Outcome analysis of prostate cancer patients with pre-treatment PSA greater than 50 ng/ml

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Introduction: *The optimal management of prostate cancer patients presenting with prostate specific antigen (PSA) levels greater than 50 ng/ml is controversial. The purpose of this study was to investigate factors associated with overall survival and biochemical outcome in a high-risk prostate cancer population with PSA > 50.0 ng/ml at time of diagnosis, and no clinical or radiological evidence of metastatic disease.*

Materials and methods: *A single institution chart review was conducted at the London Regional Cancer Program on 138 patients who presented with PSA levels greater than 50 ng/ml. Forty-eight (34.8%) of these patients had no clinical or radiological evidence of metastatic disease at time of diagnosis. Patient, tumor, and treatment related variables and biochemical/clinical outcomes were collected for analysis. Median follow-up was 49.4 months. Descriptive and univariable/multivariable analyses were performed in order to assess prognostic factors for freedom from biochemical failure and overall survival.*

Results: *On univariate analysis, clinical T-stage, Gleason score, primary RT, and PSA measurements including initial PSA, nadir PSA, change in PSA and respective log values were prognostic of biochemical failure. On multivariate analysis, log nadir PSA was prognostic of biochemical failure. No prognostic variables were significant for overall survival in this analysis.*

Conclusions: *High-risk prostate cancer patients with PSA > 50 ng/ml and no evidence of metastatic disease have survival characteristics are similar to other high-risk populations reported in the literature, and should be considered for aggressive therapy. The logarithm of the PSA nadir was found to predict for durable biochemical control on multivariable analysis.*

Key Words: high-risk, prognostic factor, prostate cancer, PSA

Introduction

Optimal management of high-risk prostate cancer is debatable. High pre-treatment PSA values have been correlated with increased risk of extracapsular disease, seminal vesicle involvement, and nodal spread as well as adverse biochemical and clinical outcomes.[1] Despite negative staging investigations such as CT and bone scans, there is a significant concern for micro-metastatic disease beyond the local-regional area in patients who present with PSA > 20 ng/ml. This concern is intensified in the subset of patients who have PSA > 50 ng/ml.[2] Integration of surgery, radiation therapy, and hormonal therapy can be challenging given the uncertainty of the individual patient risk for micrometastatic disease and future biochemical and clinical relapse.[3] In this challenging clinical situation, the utility of aggressive local and regional therapy is unclear. Appropriate options for initial treatment may include either radical radiation therapy with adjuvant androgen suppression, or androgen suppression alone. In addition, the clinical criteria for the appropriate integration of radical prostatectomy in this patient population are unknown.

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The objective of this study was to assess for prognostic factors for both biochemical and clinical outcomes in patients presenting to a tertiary care cancer clinic with PSA > 50 ng/ml and no evidence of metastatic disease at the time of initial diagnosis.

Patients and methods

Patient selection

A single institution cohort of 187 cases of pathologically confirmed prostate adenocarcinoma presenting to the London Regional Cancer Program (LRCP) with PSA > 50 ng/ml was reviewed for this study. The patients were from LRCP's southwestern Ontario catchment area (estimated population of 1.5 million). The study group represents 187 (5.9%) of a total of 3160 patients with prostate cancer referred to the LRCP between January 2001 and October 2005, inclusive. This specific study time period was selected due to readily accessible electronic prostate cancer and baseline PSA clinical data (OPIS, Cancer Care Ontario), as well as to allow for follow-up time to assess patient outcomes. Patients with treatment for prostate cancer prior to presenting with a PSA > 50 ng/ml were excluded (twenty-five cases). Twenty-four additional cases were excluded because of incomplete patient profile (two cases), PSA over 50 ng/ml not identified (two cases), or follow-up outside of the LRCP catchment area (twenty cases). The remaining 138/187 (73.8%) cases of prostate cancer were reviewed. Of these, 48/138 (34.8%) had no clinical or radiological evidence metastatic disease and were submitted to analysis of prognostic variables.

Information obtained from the charts included clinical staging (T, N, M), pathological staging (pT, pN, pM), Gleason score, baseline PSA value, treatment (modality, date, extent) including surgery, hormone manipulation, radiation treatment, and chemotherapy. The dates of follow-up and subsequent PSA measurements were recorded.

