

## American Brachytherapy Society consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy

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### ABSTRACT

**PURPOSE:** To provide updated American Brachytherapy Society (ABS) guidelines for transrectal ultrasound-guided transperineal interstitial permanent prostate brachytherapy (PPB).

**METHODS AND MATERIALS:** The ABS formed a committee of brachytherapists and researchers experienced in the clinical practice of PPB to formulate updated guidelines for this technique. Sources of input for these guidelines included prior published guidelines, clinical trials, published literature, and experience of the committee. The recommendations of the committee were reviewed and approved by the Board of Directors of the ABS.

**RESULTS:** Patients with high probability of organ-confined disease or limited extraprostatic extension are considered appropriate candidates for PPB monotherapy. Low-risk patients may be treated with PPB alone without the need for supplemental external beam radiotherapy. High-risk patients should receive supplemental external beam radiotherapy if PPB is used. Intermediate-risk patients should be considered on an individual case basis. Intermediate-risk patients with favorable features may appropriately be treated with PPB monotherapy but results from confirmatory clinical trials are pending. Computed tomography–based postimplant dosimetry performed within 60 days of the implant is considered essential for maintenance of a satisfactory quality assurance program. Postimplant computed tomography–magnetic resonance image fusion is viewed as useful, but not mandatory.

**CONCLUSIONS:** Updated guidelines for patient selection, workup, treatment, postimplant dosimetry, and followup are provided. These recommendations are intended to be advisory in nature with the ultimate responsibility for the care of the patients resting with the treating physicians. © 2012 Published by Elsevier Inc. on behalf of American Brachytherapy Society. All rights reserved.

### Keywords:

Prostate cancer; Brachytherapy; Quality assurance; Safety; Dosimetry; Guideline; Standard; Interstitial; Radiation therapy; Radiotherapy

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### Introduction

Prostate cancer (CaP) is the most common malignancy in men in the United States and the developed world. It is estimated that in 2010, nearly 218,000 men will be diagnosed and 32,050 will die of CaP (1). Current common treatment options for early stage CaP include radical prostatectomy,

external beam radiation therapy (EBRT), temporary and permanent brachytherapy, androgen deprivation therapy (ADT), and watchful waiting (2). Transrectal ultrasound (TRUS)-guided permanent prostate brachytherapy (PPB) is an outpatient procedure that is associated with a rapid recovery and return to normal activity. Modern PPB using sealed sources of iodine-125 ( $^{125}\text{I}$ ) with template (3) and TRUS guidance (4) was pioneered over 25 years ago. Subsequently, PPB has produced excellent 10–15-year serum prostate-specific antigen (PSA) and clinical outcome associated with relatively low morbidity (5–10). The procedure is readily acknowledged as a standard option in low-risk CaP by organizations including the National Cancer Institute (11), American Cancer Society (12), National Comprehensive Cancer Network (2), American Urologic Association (13), and radiation oncology associations (14, 15). PPB is no longer considered an experimental or investigational treatment and is reimbursed by Medicare and most health insurance organizations (16).

PPB TRUS guidance and the transperineal approach have evolved since its introduction into clinical practice. The previous American Brachytherapy Society (ABS) guideline by Nag *et al.* (17) was published over a decade ago. In the interim, it is estimated that over 250,000 patients in the United States and a half million worldwide have been treated with this modality. Clinical trials have been conducted by the Radiation Therapy Oncology Group (RTOG) (18, 19), American College of Surgeons Oncology Group (20), North Central Cancer Treatment Group, and Cancer and Leukemia Group B (21). Over 500 articles have been published in the last decade and with this as background the indications, techniques, treatment regimens, and methods of dosimetry are reviewed to provide timely updated guidelines for PPB.

Variation in the approach toward PPB is common. The guidelines presented here are intended to aid practitioners in managing patients, but not to rigidly define process or practice requirements, or to establish a legal standard of care.

We have categorized this ABS guideline into five areas: (1) patient evaluation, (2) patient selection, (3) contraindications, (4) planning postimplant dosimetry and (5) management. Where accepted practice is evolving and specific recommendations cannot be established discussion may be provided. It is emphasized that the definition of a “relative contraindication” is that a patient may be at a higher risk of complications but that this risk may be outweighed or mitigated by other considerations. Such relative contraindications do not preclude patients from undergoing PPB. Indeed, there are often substantial published studies from experienced groups, which demonstrate that such supposed relative contraindications demonstrate little or no appreciable difference in outcome.

## Methods

In 2009, the ABS Board of Directors appointed a group of practitioners with extensive clinical and research

experience in PPB to provide guidelines for current practice. Sources of recommendations include current and prior guidelines published by medical societies (13, 15, 17, 22–25), clinical trials (19, 21, 26–29), published medical literature, and the clinical experience and consensus of the committee. The guideline is designed for TRUS-guided PPB performed as primary management of CaP. Specific recommendations for further investigations and for therapy were made when there was a consensus. Where major controversy or lack of evidence persists, the ABS has declined to make specific recommendations. This report was reviewed and approved by the Board of Directors of the ABS with the acknowledgment that the management of CaP patients undergoing PPB is constantly evolving and the guidelines will be subject to modifications as new data become available.

