Hormone use after radiotherapy failure: a survey of Canadian uro-oncology specialists

D. Andrew Loblaw, MD, FRCSC;[*] Tom Pickles, MD, FRCSC;[†] Patrick C. Cheung, MD, FRCSC;[*] Himu Lukka, MD, FRCSC;[‡] Sergio Faria, MD, FRCSC;[§] Laurence Klotz, MD, FRCSC[**]

Abstract

Introduction: A survey of Canadian uro-oncology specialists was performed to assess practice patterns of patients with recurrent prostate cancer postradiotherapy and to assess the feasibility of conducting a trial in this setting.

Methods: There were 14 survey questions and 1 demographic question. Responses were reported by frequency.

Results: There were 96 respondents. Most respondents use both prostate-specific antigen doubling time (PSAdt) and PSA level when deciding to start androgen deprivation therapy (ADT) in asymptomatic patients. About half of respondents start ADT when PSA is greater than 10 ng/mL or when the PSAdt is less than 6 months. Eighty-six percent felt that the timing of ADT was an important research question. Over 1500 patients per year were estimated as being available for such a trial.

Conclusion: After radiotherapy failure, respondents initiated ADT about half of the time when PSA is less than 10 ng/mL and/or PSAdt is less than 6 months. A clinical trial examining the timing of ADT has strong support and appears to be feasible.

Can Urol Assoc J 2009;3(6):460-4

Résumé

Introduction : Un sondage mené auprès d'uro-oncologues canadiens a été mené afin d'évaluer les tendances concernant le traitement de patients atteints de cancer récurrent de la prostate après une radiothérapie et d'évaluer la faisabilité d'une étude dans ce contexte.

Méthodologie : Le sondage comportait 14 questions portant sur les traitements et 1 question de type démographique. Les réponses étaient groupées par fréquence.

Résultats : Quatre-vingt-seize médecins ont participé au sondage. La majorité des répondants se basent sur le temps de doublement de l'APS et les taux d'APS pour décider du moment optimal pour amorcer un traitement antiandrogène chez les patients asymptomatiques. Environ la moitié des répondants entreprennent un traitement antiandrogène lorsque le taux d'APS dépasse 10 ng/mL ou lorsque le temps de doublement de l'APS est inférieur à 6 mois. Quatre-vingt-six pour cent des répondants ont indiqué que le moment optimal pour l'amorce du traitement antiandrogène représentait une importante question de recherche. On estime que plus de 1500 patients par année seraient admissibles à une telle étude.

Conclusion : Après l'échec d'une radiothérapie, les répondants entreprennent un traitement antiandrogène dans environ la moitié des cas lorsque l'APS est inférieur à 10 ng/mL et/ou lorsque le temps de doublement de l'APS est inférieur à 6 mois. Un essai clinique portant sur la détermination du moment optimal pour l'amorce du traitement antiandrogène est fortement souhaité et semble faisable.

Introduction

Prostate cancer is the leading form of internal malignancy diagnosed among North American men. One in 6 men will develop[1] prostate cancer during his lifetime, and 1 in 26 will die as a result of it.[2]

According to the American Surveillance, Epidemiology and End Results (SEER) database, 91% of prostate cancer cases are diagnosed while the cancer is still confined to the primary site.[1] Most patients with localized prostate cancer are managed radically, i.e., with the intention of cure.[3] Most frequently, patients receive radical prostatectomy, external beam radiotherapy, brachytherapy (internal radiation) or combinations of these approaches.

Despite improved control rates associated with higher doses of radiotherapy,[4-7] recurrent prostate cancer after radical radiation therapy is a common problem, with often a long interval from biochemical failure to the time of symptomatic relapse (with a recognized intermediary state being asymptomatic metastatic relapse).[8] While local extirpative therapies are potential curative options for some men postradiotherapy,[9] androgen deprivation therapy (ADT) is the most commonly used palliative intervention after radiation failure. The goal of starting ADT has traditionally been long-term palliation: that is, the reversal or prevention of symptoms, although a recent study has reported improved cause-specific survival in patients with metastatic disease on presentation or who progress on conservative management.[10]

