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GEC/ESTRO recommendations

GEC/ESTRO recommendations on high dose rate afterloading brachytherapy for localised prostate cancer: An update

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ABSTRACT

Background: HDR afterloading brachytherapy (HDRBT) for prostate cancer is now established as an effective technique to achieve dose escalation in the radical treatment of localized prostate cancer. The previous guidelines published in 2005 from GEC ESTRO and EAU have been updated to reflect the current and emerging roles for HDRBT in prostate cancer. *Patients and method:* The indications for HDRBT in dose escalation schedules with external beam are wide ranging with all patients having localized disease eligible for this technique. Exclusion criteria are few encompassing patients medically unfit for the procedure and those with significant urinary outflow symptoms. *Results:* Recommendations for patient selection, treatment facility, implant technique, dose prescription and dosimetry reporting are given. *Conclusions:* HDRBT in prostate cancer can be practiced effectively and safely within the context of these guidelines with the main indication being for dose escalation with external beam. HDRBT used alone is currently under evaluation and its role in focal treatment and recurrence will be areas of future development.

Brachytherapy using both permanent seed implants and temporary high dose rate (HDR) afterloading techniques play an important role in the treatment of localised and locally advanced prostate cancer. In recent years there has been a substantial increase in the use of HDR brachytherapy (HDRBT) most commonly as a dose escalating boost delivered in combination with external beam radiotherapy. There is also increasing experience in HDRBT used alone to deliver a radical dose of radiation. Recommendations on temporary transperineal prostate brachytherapy, were first published on behalf of the GEC/ESTRO-EAU Prostate Brachytherapy Group (PROBATE) in+ 2005 [1]; an update of those recommendations is now presented in this paper.

HDRBT has several advantages:

- The use of image guided catheter or needle placement enables accurate implantation which can be extended to include extracapsular disease and seminal vesicles
- It is possible to individualise the source positions over the full length of the prostate based on a defined planning target volume and organs at risk. Dose distribution optimisation by inverse planning enables highly conformal dose delivery.
- The fixation of the prostate by the implant and rapid radiation delivery minimises the problems of target and OAR movement.
- The use of high doses per fraction has a biological dose advantage for tumors with a low alpha beta ratio of which prostate is a common example [2].
- Temporary brachytherapy (BT) using a stepping source does not need any source preparation time and there is good radiation protection for personnel.
- The use of a single source for all patients using a multipurpose facility makes HDRBT highly cost effective.

Disadvantages of HDRBT include the use of a fractionated schedule which results in more work load per patient and logistic issues related to quality assurance across several radiation exposures. To allow relevant comparative information on clinical results, it is essential that patient data and treatment parameters are described in a similar way for permanent and for temporary implants as defined in these guidelines.

Developments in remote afterloading brachytherapy (temporary BT) technology and dedicated treatment planning systems as well as transrectal ultrasonography have resulted in highly sophisticated tools being available in the field of interstitial

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Table 1
Published outcome data for temporary high-dose-rate brachytherapy (HDR) with external beam radiotherapy in prostate cancer (most recent data cited where recurrent publications from the same group).

First author	Patient numbers	HDR dose	bRFS (%)				G3/4 toxicity (%)
			Low	Inter	High		
Borghede 1997	50	10 Gy × 2		84%		45 mo	10:GI 12:GU
Degar 2002	230	9–10 Gy × 2	100%	70%	65%	40 mo	12.2: GU
Pellizon 2003	209	4–6 Gy × 4	91%	90%	89%	64 mo	
Hiratsuka 2004	71	5.5 Gy × 3–4		93%		44 mo	1:GI 7:GU
Chiang 2004	42	4.2 Gy × 3					
Astrom 2005	214	10 Gy × 2	92%	88%	61%	48 mo	6:GU
Martinez 2005	1260	5.5 Gy × 3–15 Gy × 2		85%		54 mo	
Yamada 2006	160	7 Gy × 3		100%	98%	93%	47 mo
Vargas 2006	197	5.5 Gy × 2–6.5 Gy × 4		86%	69%	59 mo	
Chin 2006	65	8.5 Gy × 2		91%		42 mo	8:GU
Phan 2007	309	6 Gy × 4	98%	90%	78%	64 mo	0.3:GI 4:GU
Chen 2007	85	5.5 Gy × 3	100%	91%	81%	49 mo	
Kalkner 2007	154	10 Gy × 2	97%	83%	51%	73 mo	
Sato 2008	53	7.5 Gy × 2	100%		43%	61 mo	
Demanes 2009	209	5.5–6 Gy × 4	90%	87%	69%	84 mo	8:GU
Zwahlen 2010	196	4–5 Gy × 4	94% (includes 3DCRT alone group also)	83%	76%	65 mo	7:GU 3:GI
Wilder 2010	284	5.5 Gy × 4	100%	100%	93%	66 mo	7:GU
Morton 2011	125	15 Gy × 1		97.9%		45 mo	1:GU
Kaprealian 2012	165	6 Gy × 3	92%	79%	89%	105 mo	2:GU
		9.5 Gy × 2	95%	81%	77%	43 mo	1:GU