## Results

### Evaluation of patients

Important elements of the initial workup include an appropriate history and investigations as required to establish the stage and risk group and to determine the appropriateness of treatment.

### Patient history

The medical assessment will determine the eligibility for PPB as a viable option for the patient with CaP. Aspects of the history that influence eligibility for PPB include, but are not limited to, items listed in Table 1. These include determining the relevant medical, urologic, and surgical histories and the International Prostate Symptom Score (IPSS) (30). The self-administered IPSS questionnaire, type American Urologic Association-7, includes seven items with scores from 0 to 5, with higher values being associated with increased urinary irritative and obstructive symptoms that could potentially be aggravated by PPB. Other elements of the urologic history include documentation of any prior

Table 1  
Elements of patient history for permanent prostate brachytherapy

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1. Urologic history including:
    - a. Prior transurethral or open resection of the prostate or other surgery on the urethra
    - b. Prior procedure for benign prostatic hyperplasia such as transurethral needle ablation (30) or microwave therapy
    - c. Medications for treatment of urinary obstructive symptoms
    - d. Erectile function
  2. Prior diagnosis of cancer, especially bladder or rectal
  3. Prior pelvic radiotherapy, surgery, or fracture
  4. Inflammatory bowel disease
  5. Connective tissue disorders
  6. Documentation of International Prostate Symptom Score
  7. Documentation of erectile function, International Index of Erectile function score preferred
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transurethral or open resection, or other invasive prostate surgeries or procedures. Medication history, especially including the use of alpha-blockers or anticoagulants, is also relevant.

The appropriate workup for patients being considered for PPB requires, among other items, determination of biopsy Gleason score, pretherapy serum PSA, and clinical tumor classification (31). In addition to establishing a patient's risk group and stage, factors relevant for planning and performing the procedure as provided in Table 2 include prostate volume determination, establishing a patient's ability to be placed in the dorsal lithotomy position and suitability for general or spinal anesthesia. If centers are experienced in performing brachytherapy under local anesthesia (32), then appropriate clearance for such an approach is also indicated.

#### Patient selection

Patients with documented localized CaP as established by prostate biopsy and metastatic workup for non-low-risk presentations where the history and minimum elements of the workup have been completed, may then be considered as potential candidates for PPB, provided the absolute and relative contraindications, as given in Tables 3a and 3b have been considered and addressed.

#### Absolute contraindications

Patients who are considered poor candidates for an outpatient procedure requiring general or spinal anesthesia because of comorbid medical conditions may not be candidates for PPB. Although the committee declines to recommend any absolute lower or upper age limit, patients should have an acceptable performance status and life expectancy, typically of 10 years or more.

Assessment for the presence of regional or distant metastases is essential in patients with two or three intermediate-risk factors or high-risk presentations. Both a bone scan and cross-sectional imaging of the abdomen and pelvis are appropriate. Patients with metastases are not candidates for curative PPB. Obesity is not a contraindication provided that performance status and life expectancy are acceptable (33–36). Obese patients may be better

Table 2

Minimum required elements of workup for permanent prostate brachytherapy

1. Prostate biopsy indicating adenocarcinoma within the preceding 12 months of planned permanent prostate brachytherapy. Additional synoptic information is required and includes the Gleason grading and percent cancer in the biopsy specimen.
2. Pretherapy serum prostate-specific antigen
3. Digital rectal exam with clinical tumor classification, "T stage"
4. Prostate volume determination, transrectal ultrasound preferred
5. Determination of a patient's ability to tolerate an extended dorsal lithotomy position
6. Determination of suitability for general or spinal anesthesia

Table 3a

Absolute contraindications to TRUS-guided PPB

Limited life expectancy
Unacceptable operative risks
Distant metastases
Absence of rectum such that TRUS guidance is precluded
Large TURP defects, which preclude seed placement and acceptable radiation dosimetry
Ataxia telangiectasia

TRUS = transrectal ultrasound; PPB = permanent prostate brachytherapy; TURP = transurethral resection of the prostate.

suiting to PPB than the alternative options. Clearly, lack of a rectum, because of prior abdomino-perineal resection, rules out feasibility of a TRUS-guided procedure (37).

