JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2010;40(7)652–657
doi:10.1093/jjco/hyq032
Advance Access Publication 8 April 2010

Outcome of Patients with Localized Prostate Cancer Treated by Radiotherapy After Confirming the Absence of Lymph Node Invasion

Noriyuki Suzuki[1], Masaki Shimbo[1], Yoshiyasu Amiya[1], Susumu Tomioka[1], Takayuki Shima[1], Shino Murakami[1], Hiroomi Nakatsu[1], Sayako Oota[2] and Jun Shimazaki[3,*]

[1]Department of Urology, Asahi General Hospital, Asahi, Chiba, [2]Department of Radiology, Asahi General Hospital, Asahi, Chiba and [3]Department of Urology, Graduate School of Medicine, Chiba University, Chiba, Japan

*For reprints and all correspondence: Department of Urology, Graduate School of Medicine, Chiba University, Inohana, Chuoku, Chiba-shi 260-8670, Japan. E-mail: shimajun@opal.famille.ne.jp

Received November 27, 2009; accepted February 23, 2010

Objective: Management of lymph nodes in radiotherapy for prostate cancer is an issue for curative intent. To find the influence of lymph nodes, patients with T1–T3 prostate cancer and surgically confirmed negative nodes were treated with radiotherapy.
Methods: After lymphadenectomy, 118 patients received photon beam radiotherapy with 66 Gy to the prostate. No adjuvant treatment was performed until biochemical failure. After failure, hormone therapy was administered. Follow-up period was 57 months (mean).
Results: Biochemical failure occurred in 47 patients. Few failures were observed in patients with low (24%) and intermediate risks (14%). In contrast, 64% of high-risk patients experienced failure, 97% of whom showed until 36 months. Most patients with failure responded well to hormone therapy. After 15 months (mean), a second biochemical failure occurred in 21% of patients who had the first failure, most of them were high risk. Factors involving failure were high initial and nadir prostate-specific antigen, advanced stage, short prostate-specific antigen-doubling time and duration between radiation and first failure. Failure showed an insufficient reduction in prostate-specific antigen after radiotherapy. Factor for second failure was prostate-specific antigen-doubling time at first failure.
Conclusions: Half of high-risk patients experienced biochemical failure, indicating one of the causes involves factors other than lymph nodes. Low-, intermediate- and the other half of high-risk patients did not need to take immediate hormone therapy after radiotherapy. After failure, delayed hormone therapy was effective. Prostate-specific antigen parameters were predictive factors for further outcome.

Key words: prostate cancer – radiotherapy – biochemical failure – high risk – PSA-doubling time

INTRODUCTION

Localized prostate cancer has been treated with various methods, and the results were improved gradually. Of these technologies, surgical and radiological treatments play a leading part in the field (1). An important issue in radiotherapy is conjecture of the status of regional lymph nodes. There are many guidelines for the estimation of possible invasion in the lymph nodes, where they are estimated from the stage, prostate-specific antigen (PSA) and histological findings from biopsy (2,3). The predictive score obtained by assuming these guidelines, however, may be indefinite (4,5). On the basis of the uncertainty for predicting invasion, whole pelvic radiotherapy has been discussed to improve PSA-free survival (6). In order to exclude the influence of regional lymph nodes on whether invasion may be present,

extirpation of them before radiotherapy seems to be advisable. The present study was undertaken first to perform the lymphadenectomy in patients with localized prostate cancer. Thereafter, the patients with N0 received radiotherapy alone.