Staging criteria

Metastatic disease was diagnosed by radiological evidence of nodal or distant spread was required to be detected by means of bone scan, CT scan or plain film x-ray. On CT evaluation, abdominal or pelvic lymph nodes > 1.5 cm were considered indicative of malignant lymphadenopathy. Equivocal bone scans or CT scans were considered negative unless confirmatory testing with other radiologic modalities (e.g. MRI, CT, x-ray) were positive. Patients with clinical and/or pathological staging of T1-T4 N0 M0 were classified as having no evidence of metastatic disease, for the purposes of this study. All patients with N1 or M1 disease were considered to have metastatic disease for the purpose of this study. Initial staging investigations that were completed include bone scans (45/48), CT pelvis (34/48), CT abdomen (33/48), and chest x-ray (16/48).

Statistical analysis

Descriptive statistics were expressed as mean +/- standard deviation and 95% confidence interval (CI) of the mean difference, or as median with range. Prognostic variable analyses were carried out using the Phoenix (Houston) (nadir + 2.0 ng/ml at call date) of biochemical failure[4] and overall survival as endpoints. The prognostic (explanatory) variables assessed in this study included: presenting PSA (continuous variable), age (continuous variable), clinical T stage (T1T2 vs. T3T4), Gleason score (2-7 versus 8-10), percentage of biopsy core positive (continuous variable), prostate volume (continuous variable), primary radiotherapy (presence/absence), total androgen blockade (yes/no), PSA (and log PSA) at time of presentation (continuous variable), nadir PSA (and respective log, continuous variable), and absolute change in PSA (and respective log, continuous variable).

Descriptive statistics and testing of proportional hazards assumptions, univariable, and multivariable analyses for time to Phoenix biochemical failure and overall survival (using the Cox proportional hazards model) were performed using SAS/STAT version 8.2 software (SAS Institute Inc., Cary, NC, USA). Actuarial freedom from biochemical failure and overall survival were calculated by the Kaplan-Meier methods for illustrative purposes.

Results

Patient population

The mean age of the study population was 66.6 years (SD 8.8 years). Median PSA at time of diagnosis was 112.7 ng/ml (mean 108.2 ng/ml, range 51.23-668 ng/ml). The average prostate volume determined by TRUS was 55.13 cc (SD 35.50 cc). Median Gleason score was 8 (range 6-10), Table 1. Clinical T-stage was stage T1 6/48 (12.5%), T2 16/48 (33.3%), T3 19/48 (39.6%), T4 3/48 (6.25%) and Tx 4/48 (8.33%).

Treatment

A total of 46/48 (95.8%) patients received initial hormonal management with 41 (85.4%) receiving LHRH agonists (median 36 months, range 3-72 months), 17 (35.4%) receiving anti-androgenic therapy,

TABLE 1. **Patient, tumor, and treatment demographics n = 48**

Mean presenting age, years (SD)	66.6 (8.8)
Mean initial serum PSA, ng/ml (SD)	112.7 (108.2)
Median Gleason score, (range)	8 (6-10)
Prostate volume, cc (SD)	55.13 (35.30)
Biopsy core involvement, % (SD)	70.78 (25.49)
Primary radiotherapy, %	50.0

SD = standard deviation; PSA = prostate specific antigen, cc = cubic centimeters

and 5 (10.4%) managed by orchidectomy. Twenty-four (50.0%) patients received local-regional radiation (median dose/fractions was 70 Gy in 35 fractions to the prostate, with 44 Gy in 22 fractions to the pelvis). Three (6.3%) patients received radical prostatectomy with postoperative radiation therapy.

A total of 13 patients (27.1%) received palliative chemotherapy, and 6 (12.5%) received palliative radiation therapy during their treatment.

Survival analysis

Median follow-up was 49.4 months (range 12.6 to 120.9 months) from time of initial diagnostic PSA test. A total of 24 (50.0%) patients had Phoenix criteria biochemical failure during follow-up. Median time to Phoenix criteria biochemical failure was 60.5 months, Figure 1. A total of 25/48 patients (not including five orchidectomy patients) remain on hormonal therapy at last follow-up.