#### Relative contraindications

It is recommended that the IPSS value be determined and recorded for each patient before the procedure so as to facilitate assessment and treatment of postimplant urinary symptoms. Patients with a high IPSS for urinary irritative and obstructive symptoms are at increased risk of developing postimplant urinary retention (38–41). Numerous studies have demonstrated a correlation between high IPSSs and increased toxicity after PPB (38, 42–45). The recommended cutoff values for recent RTOG clinical trial eligibility range from 15 to 18 (18). Detailed analyses by Terk *et al.* (40) and Gutman *et al.* (46) of patients with IPSS less than 20 demonstrates acceptable rates of urinary toxicity. In men with an elevated IPSS, it is important to review the questions with the patient to determine validity of the score. Other medical conditions associated with increased urinary frequency, such as diabetes, or the use of diuretics, may result in increased IPSSs, which are unrelated to prostate morphology and urinary obstruction. These patients may undergo PPB without increased risk of post-PPB toxicity. Other factors that should be considered in evaluating an elevated IPSS include (1) prostate volume, (2) urodynamic study to evaluate the postvoid residual volume, volume voided, and peak flow, (3) cystoscopic

Table 3b

Relative contraindications for TRUS-guided PPB

The items listed below are considered as essential elements of the history in determining eligibility, but the criteria by themselves do not necessarily preclude therapy. They should, however, be considered closely in electing to proceed with PPB. Published experience demonstrates that patients with such conditions may undergo PPB if appropriately evaluated by an experienced team.
High IPSS (typically defined as >20)
History of prior pelvic radiotherapy
Transurethral resection defects
Large median lobes
Gland size >60 cm <sup>3</sup> at time of implantation
Inflammatory bowel disease

TRUS = transrectal ultrasound; PPB = permanent prostate brachytherapy; IPSS = International Prostate Symptom Score.

evaluation to determine anatomic obstruction such as a stricture, bladder neck contracture or prominent obstructing median lobes (38, 40, 47–49). Urinary flow studies characterize the degree of a patient's preimplant urinary obstruction and subsequent risk of acute urinary retention (38, 47, 50–52). Caution and appropriate patient consent are indicated if the peak flow rate is <10 cc/s and postvoid residual volume >100 cc, but these factors by themselves do not preclude PPB as a treatment option.

Previous pelvic irradiation such as that given for rectal cancer may increase the risk of postimplant toxicity. However, options other than PPB may be associated with an even greater risk of complications. In patients with prior pelvic radiotherapy, the dose delivered to the prostate, rectum, and bladder should be considered and any symptoms of late gastrointestinal or genitourinary radiation toxicity. Cystoscopy and sigmoidoscopy may be useful in evaluating such patients.

Although it is not an absolute contraindication, a prior TURP is an important aspect of the urologic history, which impacts on recommending PPB (53–56). Because prior TURP may be associated with increased technical difficulties, such patients should be evaluated carefully. A large TURP defect may not permit implantation of seeds throughout the entire gland, resulting in unacceptable dosimetry. Opacification of the TURP defect with aerated gel at the time of prostate mapping allows clear visualization of the extent of the defect and assessment as to the advisability of PPB. After a TURP, it is appropriate to defer PPB for 2–4 months to allow healing.

Pubic arch interference depends on many factors such as pelvic anatomy, prostate size, patient position, and technique (57–61). When a patient has a prostate >60 cc, and pubic arch interference is a concern, a short course of ADT will reduce prostate volume by an average of approximately 30% in 3–4 months (62–66). There is no absolute upper limit for prostate volume with regard to PPB eligibility (67). Larger prostates, up to 100 cc or more, are technically challenging, but toxicity and cancer control outcomes are acceptable (68, 69). Orientation of the TRUS probe and template, use of an exaggerated dorsal lithotomy position, and implantation of a portion of the anterior prostate “free-hand” (61) are all known to circumvent pubic arch interference. Nevertheless, practitioners with limited experience should avoid PPB on large prostates, or in patients with restrictive pelvic anatomy. In cases with prior pelvic fracture, irregular pelvic anatomy, or a penile prosthesis, ultrasound, computed tomography (CT) or magnetic resonance (MR) imaging may help in assessment of the pubic arch, but are not completely reliable in predicting pubic arch interference.

#### *Disease-specific characteristics, stage, and risk grouping*

The appropriate workup for patients with localized CaP being considered for PPB requires, among other items,

determination of biopsy Gleason score, pretherapy serum PSA, and clinical tumor classification (31). These three prognostic factors are combined to determine low-, intermediate-, or high-risk classification. The ABS recommends the use of the National Comprehensive Cancer Network guidelines (2):

*Low risk:* Gleason score  $\leq 6$ , and PSA <10 ng/mL, and clinical tumor classification, T1, T2a.

*Intermediate risk:* Gleason score 7, or, PSA >10 ng/mL < 20 ng/mL, or clinical tumor classification of T2b, T2c.

*High risk:* Gleason score 8–10, or, PSA >20 ng/mL, or clinical tumor classification of T3a.

Patients with seminal vesicle invasion (SVI), clinical tumor classification T3b, are considered to be high risk in terms of treatment and evaluation. Consideration may be given to performing seminal vesicle biopsies when evaluating intermediate- and high-risk patients (70).

#### *Monotherapy, combined treatment, and treatment sequencing*

##### *Low-risk patients*

Low-risk CaP may be appropriately treated with PPB alone, also known as monotherapy. Published experience demonstrates that excellent long-term outcome can be expected when optimal dosimetric parameters are achieved (71–74). Furthermore, the ABS recommends that PPB combined with EBRT is unnecessary, as is ADT, except for the purpose of prostate down sizing (63, 64, 69, 75), or in the uncommon circumstance when other factors suggest more advanced disease than is immediately evident such as high-volume disease in the biopsy specimen, or a rapidly rising PSA. For patients who undergo primary PPB for low-risk CaP and suboptimal prostate dosimetry is achieved, supplemental treatment with EBRT may be appropriate as long as tolerance of adjacent normal structures is not exceeded (Table 4).

