HDR monotherapy for man with radiotherapy contraindications and prostate cancer

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LO A, NAM RK, LOBLAW DA. HDR monotherapy for man with radiotherapy contraindications and prostate cancer. The Canadian Journal of Urology. 2011;18(4):5839-5843.

There is debate about the optimal management of high risk localized prostate cancer. Initial options include surgery or radiation combined with androgen deprivation therapy. We describe a case of a patient with contraindications to radiotherapy who was managed with high dose rate (HDR) brachytherapy as his sole treatment.
A medically operable patient presented with a T2c N0 M0 Gleason 9 adenocarcinoma with an initial PSA of 19.9 ng/mL. Previously, he had severe ulcerative colitis managed with pancolectomy and a neorectum fashioned from ileum anastomosed behind his prostate. After a negative extended lymph node dissection, a HDR brachytherapy implant of 35 Gy in 5 fractions over 3 days was delivered. No androgen deprivation therapy was used. The treatment was extremely well tolerated in the short and long term with no significant bowel or bladder side effects observed in follow up. After 7 years, his PSA was 0.04 ng/mL.
The excellent long-term biochemical control and minimal radiation toxicity observed in this patient suggests that HDR monotherapy may be a safe and effective alternative for high risk prostate cancer patients in whom EBRT is contraindicated.

Key Words: prostate cancer, HDR brachytherapy, high risk, radiotherapy contraindications

Introduction

Prostate cancer is the most prevalent malignancy in men, with 24,600 affected individuals and 4300 deaths across Canada in 2010.[1] The disease is often stratified into high, intermediate, and low risk cancer, based on factors which include tumor grading with Gleason sum; tumor bulk and extent with tumor-node (TNM) category; biopsy core mapping and percentage core involvement; and biochemical parameters such as PSA level or velocity. High risk prostate cancer is defined by D'Amico and the Genitourinary Radiation Oncologists of Canada as those having one or more of the following features: T3-T4, Gleason sum 8-10, or PSA > 20 ng/mL.[2,3]

Primary curative treatment modalities for this group can be divided into surgery versus radiotherapy. Conventionally, surgical treatment was not the preferred approach, since the morbidity involved was not justified in view of elevated rates of positive surgical margins, absence of randomized studies, suboptimal cancer

Accepted for publication February 2011

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control, and risk of subclinical metastatic disease.[4] However, surgery is now increasingly recognized as a reasonable option in selected cases, in the context of a multimodality approach combining radical prostatectomy, extensive lymphadenectomy, and when required, adjuvant external-beam radiotherapy (EBRT) and androgen deprivation therapy (ADT). While some high risk patients will be cured with surgery alone, adjuvant or salvage radiotherapy is indicated if there is pT3 disease, positive margins, and/or a detectable or rising PSA postoperatively.[5,6]

If radiotherapy is selected as the primary treatment modality for high risk prostate cancer, it is usually administered as EBRT with ADT and dose escalation by either intensity-modulated radiotherapy (IMRT), or low or high dose-rate brachytherapy boost.[7] The combination of radiotherapy and ADT has been shown to improve a number of outcomes including local failure, biochemical control and overall survival.[8] However, in a setting where a medically operable patient has a contraindication to radiotherapy, surgery is usually preferred.

We present the treatment, acute and long term side outcome of a case of a high risk prostate cancer patient who was not a candidate for the standard dose-escalated radiotherapy (RT) regimen due to a radiotherapy contraindication.

Case report

A 58-year-old gentleman was found to have an elevated PSA at 19.9 in March 2003 with no palpable abnormality. Free to total ratio was 0.04. Prostate biopsy cores revealed adenocarcinoma of the prostate, Gleason 5 + 3 = 8 in the right mid core and 3 + 4 = 7 in the right apex. The pathology was subsequently upgraded by a uropathologist to Gleason 4 + 5 = 9 in both the right mid and right apical cores. Ninety percent (90%) and sixty percent (60%) of the surface area of each of the cores, respectively, were involved. A staging CT of the abdomen and pelvis, as well as a bone scan revealed no evidence of metastatic disease.

Past medical history of the patient was significant for multiple sclerosis and ulcerative colitis. Due to complications from his ulcerative colitis, a total colectomy had been performed, followed by construction of a neo-rectum which was anastomosed to his rectal stump. The anastamosis was located immediately posterior to the mid-prostate.

