

Be it resolved that in the modern era, the best method for dose escalation is brachytherapy: The con position

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Introduction

I have been asked to take the con position on the above resolution. This will be relatively straightforward, despite Dr. Morton's bountiful skills of persuasion, passion and expertise on the subject matter. I will argue that brachytherapy is not "the best" but *only one* method of biological dose escalation. The Oxford Dictionary defines "best" as "of the most excellent or desirable type or quality." External beam radiation, particularly when delivered in an accurate and precise way, gives equally excellent outcomes, can be given safely to more men and at a lower cost.

Evidence of biological dose escalation in prostate cancer

Higher quality inputs lead to better outcomes. Evidence-based medicine is the practice of identifying and synthesizing the highest quality of data to best inform our clinical decision-making. The higher the quality of our scientific data, the less likely we are to make "incorrect" recommendations; put another way, the recommendations will be closer to the truth. In the hierarchy of evidence-based medicine, randomized controlled trials (RCTs) are considered the best "unfiltered information," while systematic reviews and evidence-based guidelines are considered the best "filtered information."

There have been five RCTs examining the benefit of dose escalation in prostate cancer using higher external beam doses,¹⁻⁵ and two looking at delivering biologically higher doses using a brachytherapy boost.^{6,7} A meta-analysis of five of these trials was done by Viani and colleagues.⁸ They found that higher doses decrease the risk of biochemical recurrence by about 1.8%/Gy of radiation (or about 18% risk reduction for an extra week of conventionally fractionated radiation). There was no increase in late genitourinary

(GU) toxicity, although more late gastrointestinal (GI) toxicity (odds ratio 1.24, $p < 0.001$) was noted. Strictly speaking, the whole concept of dose escalation being better hinges on external beam radiation (EBRT), not brachytherapy.

Conceptually, treating cancer with radiation or chemotherapy is akin to a boxing match. If you provoke your opponent by hitting him repeatedly but fail to knock him out, he will likely get angry, strike back and be harder to beat. Cancer cells are similar. Delivering an extra week of radiation does increase the dose delivered, but taking too long allows the cancer cells to start repopulating. Thames and colleagues looked retrospectively at the importance of overall treatment time.⁹ They confirmed that the extra 9 Gy (or about 1 week of traditional radiation) did improve biochemical control by 23%, but each week over 7.5 weeks decreased biochemical control by 6% (which is consistent with Viani and colleagues, who found that the extra week of radiation improved biochemical control by 18%).⁸ In combination, these findings support the concept of delivering biologically higher doses of radiation and that completing the treatment in a shorter period of time will improve prostate cancer control rates. It should be noted that the most common type of brachytherapy (permanent seed or low-dose rate [LDR]) delivers only half the dose in the first 52 days (the total dose is delivered in about 365 days).

Biologically, prostate cancer has a weakness – the equivalent of its Achilles' heel. Prostate cancer cells are more effectively killed by using fewer, but larger, doses of radiation rather than the traditional method of delivering many smaller doses. A few large doses of radiation are called "hypofractionation;" delivering treatment in a shorter period of time is called "accelerated" treatment. Three RCTs have been published¹⁰⁻¹² and two RCTs presented in abstract^{13,14} that confirm hypofractionated accelerated radiation is equally or more effective than standard fractionation radiation. Theoretically, one worries about hypofractionated accelerated radiation causing more toxicity. However, by delivering the radiation using our new high-precision techniques,

biologically *higher doses* can be delivered to the tumour with biologically *similar or lower doses* delivered to the adjacent normal tissues.

The importance of patient selection for brachytherapy

Not everyone can or should have brachytherapy. Brachytherapy or “internal radiation” is a transperineal technique where seeds are permanently or temporarily placed into the prostate. Several studies have shown that a critical predictor of biochemical control is the dose that 90% of the prostate receives (called the “D90”). If the prostate is too wide or the pubic arch too narrow, part of the prostate cannot be treated and the D90 will be lower. We know that the prostate volume can be reduced using neoadjuvant cytoreduction,¹⁵ but this introduces unwanted side effects and cost. The risk of acute urinary retention (AUR) should also be minimized. Not surprisingly, men who have AUR have worse quality of life short-term; interestingly, studies show that compared to men without AUR, men have inferior global quality of life long-term.¹⁶ A prominent median lobe, common in men over 50 years, makes it more difficult to achieve a good quality implant and increases the risk of AUR.¹⁷ Other predictors of AUR are use of neoadjuvant cytoreduction and worse International Prostate Symptom Scores (IPSS).¹⁷ EBRT does not have any of these restrictions.