##### *Intermediate-risk patients*

The presence of one or more intermediate-risk factors is associated with adverse pathologic features including substantial extraprostatic extension (EPE), SVI, or occult lymph node involvement. However, certain intermediate-risk patients with otherwise low-risk features such as low-volume disease, predominant pattern 3, and only one

Table 4  
Suggested treatment schema for low-, intermediate-, and high-risk disease for PPB

Risk group per NCCN	Brachytherapy alone?	Combined with EBRT?	Combined with androgen deprivation?
Low	Yes	Not favored	Not favored
Intermediate	Optional	Optional	Optional
High	No	Yes	Favored

NCCN = National Comprehensive Cancer Network; EBRT = external beam radiation therapy; PPB = permanent prostate brachytherapy.



adverse feature, can be effectively treated with PPB monotherapy, without supplemental EBRT or ADT. The ongoing RTOG clinical trial 0232 randomizes men with intermediate-risk disease and only one adverse factor, to PPB monotherapy or PPB combined with EBRT.

The appropriateness of PPB monotherapy depends on many factors including the required treatment margin. In pathologic series of whole-mount prostatectomy specimens (76–79), the radial extension of extraprostatic CaP infrequently extends beyond 5 mm in patients with clinically organ-confined CaP. The posterolateral prostate is at highest risk for EPE; a site where the treatment margin may readily be expanded laterally without increased dose to neighboring organs. Sengupta *et al.* (80) analyzed the risk of adverse pathologic features in the clinical scenario of low-risk disease (T2a, Gleason 6, and PSA of 10 ng/mL) and found that many intermediate-risk tumors had equivalent or even lower risk of adverse pathologic features such as significant EPE, SVI, or lymph node involvement. Consequently, the recommended margin of 5 mm around the prostate to form the planning target volume in all directions except posteriorly should readily encompass the vast majority of occult EPE in intermediate-risk disease. Furthermore, the radiation dose profile provides coverage for microscopic disease beyond the prescription isodose for several millimeters (81, 82).

The largest published series of PPB monotherapy is a multi-institutional analysis of 2693 CaP patients, which included 960 intermediate-risk patients with a reported 8-year biochemical control rate of 70% (74). However, most of these patients were treated before 1999 and fewer than 25% had formal postimplant quality assurance. Among those patients in all risk groups who had postimplant dosimetry with a  $D_{90} > 130$  Gy for  $^{125}\text{I}$ , or  $> 115$  Gy for  $^{103}\text{Pd}$ , the 8-year PSA relapse free survival was 92–93%. In a more recent series of 144 intermediate-risk patients treated by PPB monotherapy with detailed dosimetry available, the 12-year cause-specific and biochemical progression-free survival were reported as 100% and 96%, respectively (10).

In examining present day practice patterns, a pattern-of-care study by Frank *et al.* (83) surveyed 18 brachytherapy practitioners with cumulative experience of over 10,000 cases. Factors influencing selection of intermediate-risk patients treated with brachytherapy monotherapy included the standard three risk factors of clinical tumor classification, PSA level, and Gleason score, along with percent cores positive and presence of perineural invasion on the biopsy specimen. Various combinations of these factors were examined revealing that more than half of the practitioners would treat certain intermediate-risk cases with PPB monotherapy depending on the number and type of risk factors. This survey demonstrated that experienced practitioners examine intermediate-risk patients on a case-by-case basis and use monotherapy judiciously. Consistent with these observations, the ABS recommends that intermediate-risk patients may be considered for PPB monotherapy at the discretion of the treating physicians. Until long-term followup of

randomized controlled clinical trials is available, this recommendation is viewed as prudent in view of acceptable reported outcomes, pathologic analysis of prostatectomy specimens, and current practice.

#### *High-risk patients*

Patients with high-risk features being considered for primary EBRT are known to benefit from treatment combined with ADT from multiple randomized prospective trials (84, 85). Patients with high-risk features are also known to have substantial risk of EPE such that clinically occult CaP exists beyond the tumoricidal range of a PPB implant. Indeed, early series of PPB monotherapy for high-risk CaP revealed poor outcome compared with contemporary series (86). Therefore, it is considered standard to combine EBRT with PPB for high-risk disease. There is increasing evidence from single- and multi-institutional retrospective series that the increased radiation dose achieved with a PPB boost in combination with EBRT is advantageous for local control of CaP and metastasis-free survival. When compared with EBRT trials combined with ADT, however, the data are less robust in demonstrating that ADT provides improvement in clinical endpoints for high-risk CaP. In a series by Merrick *et al.* (87), no ADT-related improvements in cause-specific and overall survival were observed, but high-risk disease had improved 10-year biochemical progression-free survival. Furthermore, in a multi-institutional series reported by Stone *et al.* (88), patients with Gleason score 8–10 demonstrated improved overall and metastasis-free survival if a greater biologically effective dose was delivered. Given these data, it is appropriate to combine ADT with EBRT and PPB for high-risk patients although further study is warranted.