brachytherapy. In prostate cancer real-time transrectal ultrasound (TRUS) guided transperineal template implant techniques represent the standard of care [3].

HDRBT as a boost with external beam treatment is now established as an effective means of dose escalation in the radical treatment of prostate cancer [4] supported by level 1 evidence from one randomised trial [5] and a large body of published case series [6–24] (Table 1). These long-term follow-up data confirm that temporary BT boost combined with EBRT represents a successful treatment of choice and results in excellent bNED, local control and survival rates (Table 1). There are systematic reviews and case control series published showing superior outcome of EBRT combined with HDR boost compared to EBRT alone [21,25,26].

Pre-treatment investigations

Pre-treatment investigations for HDRBT should be no different from those for other forms of radical prostate treatment and should follow the EAU guidelines [27].

Diagnostic tests

The diagnosis of prostate cancer will in general be defined by the following:

- Digital rectal examination.
- Prostate-specific antigen (PSA) level.
- Transrectal ultrasound (TRUS) examination and biopsy.

All patients should have histological confirmation of malignancy before consideration for radical treatment based on a standard 10–12 biopsy cores or image guided biopsies. The latter procedures are particularly indicated for more anterior lesions which may be missed by the conventional transrectal approach. The histology report should record the Gleason score, the percentage of positive biopsies and the proportion of each core involved and the presence or absence of perineural infiltration all of which are important prognostic factors [27].

Staging tests

Isotope Bone Scan should be considered for all patients with a Gleason score of 4+3 or greater and those with a PSA > 20 ng/ml [28].

For intermediate and high risk patients where there is a significant risk of extracapsular spread, seminal vesicle involvement and lymph node metastases, optimal staging of the prostate gland and pelvic lymph nodes will be achieved using MR; T2 weighted sequences provide the best images to define the peripheral zone, tumour and areas of extracapsular and seminal vesicle spread. Further information is obtained by incorporating multiparametric MR sequences to include diffusion weighted and dynamic contrast enhanced imaging techniques [27].

Nomograms are published [29,30] to evaluate the likelihood of node involvement for any individual patient. Contrast enhanced CT is recommended for staging the pelvic and para-aortic lymph nodes. In equivocal cases ^{18}FDG and ^{11}C- or ^{8}F Choline PET may be helpful [31] and laparoscopic surgical sampling should be considered.

Functional assessments

Urodynamic studies

Lower urinary tract function should be evaluated using an International Prostate Symptom Score (IPSS) or AUA symptom-scoring sheet and urinary flow tests. These tests are a valuable baseline to identify patients with significant urinary obstruction and to evaluate the results of treatment.

Sexual function assessment

Since sexual function is an important outcome measure a baseline score using a standard scale such as the International Index of Erectile Function scale (IIEFS) should be obtained.

Table 2
Patient selection criteria for a curative combined HDRBT and external beam treatment.

