Review paper

High-dose-rate brachytherapy boost for prostate cancer: rationale and technique

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Abstract

High-dose-rate brachytherapy (HDR) is a method of conformal dose escalation to the prostate. It can be used as a local boost in combination with external beam radiotherapy, with a high degree of efficacy and low rate of long term toxicity. Data consistently reports relapse free survival rates of greater than 90% for intermediate risk patients and greater than 80% for high risk. Results are superior to those achieved with external beam radiotherapy alone. A wide range of dose and fractionation is reported, however, we have found that a single 15 Gy HDR combined with hypofractionated radiotherapy to a dose of 37.5 Gy in 15 fractions is well tolerated and is associated with a long term relapse-free survival of over 90%. Either CT-based or trans-rectal ultrasound-based planning may be used. The latter enables treatment delivery without having to move the patient with risk of catheter displacement. We have found it to be an efficient and quick method of treatment, allowing catheter insertion, planning, and treatment delivery to be completed in less than 90 minutes. High-dose-rate boost should be considered the treatment of choice for many men with high and intermediate risk prostate cancer.

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Key words: boost, brachytherapy, external beam radiotherapy, HDR, intermediate risk, prostate cancer.

Purpose

Patients diagnosed with localized prostate cancer face a myriad of established treatment options including active surveillance, radical prostatectomy, external beam radiotherapy, brachytherapy, androgen deprivation therapy or combinations of two or more of the above. The choice of therapy depends on such factors as risk grouping (based on stage, Gleason score, and prostate specific antigen [PSA] level), bulk of disease (e.g. percentage of core positivity), urinary symptoms, patient age, and co-morbidities, patient preference and access to treatment. For patients being treated with radiation, decisions include whether to use external beam alone, brachytherapy alone, a combination of both, and the additional value of adjuvant androgen deprivation therapy. If brachytherapy is a component of treatment, either permanent seed or high-dose-rate (HDR) options are possible.

This review will focus on the use of HDR brachytherapy as a boost in combination with external beam radiotherapy, with particular attention to rationale, choice of dose, and technique.

Material and methods

Online searches through PubMed and MEDLINE were conducted using the search terms "brachytherapy", "high-dose-rate", "prostate cancer", "HDR", and "boost". Abstracts were reviewed and suitable full texts manuscripts obtained. Priority was given to publications within the past 5 years, with a minimum of 100 patients, and median follow-up of at least 5 years. Data was complemented by personal and institutional experience.

Results

Interstitial brachytherapy using remote afterloading of a small, very high activity iridium-192 (^{192}Ir) source has been used to treat prostate cancer since the 1980's [1]. In contrast to seed brachytherapy where there was a risk of inadequate post-implant dosimetry due to seed loss or misplacement, HDR dosimetry was performed with the catheters in place resulting in consistently higher target coverage [2]. Results of early clinical trials using HDR as a conformal boost in combination with external beam radiotherapy (EBRT) were encouraging, demonstrating low rates of acute toxicity [3], and a high rate of cancer control [4]. Early data reported that HDR boost resulted in lower nadir PSA values and higher cancer control rates than EBRT alone [5].

Rationale for high-dose-rate boost

High-dose-rate is used as a method of conformal dose escalation in combination with EBRT for the following reasons: 1) external beam dose escalation above 70-76 Gy is

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required to optimize probability of cancer control; 2) HDR allows an unequalled degree of dose conformity to target and sparing of adjacent organs at risk; 3) the postulated low α/β ratio of prostate cancer provides radiobiological rationale for hypofractionation or HDR; 4) a wealth of clinical data supports its use.

The importance of external beam dose has been firmly established with mature results from several randomized controlled trials [6-10]. These demonstrate that external beam dose escalation from 68-70 Gy to 78-80 Gy results in a 10-15% decrease in risk of biochemical failure, albeit with uncertain effect on other clinically meaningful endpoints such as local control, risk of metastases and survival. Furthermore, the improvement in biochemical recurrence rate usually comes at a cost of increased rectal toxicity, although it is hoped that advances in external beam technique will enable dose escalation without an increase in adverse events [11]. The improvement in biochemical control with external beam dose escalation appears to be greatest for patients with intermediate or high risk disease [12,13], with clinical benefit particularly for those under the age of 70 years. The dose to which patients can safely be treated with external beam radiotherapy is limited by the tolerance of surrounding organs at risk and limitations due to inter and intra-fraction organ movement. Hypofractionation has been investigated as a method of external beam biological dose escalation, but randomized trials still make the relative efficacy of this approach uncertain [14].

