

**Transperineal Permanent Seed Implantation
of “Low Risk” Prostate Cancer:
5 Years Experiences in 118 Patients**

**Transperineale permanente Seedimplantation
des Prostatakarzinoms “niedrigen Risikos”:
5 Jahres Erfahrungen bei 118 Patienten**

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Summary:

Purpose: To evaluate 5-year prostate-specific antigen (PSA) relapse-free survival of transperineal permanent seedimplantation (TPSI) in 118 patients with “low risk” prostate cancer, that means stage cT1c-T2a, Gleason-score < 7, and initial PSA-value not above 10 ng/ml.

Patients/Methods: From 04/1999 – 06/2002, a total of 118 patients underwent a mono TPSI, using ultrasound-based preplanning and intraoperative verification by both ultrasound and conventional fluoroscopy as well as postoperative CT-planning. Patients were monitored during the first year in 3 month intervals, and in 6-monthly intervals from then onwards. Biochemical failure was defined according to ASTRO criteria with 3 consecutive PSA rises observed from a post-treatment nadir PSA-value, or with clinical and/or histologically proven tumor recurrence, or initiating hormonal therapy. The median follow-up is 48.9 (range: 37.0-80.2) months. 114 patients are eligible, 4 patients were lost to follow-up.

Results: For the entire group, PSA relapse free survival at 5 years is 94.7 %, with 6 patients (5.3 %) having a PSA relapse between and 20 months after implantation. In the bNED-patients PSA values were: <0.2 ng/ml in 82.5% (94/114 patients), <0.5 ng/ml in 13.2% (15/114 patients), <1.0 ng/ml in 2.6% (3/114 patients) and <1.5 ng/ml in 1.7% (2/114 patients). In summary PSA values <0.2 ng/ml, <0.5ng/ml and <1.0 ng/ml occurred in 82.5%, 95.7% and 98.3%, respectively. Out of the 6 patients with recurrent disease, three had a local tumor recurrence only, and three developed distant metastases.

Conclusions: In low risk prostate cancer patients, TPSI with intraoperative ultrasound-based treatment planning and fluoroscopy leads to excellent local tumor control and PSA relapse-free survival.

Zusammenfassung:

Ziel: Evaluation der Wirksamkeit einer transperinealen permanenten Seedimplantation (TPSI) bei 118 Patienten mit Prostatakarzinomen "niedrigen Risikos" (cT1c-T2a, Gleason-score < 7, and initial PSA-value <10 ng/ml).

Patienten/Methode: Von 04/1999 bis 06/2002 erhielten 118 Patienten eine alleinige TPSI. Die TPSI erfolgte mit Prä-, Online- und CT-Nachplan. Die Patienten wurden im 1. Jahr dreimonatlich und vom 2.-5. Jahr sechsmonatlich nachuntersucht. Kriterien für das Vorliegen eines Tumorrezidivs waren 3 konsekutive PSA-Anstiege (ASTRO-Kriterien) nach Erreichen des posttherapeutischen PSA-Nadirs oder bei klinischem und/oder histologischem Nachweis eines Tumorrezidivs. Die mediane Nachbeobachtung betrug 48.9 (37.0-80.2) Monate. 114 Patienten waren auswertbar, 4 Patienten entzogen sich der weiteren Nachkontrolle.

Ergebnisse: Für das gesamte Patientenkollektiv ergab sich eine PSA-freies Überleben nach 5 Jahren von 94.7%, 6 Patienten (5.3%) entwickelten ein PSA-Rezidiv in einem Intervall von bis zu 20 Monaten nach TPSI. Bei den bNED-Patienten betragen die PSA-Werte: <0.2 ng/ml in 82.5% (94/114 Patienten), <0.5 ng/ml in 13.2% (15/114 Patienten), <1.0 ng/ml in 2.6% (3/114 Patienten) und <1.5 ng/ml in 1.7% (2/114 Patienten). Demgemäß fanden sich PSA Werte <0.2 ng/ml, <0.5ng/ml und <1.0 ng/ml in 82.5%, 95.7% und 98.3% der Patienten. Bei den 6 -Patienten mit Tumorrezidiv hatten drei ein lokales und drei ein systemisches Wiederauftreten der Erkrankung..