Inclusion criteria
Stages T1b–T3b
Any Gleason score
Any PSA level
Exclusion criteria
TURP within 3–6 months
Maximum urinary flow rate (Qmax) <10 ml/s
IPSS > 20
Pubic arch interference
Lithotomy position or anaesthesia not possible
Rectal fistula

Patient selection for HDRBT with external beam

The main indication for treatment is histologically proven localised or locally advanced prostate adenocarcinoma in a patient considered otherwise suitable for radical treatment who is able to undergo the required anaesthetic procedure. It is not clear whether any particular risk group is better treated with HDRBT and indeed it is suitable for all. However most low risk patients will undergo radical prostatectomy or LDR seed brachytherapy and therefore HDRBT is mainly employed for intermediate and high risk patients. The most important prognostic factors with the highest impact on disease free survival are initial PSA, Gleason score and T stage. Functional outcome is predicted by the baseline urinary and sexual function scores. Specific selection criteria are shown in Table 2.

Further considerations:

- Previous guidelines suggested that the gland volume should be smaller than 60 cm^3 however with greater experience and high quality transrectal ultrasound imaging this is no longer an absolute stipulation and larger volumes may be implanted [32].
  - o where there is the possibility of compromising coverage of the gland because of size then a period of androgen deprivation therapy may be used,
  - o where a prominent median lobe is encountered then limited resection should be considered.
- A minimum distance from the posterior gland margin to the rectal mucosa of 5 mm has been another recommendation which again with greater experience is no longer absolute, although the placement of posterior catheters must respect the distance to the anterior rectal wall to enable attainment of realistic dose constraints. This is to be checked in three dimensions by TRUS. Direct contact between applicators and the rectal mucosa must be avoided.

Requirements for HDRBT

Equipment

Equipment for temporary BT for prostate is that required for any transperineal transrectal ultrasound guided procedure and includes the following:

- Operating room or brachytherapy suite suitable for sterile procedures and access to anaesthetic support.
- HDR afterloader.
- TRUS unit with template; the ultrasound should be capable of both transaxial and sagittal (longitudinal) image acquisition.
- TRUS fixation and stepping unit.
- Interstitial implant catheters of a suitable design compatible with the TRUS based template; they should also be CT or MR compatible if this imaging method is to be used.
- Appropriate software to enable importation of post implant TRUS or CT or MR imaging with image fusion.
- A planning system which can achieve accurate implant reconstruction and three dimensional dosimetry.
- A brachytherapy suite with adequate shielding to perform the HDR treatment, according to national radiation protection rules.
- Access to appropriate imaging post implant with either TRUS, CT or MR.

The clinical team

HDR brachytherapy needs an experienced team to perform treatment planning and delivery, and to control all issues necessary for successful clinical treatment. The decision to offer HDRBT should be taken by a multidisciplinary team having access to all the diagnostic information defined above. The implant team should be experienced in prostate interventional procedures, in TRUS and should include specialists skilled in the following:

- Transrectal ultrasound imaging.
- Transrectal ultrasound guided transperineal procedures.
- CT or MR interpretation (if used).
- Use of planning software and dosimetric calculations.
- Use of afterloader and treatment delivery.
- Patient care and comfort throughout the procedure.

The team is therefore likely to include an imaging specialist, radiation oncologist, medical physicist, radiotherapy technician (radiographer) and urologist.

Documentation of the brachytherapy treatment must be performed according to national standards. It is helpful, when starting with this treatment modality to have a radiotherapist and medical physicist both experienced in prostate temporary brachytherapy on-site during the first 3–5 implant procedures. In addition, a centre with sufficient experience in the use of TRUS and brachytherapy should have been visited.

Implant procedure

Catheter insertion

Rigid steel or flexible plastic catheters can be used for the implant procedure. Insertion will be undertaken with general or spinal anaesthesia. The patient is placed in lithotomy position and a urinary catheter is placed into the urinary bladder. To enhance TRUS contrast the catheter can be filled with a foamy ultrasound-gel/air mixture. The TRUS probe is mounted on a table- or floor-mounted stepping unit and inserted into the patient's rectum. The use of a water filled ultrasound balloon can enhance image quality, but should be employed with care as overfilling of the balloon might result in displacement and distortion of the prostate.

The position of the patient and the template position are critical before implantation is commenced. The urethra should be identified and positioned along the central row of the template (usually 'row D'); the inferior row of applicator positions must reflect the lowest part of the gland to be implanted and if seminal vesicles are to be included in the PTV it is essential these are also considered in the set up as shown in Fig. 1.

