External beam irradiation for localized prostate cancer – the promise of hypofractionation

D. Andrew Loblaw, MD, Patrick Cheung, MD

Department of Radiation Oncology, University of Toronto, Sunnybrook and Women's College Health Sciences Centre, Toronto, Ontario, Canada

LOBLAW DA, CHEUNG P. External beam irradiation for localized prostate cancer – the promise of hypofractionation. The Canadian Journal of Urology. 2006;13(Supplement 1):62-66.

Within the field of radiation oncology in the last 10 years, there have been two major thematic advances in the understanding and treatment of prostate cancer. Computerized treatment planning and high precision delivery techniques have already revolutionized the treatment of this disease. Three randomized studies have reported improved biochemical disease-free survival rates in patients from low- to high-risk disease with higher radiation doses. When given conformally, the higher doses do not appear to increase severe toxicity. The second important discovery was that prostate cancer reacts differently than other tumors to radiation whereby higher doses of radiation per day ("hypofractionated radiation") seem to be more effective in killing prostate cancer cells. A meta-summary of four reports summarizing 21 studies presented herein produced an alpha/beta ratio of 1.3 Gy. The early experience of two hypofractionated trials in intermediate- and high-risk prostate cancer where the equivalent of > 80 Gy (in 2 Gy per day fractions) delivered in 5-6 weeks is reported. In summary, hypofractionated radiation coupled with high-precision techniques may allow for better prostate cancer control rates, shorter treatment times and less toxicity.

Key Words: prostate cancer, radiotherapy, hypofractionation, radiobiology

Prostate radiotherapy

Radiotherapy planning

Technology has had a major impact in the way that external beam radiotherapy (RT) is delivered. Previously, the knowledge about where the prostate was located was determined from a series of patients where the relationship of the average prostate location and size was documented with respect to bony landmarks and/or cystograms/contrast enemas. This data was then used as the individual patient was undergoing the planning process on a conventional simulator (a diagnostic x-ray machine set up in the same way as the treatment units). Due to the large uncertainty about the actual size and location of the prostate for the individual patient, a large margin had to be added around the prostate to confidently encompass it in the high dose volume.

Address correspondence to Dr. D. Andrew Loblaw, Department of Radiation Oncology, Sunnybrook and Women's College Health Sciences Centre, T2-107, 2075 Bayview Avenue, Toronto, Ontario M4N 3M5 Canada

The consequence of these large margins was that the high dose region also encompassed a large volume of bowel and bladder, which limited the dose that could be given safely to the patient. Typically using conventional RT, a patient was prescribed between 60 and 66 Gray (a unit of RT dose) in 30 – 33 treatments over 6 – 6.5 weeks. In addition, there were significant side effects (both acutely and long-term) and the tumor control rates were poor.

With the introduction of CT-based simulation, the actual position of the prostate (at the time of simulation) for the individual patient could be determined. In addition, research about prostate motion from day to day and during the time of RT helped better define the margins around the prostate. Electronically controlled shields ("multi-leaf collimators") in the head of the treatment units, allow shaping of the normally rectangular RT fields in order to further minimize dose to normal structures. Because the target and the margins around the target are defined in three dimensions, the technique is referred to as three-dimensional conformal RT (3D-CRT).

Sophisticated planning systems now allow the physician to determine, before treatment, what dose will be delivered to the target and the surrounding critical normal tissues so that the plan can be modified if it doesn't meet the safety constraints. This is called a forward planning process and sometimes several iterations are required to meet these constraints.

Typically for forward planned 3D-CRT, each treatment (or "fraction") involves directing the external beam at target volume from four – six different directions (or "fields"), usually in the same axial plane. Each beam has a custom aperture shaped by the multi-leaf collimators (MLCs).

The more sophisticated approach is to use intensity modulated radiotherapy (IMRT) and inverse planning where each beam is split into numerous beamlets of varying intensity. Because the MLCs are pushed in from the outside of the RT beam, shielding cannot be done within a target volume. Figure 1 illustrates how by breaking the volume up into two segments, this limitation can be overcome. Adding segments 1 and 2 together results in the desired "H" volume. As the MLC are electronically controlled, multiple segments can be delivered for each field in a time-efficient manner.

