0.545	0.931	0.739	1.173

Table 4. Acute and late gastrointestinal and genitourinary toxicity

RTOG grade	*0*	*1*	*2*	*3*	*4*
Acute GI (%)	26.5	38.1	34.8 Diarrhea	0.5 Diarrhea with parenteral support	0
Acute GU (%)	27	46.5	20.5 Frequency, dysuria	3.8 Frequency, dysuria, bladder spasm	2.2 Acute obstruction
Late GI (%)	54.7	12.8	26.2 Rectal bleeding	5.2* Rectal bleeding with laser coagulation	1.1 Bleeding with perforation
Late GU (%)	80.2	8.0	10.2 Intermittent macroscopic hematuria	0.5 Frequent macroscopic hematuria	1.1 Severe hemorrhagic cystitis

*argon-laser coagulation was considered as grade 3 late rectal toxicity
GI: gastrointestinal, GU: genitourinary

Discussion

Analysis of treatment results revealed bDFS comparable with the majority of published reports. Treatment toxicity was acceptable. It is concluded that radical treatment combining short term neoadjuvant hormonal therapy, high dose radiotherapy and post-radiation adjuvant hormonal therapy in a specified group of patients is an effective and well tolerated treatment option.

Analysis of variables influencing the disease outcome was disappointing. We confirmed a significant influence of tumor-related variables (PSA and Gleason score). This information has been previously published by other authors [6,7]. The combination of risk factors is also used for determination of the extent of the disease (for example Roach's equation).

Only adjuvant hormonal treatment significantly influenced bDFS in the analysis of treatment-related factors. Interestingly, the subgroup of patients with worse prognostic factors and adjuvant treatment had better outcomes than the subgroup with better prognostic factors but without adjuvant treatment. However, we suspect that the effect of adjuvant hormonal treatment may be lost with longer follow-up time. Intensification of local therapy (dose escalation and pelvic irradiation) does not influenced outcome. On the other hand, symptomatic local-regional failures are rare. We cannot exclude local persistent disease, which may be the source of PSA relapse and distant metastasis during the disease course, since we didn't perform biopsy of the prostate after radiotherapy in case of rising PSA. We suppose that some patients with relapse had undetected or undetectable dissemination at the time of diagnosis and others had undetectable locally persistent disease.

There are two possible solutions for this group of patients. The first is centered on better diagnostics before treatment. Cholin-PET/CT examination, MRI and a sodium fluoride PET bone scan [8-11] are new methods, which can be potentially useful in this setting. Unfortunately, these methods aren't ready for routine clinical use yet.

The second strategy consists of intensification of primary or adjuvant therapy. Dose escalation is controversial in high risk prostate cancer. Due to a high risk of dissemination outside the treated volume and potential late effects of radiotherapy some authors prefer moderately high doses [12]. On the other hand, excellent results have also been achieved after very intensive local radiotherapy [2,13] and the effect of adjuvant hormonal treatment may be lost with dose escalation [13]. The potential for dissemination from a suboptimally treated primary disease still exists. We did not observe any dependence between radiotherapy dose and bDFS. It can be speculated that doses between 70–78 Gy are still low in high risk prostate cancer [14,15]. Treatment volume also had no impact on bDFS in our group of patients, although some data support the use of whole pelvic radiotherapy [16-20]. Evaluation of this parameter was compromised because of selection bias in our patient group. Some authors indicated that prolonged neoadjuvant hormonal treatment was more effective than short-term hormonal treatment in the high risk group [21,22] and a PSA decline after neoadjuvant hormonal treatment had positive prognostic value [23]. Today neoadjuvant hormonal treatment is administered for 3-9 months, based on PSA response. Adjuvant hormonal therapy is a standard option in patients with high risk prostate cancer and improves OS within the high risk group by 16% [24]. However, long-term adjuvant hormonal treatment is accompanied with many side effects, including cardiovascular, and a higher incidence of diabetes mellitus [25,26], although recent reports dispute the cardiovascular risks [27]. Prolonged adjuvant hormonal treatment is therefore controversial. Adjuvant chemotherapy is another possibility which has been discussed in the literature. Some authors described the feasibility and effectiveness of neoadjuvant chemotherapy before surgery [28,29]. The combination of radiotherapy and chemotherapy seems to achieve 5-year bDFS of 66% [30]. Randomized studies evaluating this issue are currently underway [31]. Adjuvant immunotherapy based on dendritic cells vaccination also appears to be very promising; however, the effectiveness of this modality has only been demonstrated in metastatic forms of the disease [32].