The applicators are inserted transperineally under direct ultrasound control. Their positions may be predefined from an initial volume study but since dosimetry is undertaken post implant in most centres applicators are inserted in a fixed sequence to ensure good peripheral coverage of the gland including any extracapsular regions and seminal vesicles if desired. Immobilisation or anchor needles may reduce movement of the prostate during applicator insertion [33]. Where homogenous cover of the gland is required then catheters should be placed with no greater than 1 cm intervals between applicators. It is also important to remember that

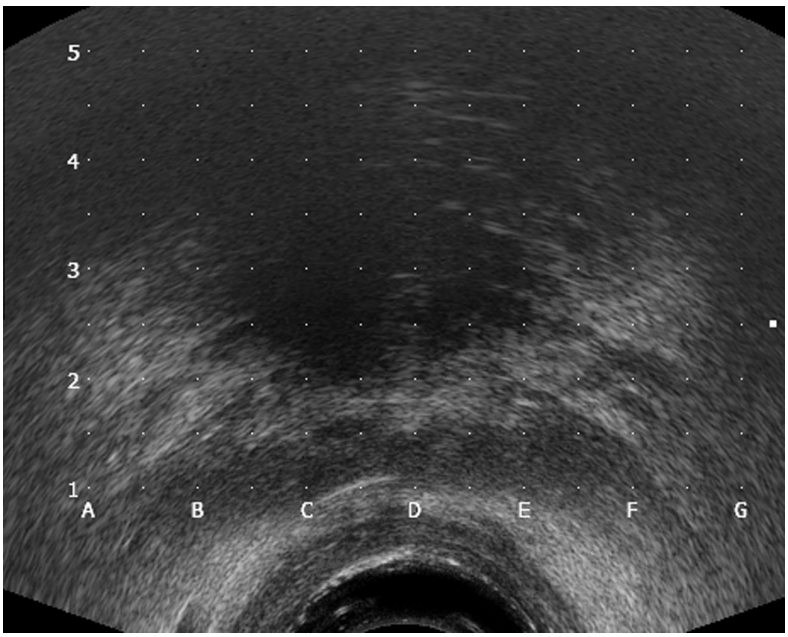

Fig. 1. Transaxial transrectal ultrasound image with template positions identified on image showing set up for HDR prostate brachytherapy to include seminal vesicle.

applicators placed closer than this to the urethra and rectum may not be able to contribute maximally to the dose distribution due to the OAR constraint. Peripheral coverage is most important so it is vital to have a ring of catheters around the edge of the peripheral zones, with a distance of about 3 mm from the prostate CTV border. It is advantageous to start to implant with the anterior catheters. This allows early checking of interference with the pubic arch so that adjustments can be made to set up early on to overcome this. It also minimises problems from the ultrasound shadowing effect behind the implant needles which decreases the image quality. It is also important to scroll up and down the ultrasound images during implantation to ensure there is not only good cover at the centre of the gland but also at the base and apex where the volume tapers and may require a second inner ring of applicators to deliver an adequate dose to this region. The position of the needles should be recorded during the TRUS guided implantation and correlated with the position in the treatment plan. An example of a typical applicator distribution is shown in Fig. 2(a). If specific biological subvolumes have been defined then optimal coverage of these may require closer clustering of applicators in these regions.

After completing the implant, in vivo dosimetry catheters may be used for quality assurance [34].

Orthogonal radiographs of the implant may be required for documentation purposes if no other permanent radiographic record is to be obtained with CT or MR.

Imaging for dosimetry

After completion of the implant procedure a three dimensional image set is acquired for treatment planning. This should adopt one of the following approaches:

- Transrectal ultrasound obtained whilst the patient remains in the lithotomy position under anaesthetic or sedation; a maximum image interval of 5 mm should be used. The whole prostate should be covered and in addition at least 5 mm cranially and caudally outside the gland.
- CT or MR images obtained following recovery from anaesthetic and transfer to the imaging department as shown in Fig. 2(b):
  - CT acquisition should be at no more than 3 mm overlapping intervals
  - T2 weighted MR images will provide optimal anatomical definition but T1 weighted images will provide more accurate catheter reconstruction
  - Image fusion may be used to maximise information from different imaging modalities.