Inverse planning performed by a computer automates the iterative process of determining the optimal plan. The goals, normal tissue and target volumes of the treatment are entered into the IMRT planning system and the system determines the optimal number of fields, the direction and weighting of those fields, and the number and shape of the segments within each field. The resulting dose distribution is then reviewed and approved by the radiation oncologist. Up to 63 segments or beamlets can be generated per treatment plan so one can see how IMRT allows the radiation oncologist to sculpt the RT dose even more than a forward planned technique. The Toronto Sunnybrook Regional Cancer Centre was the first Canadian center to introduce both 3D-CRT and IMRT.

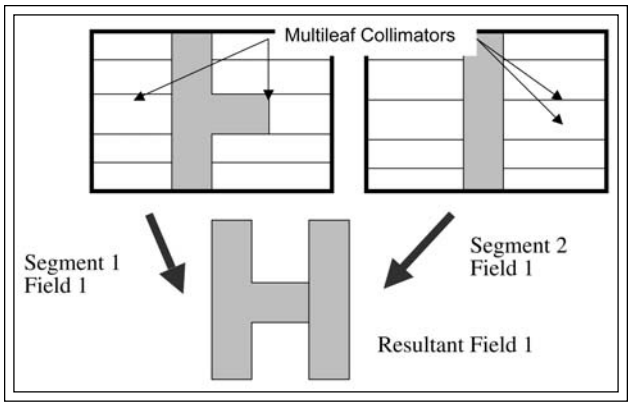

Figure 1. An illustration of the principles of intensity modulated radiotherapy (IMRT). In order to make the resultant field shape "H" using the multileaf collimators which can be advanced from each side, two shapes, "segments" 1 and 2 can be added together.

Clinical trials of dose escalation

These techniques have allowed much higher doses of RT to be safely given to the prostate, with doses ranging from 75 Gray – 86 Gray. Three published randomized studies with mature results have shown that higher doses of RT correspond with better biochemical control (13%-32% improvement at 5 years).[1-4] Table 1 summarizes these three studies.

TABLE 1. **Radiation doses, patients characteristics and outcomes for randomized studies of dose escalation in**

Trial	RT dose	N	Median follow-up	Patient characteristics			
				% T stage (T1-2 v 3-4)	% Gleason sum (2-6 v 7 v 8-10)	% PSA (<10 v 10-20 v >20)	% Risk category (low v intermediate v high)
Pollack 2002	78 Gy	151	5 y	78 v 23	50 v 33 v 17	65 v 32 v 3	NR
	70 Gy	150		83 v 17	48 v 34 v 17	65 v 32 v 3	
Sathya 2005	40 Gy EBRT + 35 Gy brachy boost 66 Gy	51	8.2 y	61 v 39	37 v 45 v 18	30 v 33 v 37	0 v 41 v 59
		53		60 v 40	34 v 53 v 13	43 v 23 v 34	0 v 40 v 60
Zeitman 2005	79.2 GyE‡	195	5.5 y	100 v 0	75 V 15 V 8*	85 v 15 v 0	60 v 31 v
	70.2 GyE†	197		100 v 0	75 v 15 v 9*	86 v 14 v 0	56 v 35 v 9

NR – not reported; † proton boost of 19.8 Gray equivalent (GyE) given; ‡ proton boost of 28.8 Gray equivalent (GyE)