Conclusion

A combination of neoadjuvant hormonal treatment, radiotherapy with moderately high doses and post-irradiation adjuvant hormonal treatment leads to a relatively high rate of long-term biochemical DFS and high locoregional control rate in high risk prostate cancer patients. Only the administration of adjuvant hormonal treatment showed a statistically significant impact on bDFS. Nonetheless, approximately one quarter of high risk patients had biochemical dis-

ease relapse. Part of this group can benefit from radiotherapy dose escalation, others would benefit from clinical trials with new strategies based on systemic adjuvant treatments, such as prolonged adjuvant hormonal treatment, chemotherapy or immunotherapy.

References

1. Pilepich MV, Caplan R, Byhardt RW et al. Phase III trial of androgen suppression using goserelin in unfavorable-prognosis carcinoma of the prostate treated with definitive radiotherapy: report of Radiation Therapy Oncology Group Protocol 85-31. J Clin Oncol 1997;15:1013-1021.
2. Deutsch I, Zelefsky MJ, Zhang Z et al. Comparison of PSA relapse-free survival in patients treated with ultra-high-dose IMRT versus combination HDR brachytherapy and IMRT. Brachytherapy 2010; 9:313-318.
3. D'Amico AV, Whittington R, Malcowicz SB et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or intestinal radiation therapy for clinically localized prostate cancer. JAMA 1998; 280: 969-974.
4. Roach M 3rd, Marquez C, Yuo HS et al. Predicting the risk of lymph node involvement using the pre-treatment prostate specific antigen and Gleason score in men with clinically localized prostate cancer. Int J Radiat Oncol Biol Phys 1994;28:33-37.
5. Eifler JB, Feng Z, Lin BM et al. An updated prostate cancer staging nomogram (Partin tables) based on cases from 2006 to 2011. BJU Int 2013;111:22-29.
6. Ploussard G, Masson-Lecomte A, Beauval JB et al. Prostate Cancer Committee of the French Association of Urology. Radical Prostatectomy for High-risk Prostate Cancer Defined by Preoperative Criteria: Oncologic Follow-up in National Multicenter Study in 813 Patients and Assessment of Easy-to-use Prognostic Substratification. Urology 2011;78:607-613.
7. Stone NN, Stone MM, Rosenstein BS et al. Influence of pretreatment and treatment factors on intermediate to long-term outcome after prostate brachytherapy. J Urol 2011;185:495-500.
8. Eschmann SM, Pfannenberg AC, Rieger A et al. Comparison of 11C-choline PET/CT and whole body-MRI for staging of prostate cancer. Nuklearmedizin 2007; 46:161–168.
9. Scattoni V, Picchio M, Suardi N et al. Detection of lymph-node metastases with integrated [11C]choline PET/CT in patients with PSA failure after radical retropubic prostatectomy: results confirmed by open pelvic-retroperitoneal lymphadenectomy. Eur Radiol 2007;52:423–429.
10. Schirrmeister H, Guhlmann A, Kotzerke J et al. Sensitivity in detecting osseous le-sions depends on anatomic localization: planar bone scintigraphy versus 18F PET. J Nucl Med 1999; 40: 1623-1629.
11. Even-Sapir E, Metser U, Mishani E et al. The detection of bone metastases in patients with high risk prostate cancer: 99mTc MDP planar bone scintigraphy, single and multi field of view SPECT, 18F-fluoride PET and 18F-fluoride PET/CT. J Nucl Med 2006; 47: 287-297.
12. Bolla M, Collette L, Blank L et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. Lancet 2002;360(9327):103-106.
13. Valicenti RK, Bae K, Michalski J et al, Does hormone therapy reduce disease recurrence in prostate cancer patients receiving dose- escalated radiation therapy? An analysis of Radiation Therapy Oncology Group 94-06. Int J Radiat Oncol Biol Phys 2011 ;79:1323-1329.
14. Zelefsky MJ, Pei X, Chou JF et al. Dose Escalation for Prostate Cancer Radiotherapy: Predictors of Long-Term Biochemical Tumor Control and Distant Metastases-Free Survival Outcomes. Eur Urol 2011; 60:1133-1139.
15. Cahlon O, Zelefsky MJ, Shippy A et al. Ultra-high dose (86.4 Gy) IMRT for localized prostate cancer: toxicity and biochemical outcomes. Int J Radiat Oncol Biol Phys 2008; 71:330-337.
16. Mantini G, Tagliaferri L, Mattiucci GC et al. Effect of Whole Pelvic Radiotherapy for Patients With Locally Advanced Prostate Cancer Treated With Radiotherapy and Long-Term Androgen Deprivation Therapy.Int J Radiat Oncol Biol Phys 2011; 81:721-726.
17. Aizer AA, Yu JB, McKeon AM et al. Whole pelvic radiotherapy versus prostate only radiotherapy in the management of locally advanced or aggressive prostate adenocarcinoma. Int J Radiat Oncol Biol Phys 2000; 75:1344-1349.
18. Roach M 3rd, DeSilvio M, Lawton C et al. Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413. J Clin Oncol 2003; 21: 1904–1911.
19. Garipagaoglu M, Sengoz M, Senkesen O et al. Does pelvic lymph nodes irradiation using intensity modulated radiation therapy increase rectal and bladder toxicities in patients with prostate carcinoma? J BUON 2010;15:668-673.
20. Seaward SA, Weinberg V, Lewis P et al Improved freedom from PSA failure with whole pelvic irradiation for high-risk prostate cancer. Int J Radiat Oncol Biol Phys 1998; 42: 1055–1062.

