Practice patterns for post-prostatectomy hormonal therapy amongst Canadian radiation oncologists

Siddhartha Baxi, MBBS, Charles Catton, MD
Department of Radiation Oncology, Princess Margaret Hospital, Toronto, Ontario, Canada

BAXI S, CATTON C. Practice patterns for post-prostatectomy hormonal therapy amongst Canadian radiation oncologists. The Canadian Journal of Urology. 2010;17(6):5436-5441.

Introduction: *Level 1 evidence demonstrates the benefit of postoperative radiotherapy (PORT) for pT3 disease and positive margins. The role of androgen deprivation therapy (ADT) after PORT remains to be defined from results of ongoing randomized trials. This study was undertaken to determine the factors influencing the current use of ADT after PORT amongst Canadian radiation oncologists.*
Methods: *An institutional survey was emailed to the Genito-urinary Radiation Oncologists Group of Canada (GUROC), designed to assess the likelihood of prescribing ADT in early and delayed PORT scenarios with variations in disease prognosticators. Analysis used descriptive statistics.*
Results: *Majority (94%) do not routinely advocate ADT with PORT. With early PORT and undetectable prostate-specific antigen (PSA), respondents (n = 53) indicated that Gleason score 8-10 (89%), pT3b disease (80%) and high risk D'Amico category (76%) were important considerations. With early PORT and a detectible PSA, important considerations were PSA doubling time (90%), high risk disease (85%), pT3b category (82%) and time to relapse (TTR) of < 3 months (90%). Similar patterns were observed in the context of delayed PORT with importance given to TTR and PSA velocity. Category pT3b was consistently perceived as a poor prognosticator. The majority of respondents prescribe ADT for > 6 months (72%) or > 24 month (48%).*
Conclusions: *Wide variation was identified among respondents in the importance given to pathological, clinical and biochemical parameters and in considering therapy duration when prescribing ADT with PORT. This demonstrates a need for consensus guidelines and lends support to currently accruing phase III trials designed to answer these questions.*

Key Words: postoperative radiotherapy, prostate cancer, androgen deprivation therapy

Introduction

The role of postoperative radiotherapy (PORT) has been elucidated in three prospective randomized control trials for patients with pT3 category disease or those with positive margins.[1-3] These trials compared immediate postoperative therapy to no therapy for high risk individuals, and demonstrated a benefit to immediate PORT in biochemical control and progression free survival, with one also identifying an overall survival advantage.[2] The optimal timing of postoperative radiotherapy remains a subject of debate and ongoing study,[4] but prognostic factors for progression free survival following radical prostatectomy (RP) have been established.[5] In particular Stephenson et al has demonstrated the impact of preradiotherapy prostate-specific antigen (PSA) level, PSA doubling time, margin status, seminal vesicle involvement and Gleason score on PORT outcomes. Overall biochemical control rates with immediate or delayed radiotherapy remain suboptimal and many patients will receive further systemic treatment.[6] Adjuvant androgen deprivation therapy (ADT) following definitive radiotherapy with prostate in situ has been shown to reduce relapse rates and prolong survival, and it is reasonable to also consider adjuvant ADT for appropriate patients

Accepted for publication August 2010

Acknowledgement
The authors acknowledge the GU Radiation Oncologists of Canada members who contributed their time and expertise to completing this survey.

Address correspondence to Dr. Charles Catton, Department of Radiation Oncology, Princess Margaret Hospital, 610 University Avenue, Toronto ON M5G 2M9 Canada

in the postoperative setting.[7] However, the timing, duration and overall benefit of ADT in this situation remains undefined. Non-randomized data suggest a benefit for hormonal therapy in conjunction with postoperative radiotherapy or as sole adjuvant therapy.[8-10] However ADT use must be balanced with toxicity, since ADT is associated with osteoporosis, the metabolic syndrome and may increase the risk of cardiac events.[11,12] Prospective randomized trials are underway to investigate the role of postoperative ADT with PORT (NCIC CTG PR13, JCOG 0401, and EORTC Trial 22043-30041).[13-15] It will be a number of years before mature data are available and consistent treatment guidelines for the use of postoperative ADT are required in the interim. Patterns of practice surveys in the United Kingdom have identified a broad variation in practices in different postprostatectomy high risk scenarios.[16,17]

This study was undertaken to evaluate the patterns of practice in the use of postoperative ADT amongst Canadian uro-radiation oncologists, the results of which could provide the initial step towards creating national treatment guidelines for these patients.

Methods

This study was conducted with the approval of the University Health Network Research Ethics Board. An in-house internet survey was created at the Princess Margaret Hospital. The survey was based on a secure intranet platform for purposes of security, data control and monitoring but with similar constructs to commercially available survey engines.