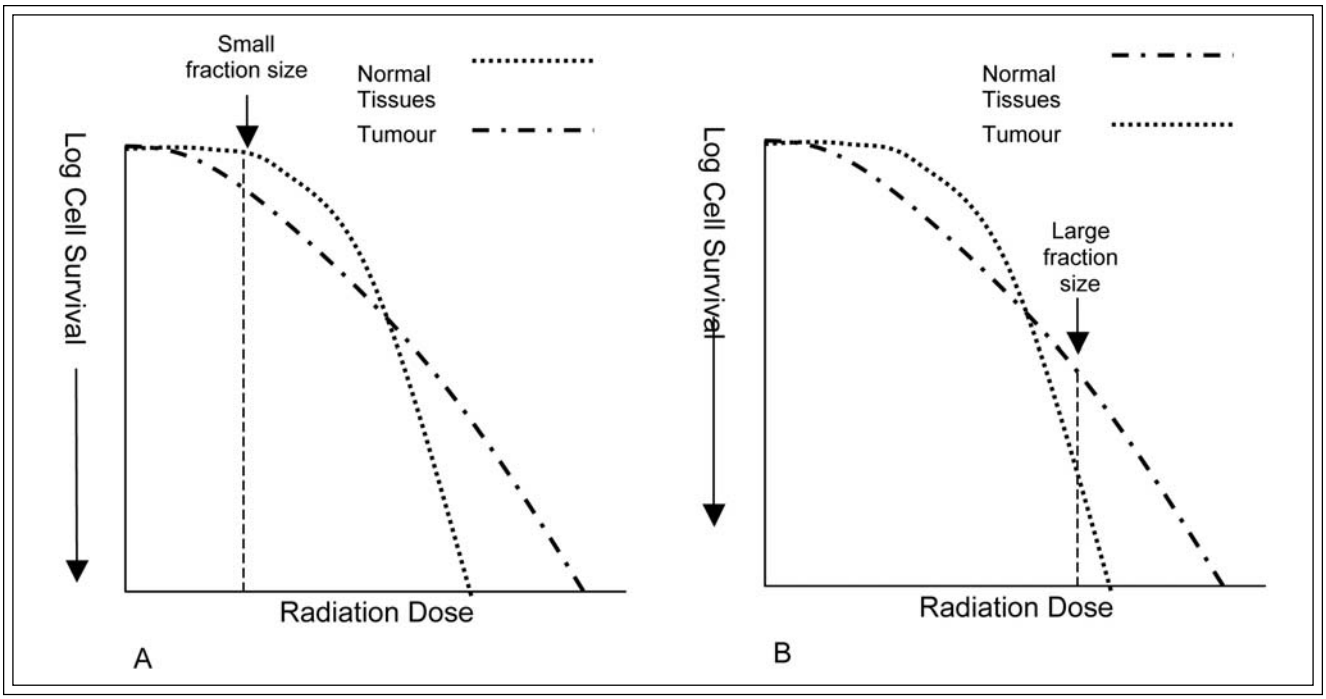

Figure 2. Cell survival curves where the log of the proportion of cells remaining for increasing doses of radiation are plotted. Figure A – where the α/β ratio for the tumor is greater than normal tissues (e.g. breast cancer), then smaller doses of radiation per day kill more tumor cells than normal tissue cells. Figure B – where the α/β ratio for the tumor is less than normal tissues (e.g. prostate cancer), then larger doses of radiation per day kill more tumor cells than normal tissue cells.

Prostate radiobiology

These three trials used daily external beam doses of 1.8 Gray – 2.0 Gray (Gy) per day which was historically determined to be a well tolerated daily dose for both acute and late toxicity. Bear in mind that these fractionation schedules were determined in an era of conventional i.e., non-conformal RT.

prostate cancer

5-Year biochemical disease-free survival		**% Grade 3 late toxicity**	
%	**P value**	**GI**	**GU**
76	0.03	10	4
63		1	2
70	0.002	4	14
38		2	4
80	<0.001	1	1
61		1	2

Two studies of the radiobiology of prostate cancer were published approximately 5 years ago and have subsequently been confirmed by two randomized controlled trials that involved over 1000 men. The observation was that prostate cancer is more sensitive to lethal damage from higher daily doses of radiotherapy compared to other tumors.

Because there is a differential cell kill between the tumor and normal tissues, a favorable therapeutic ratio can be achieved with RT. The degree of cell kill as it relates to increasing doses of radiation, can be described using the cell survival curve, see Figure 2. The shape of the cell survival curve can be modeled using the linear-quadratic equation:

$$S = \alpha D + \beta D^2 \quad (1)$$

where S = the proportion of surviving cells, D is the RT dose/fraction and α and β are constants which are thought to relate to the cell kill that is due to ionizing RT causing double- and single-strand DNA breaks, respectively. One double-strand break or two adjacent single-strand breaks constitute a lethal event.

Tissues or tumors with higher α/β ratios appear have survival curves which are more curvilinear; those

with lower α/β ratios appear straighter. A biologically equivalent dose (BED) of RT, for a given α/β ratio, can be calculated by the following formula:

$$BED_{\alpha/\beta} = nd * (1 + d/\alpha/\beta) \quad (2)$$

where n is the number of fractions, d is the daily dose of RT and α/β is the alpha to beta ratio for the outcome of interest.

Typically the α/β ratio for tumors is approximately 10 Gy,[5] while the late effects of normal tissues are typically 2 Gy – 4 Gy. One can see from Figure 2A that if the α/β ratio for prostate is like other tumors, i.e., higher than normal tissue, smaller doses per day kill more tumor cells than normal tissue cells. Higher doses per day would do the opposite and lead to serious late toxicities. Conversely, if the α/β ratio for prostate cancer is lower than normal tissues, then higher doses per day would be more effective, Figure 2B.

