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Interstitial Brachytherapy (LDR-Brachytherapy) in the Treatment of Patients with Prostate Cancer

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Abstract

Objectives: As the number of patients with prostate cancer treated with permanent radioactive implants is increasing world wide, long-term data on tumor control and treatment morbidity become available.
Materials: Biochemical and clinical tumor control appears to be as effective as after radical prostatectomy or external beam radiation therapy in early prostate cancer.
Results: The risk of posttreatment urinary incontinence and bowel dysfunction is low and erectile function can be preserved in the majority of patients. However, prostate brachytherapy requires a careful selection of patients as pretreatment factors predict for long-term outcome.

The need for combined modality approaches in intermediate and high risk patients remains controversely discussed.

The continuous refinement of intraoperative planning techniques and the elucidation of the etiology of urinary, sexual and bowel dysfunction should result in further improvements in biochemical outcomes and decreased morbidity.
Conclusions: Improved and standardized postimplantation evaluation will make outcome data more reliable and comparable.

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1. Introduction

Prostate brachytherapy has become an increasingly popular treatment for localized prostate cancer. Dose escalation has become an essential component of radiotherapeutic advances for the treatment of prostate cancer. Prostate brachytherapy represents the ultimate three-dimensional (3-D) conformal therapy permitting dose escalation exceeding other radiation modalities. Increased dose of radiation yields improved biochemical control, particularly for locally advanced prostate carcinoma. This led to the further development of brachytherapy especially in the past fifteen years and made the technique to a widely available mainstream treatment. In the US, its application

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is almost as common as radical prostatectomy. It is either applied as low dose rate (LDR) permanent implants or high dose rate (HDR) temporary implants. In this article literature on permanent prostate brachytherapy is summarized, including biochemical and clinical outcomes, quality of life issues like urinary, bowel and sexual function.

2. Technique

There are several modifications applied either in the planning or the placement of permanent interstitial seeds. When looking at the long-term results achieved in LDR-Brachytherapy the knowledge about these technical variations is of essential importance.

2.1. *Radioactive isotopes*

Contemporary approaches of permanent brachytherapy employ the radioisotopes Iodine-125 (I-125) or Palladium-103 (Pd-103). The choice of radioactive isotopes for implantation is based on the isotope half-life and dose rate. The physical advantage of permanent sources lies in their inherent low energy (21–28 keV). I-125 has a half-life of 60 days and energy of 0.028 keV. With a half-life of 60 days, the radioactive decay will occur over 1 year following the implant especially during the first six months. The half-life of Pd-103 is 17 days and it has a dose rate higher than I-125. The average energy produced by the emitted rays is 0.021 keV. Compared to EBRT, the radiobiological equivalent dose with either isotope is tumor dependent but is generally 100–120 Gy delivered in 2 Gy fractions [1]. Dose recommendations have recently changed for I-125 and Pd-103.

The American Association of Physicists in Medicine (AAPM) Task Group 43 (TG43) has recommended changes in the calculated dose rates for both isotopes [2]. Additional changes in the dose rate constant and prescription dose for Pd-103 were recommended by the National Institute of Standards and Technology (NIST-99) and the American Brachytherapy Society (ABS) [3,4].

The new prescription dose for I-125 used as a monotherapy is 145 Gy and 110 Gy when it is applied as a boost with external beam radiation (EBRT). The prescribed dose for Pd-103 in a monotherapeutic setting is 125 Gy and 100 Gy in a combination therapy with EBRT.

Both isotopes are delivered in cylinder-shaped titanium shells measuring 4.5 mm $\times$ 0.8 mm.