Brachytherapy boost has also been investigated as a method of dose escalation in randomized trials. Sathya *et al*. performed an early randomized trial comparing a boost using low-dose-rate ^{192}Ir to external beam radiotherapy alone in patients with locally advanced prostate cancer [15]. Patients randomized to receive 40 Gy EBRT and a 35 Gy brachytherapy boost had a biochemical failure rate of 29% compared to a failure rate of 61% in those randomized to receive 66 Gy with EBRT alone. Although the EBRT dose is low by modern standards, the study confirmed the principle that brachytherapy boost in combination with moderate dose EBRT resulted in higher cancer control rates than that achievable with EBRT alone. Hoskin *et al*. have completed a randomized trial of HDR boost in a cohort of patients with mostly intermediate and high risk disease [16]. Patients were randomized to receive either EBRT alone to a dose of 55 Gy in 20 fractions, or HDR boost (17 Gy/2 fractions) combined with EBRT to a dose of 35.75 Gy in 13 fractions. Those in the HDR boost arm had a 31% reduction in risk of recurrence. Once again, the EBRT dose would be considered low by contemporary standards, with an equivalent dose of approximately 68 Gy at standard fractionation.

Either HDR or permanent seed brachytherapy is capable of delivering higher dose with greater conformity than any external beam technique [17]. Yoshioka *et al*. recently detailed the rationale for HDR as monotherapy, and similar considerations hold for use of HDR as a boost [18]. The high degree of conformity achievable with HDR makes it a particularly attractive method of dose escalation. Because dose optimization is performed after placement of catheters, HDR enables more consistent target coverage than permanent seed implants with greater dose uniformity, and lower dose to urethra and rectum [19]. While there is some evidence that HDR monotherapy is associated with less toxicity than permanent seed implant monotherapy, there is a paucity of clinical outcome data comparing HDR and permanent seeds as boost [20].

High-dose-rate delivers better dosimetry than any form of external beam radiotherapy. In a dosimetric study by Georg *et al.*, radiation dose to normal tissues including rectal and bladder wall was significantly lower with brachytherapy (either HDR or permanent seeds) compared to the most advanced external techniques of volumetric modulated arc therapy (VMAT), intensity modulated proton therapy or scanned carbon-ion therapy [21]. The lowest dose to normal tissues was obtained with HDR. Spratt *et al.* drew a similar conclusion comparing HDR dosimetry with that of stereotactic body radiotherapy (SBRT) – HDR delivers a higher dose within the prostate and lower dose to adjacent organs at risk [22].

It is likely that the mean α/β ratio for prostate cancer is very low, possibly less than 1.0 [23]. This is lower than the α/β ratio of adjacent normal tissues, and would suggest that prostate cancer cells are more sensitive to radiation delivered in large fraction size than are normal tissue cells in the adjacent rectum. This provides radiobiological rationale for HDR as a method of biological dose escalation without exceeding tolerance of adjacent organs.

Perhaps the main justification for use of HDR as a boost is the wealth of clinical data supporting its use [24]. As can be seen from Table 1, many mature single centre series have been reported from around the world, including almost 5000 patients and with a median follow-up of up to 10 years [25-46]. Despite significant variability in dose and fractionation used, reported biochemical disease-free survival is consistently high – on average 95% for low risk, 91% for intermediate risk and 82% for high risk. Treatment is well tolerated – late grade 3 rectal toxicity is rare, while late grade 3 urinary toxicity (most commonly stricture) is reported in 1-14% of series.