At last follow-up, 42 (87.5%) patients were alive, 2 (4.2%) were dead of prostate cancer, and 4 (8.3%) patients were dead with unknown disease status. Median survival was not reached at the time of this report. A gradual decrease in the number of surviving patients between 24 and 48 months is demonstrated on the Kaplan-Meier plot of overall survival, Figure 2.

Prognostic factors

Freedom from biochemical failure was calculated based on the Phoenix criteria of biochemical failure. Biochemical failure after initial treatment was predicted by clinical T-stage (p = 0.0072), Gleason score (p = 0.0049), primary RT (p = 0.0388), and PSA measurements including initial PSA (p = 0.0237), nadir PSA (p = 0.0009), change in PSA (p = 0.0501) and respective log values (p = 0.0364, 0.0002, 0.0088). On multivariable analysis, log nadir PSA (p = 0.001) was found to be an independent prognostic factor (hazard ratio of 2.35), predictive for delayed biochemical failure. Table 2 summarizes the univariable and multivariable analyses for time to biochemical failure. Univariable analysis of overall survival did not identify any significant prognostic factors, Table 3.

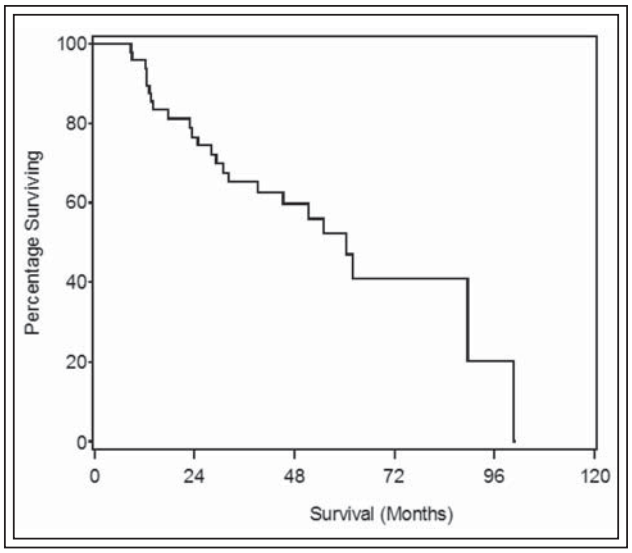

Figure 1. Kaplan-Meier plot of freedom from Phoenix (ASTRO) criteria biochemical failure.

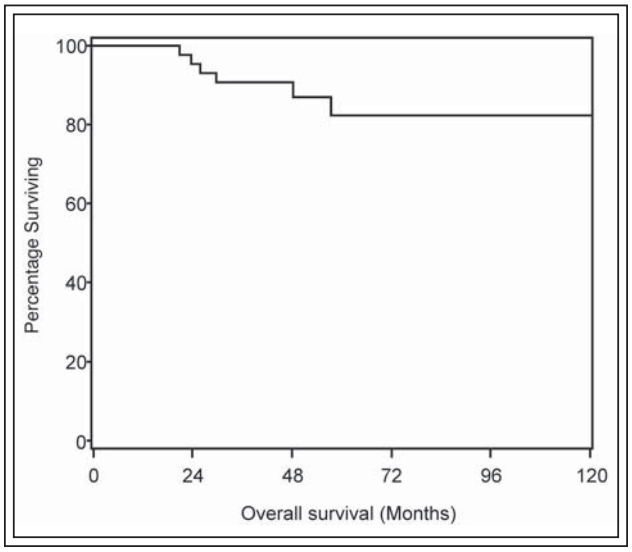

Figure 2. Kaplan-Meier plot of overall survival.