The patient's treatment options were quite limited due to his ulcerative colitis and bowel anatomy. A radical course of external beam radiation was contraindicated due to the close proximity of the small bowel to his prostate and the inherent radiosensitivity of small bowel.[9] A radical prostatectomy would have likely required postoperative radiation, which even at a lower dose (60 Gy-66 Gy) would pose significant risk to his small bowel. Another option considered was performing a defunctioning colostomy at the time of the radical prostatectomy in anticipation of the need for postoperative RT, followed by reanastamosis of the bowel after RT.

The patient's case was presented at Odette Cancer Centre GU Tumor board, and it was recommended that he undergo extensive lymph node dissection for staging purposes, followed by high dose rate (HDR) brachytherapy. If any nodes were positive, the patient would also be initiated on hormonal therapy.[10] A retroperitoneal and pelvic lymph node dissection was therefore performed in October 2003 without complications. Pathology revealed 29 non-malignant lymph nodes with no evidence of cancer.

With the goal of minimizing the biologically effective dose from HDR brachytherapy, a dose of 35 Gy in 5 fractions was administered over 3 days, completed in December 2003. The patient was planned using a CT-based planned system (PLATO, Nucletron B.V., Veenendall, The Netherlands), the details of which are reported elsewhere.[11] No bowel dose limits were prescribed nor calculated at the time but based on our current technique, typically less than 0.1 cc of adjacent bowel would receive 80% of the prescription dose. Normal small bowel would have received a negligible dose. Figure 1 shows the isodose curves approximately at the level of the anastamosis – only

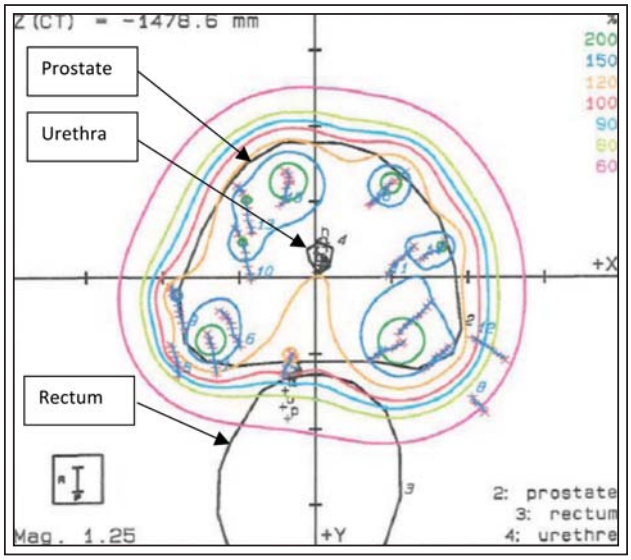

Figure 1. Isodose curves through an axial image of the mid-prostate on one of the patient's HDR treatments.

a very small volume the bowel received 100% of the prescription dose. The patient was admitted during the course of treatment with the HDR catheters remaining in place. Continuous epidural anesthesia via pump achieved excellent pain control. Before each treatment, radiographs were taken to confirm the catheter positions – in 3 of the fractions, catheters had moved more than 5 mm and the patient had to be replanned.

Acute toxicities experienced by the patient consisted of minimal urinary side effects and decreased erectile function, the latter effectively managed by PDE5 inhibitors. The patient has been followed routinely for the past 7 years -- he has had no complications with his bowel function, including hematochezia, at any time during his follow up and no bowel medications have been required. He used loperamide before RT and continued at the same dose afterwards. The patient's PSA level decreased to 4.97 in April 2004 and subsequently continued to decrease. PSA level was 0.42-0.43 between February and August 2005, 0.14 in August 2006, 0.07 in August 2007 and September 2008, 0.06 in September 2009, and 0.04 in September 2010. No ADT or 5-ARIs have ever been prescribed.

Discussion

The present case involves a high risk prostate cancer patient contraindicated for pelvic irradiation due to the close proximity of his ileum to the prostate on the background of inflammatory bowel disease (IBD). His definitive treatment with HDR brachytherapy (35 Gy/5) resulted in a successful outcome despite several unfavorable features: 1) his abnormal bowel anatomy, 2) the exclusion of external beam radiation, and 3) the exclusion of androgen deprivation therapy.