Schlussfolgerung: Bei Patienten mit einem Prostatakarzinom „niedrigen Risikos“ führt die ultraschallgestützte und fluoroskopisch kontrollierte TPSI zu einer exzellenten lokalen Tumorkontrolle und PSA-freien Überleben.

Key words: Transperineal Permanent Seed Implantation, Low Risk Prostate Cancer, Efficacy

Introduction:

In the past, radical prostatectomy (RP) and external beam radiotherapy (EBRT) – with or without hormonal therapy – has been the treatment strategies of choice for all locally confined prostate cancer patients. This was due to the fact that initial data on brachytherapy have been suboptimal. Meanwhile, permanent transperineal interstitial brachytherapy has become a competitive therapeutic option for patients with „low risk“ prostate cancer (cT1-2 Gleason Score <7 iPSA <10 ng/ml). Concerning biochemical evidence of disease (bNED) these treatment modalities supposed to be equieffective, although randomized clinical trials are still lacking [7,10,11,13,22,26,29]. The resurgence of interest in TPSI was a result of several technological advances, especially evolution in transrectal sonography and sophisticated treatment planning computer software. The accuracy of seed placement was significantly improved due to imaging and planning advances. Furthermore, computer tomography (CT)-based dosimetry after TPSI increases treatment quality and proactively predict outcome and complication [16]. Excellent TPSI results were obtained using a variety of planning and implantation techniques, with no method being proven superior.

In principle, TPSI can be performed in patients with low, intermediate and high risk prostate cancer. A mono TPSI is not recommended in intermediate and high risk prostate cancer, achieving bNED of less than 60 % in subgroups. Therefore, this study evaluated only patients with “low risk” prostate cancer who underwent TPSI [2,14,30].

MATERIAL AND METHODS:

Patients:

Between 04/99 and 06/02, 118 patient underwent TPSI in an interdisciplinary approach for low risk adenocarcinoma of the prostate. The median age of the total cohort was 65.1 (52.3-77.5) years. 114 patients were closely monitored and eligible. 4 patients were lost during follow up. The median follow up was 48.9 (37.0-80.2) months.

The prostate cancer was clinically staged by medical history, a physical examination including digital rectal examination, and serum PSA determination. A sceleron scintigraphy was obtained if the patient had clinical symptoms suspicious for bone metastases. Transrectal ultrasound was used for staging and biopsy guidance as well.

All patients had a low risk prostate cancer with PSA-values not beyond 10 ng/ml, Gleason score below 7 and tumour stage not beyond cT2a (Tab. 1).

T-Stadium:	
cT1c:	78 (66.1%)
cT2a:	40 (33.9%)
Combined Gleason Score:	
<5:	31 (26.3%)
5:	32 (27.1%)
6:	55 (46.6%)
Initiale PSA (ng/ml):	
0-4:	12 (10.2%)
4-10:	112 (89.8%)
Neoadjuvant androgendeprivation therapy	69 (58.5%)

Tab. 1: Characteristics of patients (n=118)

69 patients (58.5%) underwent a 3-6 monthly neoadjuvant androgen deprivation therapy, mainly introduced by transferring urologists to overcome delayed treatment decisions. No patient received an adjuvant androgen deprivation treatment. No supplemental EBRT was given.

Transperineal permanent seed implantation:

Using the peripheral loading method, embedded ^{125}I iodine seeds ("Strand") were implanted.

2-3 weeks prior to TPSI a preplan was created in the same manner as described for the online plan procedure. Main targets of the preplan are:

- a) Ordering of a defined number of seeds,
- b) exclusion of pubic arch interference,
- c) "internal quality control" with comparison of pre- and online-plan data to exclude major differences in these both planning procedure (prostate volume, number of seeds for TPSI).