TABLE 2. **Univariable and multivariable analysis of time to Phoenix (ASTRO) biochemical failure**

Variable	Univariable			Multivariable		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Age at presentation	0.900	0.545-1.486	0.6796			
Clinical T-stage	3.832	1.440-10.199	0.0072			
Gleason score	1.704	1.176-2.471	0.0049			
Prostate volume	1.014	0.998-1.030	0.0962			
Biopsy core involved (%)	1.020	0.982-1.060	0.3089			
Primary RT	2.579	1.050-6.336	0.0388			
LHRH	0.993	0.293-3.361	0.9907			
Antiandrogen	0.935	0.395-2.212	0.8776			
PSA at presentation	1.004	1.001-1.007	0.0237			
Log presenting PSA	1.970	1.044-3.717	0.0364			
Nadir PSA	1.025	1.025-1.102	0.0009			
Log nadir PSA	1.717	1.286-2.291	0.0002	2.350	1.415-3.903	0.001
Change PSA	1.004	1.000-1.007	0.0501			
Log change PSA	0.666	0.492-0.903	0.0088			

TABLE 3. **Univariable and multivariable analysis of overall survival**

Variable	Univariable		
	Hazard ratio	95% CI	P value
Age	1.035	0.394-2.718	0.9438
Clinical T-stage	6.380	0.741-54.90	0.0915
Gleason score	0.878	0.401-1.923	0.7441
Prostate volume	1.012	0.993-1.031	0.2284
Biopsy core involved (%)	0.992	0.956-1.029	0.6548
Primary RT	5.112	0.597-43.80	0.1366
Antiandrogen	0.727	0.132-4.010	0.7143
Log presenting PSA	1.507	0.447-5.080	0.5084
Log nadir PSA	1.631	0.909-2.928	0.1011
Log change PSA	0.656	0.349-1.234	0.1908

Discussion

PSA has consistently been identified as a useful predictor of prostate cancer disease burden. Correlating preoperative serum PSA, clinical (TNM) stage, and Gleason score with surgical pathology results, Partin et al have created tables to summarize predictive risks of extra-capsular spread, seminal vesicle extension and lymph node involvement.[5] Similarly, patients diagnosed with localized prostate cancer with characteristics of PSA > 20 ng/ml, Gleason > 7 and clinical stage > T2c are at the highest risk of clinical and/or biochemical progression of disease after therapy.[3,6] Given the high risk of biochemical failure with PSA > 20 ng/ml at the time of diagnosis, the concern of occult micrometastatic disease is intensified when PSA values are found to be greater than 50 ng/ml at time of diagnosis.[2]

Within the context of this study, patients were assessed for factors prognostic of durable biochemical

response and overall survival. By univariate analysis, several factors including clinical T-stage and Gleason score, use of primary radiation therapy, and PSA values including the presenting PSA and PSA kinetics were prognostic for freedom from biochemical. In patients with clinical stage T1b-T2, M0 prostate cancer, Ray et al observed that low PSA nadir predicted for improved disease-free survival, and lower rate of distant metastasis.[7] The observation that low PSA nadir predicts for improved disease-free survival was also true in our study population in which 45.9% had T-stage > T2. Primary radiation therapy, given in addition to hormonal therapy, was also predictive for improved freedom from biochemical failure. This suggests that patients may derive benefit from the combination of total androgen blockade with local therapy, where appropriate. Furthermore, patients who respond well to therapy have longer freedom from biochemical failure.

The rate of disease progression occurred over a prolonged period of time in the study population. Median biochemical failure-free survival was reached at 60.5 months, and 87.5% of this group was alive at time of last follow-up. These values are in accordance with biochemical failure rates of high-risk prostate cancer patients reported in recent literature; patients with localized prostate cancer and high pretreatment PSA who received radical prostatectomy with or without adjuvant hormone therapy, experienced 5-year biochemical failure-free survival rates range from 24% to 58%.[8-11] In the current study, a plateau in patients developing biochemical failure cannot be excluded, suggesting that there is a potentially curable cohort within this ultra-high risk prostate cancer population.

The Kaplan-Meier plot of overall survival in this patient population was plotted, Figure 3 against historical controls for comparison of survival data.[12-15] Historical control groups included either primary radiation therapy ± adjuvant hormonal therapy or radical prostatectomy with pelvic lymph node dissection ± adjuvant hormonal therapy. Comparator patient populations included patients with high-risk localized disease[12-14] and node positive disease.[15] Half of the current study patients received primary radiation therapy followed by hormone therapy, and approximately half received hormone therapy alone. Study patients had survival rates surpassed only by the comparison group with localized disease selected for radical prostatectomy and adjuvant hormone treatment in the study by Messing et al.[14] Therefore, patients with PSA > 50 ng/ml at presentation will benefit from initial clinical and radiological staging to exclude patients with metastatic disease from aggressive combined hormonal therapy and local therapy. The risk of micrometastatic disease in this group of patients did not preclude benefit from local treatment within the time frame of this study.