As yet there are no completed randomized trials comparing outcome of HDR boost with that of modern dose-escalated image-guided external beam radiotherapy. An ongoing trial of the National Cancer Institute of Canada (Clinical Trials.Gov identifier NCT01982786) randomizes men with intermediate risk prostate cancer to receive either an HDR boost of 15 Gy combined with 37.5 Gy image guided EBRT in 15 fractions, or else image guided EBRT alone to either a dose of 78 Gy in 39 fractions or 60 Gy in 20 fractions. The available data to date, however, strongly suggests that HDR boost results in a higher disease-free survival than dose escalated external beam alone for most men with prostate cancer. Spratt *et al.* reported outcome data on 870 consecutive patients with intermediate risk prostate treated with either IMRT alone to 86.4 Gy, or 50.4 Gy IMRT with a brachytherapy boost – either permanent seed or HDR [47]. With a median follow-up of 5.3 years, both the biochemical disease-free survival and distant metastases-free survival rates were significantly higher in the brachytherapy boost

Table 1. Biochemical disease-free survival (bDFS) by risk grouping and late grade 3 urinary (GU) and gastrointestinal (GI) toxicity in modern series of prostate cancer patients treated with combined external beam radiotherapy and HDR boost

Author	*N*	Median; follow-up (months)	Late grade 3 toxicity		bDFS by risk group			Dose/fraction (EBRT + HDR) in Gy
			GU	GI	Low	Intermediate	High	
Agoston [25]	100	62	14%	2%		84%	82%	60/30 + 10/1
Aluwini [26]	264	75	4%	1%	97%			45/25 + 18/3
Bachand [27]	153	44				96%		44/22 + 18/2-20/2
Cury [28]	121	63	2%	2%		91%		50/20 + 10/1
Deutsch [29]	160	53			100%	98%	93%	50.4/28 + 21/3
Galalae [30]	122	117	5%	3%	88%	71%	72%	50/25 + 18-30 Gy*/2
Ghadjar [31]	64	61	14%	0%		100%	91%	50/25 + 21/3
Kaprealian [32]	64 101	105 43	1%	0%		84% 94%	80% 82%	45/25 + 18/3 45/25 + 19/2
Khor [33]	344	61	2%	0%		84%	74%	46/23 + 19.5/3
Kotecha [34]	229	61	5%	0.4%	95%	90%	57%	50.4/28 + 16.5-22.5/3
Lilleby [35]	275	44				100%	98.8%	50/25 + 20/2
Marina [36]	282	96				91%		46/23 + 19-23 Gy/2
Martínez-Monge [37]	200	44	5%	2%			85%	54/27 + 19/4
Morton [38]	60 123	72 45	4% 1%	0% 0%		98% 95%		45/25 + 20/2 37.5/15 + 15/1
Neviani [39]	455	48	8%	1%	92%	88%	85%	45/25 + 16.5/3-21/3
Pellizon [40]	209	64			92%	90%	89%	45/25 + 20/2
Phan [41]	309	59	4%	0.3%	98%	90%	78%	36/18-50.4/28 + 15/3-26/4
Pistis [42]	114	32					97%	60/30 + 10/1
Prada [43]	313	68	2%	0%	100%	88%	79-91%	46/23 + 23/2
Savdie [44]	90	95					80%	45/25 + 16.5/3
Whalley [45]	101	56	2%	0%		95%	66%	46/23 + 19.5/3-17/2
Zwahlen [46]	196	66	7%	0%		83%		46/23 + 20/4-18/3

**30 Gy to peripheral zone, 18 Gy to anterior prostate.*

patients at 92% vs. 81%, and 97% vs. 93% for brachytherapy boost and IMRT, respectively. The IMRT dose used in this report is the highest that can safely be delivered. Late genitourinary toxicity rates were similar in both arms, suggesting that the improved clinical outcomes were obtained without an increase in side-effects.

In summary, HDR brachytherapy boost results in a high disease control rates for men with localized prostate cancer, with a strong suggestion that it is more effective than external beam radiotherapy alone.

High-dose-rate dose and technique

The consensus guidelines of the American Brachytherapy Society notes that similar excellent clinical outcomes are reported by investigators using a wide range of dose and fractionation, and as such is unable to recommend a particular dose fractionation schedule [48]. GEC/ESTRO have updated their recommendations on prostate HDR [49]. They also acknowledge that it is not possible to recommend one specific dose prescription, but reference the

Table 2. Dose recommendations for combined treatment proposed by ABS and GEC-ESTRO [48,49]

One of the schemes below	
External beam radiotherapy	Brachytherapy
45 Gy in 25 fractions over 5 weeks	15 Gy in 3 fractions
46 Gy in 23 fractions over 4.5 weeks	11-22 Gy in 2 fractions
35.7 Gy in 15 fractions over 3 weeks	12-15 Gy in 1 fraction
37.5 Gy in 15 fractions over 3 weeks	