The patient's history of IBD is an important factor in deciding his management. Pelvic EBRT has been considered a relative contraindication in inflammatory bowel disease due to its exacerbation of inflammatory processes in the rectal mucosa.[12] This notion is supported by a study of 28 IBD patients receiving abdominal or pelvic EBRT to an intended dose of ≥ 40 Gy: the overall incidence of severe toxicity was 46% (21% acute, 29% late – 1 patient had both severe acute and late toxicities).[13] However, other studies have suggested a more modest risk of gastrointestinal complications. Green et al determined in a series of 47 patients with IBD and rectal cancer receiving EBRT, that while 20% experienced acute Grade 3-4 toxicity, none experienced long term severe complications; they concluded that toxicity rates of IBD and non-IBD rectal cancer patients were comparable.[14]

In addition to EBRT, the question of an increased rectal toxicity rate in IBD compared to non-IBD patients has also been investigated in the setting of prostate brachytherapy. In a case series of six patients treated with ^{125}I prostate brachytherapy, Grann and Wallner observed that none of these patients experienced unusual or significant gastrointestinal side effects.[15] Peters et al determined that brachytherapy rectal toxicity rates in IBD patients are similar to that in non-IBD patients: only 4 of 24 patients in their study treated with low dose rate brachytherapy with or without EBRT experienced Grade 2 late rectal toxicity, while none of them experienced Grade 3 or 4 rectal toxicity.[12] However, Chen and D'Amico report contradicting results in a large study assessing the prevalence and predictors of brachytherapy complications in 5621 men (of whom 60% were treated with brachytherapy alone, and 40% treated with brachytherapy and EBRT): a bowel complication rate of 42% was seen in IBD patients, compared to 21% in non-IBD patients (on multivariable analysis OR 2.60, $p < 0.01$).[16]

Besides a history of IBD in the patient presented, a pan-colectomy left him with a section of small bowel directly posterior to his prostate, introducing an additional challenge to his management. Our clinical consensus was that a radical course or post prostatectomy course of EBRT could not be effectively delivered. Emami et al, estimated that for 1/3 the volume of small bowel, the TD5/5 (the total RT dose that would produce a 5% risk of perforation / obstruction / fistula within 5 years of treatment) was 50 Gy while the TD50/5 (50% probability of complication) was 60 Gy.[17] Subsequently, Roeske et al, found that the volume of small bowel receiving 45 Gy was predictive of acute severe toxicity on multivariate analysis of women getting whole pelvic RT.[18] They predicted that a small bowel volume of 100 cc receiving 45 Gy would have an estimated 2% acute toxicity rate (typical rectal volumes are 30 cc-50 cc total). However, there appears to be a paucity of published data for dose-volume normal tissue complications for higher doses of RT to justify accepting high dose RT to even a portion of small bowel.

Another treatment consideration is prostate seed brachytherapy with supplemental EBRT (45 Gy), offering high rates of disease control,[19] but in this patient, would be associated with significant GI toxicity risk, including rectal bleeding.[16] Of more pragmatic consideration for this patient, seed brachytherapy was not and is still not funded for high risk patients in the province of Ontario.

In the treatment of high risk prostate cancer, multiple randomized controlled trials (RCTs) have established a role for combining ADT with RT. For example, the

European Organization for Research and Treatment of Cancer (EORTC) conducted a study comparing RT alone versus RT with 3 years of ADT in patients with T1-T2 World Health Organization Grade 3 or T3-T4 N0-N1 M0 tumors. The study concluded that the addition of ADT to RT results in increased 5 year biochemical disease-free survival (bDFS, 74% versus 40%), 5 year overall survival (78% versus 62%), and 5 year specific survival (94% versus 79%).[20] As in other RCTs that support the use of ADT with RT,[21-23] the prescribed radiation dose was ≤ 70 Gy delivered using EBRT. There is increasing evidence in a number of RCTs that higher biologically effective doses increase bDFS, even in high risk tumors.[24-30] In the setting of dose-escalated RT, the specific value of ADT has not been investigated in any RCT to date.

HDR brachytherapy offers three ways of safely biologically dose-escalating. The first is through hypofractionation,[31] where there is increasing evidence of a low alpha/beta ratio. In the study by Miralbell et al, patients with low, intermediate and high risk prostate cancer had alpha/beta ratios of 1.3, 1.6 and 1.8, respectively.[32] The dose given to this patient would have been a minimum equivalent dose in 2 Gy fractions (EQD2) of 81 Gy. As approximately 50% of the volume would have received 150% of the prescription dose, half the target volume would have received an EQD2 of 113 Gy. The second benefit is acceleration. Thames et al, showed that while doses above 70 Gy were associated with 2.5% less bDFS/Gy, overall treatment time was associated with an increased risk of bDFS of 1% per day above 52 days.[33] The third advantage is the sparing of the normal tissues due to the physical properties of the HDR source and sophisticated planning software programs.