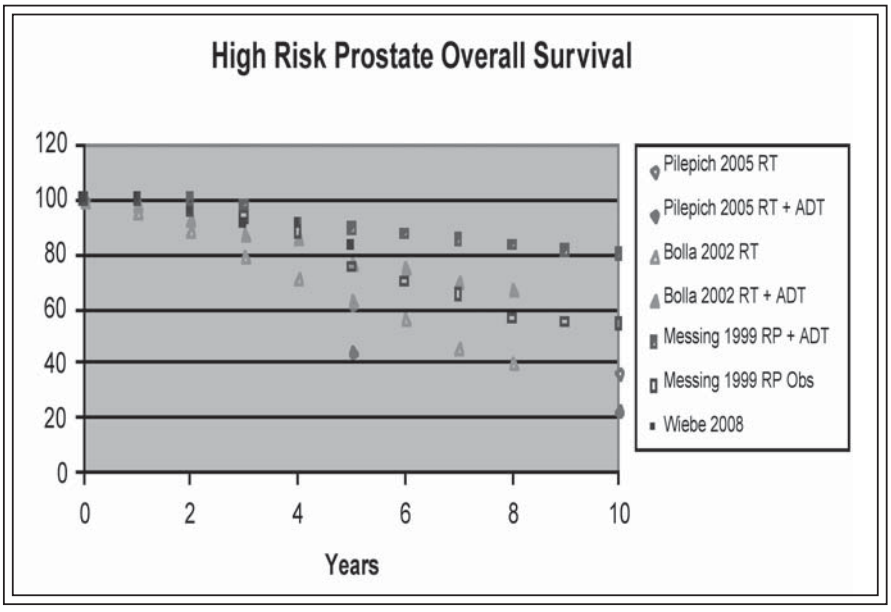

Figure 3. Comparison of estimates of 5-year overall survival in high-risk prostate cancer patients followed in recent study protocols. Hollow markers: primary treatment followed by observation. Solid markers: primary treatment followed by androgen deprivation therapy.

Limitations of this study included the single institution nature of this study. Due to the limited sample size and low event rate in the study population, further follow-up is required for robust prognostic analysis of biochemical and overall survival endpoints. A larger multi-institutional database would be valuable in further assessing the strength of prognostic variables in ultra-high risk prostate cancer. We intend to update this database at 10 years median follow-up to further describe this patient population.

In high-risk localized disease, treatment with definitive local therapy and androgen suppression provides the best results in PSA control. Androgen deprivation therapy of 3 years duration is standard therapy and confers improvement in both biochemical

control and overall survival.[8-9] Longer courses of androgen deprivation therapy may improve outcome, even in the setting of combined modality therapy. Recent studies in external beam radiation therapy indicate that dose-escalation represents an improvement over conventional radiation therapy in obtaining PSA control, and in decreasing incidence of distant metastases.[16,17] Multimodality approaches figure prominently in the evolving management of these high-risk patients; concurrent radio-chemotherapy, particularly with docetaxel-based treatment, is under study as a new approach to unfavorable localized prostate cancer.[18]

Conclusions

In conclusion, biochemical control and survival can be achieved in a subset of the patients population that presents with PSA > 50 ng/ml. Overall survival in this patient population was 87.5% at median follow-up of 49.4 months. It is hypothesized that long-term biochemical control and overall survival may be possible in a large subset of this population by comparison to published historical control groups. The kinetics of PSA response, particularly log nadir PSA, may be indicative of durability of biochemical disease-free survival. Aggressive adjuvant androgen deprivation therapy combined with primary local therapy is indicated for appropriate high-risk patients without evidence of metastatic disease. □