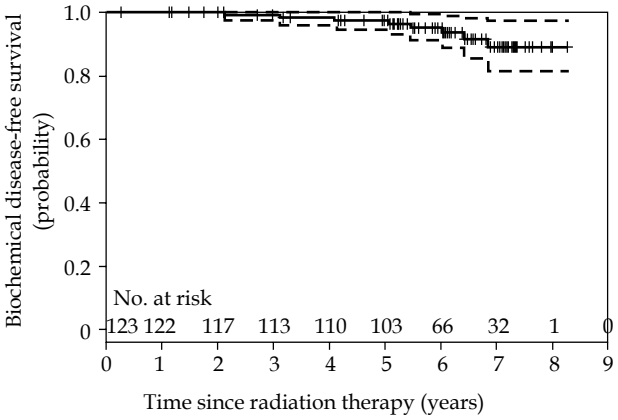

Fig. 1. With a median follow-up of 6.2 years, the 5-year biochemical relapse – free survival for patients with intermediate risk prostate cancer following 15 Gy HDR and 37.5 Gy EBRT is 97.4% (95% CI: 95-100%)

following external beam schedules (Table 2). The choice of dose and fractionation should be safe, effective, acceptable to patients, and make efficient use of available resources.

At Sunnybrook Odette Cancer Centre in Toronto, we have adopted a boost policy of 15 Gy HDR as a single fraction, combined with EBRT to a dose of 37.5 Gy in 15 fractions over 3 weeks. This protocol began as a Phase II clinical trial for patients with intermediate risk prostate cancer in 2005 [38]. At a median follow-up of 6.2 years, the 5-year biochemical disease-free survival (Phoenix definition) is over 97% (95% confidence intervals: 93-99%) (Fig. 1). Clinical efficacy and toxicity are similar to that of our previous protocol of HDR delivered in two fractions of 10 Gy and an external beam dose of 45 Gy in 25 fractions. It is, however, more acceptable to patients and makes more efficient use of resources. The protocol has been widely adopted across Canada, the United Kingdom, and in many U.S. centers. A single 15 Gy has become the standard HDR boost dose in current Radiation Therapy Oncology Group clinical trials (RTOG 0924 and RTOG 1115). It remains well tolerated with a Grade 3 or higher late toxicity rate of < 5%.

Technique

The choice of HDR technique will depend on physician preference and local resources. Key steps are: 1) catheter placement under image guidance; 2) imaging with catheters in place; 3) contouring of target(s), organs at risk, and catheter reconstruction on planning system; 4) dwell time optimization to achieve dosimetric constraints; 5) quality assurance, including second checks on plan and catheter positions; 6) treatment delivery.

For single fractions, treatment is usually delivered on an outpatient basis, allowing the patient to go home once recovered from the anesthetic. If multiple fractions are to be delivered with the same implant, the patient is usually admitted with appropriate analgesia. It is vitally important to check on catheter position, and re-position or re-plan if necessary, before each fraction delivery.

Catheters are most commonly placed under TRUS guidance. This is cheap, quick, and readily available. Computed tomography or MR guided insertions have also been reported [50]. Either rigid (steel or titanium) or flexible catheters may be used. Rigid catheters are sharper and easier to steer, but tend to cause more artifact, usually have a larger "dead space" at the tip and need to be re-sterilized. Flexible catheters are more comfortable for the patient if they are to be left in place and are disposable. Most centers use a template to help guide the catheters to desired location, although a free-hand technique using dental putty to fix catheters in place is an alternative [51].

At Sunnybrook, our technique involves using flexible catheters inserted with a template fixed to the ultrasound stepper. Rather than optimizing placement of each catheter, a standard catheter arrangement is used as indicated in Figure 2. An arrangement of 16 catheters is suitable for most patients. Catheters are placed symmetrically. The anterior 4 catheters define the anterior anatomic border of the prostate at the mid-plane. The next 2 rows of catheters are placed approximately 1 cm apart, with the medial catheters 1 cm away from the urethra. Ideally, the fourth and final row is 5 mm away from the posterior border of the prostate. This arrangement of catheters allows for consistently high target coverage with adequate sparing of the urethra and rectum.