PATIENTS AND METHODS

Patients

Between January 1999 and January 2006, pelvic lymphadenectomy was performed in 168 patients with T1–T3 prostate cancer who selected rather non-aggressive treatment at Asahi General Hospital. For lymphadenectomy, the obturator, external and internal iliac lymph nodes were removed via an abdominal incision or laparoscopic surgery. Of these cases, 144 cases (86%) showed negative findings. Stage was defined with UICC TNM classification (6th edn, 2002). Risk was classified into low (T1bc and T2a, $<$10 ng/ml of PSA and $\leq$6 of Gleason score), intermediate (T2b,c or 10–20 ng/ml of PSA or 7 of Gleason score) or high ($\geq$ T3 or $\geq$20 ng/ml of PSA or $\geq$8 of Gleason score) according to NCCN criteria (7). After radiotherapy, no adjuvant hormone therapy was administered until biochemical failure. PSA was determined every 3 or 6 months, and when elevation occurred, duration of determination was shortened. Biochemical failure was judged with Phoenix criteria (elevated 2 ng/ml of PSA or more from baseline, or clinical relapse) (8). Some patients with biochemical failure experienced second failure, which was judged with increase in PSA from baseline. Prostate biopsy was carried out with 8–12 cores via a perineal route. Gleason score was determined according to ISUP (9). Records of all patients were collected in June 2009 (follow-up, mean 57 months, median 52 months and range 9–119 months). After biochemical failure, most patients received hormone therapy with luteinizing hormone–releasing hormone agonist and 80 mg of bicalutamide daily until the hormone therapy failed. Evaluation for hormone therapy was determined from response to the therapy: decrease of $\geq$50% from baseline in the PSA (partial response, PR), increase of $\geq$25% from baseline in the PSA (progressive disease, PD) or change between PR and PD (no change, NC).

PSA Kinetics

PSA was determined as total PSA using AxSYM PSA Dainapack (Abbot, Tokyo, Japan). PSA-doubling time (PSA-DT) and velocity were calculated by linear regression. A slope was obtained by the least-square test with values of ln PSA (PSA-DT) or those of PSA (velocity) from three or more points. PSA-DT was obtained from ln 2/slope (10). Velocity was determined as a difference per year (11).

Radiation

Conformal radiation with a photon beam at 10 MV was used with a multileaf collimator (leaves 10 mm at isocenter). The clinical target volume was the whole prostate and the planning target volume was created by adding 10 mm anteroposterior and lateral margins. A conventional fractionation of 2 Gy/fraction was administered five times per week for 66 Gy of total radiation dose.

Statistical Analysis

Overall survival was calculated with the Kaplan–Meier method. Statistical difference was determined by the unpaired two-group *t*-test. Odds ratio was calculated by the logistic regression analysis. Values of $P \leq 0.05$ were considered to be significant. All calculations were used with the StatView program.

RESULTS

Biochemical Failure

Of 144 patients with negative node, 118 cases received radiation after confirming no distal metastatic disease using bone scan and abdominal echogram (Table 1). The other 26 cases were treated surgery or hormonal therapy as chosen by the patients. Of 118 patients who received radiation, 47 patients experienced biochemical failure (47 of 118, 40%). Until 36 months after radiation, 42 patients showed biochemical failure, in which high-risk patients were 34 (81%). Occurrence of biochemical failure gradually decreased in number and there was no failure in the remaining patients after 55 months of the latest failure. Duration of biochemical failure was mean of 21 months (median 17 months and range 4–55 months). Rate of failure was 24% in low-risk, 14% in intermediate-risk and 64% in high-risk patients.

The profiles of patients with biochemical failure and failure-free patients were compared (Table 2). Patients with biochemical failure showed the initial, 12 months later and nadir PSA values higher than those in failure-free patients and had a short duration between radiation and nadir. Influences on biochemical failure were the initial PSA values, stage and duration between radiation and nadir (Table 3). Since PSA-DT is a parameter for tumor growth, patients with failure were divided by PSA-DT. A positive relation between duration until nadir and PSA-DT was confirmed (Table 4).

Of 47 patients with biochemical failure, four cases did not receive an additional hormone therapy because of a slow rise in PSA. The other 43 patients received hormone therapy after failure, and responded well as PR, except for one patient who showed NC temporarily then showed a rapidly rising PSA and died of prostate cancer 46 months after the start of radiation.

Second Biochemical Failure and Outcome

Among 47 patients with first failure, 10 cases showed a second increase in PSA (21%). Risks of these 10 patients

Table 1. Patients' characteristics

Age (years)	
≤60	4
61–70	7
71–80	102
≥81	5
Initial PSA (ng/ml)	
<10	60
10.1–20	25
20.1–30	10
30.1–40	5
40.1–50	3
50.1–60	4
≥60.1	11
Stage	
T1b	3
T1c	45
T2a	18
T2b	4
T2c	5
T3a	33
T3b	10
Gleason score	
≤6	56
7	37
≥8	25

PSA, prostate-specific antigen.

were 1 of low (1 of 8, 13%) and 9 of high (9 of 35, 26%). Duration between hormone treatment and the second failure was mean of 15 months (median 14 months and range 3–28 months). Factors estimated at first failure were compared between patients with second failure and those without second failure (Table 5). Patients with second failure showed shorter PSA-DT, shorter duration between radiation and first failure. These patients were treated with second-line hormone therapy and/or chemotherapy. Except for one dead patient, the other nine patients included seven showing favorable responses and two revealing slowly progressive disease. These nine patients were alive in June 2009.