Using a transurethral catheter for visualization of the urethra the TRUS-online planning was performed under general anaesthesia (Biplane-probe 5.0, 6.5, 7.5 MHz, Hawk 2102 xdi Extended Diagnostic Imaging™, Biplane probe 8658 MDI™, B-K Medical, Medizinische Systeme GmbH).

If necessary, the posterior area of the prostate was elevated with a water bag cover (Brachyballoon™, Barzell-Whitmore Maroon Bells). The gland was fixed using 2 fixation needles (Cook-localisations needle™, Cook Urological) which were inserted in anterior areas of the prostate.

Patients were placed in lithotomy position and, after correct positioning of the transrectal probe, the volumetry began in 5 mm increments with inclusion of one above the first ("Cut above Zero-retraction") and one below the last plan ("Cut below"). During the online plan procedure the sonography images were directly transferred into the planning computer software VariSeed™ (/6.7/7.0) PSID™ (3.0/3.5).

Seeds with defined activity were placed creating an isodose of 145 Gy surrounding the prostate with a 5 and 3 mm safety margin in the apical and basal areas as well as in central zones of the gland.

After achieving the critical dose parameters (Tab. 2) the number of seeds were determined.

V100 (% of prostate volume that receives the prescription dose)	>98%
D90 (Dose that covers 90% of prostate volume)	>180 Gy
D100 (Dose that covers 100% of prostate volume)	>140 Gy
D1/D30 Urethra (Dose that covers 1% and 30% of the urethra)	<230/210 Gy
D100 Rektum (Dose that covers 100% of of the anterior rectal wall)	<200 Gy

Tab. 2: Indices used to quantify implant quality [12]

Implant quality was defined using the dose volume histograms for the target volume prostate and the organs at risk (urethra, rectum) [20,25]. During the implantation, the position of the needle was controlled by ultrasound and fluoroscopy before implanting the seeds. In all patients, the TPSI procedure was done with interdisciplinary cooperation of urologist, radiation oncologist and medical physicist.

After completion of the procedure a flexible cystoscopy was performed in order to exclude seed dislocation into the urinary bladder which would result in under dosage of the prostate and problems in radiation protection (loss of seeds during urination).

CT-Postplanning:

Postimplant evaluation or dosimetry is a key part of the procedure. Dosimetry is *the legal document* regarding the procedure [21].

CT postplanning was performed at day 28-35 after TPSI with a pelvic CT scan [2,17,30]. The prostate and seeds were visualized at 3 mms interval and using a layer thickness of 3 mm as well. After transferring the DICOM-data into the dosimetry software the CT postplanning procedure was performed. Seeds were automatically identified due to differences in Hounsfield units and gray scale appearance. After determination of dose distribution the implant quality was determined.

On the day of CT scan a transrectal ultrasound in lithotomy position of the patient in 5 mm increments was performed, too. This TRUS based volume

data led to a better definition of prostate volume and boundaries relative to the CT scan data where the gland volume is overestimated in up to 30-40% [1].

Characteristics of seeds, prostate volume and number of implantation needles:

¹²⁵Iodine seeds were administered with a median activity of 0.712 (0.521-0.737) mCi/26.37 (19.28-27.27) MBq. The median prostate volume was 31.5 (15.8-59.3) ml. In median 18 (12-28) needles within median 48 (30-76) seeds were implanted.

Definition of biochemical recurrence:

After TPSI, patients were controlled in the first year every 3 months, in year 3 to 5 every 6 month and thereafter once a year. Follow up was performed by referring colleagues, personal examination or telephone questioning. Biochemical recurrence was defined as 3 consecutive increases of PSA after reaching the PSA-Nadir ("ASTRO-Definition") [1], or with clinical and/or histologically proven tumor recurrence, or initiating hormonal therapy. bNED was defined for patients who had no biochemical evidence of tumor progression.

RESULTS:

PSA-results:

After a median follow up of 48.9 (37.0-80.2) months, PSA values <0.2 ng/ml, <0.5 ng/ml and <1 ng/ml were found in 94/114 (82.5%), 109/114 (95.7%) and 112/114 (98.3%) respectively. 2/114 (1.7%) patients show stable PSA-values <1.5 ng/ml.