Imaging is then performed with the catheters in place for planning. Computed tomography or TRUS is most commonly used. Computed tomography has the advantage of high catheter visibility, but in most institutions requires transfer of the patient to another room or department following fixation of the catheters and template to the perineum (Fig. 2). The patient then needs to be transported back to the brachytherapy room for treatment. Each patient transfer and change in position (e.g. lowering of legs) risks catheter displacement, which needs to be evaluated and corrected for. At the Sunnybrook Odette Cancer Centre, we reported an average catheter displacement of over 1 cm between the time of CT and treatment delivery despite careful suturing of the template to the perineum [52]. If uncorrected, this would have resulted in a significant degradation of the plan, with a 20% decrease in target coverage and a significant increase in urethral dose – particularly the bulbomembranous urethra (Fig. 3). If CT planning is being utilized, a careful quality assurance process is required to correct for any such displacement.

TRUS-based planning is usually performed in real time in the operating room with the ultrasound probe in place and the patient still under anesthetic (Fig. 4). The patient is then treated in the same position. There is therefore no risk of catheter displacement, and the planned dosimetry is that delivered. TRUS-based planning is particularly suitable for single fraction treatments. Ideally however, it requires a shielded operating room, so that the treatment can be delivered without moving the patient. This is not always a possibility. Further disadvantages of TRUS-based planning include occasional difficulty identifying the catheters and inability to contour the bladder. However, if a shielded operating room is available, TRUS-based planning is a more efficient, reliable, and accurate method of HDR planning than CT. In our experience, the average time between catheter inser-

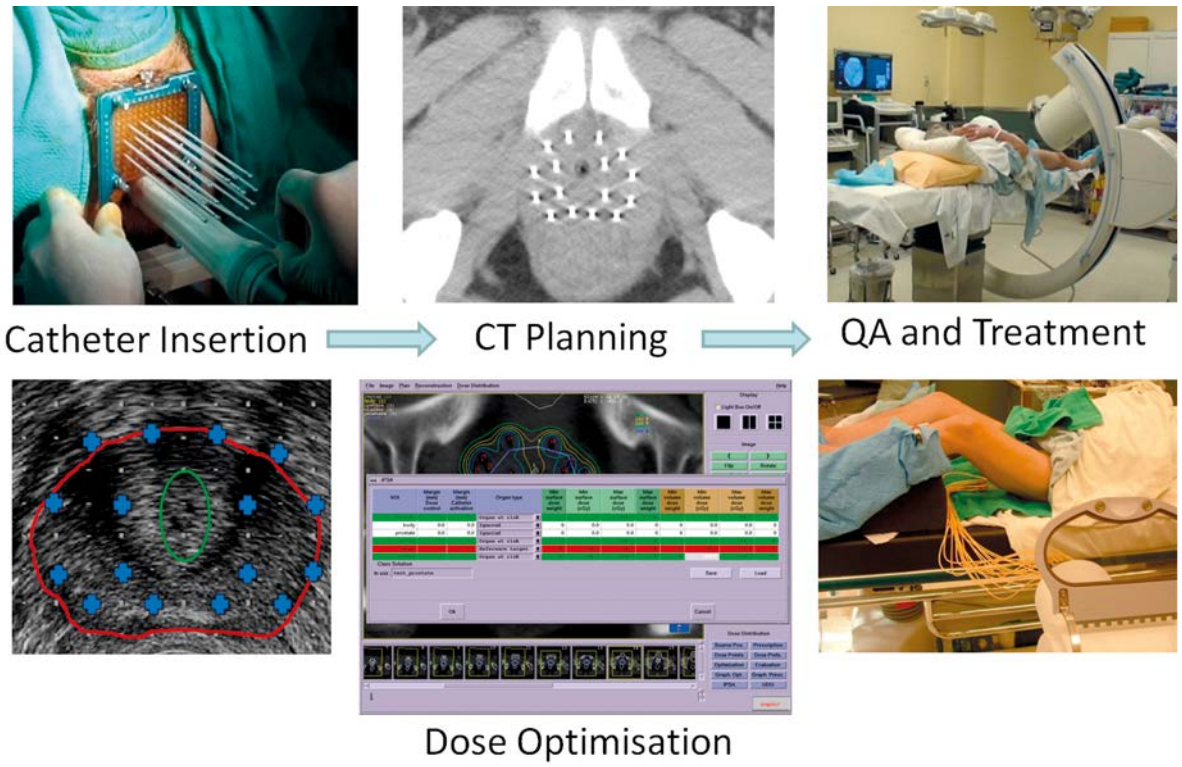

Fig. 2. For a CT planned technique, catheters are inserted under TRUS guidance and the template fixed to the perineum. Acquisition of CT images for planning usually requires transfer of patient and change in leg position. Following plan optimization and prior to treatment delivery, repeat imaging is required to correct for any catheter displacement

tion and treatment delivery was 6 hours with CT based planning and 1.5 hours with TRUS-based planning.