Biochemical failure-free survival rate was 52% (61 of 118) at 3 years after radiation. Overall survival rate at 5 years was 87% (Fig. 1). There was only one patient due to prostate cancer-specific death. Eight patients died of other causes except for prostate cancer. There was no complication due to lymphadenectomy. Concerning the toxicity after radiation according to scoring of Radiation Therapy Oncology Group, 34% and 5% of early and late Grade 1–2 morbidity, respectively, showed in the genitourinary system, with 25% and 5% of early and late Grade 1–2 morbidity, respectively, in the rectum. No toxicity was developed for Grade 3 or higher.

DISCUSSION

Survival of patients with prostate cancer after radical treatment is influenced by the status of the regional lymph nodes. The number and findings of invasive nodes correlate with subsequent outcome (12,13). As a curative treatment with radiotherapy, aggressive radiation which includes the pelvic lymph nodes is controversial (14,15). In this discussion, the adverse effects caused by radiation to the outside of the prostate may be a serious consideration. Alternatively, lymphadenectomy before radiation may be proposed. The result from lymphadenectomy may help to determine the strategy of further treatment (16). Moreover, this procedure serves to make a contribution to the relationship between stage and status of lymph nodes.

Surgical lymphadenectomy causes slight, if any, complications such as intraoperative injury and postoperative events (17). The most common complications are lymphocysts or lymphoceles after radical prostatectomy, but the present series performed lymphadenectomy alone, so such that adverse effect may be less likely to occur.

Biochemical failure occurred in more than 50% of patients with high risk at 5 years after radiotherapy (18). For extended radiotherapy including pelvic area, biochemical failure in patients with high risk was 43% at 5 years (19). Patients receiving radical prostatectomy whose regional lymph nodes had been removed showed elevation of PSA a few years later. It was reported that the obturator, external and internal iliac nodes may be insufficient for the removal of all suspicious nodes (20,21). The limitation of lymph node management for curative treatment remains to be resolved.

The similar biochemical-failure rate was noticed after radiation to patients with N0 in the present study. Together with the reports, it suggests that patients with high risk already have the small foci in the distant places. As most biochemical failure in high-risk patients occurred by 36 months, their tumors may be rapidly growing with an increase in 2 ng/ml or more of PSA in this term. Although late recurrence cannot be ruled out, incidence of biochemical failure slowly diminished thereafter.

A plausible cause of biochemical failure may be an insufficient dose of radiation to the prostate. It has been claimed that a radiation dose of <70 Gy is insufficient for cure of prostate cancer (22,23). It is recommended that >72 Gy of radiation is administered to the prostate of patients with high risk. Although no cancerous mass in the prostate was found in the present study, an insufficient dose of radiation cannot be ruled out.

Table 2. Patient characteristics, PSA and duration to nadir in patients with or without biochemical failure

	Failure (47)	Failure-free (71)	*P* value
Age (years)	74, 75 (54–83)	75, 75 (61–82)	ns
No lymph node	9.3, 8, (–21)	9.1, 8, (2–28)	ns
Risk			
Low	8	26	
Intermediate	4	25	
High	35	20	
Initial PSA (ng/ml)	43.0, 23.4 (4.1–290)	11.6, 7.5 (3.1–79.8)	0.0009
12 months PSA (ng/ml)[a]	3.1, 1.9 (0.1–14.5)	1.2, 0.8 (0.3–4.8)	0.019
Nadir PSA (ng/ml)	4.3, 1.9 (0.2–51.9)	0.8, 0.5 (0.01–5.5)	0.004
Radiation–nadir (months)	14.3, 12 (2–45)	27.5, 26 (1–69)	<0.0001

Data are shown as mean and median (range), except 'risk' (number of cases).
[a]PSA 12 months after radiation.