Physicians were asked the importance of certain clinico-pathological parameters in influencing their likelihood of prescribing ADT in the following scenarios: (1) early postoperative setting (< 6months) with an undetectable PSA; (2) early postoperative setting with a detectible PSA; (3) delayed postoperative setting (> 6 months) with a detectible PSA with and without clear evidence of biochemical progression; (4) clinical, radiological or biopsy confirmed evidence of local recurrence; (5) duration of ADT use, with the options of short term up to 6 months duration; intermediate term more than 6 months to 2 years duration; and long term more than 2 years duration.

The clinico-pathological parameters proposed in the various situations were: margin positivity, pathological stage, Gleason score, presurgical D'amico risk category, absolute PSA and PSA kinetics (doubling time, time to relapse). For the purposes of the survey, an effective postoperative radiation dose was considered to be at least 64 Gy, based upon the minimum dose recommended in the five active postoperative trials that include the use of postoperative radiotherapy with or without ADT [Trans-Tasman Radiotherapy Group (RAVES; NCT00860652); Groupe d'Étude des Tumeurs Uro-Génitales trial (GETUG-16; NCT00423475); Medical Research Council/NCIC-CTG RADICALS; NCT00541047); Japan Clinical Oncology Group (JCOG 0401; NCT00138008), and European Organization for Research and Treatment of Cancer (EORTC 22043-30041; NCT00949962].

Respondents were asked to rate the likelihood of prescribing ADT as frequently, sometimes or rarely. For questions relating to importance of a certain parameter, respondents were asked to answer as not very important, somewhat important and very important.

The survey was sent to the members of the Genito-urinary Radiation Oncologists of Canada (GUROC). This is a national academic organization of Canadian Radiation Oncologists who have an interest in treating genitourinary malignancies, and presently has a membership of 138. The emails were sent twice, 2 weeks apart and results collated at the 1 month mark. The software was designed to not accept a response from the same email more than once.

Results were analyzed using descriptive statistics.

Results

One hundred and thirty eight radiation oncologists comprising the membership of GUROC were surveyed, with 52% (n = 72) responding. Overall, 49% of respondents rarely prescribe ADT routinely in the postoperative setting while 50% stated that they would sometimes.

Early (< 6 months) postoperative radiotherapy with a undetectable PSA

Pathological category T3b, Gleason score 8-10 and high risk D'Amico presurgery category were considered to be important considerations in prescribing ADT with 61% considering Gleason score 8-10, 50% considering category pT3b or high risk category to be important, Table 1. Equipoise was seen in considerations of category pT3a disease and inadequate radiation dose delivery with approximately half saying that those factors were somewhat/very important. Approximately two thirds would consider ADT if more than one factor was present (67%). An unimportant factor was margin status (focal margins - 87.3% not very important, extensive margins - 62.9% not very important).

TABLE 1. **Factors influencing use of ADT**

	Not very important (%)	Some what important (%)	Very important (%)
Early (< 6 months) postoperative radiotherapy with undetectable PSA			
Focal positive margins	87.3	12.7	0.0
Extensive positive margins	62.9	24.3	12.9
Stage pT3a	53.5	29.6	16.9
Stage pT3b	20.0	30.0	**50.0**
Gleason score 8 to 10	11.3	28.2	**60.6**
High risk D'amico presurgery risk category	23.9	40.8	**35.2**
Unable to delivery at least 64 Gy to the PTV	50.7	26.8	22.5
More than 1 of the above risk factors present	33.3	37.7	29.0
Early (< 6 months) postoperative radiotherapy with detectible PSA			
Absolute preradiotherapy PSA	9.9	32.4	**57.7**
Intermediate risk D'amico presurgery risk category	67.1	25.7	7.1
High risk D'amico presurgery risk category	15.5	32.4	**52.1**
Positive margins - focal or extensive	64.3	25.7	10.0
Stage pT3a	47.9	36.6	15.5
Stage pT3b	18.3	28.2	**53.5**
PSA doubling time < 3 months	9.9	11.3	**78.9**
Time to biochemical relapse < 3 months	18.6	37.1	**44.3**
Time to biochemical relapse > 3 months	52.9	42.6	4.4
Unable to delivery at least 64 Gy to the PTV	48.6	32.9	18.6
More than 1 of the above risk factors present	31.4	42.9	25.7
Delayed (> 6 months) postoperative radiotherapy with a detectible PSA			
Absolute PSA	18.3	32.4	**49.3**
Time to biochemical relapse < 6 months	28.2	31.0	40.8
Unable to delivery at least 64 Gy to the PTV	50.0	31.4	18.6
Biochemical progression	33.8	38.0	28.2
PSA doubling time < 6 months	21.1	33.8	**45.1**
PSA doubling time < 3 months	12.9	20.0	**67.1**
Delayed (> 6 months) postoperative radiotherapy with biochemical progression			
Stage pT3a	57.1	28.6	14.3
Stage pT3b	25.4	31.0	**43.7**
Positive margins - focal or extensive	60.0	32.9	7.1