The use of ADT is associated with a number of side effects that offset its palliative benefits.[11,12] In addition, ADT has recently been linked to an increased risk of bone fracture[13-15] and metabolic syndrome, both of which are associated with high mortality rates.[16-18] When patients are suffering from *symptomatic* prostate cancer, virtually all practitioners would agree that the benefits of ADT in improving symptoms outweigh the side effects, and men should be placed on ADT; however, what is not clear is whether

to start ADT before the patient develops symptoms of progressive prostate cancer postradiotherapy. Since there can be a long interval from the diagnosis of prostate cancer to the onset of symptomatic disease, many physicians believe that a significant benefit in overall or cause-specific survival is needed to justify the decrease in quality of life seen with the long-term use of ADT in men with *asymptomatic* recurrent prostate cancer. Those physicians who argue for the immediate use of ADT hypothesize that when a patient's prostate-specific antigen (PSA) is lower, there are fewer prostate cancer cells present; therefore, the immediate use of ADT will control these tumours for a longer period of time.

In 2004, the American Society of Clinical Oncology (ASCO) published an evidence-based clinical practice guideline on the initial hormonal management of patients with progressive, metastatic or recurrent prostate cancer.[19] The group recommended starting ADT when the patient has symptomatic prostate cancer. The authors were unable to issue a recommendation for the immediate use of ADT due to methodological limitations of the available evidence. The authors also strongly recommend that research be completed on the question of the optimal timing of ADT for patients who experience radiotherapy failure. Based on those data, we assessed practice patterns of patients with recurrent prostate cancer postradiotherapy among Canadian uro-oncology specialists. The results of this survey will inform us on the feasibility of performing a randomized controlled trial of immediate versus deferred ADT in these patients. We did not assess whether the development of asymptomatic metastases was a trigger, as our own clinical practice and the literature we were aware of suggested that it was infrequently used as a decision point.

Methods

In October 2004, an email survey was sent to all active Canadian members of the Genitourinary Radiation Oncologists of Canada (n = 136) and the Canadian Urological Association (n = 583 active Canadian members, 167 of whom had an email address in the CUA database). Email reminders were sent to improve the response rate. There were 7 questions about current practice, and 7 additional questions about feasibility issues within a clinical trial. There was 1 question regarding demographics (the speciality of the respondent). All questions had categorical response sets, with the exception of 4 questions, which allowed for individual, open-ended responses. Responses were reported by frequency.

Results

There were a total of 96 respondents, representing a 32% response rate. Respondents were categorized as follows: 50 urologists, 42 radiation oncologists and 4 medical oncologists.

Questions about clinical practice

Sixty-nine percent of respondents felt that PSA doubling time (PSAdt) and PSA threshold were important triggers for starting ADT among men with rising PSA levels and without symptoms of recurrent disease. A little over a quarter of the respondents felt that PSAdt was the more important factor, while 3% of respondents felt that absolute PSA was the more important factor.

Nineteen percent of respondents do not use a PSA threshold to determine when to start ADT. Of the remaining 81% of respondents (5 did not respond), 11% start ADT with PSA less than 5 ng/mL; 42% start ADT between 5 and 10 ng/mL; 36% start between 10 and 20 ng/mL; 10% start between 20 and 30 ng/mL and 1% start between 30 and 40 ng/mL. None of the respondents reported waiting to start ADT until the PSA was above 40 ng/mL (Table 1).

Respondents were asked what PSAdt they typically started using. Seventeen percent of the respondents reported that they did not use a PSAdt threshold (or started ADT even if the PSAdt was greater than 24 months). Of the remaining 78 respondents (1 did not respond), 8% reported that they generally started ADT if the patient's PSAdt was greater or equal to 3 months; 44% started ADT if PSAdt was less than or equal to 6 months; 43% started ADT if PSAdt was less than 12 months; and 5% started ADT if PSAdt was less than 24 months (Table 1).