21. Crook J, Ludgate C, Malone S et al. Final report of multicenter Canadian Phase III randomized trial of 3 versus 8 months of neoadjuvant androgen deprivation therapy before conventional-dose radiotherapy for clinically localized prostate cancer.Int J Radiat Oncol Biol Phys 2009;73:327-333.
22. Denham JW, Steigler A, Lamb DS et al. Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised trial. Lancet Oncol 2011;12:451-459.
23. Alexander A, Crook J, Jones S et al. Is biochemical response more important than duration of neoadjuvant hormone therapy before radiotherapy for clinically localized prostate cancer? An analysis of the 3- versus 8-month randomized trial. Int J Radiat Oncol Biol Phys 2010; 76:23-30.
24. Bolla M, Gonzalez D, Warde P et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. N Engl J Med 1997;337:295–300.
25. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol 2006;24:4448–4455.
26. Saigal CS, Gore JL, Krupski TL et al. Long term androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. Cancer 2007;110:1493–1500.
27. Alibhai SM, Duong–Hua M, Sutradhar R et al. Impact of androgen deprivation therapy on cardiovascular disease and diabetes. J Clin Oncol 2009;27:3452–3458.
28. Dreicer R, Magi-Galluzzi C, Zhou M et al. Phase II trial of neoadjuvant docetaxel before radical prostatectomy for locally advanced prostate cancer.Urology 2004;63:1138–1142.
29. Hussain M, Smith DC, El-Rayes BF et al. Neoadjuvant docetaxel and estramustine chemotherapy in high-risk/locally advanced prostate cancer.Urology 2003;61:774–780.
30. Bolla M, Hannoun-Levi JM, Ferrero JM et al. Concurrent and adjuvant docetaxel with three-dimensional conformal radiation therapy plus androgen deprivation for high-risk prostate cancer: preliminary results of a multicentre phase II trial. Radiother Oncol 2010; 97:312-317.
31. Rosenthal SA, Bae K, Pienta KJ et al. Radiation Therapy Oncology Group Trial 9902. Phase III multi-institutional trial of adjuvant chemotherapy with paclitaxel, estramustine, and oral etoposide combined with long-term androgen suppression therapy and radiotherapy versus long-term androgen suppression plus radiotherapy alone for high-risk prostate cancer: preliminary toxicity analysis of RTOG 99-02. Int J Radiat Oncol Biol Phys 2009;73:672-678.
32. Kantoff PW, Higano CS, Shore ND et al. IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010; 363:411-422.