Two radiobiologic studies of prostate cancer have concluded that the α/β ratio is around 1.5 Gy. The first study to publish this observation was published by Brenner and Hall in 1999.[6] They analyzed two mature radiotherapy data sets which contained data on prostate cancer tumor control to extract the sensitivity to changes in fractionation of prostatic tumors. Overall there were 367 patients who were treated using external beam RT (EBRT) or permanent seed implants. They concluded that prostatic cancers appear significantly more sensitive to changes in fractionation than most other cancers and estimated the α/β ratio to be 1.5 Gy (95% confidence interval (CI) 0.8 – 2.2).

The second study contained data on 735 patients with prostate cancer from 17 papers of EBRT or seed brachytherapy published between 1995 and 2000. Several methods were used to calculate the α/β ratio; the authors felt that the most accurate method produced an α/β ratio of 1.49 Gy (95% CI 1.25 – 1.76).

These results were not too surprising as there is a documented relationship between cellular proliferative status and sensitivity to changes in fractionation, and prostate tumors contain exceptionally low proportions of proliferating cells.

Randomized hypofractionated studies

Since then, two randomized studies of hypofractionated RT have been published which validate the above studies. The largest study was the NCI Canada PR5 randomized study of 66 Gy in 33 fractions over 6.5 – 7 weeks versus 52.5 Gy in 20 fractions over 4 – 4.5 weeks for patients with localized prostate cancer. There were 935 patients, predominately with low and intermediate-risk prostate cancer, randomized between the two arms and followed for a median of 5.7 years. There was a hazard rate of 1.18 for the primary endpoint biochemical disease-free survival (bDFS) favoring the 66 Gy arm, which did not reach statistical significance (95% CI 0.99 – 1.41).

If the two arms are considered to have an equivalent biologically equivalent dose (BED), then equation (2), above, can be used:

$$n_1d_1 (1 + d_1/\alpha/\beta) = n_2d_2 (1 + d_2/\alpha/\beta) \quad (3)$$

where n_1 and d_1 are the number of fractions and daily dose for the first fractionation schedule and n_2 and d_2 are those values for the second schedule. Solving for α/β gives a value of 0.43 Gy.

However, if one believes that there truly exists a small difference in biochemical disease-free survival between these two dose regimens that the trial was insufficiently powered to detect, a slightly different α/β can be calculated. In the Lukka trial, the 5-year bDFS was 47% and 40%, respectively for the long and short arms. Using the dose response curve reported in the Wang meta-analysis, 5-year bDFS rates like the above would correspond to 67 Gy and 65 Gy, respectively.[7] Adding this factor to equation (3) and solving, the α/β ratio would be 0.86 Gy. This is biologically more plausible and more consistent with the previous radiobiologic studies.

The second RCT hypofractionated RT trial in prostate cancer was published by Yeoh et al.[8] One hundred twenty patients were randomized between 64 Gy in 32 fractions over 6.5 weeks versus 55 Gy in 20 fractions over 4 weeks. The median follow-up was 3.6 years at the time of publication. The 4-year bDFS was 85.5% and 86.2%, respectively. While smaller and less mature than PR5, its results are also consistent with a low α/β ratio. Assuming the biologically effective dose is the same for both arms of this study, solving equation (3) results in an α/β ratio of 2.6 Gy.

Overall there are 2158 patients in the four studies reporting an α/β ratio for prostate cancer of less than 2.6 Gy. While the first studies used retrospective and prospective datasets to formulate their hypothesis, this observation has been confirmed in a meta-analysis of 17 published studies and now in two prospective randomized studies involving 1055 patients. Averaging these results weighted by the number of patients in each study gives an α/β ratio of 1.28 Gy.

Hypofractionation trials with modern dosing

The criticism of the former two trials, while validating an important radiobiological principle, is that the doses in both of the conventionally fractionated arms would be considered inadequate by modern standards. Developed in 2000 and confirmed in 2004, the Canadian consensus is to prescribe 70 Gy for patients with low-

and high-risk disease (the latter with 2-3 years of adjunctive hormonal therapy), and to prescribe 74 Gy-76 Gy for those with intermediate-risk disease.[9]

At Sunnybrook & Women's College Health Science Center, the Genitourinary Group has explored the principle of hypofractionation in two trials using a hypofractionated IMRT boost. The first trial prospectively enrolled 33 men with intermediate risk[9] disease and placed gold fiducial markers into the prostate in order to determine an individualized margin around the prostate (normally population-based data are used).[10] The initial dose was 42 Gy in 21 fractions over 4 weeks using a 3D-CRT treatment approach and standard margins. It was during this time that the prostate position was measured and the individualized margin calculated for the subsequent boost. The dose for this boost was 30 Gy in 10 fractions over 2 weeks.