No one reported using orchiectomy as a form of ADT; all but 2 respondents used some form of luteinizing-hormone releasing hormone (LHRH) agonist (anti-androgen monotherapy). Of the 94 who used an LHRH agonist, 75%

Table 1. Prostate-specific antigen (PSA) values and PSA doubling time thresholds for starting androgen deprivation therapy for recurrent disease postradiotherapy

	1994 Canada[22]	2000 USA[24]	2004 Canada*
Trigger PSA, ng/mL			
<10, %	20	28	53
10 to 20, %	18	50	36
20 to 50, %	32	20	11
>50, %	24	2	0
PSAdt trigger, mos**			
<3 (%)			8
3 to 6 (%)			44
6 to 12 (%)			43
12 to 24 (%)			5

PSA = prostate-specific antigen; PSAdt = prostate-specific antigen doubling time; * = present study; ** = total number included in study is 78; 17 respondents did not use PSAdt as a trigger or used a PSAdt trigger > 24 months; 1 respondent did not complete this question.

used them alone, 19% used them with a nonsteroidal anti-androgen (NSAA), and 5% used them with a steroidal anti-androgen. Intermittent androgen blockade (IAB) was used fairly commonly outside of trial settings. Only 16% of respondents almost never used IAB, while 36% used it infrequently, 36% used it frequently, and 12% used it almost always. Sixty-five percent of respondents discussed combined androgen blockade (CAB) with patients with some regularity; 22% discussed CAB infrequently; 28% discussed it frequently; and 14% discussed it almost always. When CAB was used, 48% of respondents used it to block the testosterone flare associated with the first LHRH injection, 14% used it continuously and 58% used the anti-androgens if the PSA progressed while the patient was castrate (respondents could answer this last question more than once).

Trial design questions

There were 4 questions to inform the potential design of a randomized trial about the optimal timing of ADT for patients who recurred biochemically after radical radiotherapy. The purpose of these 4 questions was introduced to respondents.

To address the selection criteria, respondents were asked what would be the lowest PSA at which they would be comfortable starting ADT. Everyone answered this question, except for 1 respondent (n = 95). Twenty percent of respondents preferred starting ADT immediately, upon recognition of biochemical failure (the definition was not specified, but at the time of this questionnaire, the American Society of Therapeutic Radiology and Oncology (ASTRO) consensus definition of 3 consecutive rises in PSA was the most commonly used[20]); 5% wanted to start ADT at 2 ng/mL; 16% were more comfortable starting between 3 and 4 ng/mL; 28% wanted to wait until 5 ng/mL; the remaining 16% would insist on higher PSAs or another reason before starting ADT (i.e., they would not be comfortable using a PSA threshold as a trigger even in a trial situation). In all, 85% would be comfortable starting ADT in patients with PSAs between biochemical failure and 5 ng/mL.

To determine the potential trigger for ADT in the deferred arm, respondents were asked about the highest PSA (in the absence of symptoms) they would be comfortable withholding ADT in a trial setting. All respondents answered this question (n = 96). A little under a third of respondents (30%) would insist on starting ADT at 10 ng/mL, and a further 9% and 2% would be comfortable waiting until 15 and 20 ng/mL, respectively. Twenty-nine percent of respondents would wait until 25 ng/mL, while the remaining 30% of respondents would be comfortable waiting until 30 ng/mL or higher. The vast majority of respondents (92%) were comfortable withholding ADT in a selected group of patients according to their PSAdt. Table 2 summarizes the above data.

Table 2. Prostate-specific antigen levels that respondents were comfortable entering and withholding androgen deprivation therapy for recurrent disease postradiotherapy in a trial setting

	%	Cumulative %
Lowest PSA respondents comfortable starting ADT (n = 95)		
Biochemical failure*	20	20
2 ng/mL	5	25
2 to 3 ng/mL	16	41
3 to 4 ng/mL	16	57
4 to 5 ng/mL	28	85
>5 ng/mL**	15	100
Highest PSA respondents comfortable withholding ADT (n = 96)		
10 ng/mL	30	30
15 ng/mL	9	39
20 ng/mL	2	41
25 ng/mL	29	70
>25 ng/mL	30	100

PSA = prostate-specific antigen therapy; ADT = androgen deprivation therapy; * = American Society of Therapeutic Radiology and Oncology (ASTRO) definition of failure (i.e., 3 consecutive increases in PSA following treatment); ** = includes patients who would want another reason to start ADT (i.e., PSA doubling time).