Early (< 6 months) postoperative radiotherapy with a detectible PSA

In the context of a detectible PSA, importance was given to PSA kinetics over pre-treatment risk stratification or pathology, Table 1. The absolute PSA level, PSA doubling time and time to relapse < 3 months were very important to support the use of ADT respectively scoring 58%, 79% and 44%. Category pT3b disease and high risk D'Amico category was also considered very important considerations - 54% and 52%. Intermediate risk presurgical D'amico risk category, margin status, stage pT3a, inability to delivery > 64Gy and time to relapse faired as less important. Again two thirds (68.6%) would consider more than one risk factor as somewhat important or very important in influencing their decisions to use ADT.

Delayed (> 6 months) postoperative radiotherapy with a detectible PSA

In the context of delayed postoperative radiotherapy and a detectible PSA, the questions focused on PSA kinetics, Table 1. Overall 4.6% frequently use ADT in this setting, while 55.4% sometimes use it and 38.5% rarely use it. PSA doubling time < 3 months was very important for 67% of respondents, followed by absolute PSA, PSA doubling time of < 6 months and time to relapse as very important in 49%, 45% and 40% respectively. Equipoise between categories was seen in regards to the perceived importance of biochemical progression without specifying a PSA doubling time. When asked in regards to which of the established pathological factors for local relapse may persuade the use of ADT, only category pT3b was identified as very important (53.5%).

Clinical/radiological or biopsy proven residual prostate bed disease

When clinical/radiological evidence of residual prostate bed disease was evident, 47% said that they would frequently prescribe ADT, 24% stated sometimes and 21% stated rarely. 7% reported that they were not referred these patients, Figure 1. Likewise if prostate bed disease was biopsy proven the response was 36% frequently, 26% sometimes, 29% rarely and 8% were not referred these patients.

Duration of ADT

When asked the duration of recommending ADT use once prescribed, 48% indicated they would recommend it for 6 to 24 months, 24% for more than 24 months and 8% less than 6 months. Twenty percent reported that is was variable depending on the situation, Figure 2.

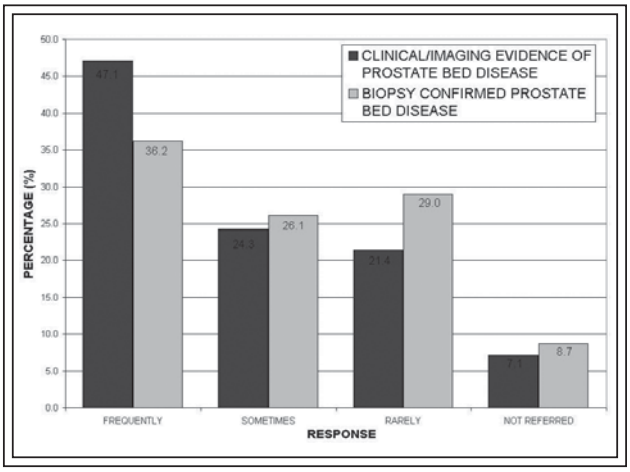

Figure 1. ADT overall frequency of use.

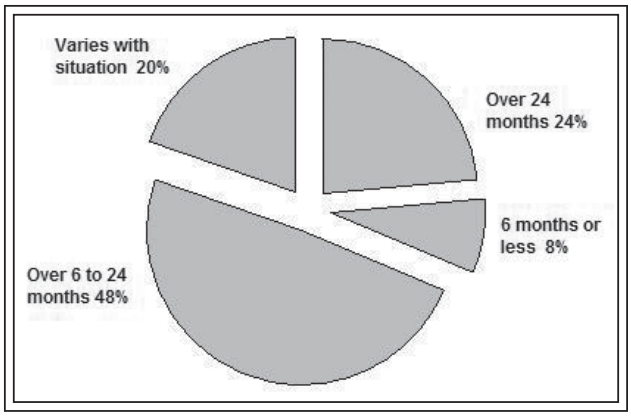

Figure 2. ADT preferred duration of use.