Fig. 1 shows the distribution of PSA-values.

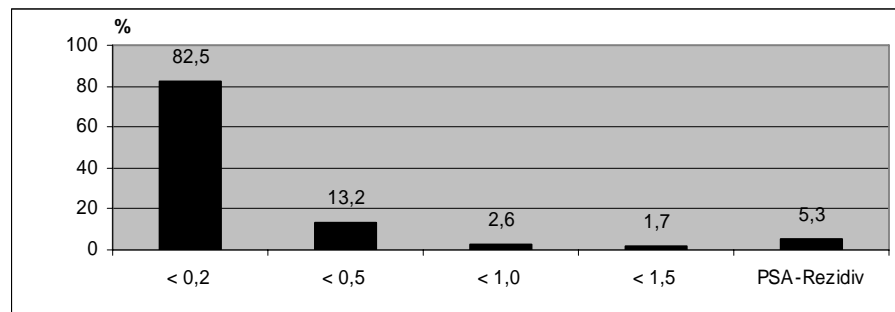


Fig. 1: Distribution of PSA values (ng/ml) and PSA failure after TPSI (n=114)

According to the ASTRO-definition bNED resulted in 94.7% of patients with a median and average PSA value of 0.1 ng/ml and 0.2 ng/ml, respectively. 3 consecutive PSA-increases were diagnosed in 6 patients (5.3%), thus defining biological evidence of disease at 6, 7, 7.5, 9, 13 and 20 months, respectively. Recurrences occurred locally in 3 and systemically in 3 patients. Fig. 2 shows the Kaplan-Meier curve of bNED, with bNED of 94.5 % at 3- and at 5-years.

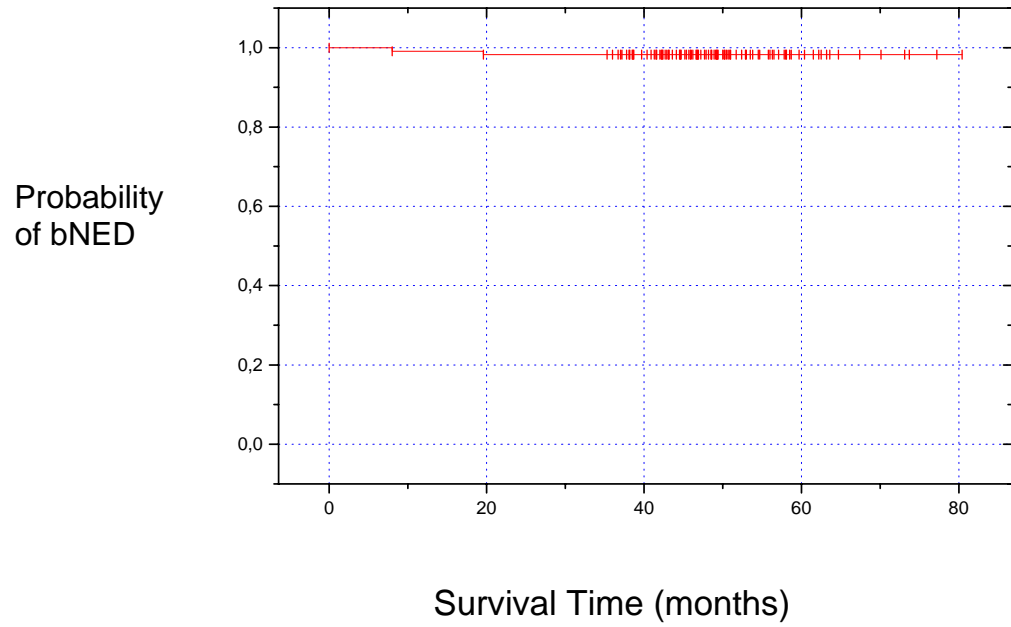


Fig. 2: bNED after TPSI

DISCUSSION:

The initial clinical data on permanent interstitial brachytherapy were disappointing. High morbidity and an inadequate dose distribution resulted in poor local control and bNED rates. With the development of ultrasound guidance and improvements in the percutaneous transperineal technique, morbidity lessened and uniform dose distribution was achievable [1,6,9,12,27]. Currently, in high volume centres with modern techniques, RP, EBRT, and TPSI are considered equivalent regarding local tumour control, bNED, and frequency of severe late side effects in the treatment of low risk prostate cancer [13,26,29]. Permanent seed implantation is by now well accepted in the management of localized early stage prostate cancer [1,2,29,30].