Table 3. Logistic regression analysis for biochemical failure

	Odds ratio	95% CI
Initial PSA (ng/ml)	1.054	1.019–1.090
Stage		
T2[a]	5.25	1.325–20.803
T3	6.927	1.837–26.121
Gleason		
7[b]	0.462	0.128–1.666
≥8	0.739	0.160–3.416
Nadir PSA (ng/ml)	1.477	0.977–2.233
Radiation–nadir (months)	0.95	0.908–0.993

[a]Reference: stage T1.
[b]Reference: Gleason ≤6.

Table 4. Factors influenced biochemical failure divided by PSA-DT

	PSA-DT≲8.3 (24)	PSA-DT > 8.3 (23)	*P* value
Initial PSA (ng/ml)	51.3, 25 (4.1–290)	33.9, 18 (6–245)	0.322
Nadir PSA (ng/ml)	3.4, 2.0 (0.2–11.2)	5.2, 1.7 (0.4–51.9)	0.47
Radiation–nadir (months)	10.3, 9 (2–21)	18.5, 18 (5–45)	0.001
Radiation–failure (months)	18.5, 17 (4–36)	14.3, 13 (8–55)	0.06

Data are shown as mean and median (range).
Median of PSA-doubling time (DT) (8.3 months).

Table 5. Factors influencing second biochemical failure

	Second failure (10)	No second failure (37)	*P* value
Initial PSA (ng/ml)	26.8, 15.8 (4.1–82.7)	47.4, 25.2 (5.7–290)	0.148
Nadir PSA (ng/ml)	4.6, 3.3 (0.2–11.2)	4.2, 1.4 (0.3–51.9)	0.83
Failure PSA (ng/ml)	10.6,.2.0 (2.6–31.9)	6.8, 4.0 (1–56.8)	0.29
Radiation–failure (months)	14.3, 14 (4–28)	31.7, 27 (5–55)	<0.0001
PSA-DT (months)	4.8, 6 (0.9–11.2)	10.6, 9.6 (2.5–30.8)	0.0002
Velocity (ng/ml/year)	25.1, 11.5 (2.7–96.5)	6.0, 3.2 (0.4–31.9)	0.09

Data are shown as mean, median and range. All data are quoted from the first biochemical failure.

The risk for recurrence after radiotherapy was pointed out with initial PSA, Gleason score and stage, which are well-known risk factors, and risk classification is used from these factors (24). Patients judged to be high risk might have progress in unfavorable courses. Duration of time between radiotherapy and biochemical failure influences the outcome (25). Among these factors, the level of PSA is crucial since patients with >30 ng/ml of PSA showed 20% of PSA-free rate at 5 years and this rate was independent of other factors (26). After radiotherapy, insufficient decrease in PSA to reach a low nadir and a rising pattern of PSA are also considered as factors for recurrence (27). Patients showed biochemical failure in short duration from radiation have rapidly growing tumors as estimated from short PSA-DT.

Additional hormone therapy is recommended along with radiotherapy for patients especially with high risk. Radiation combined with hormone therapy decreased the biochemical failure and improved clinical progression-free and cancer-specific survival (28). According to literatures, duration of hormone therapy varies between 4 months and 5 years, or up

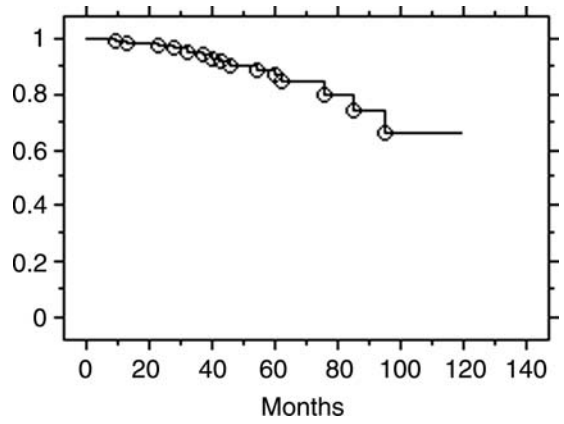

Figure 1. Overall survival of patients who received radiotherapy after confirming no lymph node invasion (118 cases).

to appearance of progression (29). The adverse effects of hormone therapy have been indicated recently (30). In the present study, the response to hormone therapy was favorable in general, and this may be attributable to a hormone-naïve condition in patients. Duration of hormone therapy after biochemical failure seems to be long, and this might be due to the presence of residual cancer foci. The treatment period of hormone therapy with radiotherapy is an issue under debate, but it might be advisable to make treatment plans adaptable to the individual situations of patients.