Discussion

The potential value of ADT in the postoperative setting is to target micro-metastatic disease outside the radiation treatment volume and to potentiate the effect of irradiation cell kill on microscopic disease within the radiation treatment volume.[18] Animal models suggests that ADT improves cell kill when lower radiation doses are employed.[19] Since postoperative radiation doses are limited by bladder and bowl toxicity issues, and are lower than the doses typically used in the in situ setting, there is a theoretical benefit for combining treatment with ADT to improve local disease control.[1-3] Combined RT and ADT have shown a survival advantage in the in situ setting. This suggests a potential effect of adjunctive ADT on micro-metastatic disease and also supports the treatment concept in the postoperative setting.[7] Non randomized data have shown an advantage in biochemical progression-free survival for patients treated with PORT and ADT.[20,21] Two key randomized studies evaluating the role of postoperative ADT are awaiting maturity. RTOG 96-01 compares PORT with and without adjuvant ADT and the Early Prostate Cancer Program trial compared surgery alone with or without adjuvant ADT. Both studies used a 2 year course of ADT in the experimental arm.[22,23]

The optimal use of androgen deprivation therapy for prostate cancer in the postoperative radiotherapy setting cancer remains to be elucidated. Our results demonstrate variable ADT use amongst responding Canadian uro-radiation oncologists, and inconsistent emphasis on various clinico-pathological parameters used to select patients for treatment. In fact half of the respondents rarely prescribe ADT in this setting. Similar variability has been observed in other jurisdictions,[16,17] and no one factor showed a high level

of agreement as an indicator for initiating hormonal treatment. In the early postoperative radiotherapy setting where patients are referred within 6 months of surgery, high risk disease and category pT3b were consistently felt to be important. When early biochemical relapse was also considered, PSA kinetics dominated as important considerations, including absolute PSA at time of referral, time to relapse, and PSA doubling time. This was also observed in the delayed postoperative setting where PSA kinetics was considered most important. Where respondents were asked if the presence of multiple risk factors would alter their preference to use ADT, approximately 1 in 4 respondents considered it important. We observed in all scenarios that category pT3b disease and PSA kinetics were considered to be an important factor throughout, reflecting that these are a strong predictor of sub-clinical metastatic disease.[24] Interestingly, there was no consensus on ADT use in the very adverse scenario of patients with clinical, radiological and biopsy proven local disease.

A response rate of 52% is comparable to other surveys in the literature and a representative sample of the field was achieved.[16] We did not present an exhaustive list of considerations that might be used to determine ADT use, for example, absolute PSA prior to surgery. In order to optimize response and applicability to the growing body of experience in this field, we grouped some factors such as risk categories and we were not overly specific in detailing the scenarios, particularly with the lack of randomized evidence. In this regard the interpretation of the scenario may vary. We did target all interested genito-urinary radiation oncologists and the results reflect the extent of ambiguity in the decision making process that exists amongst this specialist group. An unexpected finding was that time to biochemical relapse > 3 months was given very little importance compared to other PSA kinetic parameters, however this may reflect the rationale that PSA relapse after 3 months truly reflects local recurrence versus distant persistence of disease. Since up to 8% of radiation oncologists did not see patients in certain clinical scenarios, these results cannot be used to reflect the profile of ADT use in other prostate cancer specialties, which may see a different profile of patients.

This study indicates the great importance of ongoing randomized trials, particularly as postoperative radiotherapy becomes more widely accepted and employed. In the absence of data from these trials, there is a need for consensus guidelines to create a more uniform treatment paradigm based on best practice and level of evidence currently available.

Conclusions

Widespread variation in factors considered to be important in prescribing ADT in the postoperative radiotherapy setting was observed, no broad consensus was achieved, even with multiple adverse features. Duration of use is undecided. National consensus guidelines are required while randomized data to assess the efficacy of androgen deprivation therapy matures. □