The treatment was well tolerated with 0% and 10% grade 3 acute GI and GU toxicity, respectively. Using an α/β ratio of 1.3, this dose regimen would be equivalent to 81 Gy in 2 Gy per day fractions. This was a novel approach in that for men with very little prostate motion or day-to-day set up error, the RT would have been more tightly conformed, therefore theoretically leading to less late toxicity. Results initial biochemical control and late toxicity should be analyzed soon.

While the first trial compressed the equivalent of 8 weeks of RT in 6 weeks, the second shortened treatment times even further. In this prospective, phase 2 trial, 60 men with high-risk prostate cancer[9] were treated with 45 Gy in 25 fractions in 5 weeks of pelvic RT using a 3D-CRT approach and standard margins. Gold fiducial markers were also inserted into the prostate but margins based on the former trial were used. The prostate was concomitantly boosted using IMRT with 22.5 Gy over the same 5 weeks, resulting in a total prostate dose of 67.5 Gy in 25 fractions, or the equivalent of 82 Gy in 2 Gy per day fractions. As is standard in this group of patients, patients then proceed to 3 years of adjuvant hormonal therapy.

While the study has completed its enrollment, the acute toxicity on the first 45 patients was recently presented in Paris at the European Society of Therapeutic Radiology and Oncology (ESTRO).[11] The median patient age was 71 years. Two, 48 and 50% had T1, T2 or T3 disease, respectively, and 52% of patients had Gleason sum 8-10. The median PSA was 22.7 ng/ml.

There were no grade 3 gastrointestinal toxicities seen and less than 24% of patients had temporary diarrhea, proctitis or flatulence. Two patients experienced required temporary catheterization for severe urinary frequency, one patient had urge incontinence and one patient had a TURP.

A further study in the same population where the elective nodal RT will also be delivered using IMRT (in order to spare the small bowel in the pelvis) is about to open. Agreement in principle was achieved at the 2005 Early Prostate Disease Oriented Group of NCI Canada's Genitourinary Group to further develop a randomized study comparing a pelvic RT with a concomitant hypofractionated prostate boost to the conventional sequential pelvic and prostate RT in high-risk patients.

Conclusions

Improved prostate cancer control has been seen in last decade due to increased RT dose and improvement in toxicity has been greatly improved due to high-precision RT techniques. Due to a new understanding of radiobiology of prostate cancer and the implementation of novel dose fractionation schemes delivered using these high-precision techniques, the next decade may bear witness to improved cancer control and toxicity and overall shorter treatment times. □

References

1. Zeitman 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;294:1233-1239.
2. 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;23:1192-1199.
3. 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;53:1097-1105.
4. Pollack A, Zagars GK, Smith LG et al. Preliminary results of a randomized radiotherapy dose-escalation study comparing 70 Gy with 78 Gy for prostate cancer. *J Clin Oncol* 2000;18:3904-3911.
5. Hall EJ. Radiobiology for the radiobiologist. Philadelphia: JB Lippincott, 1988:535.
6. Brenner DJ, Hall EJ. Fractionation and protraction for radiotherapy of prostate carcinoma. *Int J Radiat Oncol Biol Phys* 1999;43:1095-1101.
7. Wang JZ, Guerrero M, Li XA. How low is the alpha/beta ratio for prostate cancer? *Int J Radiat Oncol Biol Phys* 2003;55:194-203.
8. Yeoh EE, Fraser RJ, McGowan RE et al. Evidence for efficacy without increased toxicity of hypofractionated radiotherapy for prostate carcinoma: early results of a Phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2003;55:943-955.
9. Lukka H, Warde P, Pickles T, Morton G, Brundage M, Souhami L. Controversies in prostate cancer radiotherapy: consensus development. *Can J Urol* 2001;8:1314-1322.
10. Cheung P, Sixel K, Morton G et al. Individualized planning target volumes for intrafraction motion during hypofractionated intensity-modulated radiotherapy boost for prostate cancer. *Int J Radiat Oncol Biol Phys* 2005;62:418-425.
11. Cheung P, Loblaw D, Morton G et al. Hypofractionation using a concomitant intensity modulated radiotherapy (IMRT) boost for localized high risk prostate cancer: acute toxicity results. *Eur J Ca Suppl* 2005;3:236(abstract 824).