#### *Seminal vesicle invasion*

Integration of PPB into the management of patients with known SVI is practiced, but there is not yet a standardized technical approach because questions of reproducibility and required extent of the SV implant volume are unanswered. Because PPB in high-risk patients is recommended only in combination with EBRT, the seminal vesicles (SVs) should be part of the target volume for both components of treatment (89). SVI is most frequent in the proximal SVs adjacent to the base of the prostate (90, 91), and as such, a substantial portion may be included in the high-dose volume of a typical PPB implant (89, 92). Implantation of the SV is feasible and results in higher doses to the SV, although dose distribution can be variable. Nevertheless, further investigation of treatment approaches with patients harboring, or at increased risk of harboring, SVI is necessary.

#### *Preimplant treatment planning*

The ABS continues to recommend that dosimetric planning be carried out for all patients before seed placement.

Preimplant treatment planning may be performed either in a separate procedure as in a preplan approach, or on the day of the procedure in the operating room as intraoperative preplanning or in an intraoperative dynamic manner (93, 94). TRUS is considered the standard imaging modality for treatment planning, yet circumstances may dictate that an initial plan be performed using other volumetric imaging data such as CT or MR. The treatment plan should indicate the needle locations according to the template, and the number, and strength of seeds in each needle using contiguous, transverse images of the prostate. Within the scope of these guidelines, the use of TRUS for guidance during needle implantation and for preimplant planning is favored. Preimplant planning with MR is acceptable in experienced hands, whereas the use of preplanning with CT alone is less reproducible than TRUS (95). A peripheral distribution of sources, frequently referred to as a “modified peripheral or modified uniform loading” is recommended so that the portion of the urethra receiving 150% dose ( $V_{150}$ ) or greater can be limited (96). The volume of the rectum ( $RV_{100}$ ) receiving the prescription dose ideally should be <1 cc (97), but is dependent on the prostate–rectal interface and body mass index.

#### Intraoperative procedure

The standard procedure for seed implantation is to use a transperineal approach under TRUS and template guidance. Patient positioning and the TRUS-probe angle should coincide with the preimplant planning study as closely as possible when a preplan approach is used. The TRUS unit used should have the electronic grid and perineal template calibrated and coincident, and use frequencies between 5 and 12 MHz. A high-resolution biplanar ultrasound system with dedicated prostate brachytherapy software is mandatory. Fluoroscopy is frequently used to monitor seed deposition as a complementary imaging modality to TRUS (98), and is used in some centers for intraoperative dose computation using image fusion (99), but it is not considered mandatory for successful PPB.

There are several acceptable approaches to seed placement including the use of a Mick applicator (98), preloaded needles (100), which may be loaded commercially according to the preplan or loaded on site, or by afterloading (101). Seeds may be loose or stranded. Pros and cons of each type of technique have been described. Loose seeds are associated with a higher rate of seed migration (102–111), but only one report suggests an untoward outcome associated with such migration (112). One multi-institutional randomized prospective trial confirmed that stranded seeds migrated less frequently to the lung than loose seeds (113). Although some authors note modest (114), or significant (115, 116) improvement in dosimetry with stranded seeds, others have found stranded seeds to be associated with intraprostatic seed movement in the weeks after implantation with adverse effects on dosimetry (117).

Nonetheless, a recent prospective study confirmed that although 15% of strands shift 5 mm or more in the 4 weeks after placement, there was little apparent effect on dosimetry (118). The ABS does not favor any particular seed deposition technique among those commonly practiced. The relevant metrics are the postimplant dosimetry. If a given technique is reproducible, consistently results in optimal dosimetry and is associated with excellent long-term outcome then differences relating to methods of seed deposition and type are of secondary importance.

#### Recommended prescription doses for approved isotopes: monotherapy and therapy combined with EBRT

The ABS supports the American Association of Physics and Medicine Task Groups No. 43 (TG-43) (119), No. 137 (TG-137) (120) dose calculation protocols, and other published recommendations (121) regarding dose prescriptions as summarized in Table 5, and consistent with prior ABS statements (122, 123). It is important to recognize that early literature on the use of  $^{125}\text{I}$  used a prescription dose of 160 Gy, which after TG-43 became equivalent to a dose of 144 Gy.

#### Dose selection

Whereas no prospective dose escalation clinical trials have been conducted in PPB for CaP, ample retrospective data exists to confirm the importance of dosimetry in outcomes. Guidelines for dose selection are based on available data and current practice.

Stock *et al.* (124) developed the concept of  $D_{90}$ , which is the minimum dose received by the “hottest” 90% of the prostate volume, also described as the isodose enclosing 90% of the prostate. Numerous studies have confirmed that this metric and the prostate  $V_{100}$  (percentage of the target volume delineated on the postimplant CT receiving 100% of the prescribed dose) are correlated with outcome (125–127). Nonetheless, investigators are cautioned that these important dosimetric parameters are not surrogates of oncologic endpoints (128).