The importance of centre/physician selection

Not every physician can or should be doing brachytherapy. Like any technical skill, brachytherapy requires expertise to optimize outcomes. The learning curve for brachytherapy (measured by the proportion of patients getting a D90 >145 Gy) is about 100 patients, and is greater for smaller prostates.¹⁸ Centres with inadequate quality assurance protocols have been met with public scrutiny and external investigation.¹⁹ Lastly, brachytherapy requires an operating room with appropriate shielding. Some centres, like the Odette Cancer Centre, are fortunate to have a dedicated brachytherapy suite. Other centres trying to do brachytherapy face costly renovations for radiation shielding; they compete with urologists who face long wait times to get their patients into the operating room. EBRT is much easier to delivery in a high quality manner and there is an abundance of EBRT machines across the country.

The alternative to brachytherapy

The Miralbell study predicts that about 100 Gy equivalent are needed to completely kill prostate cancer.²⁰ It is not surprising that LDR brachytherapy (which provides a biologically effective dose of 101 Gy) improves the seven-year biochemical disease-free survival (bDFS) compared to

Table 1. Tumour outcomes and toxicities for SBRT vs. modern IGRT

	SBRT (35/5F/29d) ²⁴	IGRT (79.6/42/60d) ^{25*}
Low-risk patients (n)	84	59
Median follow-up (months)	48	68
Acute grade 3 GI toxicity	0%	0%
Acute grade 3 GU toxicity	1.2%	0%
Late grade 3 + GI toxicity	1.2%	1.3%
Late grade 3 GU toxicity	2.3%	1.3%
Biopsy negative	97%	54%*
Biochemical control	99%	87%

d: days; F: fractions; SBRT: stereotactic body radiotherapy; IGRT: image-guided intensity modulated radiotherapy; GU: genitourinary; GI: gastrointestinal.

*This study included 59 low risk patients, 163 intermediate risk patients and 37 high risk patients. Toxicity and biopsy data was derived from all risk groups. Biochemical control was specific to the low-risk group.

68 Gy (94% vs. 74%, $p < 0.001$)²¹ and 81 Gy (94% vs. 89%, $p = 0.004$)²² of EBRT (conventionally fractionated). The safe dose limit for standard EBRT is 86 Gy, whereas with hypofractionated accelerated image-guided radiation (called stereotactic body radiation, SBRT), biologically effective doses up to 168 Gy_{1,4} are achievable safely.²³

At our centre, we conducted a phase 1/2 prospective study of SBRT (35 Gy in 5 fractions once weekly for 29 days).²⁴ This is a biologically effective dose of 87 Gy_{1,4}. We treated 84 patients with low-risk prostate cancer (83 without androgen deprivation therapy). Patients with prostate volumes up to 90cc and IPSS scores <19 were allowed. After a median follow-up of 48 months, the treatment was well-tolerated and efficacious. One patient required a temporary catheterization during treatment (grade 3 GU acute toxicity); no grade 3 GI toxicities were seen. After 6 months, one patient with history of diverticulitis had a *fistula in ano* (grade 4 late GI toxicity) and two patients required transurethral resections of bladder tumour (TURPs) (grade 3 late GU toxicity). These toxicities are similar to those reported with modern dose-escalated image-guided intensity modulated radiotherapy (IGRT) according to the Princess Margaret Hospital (PMH) experience.²⁵ Seventy patients have had a 3-year biopsy and 97% were negative. This is better than the PMH experience, where 46% of patients had positive biopsies.²⁵ One patient failed biochemically, but had a negative biopsy and a history of chronic non-bacterial prostatitis resulting in a 99% bDFS (87% bDFS for low-risk patients in PMH experience). Table 1 summarizes SBRT versus conventional dose-escalated IGRT.

Health care system issues

Health care costs are forecast to rise at 3% to 6% annually. Our health care practices are simply not sustainable and we need to identify and promote treatments that are more effective *and* cost less. At our centre, we have calculated

the per-patient departmental and disposable cost for LDR brachytherapy to be \$2864; for high-dose rate brachytherapy/EBRT, the cost is \$4569. In contrast, SBRT costs \$1470. Each patient who receives brachytherapy costs between 2 and 3 times more than if the patient received SBRT, yet their outcomes are the same.

There are about 24 000 patients diagnosed with localized prostate cancer each year in Canada.²⁶ If 25% are treated with surgery and 30% are treated conservatively, 45% (or 10 800 patients) will need some form of radiotherapy.²⁷ Currently, about 8% of patients are treated with brachytherapy.²⁷ Increasing this proportion to 23% will require operating rooms for 2300 patients (or a 50% increase over the spaces currently being used for radical prostatectomy). Surgeons and administrators are unlikely to support this proposal. Treatment costs alone for the extra 2300 patients would be an extra \$3.2M per year over SBRT. Training expert brachytherapy teams, building dedicated new brachytherapy operating rooms and associated cancer centres would take years and millions of dollars. This is simply not realistic nor the best way to spend our limited resources.

Conclusion

I believe that in the modern era, the best method of dose escalation is not brachytherapy but SBRT. It is well-tolerated, effective, higher quality, cheaper and requires resources that are already in abundance.

Competing interests: None declared.

This paper has been peer-reviewed.

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