References

1. Bolla M, van Poppel H, Collette L et al. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). *Lancet* 2005;366(9485):572-578.
2. Thompson IM Jr, Tangen CM, Paradelo J et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. *JAMA* 2006;296(19):2329-2335.
3. Wiegel T, Bottke D, Steiner U et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. *J Clin Oncol* 2009;27(18):2924-2930.
4. Chalasani V, Iansavichene AE, Lock M, Izawa JI. Salvage radiotherapy following radical prostatectomy. *Int J Urol* 2009; 16(1):31-36.
5. Stephenson AJ, Scardino PT, Kattan MW et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol* 2007;25(15):2035-2041.
6. Sia M, Pickles T, Morton G, Souhami L, Lukka H, Warde P. Salvage radiotherapy following biochemical relapse after radical prostatectomy: proceedings of the Genito-Urinary Radiation Oncologists of Canada consensus meeting. *Can Urol Assoc J* 2008; 2(5):500-507.
7. Bolla M, de Reijke TM, Van Tienhoven G et al. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med* 2009;360(24):2516-2527.
8. Katz MS, Zelefsky MJ, Venkatraman ES, Fuks Z, Hummer A, Leibel SA. Predictors of biochemical outcome with salvage conformal radiotherapy after radical prostatectomy for prostate cancer. *J Clin Oncol* 2003;21(3):483-489.
9. Song DY, Thompson TL, Ramakrishnan V et al. Salvage radiotherapy for rising or persistent PSA after radical prostatectomy. *Urology* 2002;60(2):281-287.
10. Taylor N, Kelly JF, Kuban DA, Babaian RJ, Pisters LL, Pollack A. Adjuvant and salvage radiotherapy after radical prostatectomy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2003;56(3):755-763.
11. Israeli RS, Ryan CW, Jung LL. Managing bone loss in men with locally advanced prostate cancer receiving androgen deprivation therapy. *J Urol* 2008;179(2):414-423.
12. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol* 2006;24(27):4448-4456.
13. [Internet] EORTC. Post-operative external radiotherapy combined with concomitant and adjuvant hormonal treatment versus post-operative external radiotherapy alone in pathological stage pT3a-b R0-1/pT2R1 N0M0, Gleason score 5-10 prostatic carcinoma. A phase III study.; 2009 [updated 2009; cited]; Available from: http://www.eortc.be/protoc/Details.asp?Protocol=30041.

14. [Internet] NCIC. RADICALS: Radiotherapy and Androgen Deprivation In Combination After Local Surgery.; 2009 [updated 2009; cited 2010]; Available from: http://www.ctg.queensu.ca/public/Clinical_Trials/public_ph_3_trial_summary.html#PR13.
15. Yokomizo A, Kawamoto H, Nihei K et al. Randomized controlled trial to evaluate radiotherapy +/- endocrine therapy versus endocrine therapy alone for PSA failure after radical prostatectomy: Japan Clinical Oncology Group Study JCOG 0401. *Jpn J Clin Oncol* 2005;35(1):34-36.
16. Lee LW, Clarke NW, Ramani VAC, Cowan RA, Wylie JP, Logue JP. Adjuvant and salvage treatment after radical prostatectomy: current practice in the UK. *Prostate Cancer Prostatic Dis* 2005; 8(3):229-234.
17. Morris SL, Parker C, Huddart R, Horwich A, Dearnaley D. Current opinion on adjuvant and salvage treatment after radical prostatectomy. *Clin Oncol (R Coll Radiol)* 2004;16(4):277-282.
18. Vergis R, Corbishley CM, Norman AR et al. Intrinsic markers of tumour hypoxia and angiogenesis in localised prostate cancer and outcome of radical treatment: a retrospective analysis of two randomised radiotherapy trials and one surgical cohort study. *Lancet Oncol* 2008;9(4):342-351.
19. Zietman AL, Prince EA, Nakfoor BM, Park JJ. Androgen deprivation and radiation therapy: sequencing studies using the Shionogi in vivo tumor system. *Int J Radiat Oncol Biol Phys* 1997;38(5):1067-1070.
20. Kasibhatla M, Peterson B, Anscher MS. What is the best postoperative treatment for patients with pT3bN0M0 adenocarcinoma of the prostate? *Prostate Cancer Prostatic Dis* 2005; 8(2):167-173.
21. King CR, Presti JC, Jr., Gill H, Brooks J, Hancock SL. Radiotherapy after radical prostatectomy: does transient androgen suppression improve outcomes? *Int J Radiat Oncol Biol Phys* 2004;59(2): 341-347.
22. [Internet] RTOG. A PHASE III trial of radiation therapy with or without casodex in patients with PSA elevation following radical prostatectomy for PT3N0 carcinoma of the prosatate.; 2006 [updated 2006; cited]; Available from: http://www.rtog.org/members/protocols/96-01/96-01.pdf.
23. Tyrrell CJ, Payne H, See WA et al. Bicalutamide ('Casodex') 150 mg as adjuvant to radiotherapy in patients with localised or locally advanced prostate cancer: results from the randomised Early Prostate Cancer Programme. *Radiother Oncol* 2005;76(1):4-10.
24. Walz J, Chun FK, Klein EA et al. Nomogram predicting the probability of early recurrence after radical prostatectomy for prostate cancer. *J Urol* 2009;181(2):601-607;discussion 7-8.