Table 5  
Prescription doses to the planning target volume

$^{125}\text{I}$	
Monotherapy	140–160 Gy
Combination EBRT PPB dose	41.4–50.4 Gy (1.8 Gy/d <sup>a</sup> ) 108–110 Gy
$^{103}\text{Pd}$	
Monotherapy	110–125 Gy
Combination EBRT PPB dose	41.4–50.4 Gy (1.8 Gy/d <sup>a</sup> ) 90–100 Gy

PPB = permanent prostate brachytherapy; EBRT = external beam radiation therapy.

<sup>a</sup> 2 Gy/d also acceptable.

In practice, many brachytherapists plan a dose higher than that listed in Table 5 to compensate for edema, seed placement uncertainty, and other factors. Merrick *et al.* (129) examined variability in PPB preimplant dosimetry among eight experienced brachytherapy teams. A range of  $D_{90}$  values from 112% to 151% of the prescription dose was planned. Based on the published literature, an acceptable dose range for postimplant  $D_{90}$  for  $^{125}\text{I}$  may be 130–180 Gy as long as normal structures are not overdosed.  $D_{90\text{s}} < 130$  Gy are associated with an increased risk of failure (74), whereas  $D_{90\text{s}}$  from 180 to 200 Gy seem to be well tolerated with no increased incidence of toxicity (130). High-risk CaP may benefit from a  $D_{90} > 180$  Gy (88). The ABS acknowledges that the nature of PPB precludes exact precision in final seed placement and consequently a wide range of postplan variability is not only acceptable but expected. Furthermore, while  $D_{90\text{s}} < 130$  Gy may be associated with increased failure, supplemental radiation in the form of EBRT or a second implant may be possible and ultimately yield excellent outcome while respecting normal organ tolerance. In this immediate discussion  $D_{90\text{s}}$  refer to  $^{125}\text{I}$ , but similar considerations are valid for  $^{103}\text{Pd}$ .

#### Seed activity and total activity

No consensus exists regarding optimal seed activity, seed number, or total activity. In the RTOG clinical trials, seed activity has been specified at 0.23–0.43 mCi/seed for  $^{125}\text{I}$ , and 1.0–2.0 mCi/seed for  $^{103}\text{Pd}$ . In an ongoing CALBG trial (21), seed strength for PPB combined with EBRT was similar to the RTOG trials, but 0.8–1.0 mCi for  $^{103}\text{Pd}$ . Experienced practitioners typically recommend a range of seed activities but there is variation. Aronowitz *et al.* (131) analyzed variation of implant activity for PPB among three institutions with extensive experience and found that total activity as a function of volume varied by 25% for large prostates and 40% for small prostates. Optimal equations were developed to describe the relationship between prostate volume, number of sources, and total activity in PPB (132). A randomized trial comparing low activity  $^{125}\text{I}$  seeds (0.31 mCi), vs. high activity (0.60 mCi) found excellent dosimetry in both arms (29). Although information regarding typical seed activity is useful, the ABS does not recommend a specific seed activity or total activity but does make recommendations regarding dose planning. Total activity implanted varies as a function of prostate volume and shape, and treatment margin, extraprostatic seed placement, and implant technique. As emphasized, postimplant dosimetry is paramount in evaluating the quality of an implant and satisfactory postimplant dosimetry is achievable using different techniques.

#### Sequencing of EBRT and PPB

Although EBRT is generally performed 0–8 weeks before PPB, the ABS makes no recommendation regarding the timing of PPB with respect to EBRT because of lack of

evidence. No studies have investigated either the sequencing of PPB and EBRT, or the time interval between the two. Current practice and ongoing clinical trials favor delivering EBRT first followed by PPB but there are rationales for either approach. Delivering PPB before EBRT exposes tissues to radiation simultaneously from both treatments and may theoretically increase normal tissue toxicity, but also allows assessment of the implant such that the EBRT dose may be adjusted if necessary.

#### Choice of radionuclides— $^{125}\text{I}$ , $^{103}\text{Pd}$ , and $^{131}\text{Cs}$

The ABS does not recommend the use of one specific radionuclide. Both  $^{125}\text{I}$  and  $^{103}\text{Pd}$  have demonstrated excellent long-term outcomes.  $^{131}\text{Cs}$  is an isotope introduced in 2004 (133) for PPB, which is being investigated in a multi-institutional clinical trial. It has a shorter half-life (9.7 days) compared with  $^{125}\text{I}$  (59.4 days) or  $^{103}\text{Pd}$  (17 days), but slightly higher average energy than  $^{125}\text{I}$ . Its recent introduction and short followup at this juncture prevent any recommendations regarding its use (Table 6).

$^{198}\text{Au}$  is an isotope previously used in PPB on a limited basis but is not recommended for routine practice at present.