2.2. *Planning*

Planning for a permanent implant is typically performed by using transrectal ultrasound imaging (TRUS). This information can be either obtained prior to the procedure or intraoperatively. Subsequent to imaging, the appropriate distribution of sources is determined by a computer-based dose optimization system, so that the desired radiation dosage is delivered to the prostate while assuring that neither the urethra nor the rectum receive excessive radiation. The preplanned ultrasound-guided transperineal technique relies on a comprehensive planning method. Axial prostate images, obtained at a separate patient encounter, are digitized with a software program. Later the images are reconstructed and transformed into a detailed deposition plan. In the operating room the physician follows the plan by attempting to guide the needles into the predetermined area. For this purpose it is of critical importance that the perineal template is correctly superimposed over the ultrasound image [5]. Because available perineal template systems restrict the needle to needle spacing to either 1.0 or 0.5 cm, spacing of sources is usually planned at 1.0 cm intervals.

Nowadays it is possible to perform the entire planning process intraoperatively. Intraoperative planning avoids potential discrepancies in prostate measurement between pre- and intraoperative ultrasound images [6]. Some interactive systems now provide feedback on dosimetry based on actual needle position, minimizing the impact of needle deviation.

Most recently a planning system (Varian 7.1) was introduced which allows to acquire the actual seed position as the implant progresses, allowing a real-time dosimetry based on real-time seed distribution.

2.3. *Seed placement*

There are two seed distribution techniques available. The Quimby method, first described in the 1930s, delivers the seeds equally throughout the gland [7]. This uniform distribution has generally been abandoned in favor of a peripheral loading technique, according to the principles of Paterson and Parker [8]. This technique reduces the central urethral dose to less than 120–150% of the prescription dose and is used by 75% of brachytherapists according to a survey of the American Brachytherapy Society [9].

Several modifications concerning the implant procedure are described. The needles can be loaded

prior to the procedure using spacers to separate them (preloaded technique). This technique is time-consuming and an accurate seed positioning is difficult. Alternatively, seeds can be lined up at a polyglycolic strand.

This procedure does not avoid late seed displacement as the strand dissolves. The fixed spacing does not allow variable placement of the seeds, which is often necessary during the implant procedure. The real-time technique uses the so-called Mick applicator (Mick Radionuclear Instruments, Bronx, NY, USA), which allows to deposit the single seeds under modern biplane ultrasonography. Once the correct needle position has been achieved, seeds are placed in the longitudinal view from the base to the apex.

2.4. *Postimplant dosimetry*

Postimplant dosimetry has become the gold standard for implant evaluation and it is recommended by the ASTRO/EAU/EORTC, American Brachytherapy Society, the American Association of Physicists in Medicine. The most commonly used technique for postimplant dosimetry is currently CT-based [10]. CT-slices of 3 mm thickness are taken throughout the implanted area. On every slice the prostate, the urethra, the rectum and the inner and outer wall of the bladder are contoured. The position of the seeds is identified on every CT-slice. The total number of seeds is checked on an orthogonal X-ray. All structures are reconstructed in three dimensions and dose distributions to these structures are calculated.

This technique has resulted in a good correlation between the ultrasound volume and the CT volume [11]. Prostate volume increases in an average of 20-50% after the implant. The half-life of this edema has been reported to be about 10 days [12].

For this reason the postimplant dosimetry should be performed 1 month after the implant as it has been shown that the most reproducible results will be obtained at this time.

The information obtained from the postimplant CT is used to generate dose volume histograms (DVH). Applying the DVH the amount of dose delivered to 100 (D100), 90 (D90) or 80% (D80) of the prostate can be calculated. At the same time the volume of prostate that receives 100 (V100) or 150% (V150) of the prescription dose can be evaluated. The D90 has proved to be the parameter which best describes the delivered dose and which best correlates with the PSA response [13].

3. Indication for LDR-Brachytherapy

Permanent interstitial brachytherapy as single modality therapy can only be applied with curative intent in patients with localized prostate cancers because of the physical characteristics of the isotopes.

According to this fact interdisciplinary task groups have developed guidelines for the use of LDR-Brachytherapy.

