The best method for dose escalation: Prostate brachytherapy

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Radiation dose is important. Several randomized clinical trials have demonstrated that a 10-Gy increase in external beam (EBRT) dose increases the biochemical control rate by about 10% at 5 years.[1] Even at a EBRT dose of 80 Gy, the failure rate is about 30%, and the question arises as to whether further dose escalation is of value. The only safe method of further dose escalation is with the use of brachytherapy.

Brachytherapy delivers radiation from radioactive sources placed within the prostate. The radiation dose to the cancer is much higher than that achievable with any form of EBRT, and the rapid fall-off in dose outside the prostate spares adjacent organs from radiation toxicity. Two forms of prostate brachytherapy are commonly used in Canada: (1) low-dose rate (LDR), where iodine-125 seeds are permanently implanted into the prostate; and (2) high-dose rate (HDR), where a single iridium-192 source is passed by remote control along temporarily implanted catheters. LDR is primarily used to treat patients with low- or intermediate-risk disease as sole treatment, whereas HDR is most commonly combined with EBRT to "boost" the dose within the prostate.

Either approach results in excellent disease-free survival.

LDR brachytherapy has been used to treat about 12 000 patients in Canada over the past 20 years. It is performed as a simple outpatient procedure in less than an hour, under either regional or general anesthesia. Iodine-125 emits low energy photons with a limited range in tissue, with most of the dose being absorbed within a few millimeters of the implanted seeds. Many mature series report a disease-free survival of over 90% for men with low- and intermediate-risk disease (Table 1). A dose of 145 Gy is prescribed as a minimum dose to the prostate and includes a tight 2- to 3-mm margin to cover potential extraprostatic spread. The dose within the prostate is significantly higher, with over one third of the prostate usually receiving a dose higher than 200 Gy. This dose is at least twice that achieved with the most modern of external beam techniques, and explains the high success rate and low nadir PSA values (usually <0.05 ng/mL) achieved with this ablative dose of radiation. Careful planning of seed placement allows sparing of the urethra, with a low incidence of late urinary toxicity. With modern imaging and implant techniques, low-risk patients can expect a 90% to 95% disease-free survival, while men with low tier intermediate-risk disease can expect an 85% to 95% disease-free survival. A further advantage of brachytherapy is the significant sparing of normal tissue, particularly the rectum and bladder, with a low risk of long-term morbidity or risk of radiation-induced malignancy.

Additional EBRT is sometimes used to treat more extensive disease beyond the range of the brachytherapy implant, such as seminal vesicles or nodes. Brachytherapy is used in combination with EBRT to greatly increase the radiation dose to gross cancer within the prostate and limit the amount of EBRT required. This strategy has the potential to maximize local control by dose escalating within the prostate, while limiting morbidity due to EBRT. A recently completed randomized clinical trial led by investigators at the British Columbia Cancer Agency compared the combination of LDR and EBRT to dose-escalated EBRT alone in a population with intermediate- and high-risk disease. Results of this trial have yet to be released. HDR is a more recent form of prostate brachytherapy, with over 2500 HDR implants performed in Canada over the last decade. HDR involves first placing hollow catheters into the prostate through which a highly radioactive source "steps" under computer guidance. This allows for great accuracy and precision in treatment delivery, and also easily enables dose delivery outside the prostate. Treatment is delivered in 10 to 15 minutes, and the process of catheter placement and treatment delivery may be performed in under 90 minutes. The combination of a single HDR treatment and a short course of EBRT can result in a biochemical disease-free survival of over 95% (Table

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Table 1. Reported biochemical biochemical disease-free survival in modern series of low-dose rate brachytherapy as monotherapy for low- and intermediate-risk prostate cancer

Author	n	Median follow-up	Biochemical disease-free survival	
			Low risk	Intermediate risk
Crook[7]	776	54 months	95% (7 years)	
Henry[8]	1005	4.9 years	72% (10 years)	74% (10 yrs)
Hinnen[9]	601	69 months	88% (10 years)	61% (10 yrs)
Taira[10]	463	6.2 years	97% (12 years)	96% (12 yrs)
Burri[11]	768	68 months	93% (8 years)	
Prada[12]	706	55 months	92% (10 years)	84% (10 yrs)
Morris[13]	1005	54 months	96% (5 years)	95% (5 yrs)
Martin[14]	273	60 months	95% (years)	
Potters[15]	481	82 months	88% (12 years)	
Stone[16]	964	6 years	88% (12 years)	
Sylvester[17]	128	11.7 years	86% (15 years)	80% (15 yrs)
Lawton[18]	101	8.1 years	92% (9 years)	

2), with a low rate of late toxicity.[2-4] Emerging data suggest that HDR monotherapy without EBRT is just as effective, thus questioning the need for any additional EBRT. Demanes and colleagues reported an 8-year biochemical disease-free survival of 97% for men with low- and intermediate-risk disease.[5] The optimal dose and fractionation of HDR in this setting is unknown and is the subject of ongoing clinical trials.

Brachytherapy is the ultimate form of conformal radiotherapy, whether delivered by LDR or HDR. Both forms are significantly cheaper than EBRT, and have reported cancer control rates significantly higher than those associated with EBRT, even when given in doses greater than 80 Gy.[6] The intense localized delivery of high radiation dose results in some degree of acute urinary toxicity for most men. Urinary symptoms typically last several months following LDR implants, with a urinary retention rate of 5% to 10%. With HDR, the radiation dose is delivered over a far shorter time, and so urinary toxicity is of shorter duration with a retention rate of less than 5%. By avoiding EBRT, the rectal toxicity rate is negligible, and the volume of normal tissue irradiated is far less. This may be a particular concern for younger men, where concern about potential second malignancy induction is greater. There is no evidence that brachytherapy leads to an increased risk of second cancer.

Table 2. Biochemical disease-free survival for intermediate and high risk patients treated with a combination of HDR brachytherapy and external beam radiotherapy

Author	Median follow-up	Biochemical disease-free survival	
		Intermediate risk	High risk
Galalae[19]	5 years	88%	69%
Astrom[20]	4 years	88%	61%
Demanes[21]	7.3 years	87%	69%
Pellizzon[22]	5.4 years	90%	89%
Phan[23]	5 years	90%	78%
Bachand[24]	3.7 years	96%	96%
Deutsch[6]	4 years	98%	93%
Cury[4]	5.4 years	91%	
Morton[3]	6 years	98%	

In summary, there is a wealth of mature clinical evidence that brachytherapy, either alone or combined with EBRT, results in excellent disease control rates for men with prostate cancer. Results are far superior to those reported with EBRT. Although new EBRT techniques, such as altered fractionation with stereotactic body radiotherapy, are certainly worth investigating, clinical data are very limited. There is no clinical evidence that the results with the newer techniques are superior to that with conventional EBRT. No EBRT technique can deliver radiation with as much precision as brachytherapy, and even the most modern EBRT technique still irradiates a much larger volume of normal tissue.

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