#### Perioperative and postimplantation care

##### Role of cystoscopy

Cystoscopy before, during, or after PPB may be used, but is not mandatory. Flexible cystoscopy is generally preferred over rigid cystoscopy to minimize urethral trauma (134). A cystoscopy during the pre-PPB evaluation may identify urethral or bladder abnormalities such as urethral strictures, or bladder cancer, that may affect the treatment decision. Cystoscopy after PPB may be useful for removal of blood clots or misplaced seeds, but if bladder irrigation is clear and fluoroscopy images do not show seeds that are suspected to be in the bladder, it is probably unnecessary.

##### Radiation precautions

Radiation precautions should be explained to the patient, and preferably provided in writing. Although no mandatory precautions after discharge are required by the Nuclear Regulatory Commission [10 CFR 35] (CFR, Code of Federal Regulations), it is common to advise the avoidance of prolonged close contact with children and pregnant

Table 6  
Radionuclides for permanent prostate brachytherapy

Radionuclide	Half-life (d)	Average energy (keV)	Year introduced	Typical monotherapy seed strength	
				(mCi)	(U)
$^{125}\text{I}$	59.4	28.4	1965	0.3–0.6	0.4–0.8
$^{103}\text{Pd}$	17.0	20.7	1986	1.1–2.2	1.4–2.8
$^{131}\text{Cs}$	9.7	30.4	2004	2.5–3.9	1.6–2.5

women for one half-life of the radionuclide. These recommendations are considered conservative, and exceed regulatory requirements. Smathers *et al.* (135) measured dose rate at the skin surface after either  $^{125}\text{I}$  or  $^{103}\text{Pd}$  PPB, demonstrating that patients need not be concerned about radiation risk to the general public. Radiation exposure to family members of PPB patients is well below the limits recommended by the U.S. Nuclear Regulatory Commission (136).

Similarly, intercourse may be resumed, although ejaculation may be uncomfortable initially (137). Ejaculatory volume usually declines in the months after PPB (138). Although ejaculation of a seed is uncommon (139), some practitioners advise patients to wear condoms for the first few encounters.

Postoperative anti-inflammatory drugs, antibiotics, and alpha-blockers can be used prophylactically, or prescribed as needed. The use of prophylactic tamsulosin is associated with the improvement in urinary morbidity 5 weeks postoperatively as demonstrated in a placebo-controlled blinded and randomized study by Elshaik *et al.* (140). There is insufficient evidence to provide a recommendation in this regard, although urinary anesthetics, antispasmodics, analgesics, perineal ice packs, and stool softeners may all be beneficial. Acute urinary retention is uncommon but should be managed by intermittent or continuous bladder drainage. If the problem persists more than a few days, clean intermittent self-catheterization is preferred to continuous drainage by a Foley catheter. If the patient cannot manage clean intermittent self-catheterization, suprapubic cystostomy should be considered. In most of the cases, symptoms resolve by the above temporary measures. The use of transurethral incision of prostate should be avoided in the first 6 months but if retention persists, transurethral incision of prostate or minimal TURP may be considered, recognizing the risk of urinary incontinence after these procedures (141–143).

### Evaluation of postimplant dosimetry

The ABS recommends that CT-based postoperative dosimetry be performed within 60 days of the implant. Planning systems able to generate dose–volume histograms, dose–volume statistics, and 2D and 3D isodose curves superimposed on CT and other images have become widely available over the past decade. The use of such planning systems is considered mandatory for good clinical practice and quality assurance. Careful postimplant assessment provides the brachytherapy team with objective measures of implant quality allowing for continual technical improvement. Ongoing feedback from critical review of dosimetry is a necessary link in this learning process.

It is well known that there is inter- and intraobserver variability in postimplant CT contouring of the prostate, which results in differences in computed doses to the prostate (144–146). The interval between the implant and CT

will produce differing results in postimplant dosimetry because of variable degrees of edema (147–153). Postimplant CT on Day 0 or Day 1 is more convenient for the patient, allows early identification of dosimetric problems and closes the learning loop while memory of the procedure is still recent, but undertaking dosimetry at this time will underestimate dosimetric parameters because of the presence of edema. The optimum CT timing to minimize edema-derived dosimetry error is radionuclide specific;  $16 \pm 4$  days for  $^{103}\text{Pd}$  and  $30 \pm 7$  days for  $^{125}\text{I}$ . Methods of improving reproducibility of postimplant dosimetry such as MR–CT image fusion are encouraged (154–156). Consistency in approach with respect to timing and postimplant segmentation is favored.