In the guidelines of the ASTRO, EAU and EORTC the following contraindications for this therapy are seen:

1. A life expectancy of <5 years.
2. The presence of distant metastases.
3. A recently performed TUR-P with persistent central defect.
4. Patients with bleeding disorders.
5. A prostate size >50 cc because of possible pubic arch interference.

In these guidelines a group of patients is defined which has the highest chance of cure after LDR-Brachytherapy.

The clinical stage at time of diagnosis should be $\leq$T2a, the PSA <10 ng/ml and the Gleason-score of prostate biopsy ≤ 6 [14].

An interdisciplinary German task group has recommended a pretherapeutic IPSS of ≤ 8, a maximum uroflow >15 ml/s, a residual postmicturitional volume of <50 ml and a minimum time interval between a TUR-P and the implant of six months in order to avoid severe micturition problems after the therapy [15].

4. Results

4.1. *Definition of biochemical success/failure*

The definition of biochemical success after brachytherapy is still discussed controversely. While the ASTRO Consensus panel defines three consecutive rises of PSA as a definition of biochemical failure after external beam radiotherapy, the more appropriate endpoint for a biochemical success after brachytherapy appears to be a ''nadir'' value of 0.5 to 0.2 ng/ml. The only drawback in this concept is the fact that it might be difficult to define when an individual patient has achieved an actual ''nadir''. Very often the ''nadir'' can only be defined once the PSA has risen again. Nevertheless the experiences from the Seattle group teach us that the lower the PSA

drops, the less likely a subsequent failure is, although this does not guarantee either success or failure [16].

4.2. *Tumor control*

Results of permanent implants have been reported from several institutions with a follow-up between 5–15 years. These series are difficult to compare, as there are major differences concerning the follow-up time, the disease profile at presentation, the PSA endpoints chosen and the treatment regimens, which differ from a permanent implant alone to the combination with external beam radiation and/or androgen ablation. Overall clinical survival and disease free survival differ between 66–87% after an average of 10 years [21–30]. The correlation between the implanted dose and the freedom from PSA failure (FFPF) was demonstrated by Stock et al. who were able to show that patients receiving a D90 value of $\geq$140 Gy had an improved biochemical control rate (PSA $\leq$ 1.0 ng/ml) of 92% at 4 years compared to only 68% for those patients with D90 values $<$140 Gy. Overall patients with doses of $<$140 Gy (median follow-up 66 months) had a FFPF of 60% compared to 96% for patients with doses of $\geq$140 Gy (median follow-up 35 months) [31]. The Seattle group recently analysed their treatment results according to different preoperative risk groups. They were able to demonstrate that the FFPF was 87% after 12 years for the low risk group (S-PSA $<$10 ng/ml, Gleason: $\leq$6, any T1-T2 stage), 79% for the intermediate group (either Gleason: 7–10 or S-PSA $>$10 ng/ml, any T1-T2 stage) and 51% for the high risk group (Gleason 7–10 and S-PSA $>$10 ng/ml, any T1-T2 stage) [32] (Table 1).

4.3. *Androgen ablation (AA)*

The role of androgen ablation (AA) in conjunction with permanent interstitial brachytherapy remains unclear. Stone et al. suggested an improved biochemical control rate with an addition of AA to intermediate risk cohort patients treated with I-125 or Pd-103 monotherapy [27].

In contrast Sharkey et al. initially showed that AA improved the postimplant negative biopsy negative rate and biochemical control rate. This effect vanished with prolonged follow-up [28]. Potters et al. did not demonstrate an improvement in FFPF when adding a short course of AA to permanent implant [29]. Also the Seattle group initially showed an advantage in regard to the FFPF in patients who received a short course AA in addition to the combination of external beam radiation therapy plus I-125 or Pd-103 brachytherapy [30]. This advantage also vanished in a recent reanalysis. Summarizing the literature currently available the evidence for an advantage of short-term AA to brachytherapy in regard to FFPF remains small. If long-term AA in combination with brachytherapy in high risk patients is of any benefit will be subject of further evaluations. For the purpose of gland size cytoreduction, androgen deprivation in the form of LHRH agonists is commonly used, allowing the brachytherapist easier access to the prostate by avoiding pubic arch interference [31].