In our series of low risk prostate cancer patients, the actuarial bNED rate at 3- and 5 years is 94.7 and 94.7 %, respectively. These results are in accordance with most series published so far [3,8,9,11,16,24,28]. Centers who included a high quality of implantation, that means preplanning – either based on CT or ultrasound - and an ultrasound-based intraoperative planning supported during application by fluoroscopy achieve a low local failure rate and a high bNED. The varying techniques and experience in the different groups in partial explain the different treatment results, with a range of 7-year bNED from 74 % to 98.3 %, and a 10-year bNED between 78 % and 89 % [5,9,16,24,31]. On the other hand, dose distribution has changed, with increasing dose being used more recently whilst improving the implantation techniques [12]. The question of dose prescription and target coverage is not yet finally clarified. We know that a low risk prostate cancer is carrying a very low risk of disease in seminal vesicles or lymph nodes which can be estimated using the Partin tables [18]. It is of about 2 % and 1 %, respectively. This explains only in part the 5.3 % of tumour recurrence in our series with a dose distribution that only covers the prostate sufficiently, or in other clinical series with tumor recurrences of up to 25 % at 7 years.

Nevertheless, even in low risk cancer there is a modest risk of tumor that shows capsular penetration. If capsular penetration within a short distance occurs it is easily covered by the implant volume [6]. It might not be covered, if the brachytherapy target volume consists of a 3-5 mm enlargement of the prostate gland, which is usually recommended [21]. Grimm et al. achieved a bNED at 10 years of 87 % only in low risk patients, using a discretionary margin of 2-5 mm [9]. In contrast to the recommendations, Merrick et al. used

margins up to 8 mm, and could demonstrate in a group of younger patients an extraordinary high rate of 96.1 % 7-year biochemical progression free survival [15]. This rate of bNED is definitely in the range of an optimal radical prostatectomy and can not only be explained by the young median age of the patients in this study. We have to continuously to investigate risk factors that will help us to define the optimal individual patients dose.

The only shortcoming of our series is the relatively short follow-up, with no patient being followed for more than 7 years. Nevertheless, we know that a tumor recurrence later than 5 years after implantation is rare, making about 25 % of all tumor recurrences. Radge et al. [24] reported on patients who received a TPSI between 1987 und 1989 with a follow up of up to 13 years. Some patients were treated in the “before-PSA Era”, 80% of patient had a palpable nodule. PSA recurrence was defined according the ASTRO criteria whereas the third PSA value had to be <0.5 ng/ml. Late biochemical recurrence was seldom, 75% of biochemical recurrence occurred during the first 5 years after TPSI. No patient developed a PSA relapse between the 10. and 12. year after TPSI. Initial results after a period of 4 years of experience are reported by a multiinstitutional, interdisciplinary European group: 178 patients with low risk prostate cancer underwent TPSI. The 3 year bNED was 97.7% after median follow up of 29.5 (8-56) months. It is of interest that 16 out of 18 PSA recurrences occurred within the first 18 months after TPSI [4]. If we translate these informations on our series with a relapse rate of 5.3 % at 5 years, we will expect a bNED at 10 years of about 92.8 %.

Using TPSI, besides the experience of the implanting team an optimal treatment technique in TPSI is essential. Grimm et al. [9] implanted 125 patients between 1988 and 1990 and reported a follow up of 10 years (Fig. 3).