CONCLUSION

Patients with T1–T3 prostate cancer who were surgically confirmed to be N0 were treated with radiotherapy. Few biochemical failures were observed in patients with low and intermediate risks. Patients with high risk, however, showed biochemical failure in 64%, in whom 97% of failure occurred by 3 years after radiation. Initial and nadir PSA, and duration between radiation and nadir were the factors for biochemical failure. Some patients with first failure, mostly high risk, showed the second failure, and PSA-DT was the factor for second failure, suggesting that patients with second failure had rapidly growing hormone-independent tumors. Most patients after the biochemical failure responded well to hormone therapy, showing favorable results by delayed hormone therapy. It is emphasized that half of patients with high risk can be treated with radiation and lymphadenectomy alone.

Acknowledgements

This work was approved by the Ethical Committee of the Asahi General Hospital.

Conflict of interest statement

None declared.

References

1. Hanks GE, Krall JM, Hanlon AL, Asbell SO, Pilepich MV, Owen JB. Patterns of care and RTOG studies in prostate cancer: Long term survival, Hazard rate observations, and possibilities of cure. *Int J Radiat Oncology Biol Phys* 1993;28:39–45.
2. Roach MIII, Marquez C, You H-S, Narayan P, Coleman L, Nseyo UO, 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 Oncology Biol Phys* 1993;28:33–7.
3. Partin AW, Mangold LA, Lamm DM, Walsh PC, Epstein JI, Pearson JD. Contemporary update of prostate cancer staging nomograms (Partin Tables) for the new millennium. *Urology* 2001;58:843–8.
4. Nguyen PL, Chen M-H, Hoffman KE, Katz MS, D'Amico AV. Predicting the risk of pelvic node involvement among men with prostate cancer in the contemporary era. *Int J Radiat Oncology Biol Phys* 2009;74:104–9.
5. Bhojani N, Ahyal S, Graefen M, Capitanio U, Suardi N, Shariat SF, et al. Partin tables cannot accurately predict the pathological stage at radical prostatectomy. *Eur J Surg Oncol* 2009;35:123–8.
6. Aizer AA, Yu JB, McKeon AM, Decker RH, Colberg JW, Peschel RE. Whole pelvic radiotherapy versus prostate only radiotherapy in the management of locally advanced or aggressive prostate adenocarcinoma. *Int J Radiat Oncology Biol Phys* 2009;74.
7. NCCN Clinical Practice Guidelines in Oncology V2, 2009. www.nccn.org.
8. Abramowitz MC, Li T, Buyyounouski MK, Ross E, Uzzo RG, Pollack A, et al. The Phoenix definition of biochemical failure predicts for overall survival in patients with prostate cancer. *Cancer* 2007;112:55–60.
9. Epstein JI, Allsbrook WC, Amin MB, Egevad LL, ISUP Grading Committee. The 2005 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostate carcinoma. *Am J Surg Pathol* 2005;29:1228–41.
10. Schmid H-P, McNeal JE, Stamey TA. Observations on the doubling time of prostate cancer. The use of serial prostate-specific antigen in patients with untreated disease as a measure of increasing Cancer volume. *Cancer* 1993;71:2031–40.
11. Connolly D, Black A, Murray LJ, Napolitano G, Gavin A, Keane PF. Methods of calculating prostate-specific antigen velocity. *Eur Urol* 2007;52:1044–51.
12. Cheng L, Zincke H, Blute ML, Bergstralh EJ, Schere B, Bostwick DG. Risk of prostate carcinoma death in patients with lymph node metastasis. *Cancer* 2001;91:66–73.
13. Boormans JL, Wildhagen MF, Bangma CH, Verhagen PC, van Leenders GJ. Histopathological characteristics of lymph node metastases predict cancer-specific survival in node-positive prostate cancer. *BJU Int* 2008;102:1589–93.
14. Vargas CE, Galalae R, Demanes J, Harsolia A, Meldolesi E, Nurnberg N, et al. Lack of benefit of pelvic radiation in prostate cancer patients with a high risk of positive pelvic lymph nodes treated with high-dose radiation. *Int J Radiat Oncology Biol Phys* 2005;63:1474–82.
15. Jacob R, Hanlon A, Horwitz M, Movsas B, Uzzo RG, Pollack A. Role of prostate dose escalation in patients with greater than 15% risk of pelvic lymph node involvement. *Int J Radiat Oncology Biol Phys* 2005;61:695–701.
16. Karakiewicz PI, Bhojan N, Capitanio U, Reuther AM, Suardi N, Jeldres C, et al. External validation of the updated Partin tables in a cohort of North American men. *J Urol* 2008;180:898–902.
17. Link RE, Morton RA. Indications for pelvic lymphadenectomy in prostate cancer. *Urol Clin North Am* 2001;28:491–8.
18. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998;280:969–74.
19. Morgan PB, Hanlon AL, Horwitz EM, Buyyounouski MK, Uzzo RG, Pollack A. Timing of biochemical failure and distant metastatic disease for low-, intermediate, and high risk prostate cancer after radiotherapy. *Cancer* 2007;110:68–80.
20. Weckermann D, Dorn R, Trefz M, Wagner T, Wawroschek F, Harzmann R. Sentinel lymph node dissection for prostate cancer: experience with more than 1000 patients. *J Urol* 2007;177:916–20.