4.4. *External beam therapy*

Indications for additional external beam therapy remain controversial. The indication for performing a brachytherapy as monotherapy is currently seen

Table 1 – Outcome data for patients treated with ^{125}Iodine or ^{103}Paladium implants

Author (Year of publication)	Patient number (*n*)	P/I[a]	Median follow-up (months)	% Recurrence-free survival (years)
Blasko (1995) [5]	197	I	36	93 (5)
Blasko (2000) [17]	230	P	41.5	83.5 (9)
Ragde (2000) [18]	147	I	93	66 (12)
Brachmann (2000) [19]	695	I/P	74	71 (5)
Grimm (2001) [20]	125	I	78	85 (10)
Beyer (2003) [21]	1266/73	I/P	49	76 (5) 65 (10a)
Potters (2004) [22]	733	I/P	51	74 (7)
Kupelian (2004) [23]	950	I/P	47	75 (7)
Sylvester (2004) [24]	223	I/P	120	86 (15a)
Potters (2005) [25]	1148	I/P	82	81 (12a)
Stone (2005) [26]	279	I	72	78 (10a)

[a] P/I: ^{103}Paladium/^{125}Iodine.

in patients with a clinical stage T1-T2, a Gleason score of ≤6 and a PSA ≤10 ng/ml [10].

Supplementary external beam radiation is currently applied mainly to patients who exceed these parameters. It is supposed that an additional 45 Gy will add another 4 mm beyond an implant alone [32]. Because 4 mm margins are routinely accomplished with monotherapy it appears questionable if additional external beam therapy is indicated in the intermediate risk group. So far no significant difference between seeds alone or in combination with external beam radiation in regard to recurrence-free survival in any risk group could be noticed [33].

5. Morbidity

5.1. *Micturition*

Most patients will experience some acute urinary symptoms shortly after the implant. Dysuria, frequency, urgency, a weak stream and nocturia are common during the first months after the implant [34]. Urinary retention occurs in 1.5–22% of all patients [35,36]. The risk of urinary retention is greater for patients with a prostate volume >35 cc and in case of a high preoperative IPSS [37]. The incidence of retention could be reduced by the application of α-blockers [38]. Most studies have found that about 90% of patients will have normalized their urinary complaints by 1 year postimplant [37,38]. The necessity for postimplant TUR-P ranges from 0–8.7% and should not be performed before six months after a I-125 and 2 months after a Pd-103 implant [39,40]. In case a resection is necessary it should be carried out very carefully to avoid urinary incontinence. The incontinence rates after a permanent seed implantation vary between 0–19% [41]. In case a TUR-P has been performed before the implant rates between 0–85% have been described [42]. Chronic urinary morbidity can appear as irritative voiding symptoms and urethral scarring, followed by obstruction and incontinence. Grade 3 urinary morbidity has been found to occur in 1–3% of the patients [43].

5.2. *Rectal complications*

Proctitis rates after seed implantations range from 1–21.4% [44].

Bowel and rectal complaints are normally documented using the modified Radiation Therapy Oncology Group (RTOG) rectal scoring scale [45].

Modified RTOG rectal toxicity scale	
Grade 1	Tenesmus, clear mucous discharge
Grade 2	Intermittent rectal bleeding, erythema of rectal lining on proctoscopy
Grade 3	Rectal ulcerations
Grade 4	Bowel obstruction, fistula formation, blood transfusion required

Severe rectal complications such as ulcer or fistula formation mainly occur after some kind of caustic therapy like rectal biopsies or electrocautery. Therefore it is prudent to caution the patients not to have any rectal procedures performed shortly after the implant.

Snyder et al. have demonstrated a correlation between the rectal volume receiving the prescription dose and the development of grade 2 proctitis. If ≤0.8 cc of rectal wall received 160 Gy no proctitis developed. The likelihood increased to 5% in case ≤1.3 cc received 160 Gy [46].

