Opportunity lost and found: Any easy way to improve outcomes for prostate cancer patients in the postoperative setting?

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See related article on page 89.

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Evidence-based medicine is a paradigm shift and is a key component in the provision of high-quality care. The highest quality evidence is clinical practice guidelines based on systematic reviews of the randomized controlled trial (RCT) literature. There are many challenges to successfully complete RCTs and it is problematic to synthesize recommendations when the RCTs have conflicting results.

However, in the case of the utility of adjuvant postoperative radiotherapy (ART), this is not the case. There are three RCTs showing improvements in local and biochemical control;[1-3] the study with the longest follow-up (SWOG 8794) also demonstrates improvements in distant metastatic disease-free survival and overall survival.[2] Cancer Care Ontario (CCO) published a systematic review of the literature and clinical practice guideline on the topic showing that all subgroups benefitted in biochemical control and overall survival from ART (and those with seminal vesicle involvement seemed to benefit more not less).[4]

It is very interesting to see how this evidence is applied in the pragmatic setting. In this issue of *CUAJ*, Tyldesley and colleagues have published a population-based analysis of postoperative radiotherapy in British Columbia from 2007 to 2009.[5] Many interesting facts are reported. Over the 3-year observation period, 9223 patients were identified from the tumour registry and linked to centralized radiotherapy records. Of these patients, initial therapy was radical prostatectomy in 24%. Postoperatively, 47% had one or more high-risk features (positive surgical margin: 36%; extracapsular spread: 22%; seminal vesicle involvement: 4%).[5]

Of the 47% with one or more high-risk features, 23% with any adverse features were seen by a radiation oncologist within 6 months of surgery. Only 10% of these patients received adjuvant ART (i.e., 2% of patients with any high-risk features). Of equal interest, 40% of those with adverse features who were seen were advised against ART.

Why are the rates of referral (23%) and recommendation (60%) and use of ART (2%) so low for these patients?

The first argument is a lack of knowledge. The EORTC and SWOG studies were published in 2005 and 2006, respectively (and all were presented in abstract before the observation period). Despite this, we know that evidence takes a while to diffuse into practice, particularly community practice. How long is too long when we have a treatment with a solid evidence base that improves not just biochemical, but distant metastatic disease and overall survival rates? Is there anything we could have done differently to accelerate this knowledge dissemination?

The second argument is that the treatment is too toxic. It is easy to attribute really bad side effects (such as severe hemorrhagic cystitis) to all patients who might get radiation. However, when prospectively collected, the data demonstrate that the risk of serious RT toxicity was low. In the Wiegel trial, 1% and 0% of patients had grade 3 bladder and bowel problems.[3] This is despite patients receiving 2-dimensional RT; RT has improved greatly in target localization with image-guided techniques and my experience is that modern RT has even fewer side effects.

It is true that patients would require at least 30 visits to a cancer centre for consult, planning and treatment and for some patients this is costly and inconvenient. Much progress has been made in shortening the course of primary external radiation from 34 to 49 treatments to a few as 5 treatments;[6-8] work from our group and Kruser and colleagues' has applied these same techniques in the postoperative setting to improve the convenience without increasing the toxicity.[9]

The final argument is that early salvage postoperative RT is as good as immediate ART. Non-randomized data argue

against this.[10-12] However, this question (and the question of the optimal duration of adjuvant androgen deprivation therapy) is currently being tested in the intergroup RCT RADICALS which is open in more than 20 centres across Canada. Patients with any high-risk features should be considered for this trial.

In short, ART is being underutilized. This is a lost opportunity not only for our patients, but also the health care system. There are now 6 systemic therapies which improve overall survival in the castrate-resistant prostate cancer setting, but none have improved median survival more than 5 months. A course of each treatment costs between $20 000 and $118 000 on top of the $11 000 to $32 000 of hormone therapy. In comparison, a course of ART costs about $4000 and improves median survival by 23 months. At 10 years, it offers more survival benefit than SPCG4 documented for radical prostatectomy over watchful waiting (8% vs. 5%).[2,13]

We have a tremendous opportunity to make a meaningful difference in the lives of our patients and the healthcare system – we just need to listen to the evidence and act accordingly.

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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;366:572-8. http://dx.doi.org/10.1016/S0140-6736(05)67101-2
2. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant Radiotherapy for Pathological T3NOMO Prostate Cancer Significantly Reduces Risk of Metastases and Improves Survival: Long-Term Followup of a Randomized Clinical Trial. *J Urol* 2009;22:22.
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;27:2924-30. http://dx.doi.org/10.1200/JCO.2008.18.9563
4. Morgan SC, Waldron TS, Eapen L, et al. Adjuvant radiotherapy following radical prostatectomy for pathologic T3 or margin-positive prostate cancer: a systematic review and meta-analysis. *Radiother Oncol* 2008;88:1-9. http://dx.doi.org/10.1016/j.radonc.2008.04.013
5. Tyldesley S, Peacock M, Morris JW, et al. The need for, and utilization of radiotherapy after radical prostatectomy for patients with prostate cancer in British Columbia. *Can Urol Assoc J* 2012;6:XX-XX; http://dx.doi.org/10.5489/cuaj.11158
6. Boike TP, Cho L, Lotan Y, et al. A phase I dose escalation study of stereotactic body radiation therapy (SBRT) for low- and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2009;75:S80. http://dx.doi.org/10.1016/j.ijrobp.2009.07.200
7. Loblaw DA, Cheung P, Tang CI, et al. Biochemical, Pathological, Toxicity and Quality of Life Outcomes in A Five-Fraction Hypofractionated Accelerated Radiotherapy Treatment using standard linear accelerators and gold seed fiducials. *J Clin Oncol* 2012(suppl 5; abstr 186).
8. Ritter M, Forman J, Kupelian P, et al. Hypofractionation for prostate cancer. J Cancer 2009;15:1-6. http://dx.doi.org/10.1097/PPO.0b013e3181976614
9. Kruser TJ, Jarrard DF, Graf AK, et al. Early hypofractionated salvage radiotherapy for postprostatectomy biochemical recurrence. *Cancer* 2011;117:2629-36. http://dx.doi.org/10.1002/cncr.25824
10. 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;25:2035-41. http://dx.doi.org/10.1200/JCO.2006.08.9607
11. Swanson GP, Hussey MA, Tangen CM, et al. Predominant treatment failure in postprostatectomy patients is local: analysis of patterns of treatment failure in SWOG 8794. *J Clin Oncol* 2007;25:2225-9. http://dx.doi.org/10.1200/JCO.2006.09.6495
12. Trabulsi EJ, Valicenti RK, Hanlon AL, et al. A multi-institutional matched-control analysis of adjuvant and salvage postoperative radiation therapy for pT3-4N0 prostate cancer. *Urology* 2008;72:1298-302; discussion 302-4. http://dx.doi.org/10.1016/j.urology.2008.05.057
13. Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer. *N Engl J Med* 2011;364:1708-17. http://dx.doi.org/10.1056/NEJMoa1011967

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