21. Briganti A, Blute ML, Eastham JH, Graefen M, Heidenreich A, Karns JR, et al. Pelvic lymph node dissection in prostate cancer. *Eur Urol* 2009;55:1251–65.
22. Thames HD, Kuban DA, DeSilvio ML, Levy LB, Horwitz EM, Kupelian PA, et al. Increasing external beam dose for T1-T2 prostate cancer: effect on risk groups. *Int J Radiat Oncology Biol Phys* 2006;65:975–81.
23. Goldner G, Dimopoulos J, Krisits C, Potter R. Moderate dose escalation in three-dimensional conformal localized prostate cancer radiotherapy: Single-institutional experience in 398 patients comparing 66 Gy versus 70 Gy versus 74 Gy. *Strahlenther Onkol* 2009;185:438–45.
24. Zagars GK, von Eschenbach AC, Ayala AG. Prognostic factors in prostate cancer. Analysis of 874 patients treated with radiation therapy. *Cancer* 1993;72:1709–25.
25. Denham JW, Steigler A, Wilcox C, Lamb DS, Joseph D, Atkinson C, et al. Why are pretreatment prostate-specific antigen levels and biochemical recurrence poor predictors of prostate cancer survival? *Cancer* 2009;115:4477–87.
26. Feigenberg SJ, Hanlon AL, Horwitz EM, Uzzo RG, Eisenberg DF, Pollack A. What pretreatment prostate-specific antigen level warrants long-term androgen deprivation? *Int J Radiat Oncology Biol Phys* 2005;61:1003–10.
27. Prout-Lima C, Taylor JMG, Williams S, Ankerst DP, Liu N, Kestin LL, et al. Determinations of change in prostate-specific antigen over time and its association with recurrence after external beam radiation therapy for prostate cancer in five large cohorts. *Int J Radiat Oncology Biol Phys* 2008;72:782–91.
28. Bria E, Cuppone F, Giannarelli D, Milella M, Ruggeri EM, Sperduti I, et al. Does hormone treatment added to radiotherapy improve outcome in locally advanced prostate cancer? Meta-analysis of randomized trials. *Cancer* 2009;115:3446–56.
29. Lawton CA, Bae K, Pilepich M, Hanks G, Shipley W. Long-term treatment sequelae after external beam irradiation with or without hormonal manipulation for adenocarcinoma of the prostate: analysis of radiation therapy oncology group studies 85-31 86-10, and 92-02. *Int J Radiat Oncology Biol Phys* 2008;70:437–41.
30. Taylor LG, Canfield SE, XLPrasad D. Review of major adverse effects of androgen deprivation therapy in men with prostate cancer. *Cancer* 2009;115:2388–99.