Twenty-nine percent of respondents would not be comfortable withholding ADT, even in patients with PSAdts up to 24 months. A little under half of the respondents (47%) would enter patients in a trial where half the patients would receive deferred therapy if the patient's PSAdt was 12 months or less. Twenty-three percent of respondents would be able to enter patients with PSAdt of less than or equal to 6 months. One percent of respondents would have equipoise to withhold potentially ADT in patients with PSAdt of less than 3 months. Overall, 71% would be comfortable entering patients with PSAdt less than or equal to 12 months.

In terms of using PSAdt as a potential trigger, 10% were not comfortable using PSAdt to trigger ADT. Of the remaining 86 respondents, 26% would want to start ADT if the PSAdt was less than 24 months; 28% could wait until it was 12 months or less; and 35% would still feel comfortable even if the PSAdt was as short as 6 months. Only 11% would withhold ADT when the PSAdt was as low as 3 months. About half of respondents (46 of 86, 54%) who were comfortable using PSAdt as a trigger would start ADT if the PSAdt was 12 months or less. Table 3 summarizes the data on PSAdt entry and trigger points.

When determining important outcomes to measure, quality of life (84%), overall survival (80%), time to androgen-independent prostate cancer (77%), and cause-specific survival (77%) were important outcomes (n = 94; respondents could select more than one outcome). Sixty-four percent of these respondents selected one of these outcomes as the primary outcome. Overall survival (37%) and time to androgen-independent prostate cancer (26%) were followed by

Table 3. Prostate-specific antigen doubling times that respondents were comfortable entering and withholding androgen deprivation therapy for recurrent disease postradiotherapy in a trial setting

	%	Cumulative %
Slowest PSAdt respondents were comfortable starting ADT (n = 88)		
<3 mo	1	1
3 to 6 mo	23	24
6 to 12 mo	47	71
Not comfortable withholding ADT for any PSAdt*	29	100
Fastest PSAdt respondents were comfortable withholding ADT (n = 86)		
>24 mo	26	26
12 to 24 mo	28	54
6 to 12 mo	35	89
3 to 6 mo	11	100

PSAdt = prostate-specific antigen doubling time; ADT = androgen deprivation therapy.

cause-specific survival (18%) and quality of life (16%) as the most frequently ranked primary outcome of choice.

Feasibility questions

Two questions informed the feasibility of the potential study.

Respondents were asked how important the research question of immediate versus delayed ADT was for patients who recurred biochemically after radical irradiation. All respondents felt the question was important; 51% thought it was very important, and a further 35% felt it to be moderately important. The group was then asked to estimate how many patients would qualify for such a study in their clinics annually. Over 1500 potential study candidates nationally per year were identified.

Discussion

This survey reports the practice patterns for a sample of Canadian uro-oncology specialists in managing patients who fail biochemically after radiation treatment at the end of 2004. As the response rate was approximately 30%, an appropriate level of caution should be used to generalize these data. In addition, estimates about the number of potentially eligible patients for a trial examining the timing of androgen deprivation therapy for recurrent prostate cancer postradiotherapy were not based on clinic audits and therefore should be also duly considered.

Most respondents reported using a combination of PSAdt and PSA threshold to determine whether to start ADT. Despite no direct evidence informing this decision, over time ADT appears to be started at lower PSA thresholds. Table 1 summarizes the North American trend from 1994 to 2004. This trend may reverse with the recent recognition that prolonged ADT is not only associated with vasomotor, sexual and constitutional symptoms, but also with increased risk of hip fractures,[13,15,21] diabetes, coronary heart disease, acute myocardial infarction and sudden cardiac death.[18]

Recently, several prognostic and predictive factors have emerged in the prostate cancer literature and have begun to inform today's clinical decision-making. These factors include the Gleason score,[22] PSA response to ADT[23] and age.[24] PSA doubling time is probably the most robust factor for predicting overall survival,[24] cause-specific survival[23,25] and chance of distant metastases.[22] Interestingly, the use of PSAdt as a trigger for initiating earlier use of ADT predates any evidence that this alters measurable outcomes in a positive way.

Our results also demonstrate interesting patterns of practice that were inconsistent with published evidence-based clinical practice guidelines.[19] Most respondents (84%) commonly used IAB despite insufficient evidence of equivalent tumour control or survival. Five percent used steroidal antiandrogens with LHRH, despite worse survival demonstrated in an individual patient data meta-analysis showing inferior survival (hazard ratio 1.13, $p = 0.04$ of cyproterone vs. cyproterone CAB).[26] Two-thirds of respondents routinely discussed CAB with a nonsteroidal with their patients.