Once planning images have been obtained, dwell time optimization is performed to meet the dosimetric constraints using anatomy-based inverse planning [53]. A wide range of dose constraints is used by different centers. There is evidence that maintaining a high target coverage (volume receiving 100% of prescription dose, V_{100}, or dose to 90%, D_{90}) is important for disease control, and that dose to urethra is the most important predictor of long-term urinary morbidity [54-56]. GEC-ESTRO has proposed a number of reasonable dosimetric constraints for both target and organs at risk as follows [49] (Table 3).

There was insufficient data to provide recommendations on bladder or penile bulb dose limits. Expressing

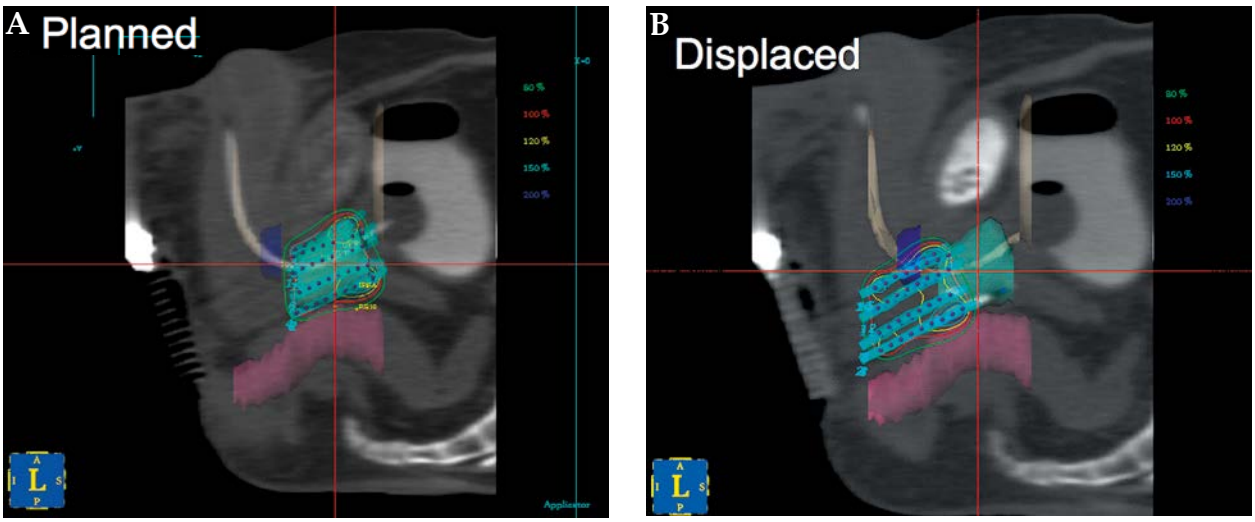

Fig. 3. Computed tomography planning allows for highly conformal dose delivery to the prostate (Fig. 3A). Unrecognized inferior catheter displacement could significantly compromise dose delivery, with underdosing of target and increased dose to urethra (Fig. 3B)