Volumes for treatment planning

There are different target and treatment philosophies in the literature. For all patients the following should be defined on the planning images:

- Clinical target volume (CTV) is defined by:
  - the prostate capsule
  - plus any macroscopic extracapsular disease or seminal vesicle involvement identified on diagnostic images expanded by 3 mm to encompass potential microscopic disease. This is usually constrained posteriorly to the anterior rectal wall and superiorly to the bladder base.
- Organs at risk (OAR) which should include as a minimum:
  - Rectum: outlining of the outer wall alone is considered adequate for brachytherapy dosimetry as defined for LDR seed techniques.
  - Urethra using the urethral catheter as the landmark on imaging for the urethral contour which should extend from bladder base to 5–10 mm below the prostatic apex. Contrast such as aerated gel within the catheter will aid visualisation on ultrasound.

Other structures which may be outlined include the following;

- Gross tumour volume (GTV) may be defined using information from previous diagnostic imaging

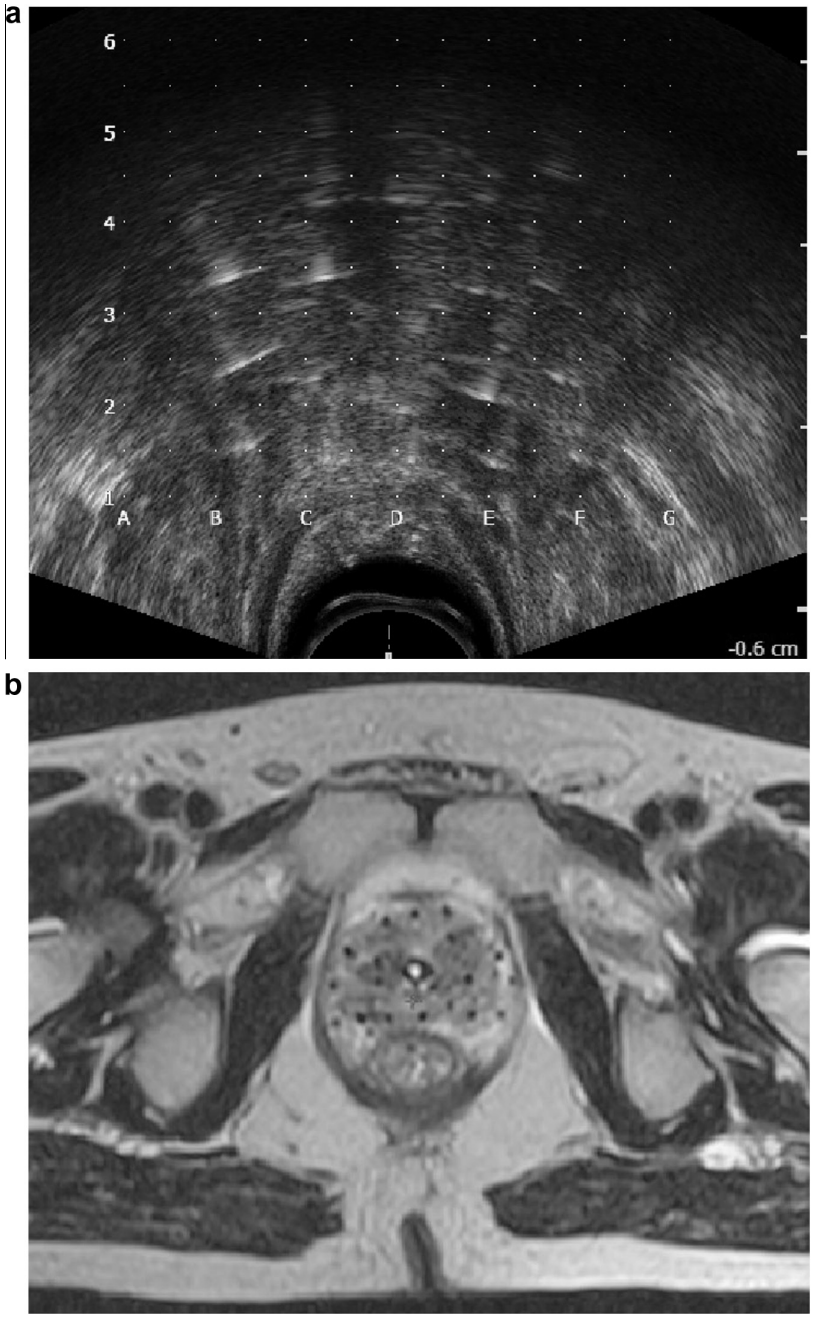

Fig. 2. Transrectal ultrasound image (a) and T2 weighted MR image (b) of HDR implant.

- CTV subvolumes. These may include boost volumes to the peripheral zones or other sites defined from imaging where it is considered there are significant tumour volumes. Each should be designated separately as CTV1, CTV2, CTV3 etc.
- Other OARs of interest may include
  - o Penile bulb.
  - o Bladder neck.
  - o Neurovascular bundle.

Consideration should be given to expanding the CTV to define a Planning Target Volume (PTV) accounting for any uncertainties in the procedure for example catheter tracking and image registration.

Planning aim and dose prescription

In order to clarify the process from defining planning aims for the treatment to final individual prescription for the patient, the concept of planning aim, prescription and reporting is described. The planning aims are the dose to specific volumes defined prior to treatment planning. The prescription dose is the finally accepted

dose value, after treatment plan optimisation which may be different from the planning aim as it may represent an individual compromise between target and OAR doses.