The ASCO guideline has subsequently been updated.[10] While improvements in cause-specific survival were reported in patients with progressive disease on conservative management or who presented with metastatic disease, there were insufficient data to make a recommendation about patients who recur after radical radiotherapy. It was urged that these latter patients enrol in clinical trials addressing the issue of the timing of ADT, if available.

There was strong support for a trial that will determine the optimal timing of ADT for recurrent prostate cancer after radical radiotherapy in Canada. These data have been used to inform the design of a Canada-wide randomized study of immediate versus deferred goserelin in this patient population. The study, called ELAAT (Early versus Late Androgen Ablation Therapy), is being carried out by the Canadian Urologic Oncology Group/Ontario Clinical Oncology Group (CUOG/OCOG). There are 1100 patients planned for this study; they have recurrent prostate cancer after radiation and are randomized to immediate goserelin or goserelin at symptom onset or PSA above 25 ng/mL, whichever occurs first. The primary outcome will be time to androgen independent disease, although QOL, survival, complications of advanced malignancy and fractures will also be measured. The study was activated in 2007 and is currently open in 15 centres.

A similar trial, called the Timing of Androgen Deprivation (TOAD), is being conducted by the Trans Tazmanian Radiation Oncology Group (TROG). The main exception is that the deferred arm will start ADT at symptom onset. The trial aims to accrue 750 patients with survival;

quality of life and morbidity are being measured as endpoints.

There was a difference observed between what respondents practiced versus what they would accept in a trial setting. For example, in practice, 11% of respondents would be comfortable waiting until the PSA was over 20 ng/mL before starting ADT, while in a trial setting, 59% would be comfortable waiting. These discrepancies may foretell a lack of equipoise for this question, which may reflect in poor accrual. Alternatively, these differences may be explained by the fact that many physicians are willing to accept widely different practices than their own within trial settings because there is demonstrable equipoise confirmed by independent research ethics boards' approvals and full disclosure to the patient through a written informed consent process.

Conclusion

About half of the respondents initiated ADT when PSA was greater than 10 ng/mL and/or PSAdt greater than 6 months for patients with biochemical failure of asymptomatic prostate cancer after radiation treatment. A clinical trial examining the timing of ADT after RT failure has strong support, appears feasible to complete and has been open to accrual to patients across Canada since 2007.

From the *Department of Radiation Oncology, Sunnybrook Health Sciences Centre, Toronto, ON; †Department of Radiation Oncology, BC Cancer Agency, Vancouver Site, Vancouver, BC; ‡Department of Radiation Oncology, Juravinski Cancer Centre, Hamilton, ON; §Department of Radiation Oncology, McGill University, Montreal General Hospital, Montréal, QC; **Department of Surgery, Sunnybrook Health Sciences Centre, Toronto, ON

Acknowledgements: The authors would like to thank Sarah Gilbert for her assistance in conducting this survey, and Hillary Montagu-Douglas-Scott for editing the manuscript.

Competing interests: Dr. Loblaw is the principal investigator for a trial sponsored by AstraZeneca through a grant-in-aid to a third party. He has also received educational grants and honoraria from AstraZeneca. Dr. Lukka has received speaker fees and educational grants from AstraZeneca, Abbott Laboratories, sanofi-aventis, Novartis and Paladin Labs.

This paper has been peer-reviewed.