The ABS recommends the following postoperative dosimetric parameters be determined:

*Prostate:*  $D_{90}$  (in Gy and percent)

$V_{100}$  and  $V_{150}$  (in percent)

*Urethra:*  $UV_{150}$  (in volume)

$UV_5$ ,  $UV_{30}$  (percent)

*Rectum:*  $RV_{100}$  (in volume)

Many critical organ dose parameters have been reported (24, 96). The ABS encourages a uniform approach to critical organ dosimetry. For urethral doses, the  $UV_5$  (urethral volume) approximates the urethral maximum dose, whereas the  $UV_{30}$  represents a clinically significant volume of urethra exposed to that dose level. Although one aims to keep the  $UV_5 < 150\%$  and the  $UV_{30} < 125\%$  in the preplan, it is recognized that this is not always possible, especially in smaller prostates (<20 cc). Similarly for rectal dosimetry, the  $RV_{100}$  is ideally <1 cc on Day 1 dosimetry and <1.3 cc at Day 30, the difference being due to changes in rectal proximity with resolution of periprostatic edema. Critical structures for postimplant erectile dysfunction have not been agreed on, although the internal pudendal artery, penile bulb, and neurovascular bundles have been studied (157–159).

### Followup

Close postoperative followup with digital rectal examinations and PSA at regular intervals is recommended. The optimal frequency of surveillance after PPB has not been established, although an interval of every 6 to 12 months is considered suitable. For purposes of reporting and comparing results among radiotherapeutic management strategies, the ABS favors the use of the Phoenix definition that dates failure at the time when the PSA has increased to 2 ng/mL above the nadir after treatment (160). For patients with higher risk features, more frequent surveillance is appropriate. Routine ultrasound-guided biopsies are not



required. If a rising PSA occurs and prostate biopsy is undertaken, it should be recognized that the biopsy result may not be interpretable before 30 months after PPB, and a false call of failure may occur when actually a benign PSA bounce is likely (161).

The use of cautery to treat rectal bleeding, or biopsies to evaluate anomalies in the rectum, may result in the development of iatrogenic rectourethral fistulas post-PPB. The ABS recommends that such procedures be avoided if possible.

### Personnel

The American College of Radiology and American Society of Radiation Oncology recently published guidelines related to PPB and reviewed qualifications and responsibilities of individuals involved in the procedure (25). As a licensed user of sealed radioactive sources, a Radiation Oncologist is essential in the workup, evaluation, and treatment of patients undergoing PPB. Similarly, a qualified Medical Physicist (162) is essential to the planning and quality assurance for PPB. In addition, the multidisciplinary team may include an Urologist, a certified Dosimetrist, Radiation Therapist, and other patient support staff.

The ABS further recommends that any facility that performs PPB be in compliance with the American College of Radiology–American Society of Radiation Oncology guidelines and have a well-documented quality improvement program that assures all staff involved in PPB are trained and competent. All junior faculty should undergo extensive training and competency review.

### Discussion

This updated ABS guideline is intended to promote the safe and efficient delivery of PPB. It is based on the current practice of PPB as reviewed from clinical trials, published literature, other, and prior guideline statements. These guidelines were developed as a consensus-based statement and have been reviewed and approved by the board of the ABS. Since the previous formal guideline statement, PPB has been broadly practiced and its use has expanded. It deserves reiterating that these guidelines are to be viewed as an aid to practitioners in managing patients, but are not to be judged as rigid practice requirements by which to establish a legal standard of care.

Progress in the clinical practice and understanding of PPB has resulted in differences reflected in the updated guidelines compared with those published by our Society over a decade ago. Recommendations regarding the use of PPB are risk group specific.

- Low-risk disease: PPB monotherapy is appropriate without the routine need for combined EBRT or ADT except for prostate down sizing or in other uncommon circumstances.

- Intermediate-risk patients may be candidates for PPB monotherapy as the spectrum of risk factors are considered, but often have PPB in combination with EBRT and/or ADT.
- High-risk patients are recommended to receive PPB combined with EBRT. ADT, as “tri-modality” therapy is also favored. There exists a need for prospective controlled clinical trials in addition to those currently underway (163).
- Patients with prior TURP may be candidates for PPB, depending on the size of TURP defect. Prostate size is generally not a contraindication to PPB for experienced practitioners, but PPB may be more readily facilitated with the use of cytoreduction by ADT.

Since the last guideline statement from the ABS in 1999, the widespread availability of prostate brachytherapy planning software enables all practices to engage in routine CT-based postimplant dosimetry in a timely manner. The ABS does not recommend one implant technique over another but insists that postimplant assessment be a requirement for all patients. Although several studies regarding a “learning curve” (101, 164, 165) have been published since the last guideline statement demonstrating a relatively short learning curve is possible and reaches a plateau after 20–30 cases (166, 167), the ABS strongly supports proctoring by experienced practitioners and appropriate training such that the learning curve manifested in substandard outcome is eliminated and that training and certification of brachytherapists is documented accordingly. Detailed analyses of outcomes with respect to cancer control and toxicity have yielded a number of parameters by which to plan and evaluate PPB, yet further study and refinement of these parameters is in order.

### Conclusion

These clinical guidelines for permanent TRUS-guided PPB represent a practical guide for clinicians performing this common procedure. Over the past decade, multi-institutional prospective clinical trials have demonstrated that PPB is a safe and efficacious procedure, acknowledged as a standard therapy for men with localized CaP. The selection criteria for patients undergoing PPB have broadened such that patients within all risk groups may be considered for PPB either as primary treatment or in conjunction with other therapies.

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