HDRBT boost with external beam

There is no consensus regarding the timing of each modality; in some centres brachytherapy is given before external beam, in others between EBRT fractions, whilst elsewhere it is given after completion of external beam.

There are a wide range of EBRT target volume concepts and treatment schedules reported in the literature, and it is not possible to recommend one specific prescription. Published schedules include the following:

- 45 Gy in 25 fractions over 5 weeks.
- 46 Gy in 23 fractions over 4.5 weeks.
- 35.7 Gy in 13 fractions over 2.5 weeks.
- 37.5.Gy in 15 fractions over 3 weeks.

HDR brachytherapy planning aim doses, defined as a minimum peripheral dose, which have been prescribed with these schedules include:

- 15 Gy in 3 fractions.
- 11–22 Gy in 2 fractions.
- 12–15 Gy in 1 fraction.

These planning aim doses do not give any indication of dose inhomogeneity within the volume.

It is not possible to make a firm recommendation on planning aim dose; the randomised trial providing level 1 evidence used 17 Gy in 2 fractions (after 35.7 Gy in 13 fractions external beam) [5]. There is evidence from a large cohort study that after 45 Gy in 25 fractions external beam a dose response exists up to 22 Gy in 2 fractions [35] and a single dose of 15 Gy is gaining increasing acceptance [36].

HDR monotherapy

HDR 'monotherapy' is associated with low acute toxicity and high biochemical control rates in the limited series published to date [37–43] but more mature data are needed to confirm its role. The schedules (planning aim) which have been used include:

34 Gy in 4 fractions.
36–38 Gy in 4 fractions.
31.5 Gy in 3 fractions.
26 Gy in 2 fractions.

Long term outcome data are not yet available from these cohorts and it is recommended that this treatment is not undertaken outside a formal study.

HDR in recurrence

There is limited experience of HDR brachytherapy for locally recurrent prostate cancer after previous irradiation and this is not recommended outside a formal prospective study. OAR constraints are critical in this setting. Published schedules (planning aim) include the following:

36 Gy in 6 fractions [44].
21 Gy in 3 fractions [45].
30 Gy in 2 fractions to peripheral zone after 30–40 Gy external beam [46].