References

1. Pisansky TM, Kahn MJ, Rasp GM, Cha SS, Haddock MG, Bostwick DG. A multiple prognostic index predictive of disease outcome after irradiation for clinically localized prostate carcinoma. *Cancer* 1997;79:337.
2. Ou YC, Chen JT, Cheng CL, Ho HC, Yang CR. Radical Prostatectomy for Prostate Cancer Patients with Prostate-specific Antigen >20 ng/ml. *Japanese J Clin Onc* 2003;33:574-579.
3. Lukka H, Warde P, Pickles T, Morton G, Brundage M, Souhami L, Canadian GU Radiation Oncologist Group. Controversies in prostate cancer radiotherapy: consensus development. *Can J Urol* 2001;8:1314-1322.
4. Roach M 3rd, Hanks G, Thames H Jr, Schellhammer P, Shipley WU, Sokol GH et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys* 2006;65:965-974.
5. Partin AW, Kattan MW, Subong ENP, Walsh PC, Wojno KJ, Oesterling JE et al. Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer: a multi-institutional update. *JAMA* 1997;277:1445-1451.
6. Stock RG, Ho A, Cesaretti JA, Stone NN. Changing the patterns of failure for high-risk prostate cancer patients by optimizing local control. *Int J Radiat Oncol Biol Phys* 2006;66:389-394.
7. Ray ME, Thames HD, Levy LB, Horwitz EM, Kupelian PA, Martinez AA et al. PSA nadir predicts biochemical and distant failures after external beam radiotherapy for prostate cancer: a multi-institutional analysis. *Int J Radiat Oncol Biol Phys* 2006;64:1140-1150.
8. Bastide C, Kuefer R, Loeffler M, de Petriconi R, Gschwend J, Hautmann R. The role of radical prostatectomy in patients with clinically localized prostate cancer and a prostate-specific antigen level >20 ng/ml. *Prostate Cancer Prostatic Dis* 2006;9:239-244.
9. Brandli DW, Koch MO, Foster RS, Bihrle R, Gardner TA. Biochemical disease-free survival in patients with a high prostate-specific antigen level (20-100 ng/mL) and clinically localized prostate cancer after radical prostatectomy. *BJU Int* 2003;92:19-22.
10. D'Amico AV, Hui-Chen M, Renshaw AA, Sussman B, Roehl KA, Catalona WJ. Identifying men diagnosed with clinically localized prostate cancer who are at high risk for death from prostate cancer. *J Urol* 2006;176:S11-S15.
11. Vanasupa BP, Paquette EL, Wu H, Sun L, McLeod DG, Moul JW. The role of radical prostatectomy in patients with pretreatment prostate-specific antigen > or = 40 ng/mL. *Urol Oncol* 2002;7:167-172.
12. Bolla M, Gonzalez D, Warde P, Dubois JB, Mirimanoff RO, Storme G et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med* 1997;337:295-300.
13. Bolla M, Collette L, Blank L, Warde P, Dubois JB, Mirimanoff RO 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;360:103-106.
14. Messing EM, Manola J, Sarosdy M, Wilding G, Crawford ED, Trump D. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. *N Engl J Med* 1999;341:1781-1788.
15. Pilepich MV, Winter K, Lawton CA, Krisch RE, Wolkov HB, Movsas B et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma--long-term results of phase III RTOG 85-31. *Int J Radiat Oncol Biol Phys* 2005;61:1285-1290.
16. Pollack A, Zagars GK, Starkschall G, Antolak JA, Lee JJ, Huang E et al. Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2002;53:1097-1105.
17. Zelefsky MJ, Yamada Y, Fuks Z, Zhang Z, Hunt M, Cahlon O, Park J, Shippy A. Long-term Results of Conformal Radiotherapy for Prostate Cancer: Impact of Dose Escalation on Biochemical Tumor Control and Distant Metastases-Free Survival Outcomes. *Int J Radiat Oncol Biol Phys* 2008 Feb 13.epub.
18. Kumar P, Perrotti M, Weiss R, Todd M, Goodin S, Cummings K et al. Phase I trial of weekly docetaxel with concurrent three-dimensional conformal radiation therapy in the treatment of unfavorable localized adenocarcinoma of the prostate. *J Clin Oncol* 2004;22:1909-1915.