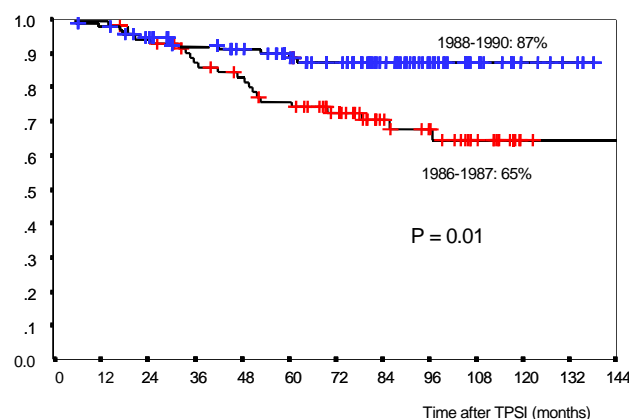


Fig. 3: Results of TPSI from 1988–1990 and 1986-1987 respectively [adopted from 18]

Concerning PSA relapse a modified ASTRO definition was used, namely 2 consecutive PSA rises. The median follow up was 81.4 months. After 10 years 87% of patients with low risk prostate cancer showed bNED. 59 patients (47%) had a follow up > 7 years with PSA values <0.2 and <0.5 ng/ml in 48 (81%) and 51 (86%) patients respectively. Local and distant failures occurred in 3% each. A further continuous PSA decrease <0.2 ng/ml occurred 7-8 years after TPSI. In this study differences in outcome was shown in patients treated between 1986 and 1987 (“learning curve”) compared with them implanted between 1988-1990 (Fig. 3). These differences of outcome did not correlate with patient selection. The increased biochemical control correlated with the technical development of treatment facilities (high resolution transrectal ultrasound, 3 D reconstructive planning procedures).

Kollmeier et al. published a 88%-bNED in 75 patients after 8 years. They analyzed in the low-, intermediate- and high-risk groups “optimal” (D90 >140 Gy) versus “suboptimal” (D90 <140 Gy) implants. After 8 years a bNED of 82% in the “optimal” versus 68% in the “suboptimal” cohorts was achieved [12].

The excellent efficacy of TPSI in patients with low risk prostate cancer is also confirmed in the most recent literature. In 2004, Battermann et al revealed a bNED in 89% of 116 patients after a median follow up of 48 (24-123) months [3]. In the same year a 92% bNED after a median follow up of 52,3 (12-108) months is published [19], which is close to our own data. Sharkey et al [26] reviewed 1707 patients with T1- and T2- adenocarcinoma of the prostate treated by ¹⁰³Pd brachytherapy or radical prostatectomy (RRP) from 1992 to 2004. In low risk patients the bNED was 99% for implanted versus 97% for operated patients which showed no statistical significance. They concluded that TPSI and RRP should be offered without bias to all men with low risk prostate cancer. Most recently the 12-year outcome following TPSI in 1449 patients with clinically localized prostate cancer was published: In the low risk cohort of 481 men the 12 year-bNED was 89% [23]

Conclusion:

According to reported results in literature and the patient cohort with low risk prostate cancer presented in this study an equiefficacy of TPSI with RP and EBRT is assumed although no prospective studies are available. Nevertheless, there are some crucial aspects of TPSI having a enormous influence of the efficacy of this treatment:

1. Strict patient selection, i. e. patients with low risk prostate cancer (cT 1-2a, Gleason score < 7, and PSA \leq 10 ng/ml) although the efficacy of mono TPSI in the intermediate and high risk groups remains controversial,
2. detailed information to each patient about the 3 definitive treatment modalities in low risk prostate cancer, thus supporting the patient`s treatment decision,
3. high implant quality and quality assurance,
4. CT postplanning with D90 >140 Gy based on the dose response: A dose response curve for patients undergoing 125 Iodine-mono-TPSI with superior biochemical results with a D90 >140 Gy was reported [18,22].

One major final conclusion is that TPSI leads only to excellent results when applied from an experienced interdisciplinary team consisting of an urologist, a radiation oncologist and medical physicist. Unfortunately, published data are not prospective or randomized, and, therefore, it is not possible to determine the superiority of one treatment over the others, but it is reasonable to state that biochemical outcomes are similar in patients with “low risk” prostate cancer. Therefore, every patient should be offered all treatment options with advantages and disadvantages without any bias.

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