OAR dose constraints

The heterogeneity of dose delivered using varying external beam and HDRBT schedules makes the definition of generalised OAR tolerances difficult. This should be related to an absolute dose volume constraint and an extrapolation for each schedule using an EQD2 total dose, including the dose from EBRT, may be the safest approach. In this setting there is uncertainty in translating LDR constraints to an EQD2 and data from the experience in gynaecological brachytherapy should be considered also [47]. Dose constraints proposed are as follows:

- Rectum: D2 cc $\leqslant$ 75 Gy EQD_2
- Urethra:
  - o D0.1 cc = $\leqslant$120 Gy EQD_2
  - o D10 $\leqslant$ 120 Gy EQD_2
  - o D30 $\leqslant$ 105 Gy EQD_2

There are no data available on which recommendations for constraints to penile bulb can currently be made and detailed long term follow up in cohorts receiving HDRBT is required.

Implant quality

Through optimisation, a balance will be reached between dose–volume constraints for OARs and for the target. The D90 will then become the prescription dose, individualised for each patient. The D90 should be higher than the planning aim, i.e. >100%. In addition, the PTV V100 should be at least 95% of the planning aim dose.

Various conformity indices have been described which evaluate the PTV coverage balanced by the OAR doses such as the COIN [48]. Within the implant the dose non-homogeneity ratio (DNR) should be documented from the ratio V150/V100.

Treatment delivery

The physicist or dosimetrist and radiation therapist calculate the dwell times and dwell positions for each applicator to deliver the required prescription dose with OAR constraints. This can be carried out by conventional or inverse planning. The standard for dose calculation is the TG-43 formalism for dose specification in terms of dose-to-water in a large water environment. This formalism should be used for dose planning. Modern model-based dose calculation algorithms should be used with care and when available in parallel to the proven TG-43 formalism, [49].

The machine treatment data are then transferred to the afterloader's computer. Treatment will be delivered in one of two scenarios:

a) In the operating room with the patient still in the lithotomy position under anaesthetic or sedation and the transrectal ultrasound in situ.
b) In a brachytherapy suite distant from the operating room after removal of the transrectal ultrasound and recovery from the anaesthetic In this setting careful quality assurance is required to identify movement of catheters and changes in OARs in relation to the images used for planning.

Before radiation exposure verification of the implant position is essential. Minimum requirements are for the position of the perineal template to be reviewed and confirmed by direct measurement to identify any displacement from the original position on the skin. Optimally a further image set will be obtained to confirm the position of the applicators within the prostate. This is essential where fractionated treatment is to be delivered with a second or

Table 3
Reporting parameters for HDR prostate brachytherapy.

1. External beam dose
2. Implant technique; number of catheters;
3. Total reference air kerma (TRAK). Total source exposure
4. Pattern of dwell times for each applicator
5. CTV: D90, V100, V150, V200
6. PTV (if defined): D90, V100, V150, V200
7. Organs at risk:
   a. Rectum: D2 cc, D0.1 cc
   b. Urethra: D0.1 cc, D10, D30

Other volumes which may be recorded but are not considered mandatory: GTV, subvolumes within CTV/PTV and Penile bulb.

third fraction delivered after some hours using the same implant. If orthogonal films are to be used then fiducial markers may be helpful to verify the relative position of applicator and prostate soft tissue.

Recording and reporting HDRBT

The ICRU recommendations for recording and reporting brachytherapy applications [50] should be followed. The recommended minimum parameters for reporting are shown in Table 3.

Summary and future directions

Numerous groups have shown that high quality treatment planning and performance of HDRBT combined with EBRT leads to good treatment results in patients with localised and locally advanced prostate cancer. Uniform approaches and data collection are essential to inform future developments. These guidelines have been produced to define minimum requirements for the safe delivery of HDRBT and provide a uniform framework for the assessment and selection of patients and minimum requirements for implantation, dosimetry and reporting. Future publications should follow these reporting parameters to enable comparison between different series.

Future developments of HDRBT will include the definition of biological subvolumes within the CTV selecting potential areas of radioresistance requiring higher doses [51]. In this setting HDR brachytherapy has a strong advantage exploiting the individual variation in source dwell time possible using modern afterloading techniques. Focal therapy is gaining popularity with the ability of modern imaging to identify dominant areas of the disease within the prostate and again HDRBT will have a major role to play in this area [52]. There is also increasing evidence for the role of HDRBT in local recurrence after external beam radiotherapy. Future guidelines will seek to explore these areas as published evidence emerges.

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