Brachytherapy-related bowel morbidity can be minimized with meticulous implant technique to minimize the radiation dose to the anterior rectal wall, careful attention to regulate postimplant bowel constipation and the judicious use of supplemental external beam radiation (Table 2).

Table 2 – Rate of Grade II/III proctitis in patients treated with implants alone or in combination with EBRT

Author (Year of publication)	Patient number (*n*)	Treatment P/I/EBRT[a]	Median follow-up (months)	% Grade II/III proctitis (RTOG)
Wallner (1995) [39]	92	I	36	5
Beyer (1997)	489	I	34	1
Merrick (1999) [47]	45	I/P	?	9
Gelblum (2000) [45]	685	I/P	48	6.5/0.4
Albert (2003) [48]	151	I	32	8
Kaye (1995) [49]	73	EBRT/I	24	4
Critz (1995) [50]	239	EBRT/I	47	15
Grado (1998) [51]	490	EBRT/I/P	30	1
Zeitlin (1998) [52]	212	EBRT/I/P	60	21.4
Gelblum (2000) [45]	140	I/P + EBRT	48	7.1/0.7

[a] P/I/EBRT: ^{103}Paladium/^{125}Iodine/External beam radiation.

Table 3 – Long-term preservation of erectile function in patients after permanent implants alone or in combination with EBRT

Author (Year of publication)	Patient number (*n*)	Treatment P/I/EBRT[a]	Follow-up (months)	% Rate of preserved erectile function
Wallner (1995) [39]	92	I	36	86
Kao (2000) [53]	236	I/P	72	70
Kaye (1995) [49]	73	EBRT/I	12	75
Dattoli (1996) [54]	73	EBRT/P	36	77
Zeitlin (1998) [52]	212	EBRT/I/P	60	62
Critz (1995) [50]	239	EBRT/I	60	76
Stock (2001) [55]	313	I/P	72	59
Potters (2001) [56]	482	I/P/EBRT	60	52.7
Merrick (2005) [57]	128	EBRT/I/P	36	50.5

[a] P/I/EBRT: ^{103}Paladium/^{125}Iodine/External beam radiation.

5.3. *Erectile function*

Brachytherapy studies demonstrate a 50–86% likelihood of preserved erectile function 1–6 years after an implant. The outcome was most significantly influenced by the pre-treatment erectile function. In case a normal erectile function was documented prior to the treatment a 70% likelihood of a maintained function after six years was noticed. If the erectile function was compromised before the implant 34% of the patients developed an erectile dysfunction. The other factor significantly influencing the postimplant erectile function was the applied dosage. Patients receiving a D90 >160 Gy for I-125 and >120 Gy for Pd-103 had a poorer outcome in regard to their erectile function [53].

Although erectile dysfunction (ED) is likely a multifactorial process, an increasing body of data implicating excessive radiation doses to the proximal penis as a possible cause is available. Recommendations to maximize potency preservation include limiting the radiation dose delivered to 50% of the bulb of the penis to less than 40% maximum prescription dose (mPD) and the crura to less than 28% mPD. Currently there are no data available which support a neurovascular bundle sparing approach in brachytherapy in order to preserve the erectile function. So far no information from retrospective or prospective studies are available, which demonstrate a correlation between ED and the radiation dose delivered to the neurovascular bundle (Table 3).

6. Conclusion

More than 15 years experience with modern transperineal prostate brachytherapy has proven the efficacy of this treatment approach. Cure rates, urinary and rectal complications, preservation of sexual potency are related to technical details of the implant procedure like various planning methods and source distribution patterns. The coming years will demonstrate if the reported favorable results of some centers of excellence can be reproduced by others. The development of treatment algorithms based on upcoming evidence will lead the way to define the place for interstitial brachytherapy in multimodality approaches to patients with intermediate and high-risk prostate cancers.

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