As such, HDR brachytherapy has been used as the sole method of administering radiotherapy, that is without EBRT, in low risk and low tier intermediate risk prostate cancer patients. In this select group of patients, excellent intermediate term results have been shown with HDR brachytherapy alone, using 4 or 6 doses of 6 Gy-9.5 Gy each, to a total dose of 38 Gy-54 Gy.[34] In all other intermediate risk and high risk patients, however, HDR brachytherapy is generally combined with EBRT. Using this combined treatment regimen, a study by Guix et al showed a 5 year biochemical-free rate survival of 96%-97% with a median follow up of 77 months.[35] While research shows that brachytherapy in conjunction with EBRT is an effective treatment for high risk patients, there is no strong evidence to support the use of HDR brachytherapy alone in this patient population.

In a prospective, non-randomized study by Demanes et al, improvement was not observed with the addition of ADT to HDR brachytherapy (4 fractions of 5.5 Gy to 6.0 Gy) and EBRT (total of 36.0 Gy to 39.6 Gy). Risk-stratified analysis of the 113 patients in the high risk group revealed no difference in rates of local control, PSA progression-free survival, distant metastasis, and cause-specific survival. Others have shown similar results.[36,37] While suggestive that ADT may not offer an added benefit in this setting, proper evaluation in a RCT needs to be performed.

The management of the patient being presented deviates from the standard management of high risk prostate cancer patients: the patient was treated definitively with HDR brachytherapy, without EBRT or hormonal therapy. Despite this conservative approach, 7 year follow up reveals an excellent outcome with PSA nearly undetectable and continuing on a downward trend. The other notable feature of the case is the minimal radiation toxicity experienced by a patient who would normally be contraindicated to RT due to inflammatory bowel disease and abnormal bowel anatomy. In spite of his increased risk for severe toxicity, the patient received 35Gy/5 of HDR brachytherapy with only minor urinary side effects, decreased erectile function, and no bowel toxicity.

Conclusion

The excellent long term biochemical control and minimal radiation toxicity observed in this patient suggests that HDR monotherapy may be a safe and effective alternative for high risk prostate cancer patients in whom EBRT is contraindicated. A significant contributor to the successful outcome of this case may be the extreme precision of image-guided radiotherapy, allowing for delivery of high doses of radiation to the targeted site with relative avoidance of normal tissues. Further studies should be conducted in order to determine which prostate cancer patients are appropriate candidates for HDR monotherapy, as well as the role of adjuvant ADT in the defined setting. □

References

1. Canadian Cancer Society/National Cancer Institute of Canada. Canadian Cancer Statistics 2010.
2. D'Amico AV, Whittington R, Malkowicz SB et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998;280(11):969-974.
3. Lukka H, Warde P, Pickles T, Morton G, Brundage M, Souhami L. Controversies in prostate cancer radiotherapy: consensus development. *Can J Urol* 2001;8(4):1314-1322.
4. Lawrentschuk N, Trottier G, Kuk C, Zlotta AR. Role of surgery in high-risk localized prostate cancer. *Curr Oncol* 2010;17(Suppl 2): S25-S32.