References

1. Ries LAG, Harkins D, Krapcho M, et al. *SEER Cancer Statistics Review, 1975-2003*. Bethesda (MD): National Cancer Institute, 2006.
2. *Canadian Cancer Statistics 2005*. Toronto (ON): Canadian Cancer Society/National Cancer Institute of Canada, 2005.
3. Cooperberg MR, Broering JM, Litwin MS, et al. The contemporary management of prostate cancer in the United States: lessons from the cancer of the prostate strategic urologic research endeavor (CapSURE), a national disease registry. *J Urol* 2004;171:1393-401.
4. Sathya JR, Davis IR, Julian JA, et al. Randomized trial comparing iridium implant plus external-beam radiation therapy with external-beam radiation therapy alone in node-negative locally advanced cancer of the prostate. *J Clin Oncol* 2005;23:1192-9.
5. Peeters ST, Heemsbergen WD, Koper PC, et al. Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. *J Clin Oncol* 2006;24:1990-6.
6. Pollack A, Zagars GK, Starkschall G, et al. Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2002;53:1097-105.
7. Zietman AL, DeSilvio ML, Slater JD, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA* 2005;294:1233-9.
8. Bianco FJ, Dotan ZA, Kattan MW, et al. Duration of response to androgen deprivation therapy and survival after subsequent biochemical relapse in men initially treated with radical prostatectomy [abstract 4552]. *Proc Am Soc Clin Oncol* 2004;23:393.
9. Touma NJ, Izawa JI, Chin JL: Current status of local salvage therapies following radiation failure for prostate cancer. *J Urol* 2005;173:373-9.
10. Loblaw DA, Virgo KS, Nam R, et al. Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. *J Clin Oncol* 2007;25:1596-605.
11. Herr HW, Kornblith AB, Ofman U: A comparison of the quality of life of patients with metastatic prostate cancer who received or did not receive hormonal therapy. *Cancer* 1993;71:1143-50.
12. Herr HW, O'Sullivan M: Quality of life of asymptomatic men with nonmetastatic prostate cancer on androgen deprivation therapy. *J Urol* 2000;163:1743-6.
13. Shahinian VB, Kuo Y-F, Freeman JL, et al. Risk of fracture after androgen deprivation therapy for prostate cancer. *N Engl J Med* 2005;352:154-64.
14. Smith MR, Lee WC, Brandman J, et al. Gonadotropin-releasing hormone agonists and fracture risk: a claims-based cohort study of men with nonmetastatic prostate cancer. *J Clin Oncol* 2005;23:7897-903.
15. Carolan H, Paszat L, Loblaw DA: Hormones May Break Their Bones. Is there an increased risk of hip fracture in men with prostate cancer treated with androgen ablation [abstract 2]? *Radiother Oncol* 2004;72:S1.
16. Riggs BL, Melton LJ, 3rd, McGraw RL, et al. The worldwide problem of osteoporosis: insights afforded by epidemiology. *Bone* 1995;17:505S-11S.
17. D'Amico AV, Denham JW, Crook J, et al. Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. *J Clin Oncol* 2007;25:2420-5.
18. Keating NL, O'Malley AJ, Smith MR: Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol* 2006;24:4448-56.
19. Loblaw DA, Mendelson DS, Talcott JA, et al. American Society of Clinical Oncology recommendations for the initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer. *J Clin Oncol* 2004;22:2927-41.
20. American Society for Therapeutic Radiology and Oncology Consensus Panel: Consensus statement: guidelines for PSA following radiation therapy. *Int J Radiat Oncol Biol Phys* 1997;37:1035-41.
21. Smith MR, Lee WC, Krupsi T, et al. Association between androgen deprivation therapy and fracture risk: A population-based cohort study in men with non-metastatic prostate cancer [abstract 4507]. *Proc Am Soc Clin Oncol* 2004;23:382.
22. Pound CR, Partin AW, Eisenberger MA, et al. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999;281:1591-7.
23. D'Amico AV, Moul JW, Carroll PR, et al. Intermediate end point for prostate cancer-specific mortality following salvage hormonal therapy for prostate-specific antigen failure. *J Natl Cancer Inst* 2004;96:509-15.
24. D'Amico AV, Kantoff P, Loffredo M, et al. Predictors of mortality after prostate-specific antigen failure. *Int J Radiat Oncol Biol Phys* 2006;65:656-60.
25. Kim-Sing C, Pickles T: Intervention after PSA failure: examination of intervention time and subsequent outcomes from a prospective patient database. *Int J Radiat Oncol Biol Phys* 2004;60:463-9.
26. Prostate Cancer Trialists' Collaborative Group: Maximum androgen blockade in advanced prostate cancer: an overview of the randomized trials. *Lancet* 2000;355:1491-8.

Correspondence: Dr. Andrew Loblaw, Department of Radiation Oncology, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, ON M4N 3M5; fax: 416-480-6002; andrew.loblaw@sunnybrook.ca