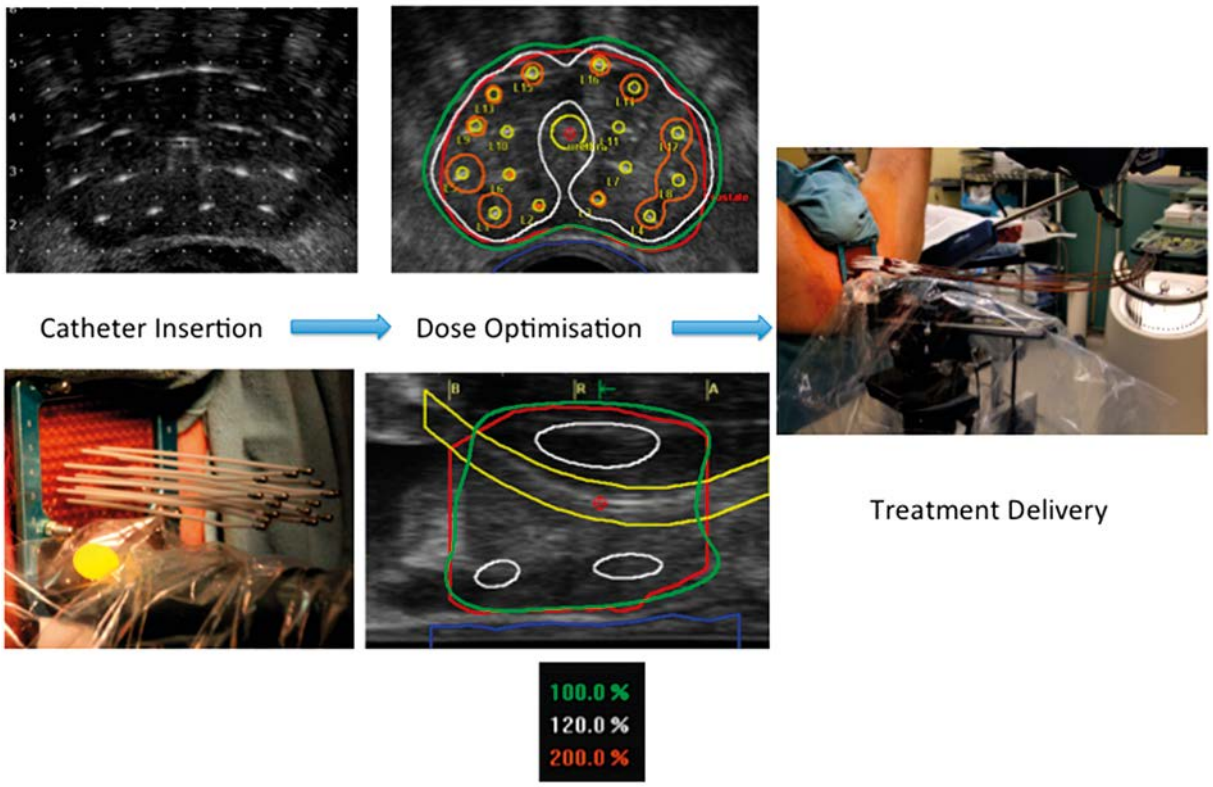

Fig. 4. For a TRUS-based technique, catheter insertion, dwell time optimization, and treatment delivery can be completed without moving the patient, changing leg position, or removing the ultrasound probe

Table 3. Dosimetric constraints for both target and organs at risk proposed by GEC-ESTRO [49]

Planning target volume	V_{100} > 95%	D_{90} > 100%
Dose to 2 cc of rectum	< 75 Gy equivalent at 2 Gy per fraction (EQD2)	
Dose to 0.1 cc or 10% of urethra	< 120 Gy EQD2	
Dose to 30% of urethra	< 105 EQD2	

dose limits in terms of EQD2 enables adjustment for different fractionation schedules and external beam dose regimens.

At Sunnybrook, HDR is delivered using a real-time intra-operative technique, and the external beam is delivered using volumetric arc therapy (VMAT). This provides greater efficiency than previous techniques, with continued low incidence of morbidity. For an HDR prescription dose of 15 Gy to the clinical target volume, the V_{100} is maintained > 95% (median 97.5%). V_{150} between 30-35% and V_{200} < 14%. The urethra D_{10} is constrained to < 118% (median 116%), maximal urethral dose < 130% (median 120%), and rectal V_{80} < 0.6 cc (median 0.1 cc). The standard external beam dose is 37.5 Gy in 15 fractions over 3 weeks to the prostate and proximal seminal vesicles.

Summary and Conclusions

High-dose-rate brachytherapy combined with external radiotherapy is associated with a high cancer control rate for patients with intermediate and high risk disease. While a wide range of dose and fractionations can be used, a single 15 Gy combined with 37.5 Gy EBRT in 15 fractions is well tolerated and associated with excellent long-term disease control rates. The role of adjuvant androgen deprivation therapy is not well established in the context of HDR boost, but is reasonable to consider for patients with higher risk disease.

Disclosure

Author reports no conflict of interest.

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