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. Morgan SC, Walker-Dilks C, Eapen LJ et al. Adjuvant radiotherapy following radical prostatectomy for pathologic T3 or margin-positive prostate cancer: updated guideline recommendations 2010. Cancer Care Ontario Evidence-based Series. July 2010.
7. Mohler J, Bahnson RR, Boston B et al. NCCN clinical practice guidelines in oncology: prostate cancer. *J Natl Compr Canc Netw* 2010; 8(2):162-200.
8. Quon H, Loblaw DA. Androgen deprivation therapy for prostate cancer-review of indications in 2010. *Curr Oncol* 2010;17(Suppl 2): S38-S44.
9. Martin E, Pointreau Y, Roche-Forestier S, Barillot I. Normal tissue tolerance to external beam radiation therapy: small bowel. *Cancer Radiother* 2010;14(4-5):350-353.
10. Messing EM, Manola J, Yao J, et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. *Lancet Oncol* 2006;7(6):472-479.
11. Morton GC, Loblaw DA, Sankreacha R et al. Single-fraction high-dose-rate brachytherapy and hypofractionated external beam radiotherapy for men with intermediate-risk prostate cancer: analysis of short- and medium-term toxicity and quality of life. *Int J Radiat Oncol Biol Phys* 2010;77(3):811-817.
12. Peters CA, Cesaretti JA, Stone NN, Stock RG. Low-dose rate prostate brachytherapy is well tolerated in patients with a history of inflammatory bowel disease. *Int J Radiat Oncol Biol Phys* 2006;66(2):424-429.
13. Willett CG, Ooi CJ, Zietman AL et al. Acute and late toxicity of patients with inflammatory bowel disease undergoing irradiation for abdominal and pelvic neoplasms. *Int J Radiat Oncol Biol Phys* 2000;46(4):995-998.
14. Green S, Stock RG, Greenstein AJ. Rectal cancer and inflammatory bowel disease: natural history and implications for radiation therapy. *Int J Radiat Oncol Biol Phys* 1999;44(4):835-840.
15. Grann A, Wallner K. Prostate brachytherapy in patients with inflammatory bowel disease. *Int J Radiat Oncol Biol Phys* 1998; 40(1):135-138.
16. Chen AB, D'Amico AV, Neville BA, Earle CC. Patient and treatment factors associated with complications after prostate brachytherapy. *J Clin Oncol* 2006;24(33):5298-5304.
17. Emami B, Lyman J, Brown A et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 1991;21(1): 109-122.
18. Roeske JC, Bonta D, Mell LK, Lujan AE, Mundt AJ. A dosimetric analysis of acute gastrointestinal toxicity in women receiving intensity-modulated whole-pelvic radiation therapy. *Radiother Oncol* 2003;69(2):201-207.
19. da Silva Franca CA, Vieira SL, Carvalho AC, Bernabe AJ, Penna AB. Localized prostate cancer with intermediate- or high-risk features treated with combined external beam radiotherapy and iodine-125 seed brachytherapy. *Brachytherapy* 2010;9(4): 307-312.
20. Bolla M, Collette L, Blank L 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(9327):103-106.
21. Hanks GE, Pajak TF, Porter A et al. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: the Radiation Therapy Oncology Group Protocol 92-02. *J Clin Oncol* 2003;21(21):3972-3978.
22. Pilepich MV, Winter K, Lawton CA 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(5):1285-1290.
23. 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.
24. Dearnaley DP, Sydes MR, Graham JD et al. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2007;8(6):475-487.
25. Hoskin PJ, Motohashi K, Bownes P, Bryant L, Ostler P. High dose rate brachytherapy in combination with external beam radiotherapy in the radical treatment of prostate cancer: initial results of a randomised phase three trial. *Radiother Oncol* 2007; 84(2):114-120.
26. 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(13):1990-1996.
27. 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(5):1097-1105.
28. 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(6): 1192-1199.
29. 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(10):1233-1239.
30. Guix B, Bartrina JM, Henriquez I et al. Dose escalation by combined treatment 3D-conformal radiotherapy plus HDR brachytherapy as treatment for intermediate- or high-risk cancer: early toxicity and biochemical outcome of a prospective randomized trial. In: American Brachytherapy Society. Toronto; 2009.
31. Loblaw DA, Cheung P. External beam irradiation for localized prostate cancer--the promise of hypofractionation. *Can J Urol* 2006; 13(Suppl 1):62-66.
32. Miralbell R, Roberts SA, Zubiazerreta E, Hendry JH. Dose-fractionation sensitivities of low/middle/high-risk prostate cancer deduced from seven international primary institution datasets. *Int J Rad Onc Biol Phys* 2009;75(3 Supp 1):S81 (abstract 171).
33. Thames HD, Kuban D, Levy LB et al. The role of overall treatment time in the outcome of radiotherapy of prostate cancer: an analysis of biochemical failure in 4839 men treated between 1987 and 1995. *Radiother Oncol* 2010;96(1):6-12.
34. Pisansky TM, Gold DG, Furutani KM et al. High-dose-rate brachytherapy in the curative treatment of patients with localized prostate cancer. *Mayo Clin Proc* 2008;83(12):1364-1372.
35. Guix B, Bartrina JM, Tello J et al. Treatment of intermediate-or high-risk prostate cancer by dose escalation with high-dose 3D-conformal radiotherapy (HD-3D-CRT) or low-dose 3D-conformal radiotherapy plus HDR brachytherapy (LD-3D-CRT+HDR-B): early results of a prospective comparative trial. *Int J Radiat Oncol Biol Phys* 2010;78(3 Suppl):S78 (abstract 167).
36. Krauss D, Kestin L, Ye H et al. Lack of benefit for the addition of androgen deprivation therapy to dose-escalated radiotherapy in the treatment of intermediate- and high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2010;2010:26.
37. Martinez A, Galalae R, Gonzalez J, Mitchell C, Gustafson G, Kovacs G. No apparent benefit at 5 years from a course of neoadjuvant/concurrent androgen deprivation for patients with prostate cancer treated with a high total radiation dose. *J Urol* 2003;170(6 Pt 1):2296-2301.