Clinical and physical determinants for toxicity of 125-I seed prostate brachytherapy

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Abstract

Background and purpose: To assess acute as well as long-term toxicity after permanent prostate seed implantation. To find predictive clinical or dosimetric factors for side effects in order to work out strategies for improvement.

Patients and methods: A group of 174 patients with localised prostate cancer was treated with permanent seed implantation between 1999 and 2001, either alone (140 patients) or in combination with external radiotherapy (34 patients). For the majority (114/174, i.e. 66%) a CT was performed four weeks after implantation and analysed in the planning system VariSeed. In the postimplant analysis, dosimetric descriptors (doses, volumes) were determined for the prostate and rectum and compared with the intraoperative values. In addition, a questionnaire was sent to all patients to assess and quantify acute and chronic toxicity (urinary, rectal, sexual) and the impact on subjective acceptance and quality of life (return rate of questionnaires 83%). The derived score changes were correlated with clinical and dosimetric factors.

Results: In the mono-brachytherapy group 14% (16/140) required a bladder catheter, of them 8% (9/140) with a manifest urinary obstruction. Long-term rectal toxicity (<5%) and impairment of potency (<30%) are moderate and obviously below other treatment options. Urinary toxicity is dominant with an overall long-term dysuria up to 30% (at a mean observation interval of ten months), and a significant trend to decline with follow-up time. Conversely, the erectile function tends to deteriorate with follow-up time. Nevertheless, quality of life is not significantly reduced and acceptance is high. Our analysis suggests that the main factor for urinary toxicity and impaired erectile function is the dose load to larger portions of the prostate ($D_{50} < 240$ Gy), which appears to be attributed to unnecessarily high numbers of seeds (for a fixed activity per seed) and needles. The rectal toxicity is correlated with the high dose regions in the rectum ($\geq 145$ Gy). Urinary toxicity is lower for combined-brachytherapy, while rectal toxicity and impairment of potency are slightly higher.

Conclusions: Toxicity spectrum and quality of life after permanent seed implantation for early prostate cancer are acceptable for nearly all patients (98%). To further improve tolerance we should attempt to achieve a better dose homogeneity, i.e. by reducing $D_{50}$. Therefore, special attention should be given to $D_{50}$ during the real-time planning process. The necessity of more homogeneous dose distributions might imply a reduction of the activity per seed, e.g. from 0.7 mCi down to 0.6 mCi.

Keywords: Early prostate cancer; 125-I seed implantation; Postimplantation analysis; Toxicity spectrum; Correlation analysis

1. Introduction

Permanent prostate seed implantation with 125-Iodine has become a third therapeutic option for early prostate cancer together with radical retropubic prostatectomy (RRP) and external beam radiotherapy (EBRT). This method has also been established at some European centres [1] and is becoming more popular in Germany since 1998 [8].

Implant dosimetry planning and its precise reproducibility has been improved considerably since 1990 based on transrectal ultrasound guided planning systems as well as localisation tools [19]. Phase II long-term studies with observation times of more than 10 years are now available [7,9,11,23,25,26] showing comparable long-term
PSA control and overall survival (age-corrected) for permanent seed implantation and radical surgery. Many patients prefer permanent seed implantation [3,16,18,24,27,33], because of an acceptable toxicity spectrum and convenient practical considerations in comparison to RRP [2,32] or EBRT [13,28]. More details about the comparison of acute and long-term side effects, reactions, or complications are given in Section 4.

It is desirable to include more data about acute and long-term side effects. In particular, correlations of side effects with various (clinical and treatment-related) parameters are a precondition to develop criteria for further improvement of the implantation technique [3,20,31,34]. Therefore, we performed the following retrospective analysis of a patient group treated with 125-I permanent seed implantation at a European centre.

2. Patients and methods

2.1. Patients and indication for seeds

During the period 6/1999–9/2001 we treated 174 patients with localised prostate cancer using 125-I permanent seed implantation (see Table 1).

| Follow-up time: 9.7 ± 4.7 months (3–21 months) |
| Age: 64 ± 7.4 years (46–86 years) |
| Prostate volume: 34 ± 14 ml (10–75 ml) |

### Table 1

Characteristics of the 174 patients treated from 6/1999 to 9/2001 by mono-brachytherapy (140 pts) or combi-brachytherapy (34 pts). Mean values ± SD are listed (in brackets the range from minimum to maximum is added)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mono-brachytherapy</th>
<th>Combi-brachytherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up time</td>
<td>9.7 ± 4.7 months (3–21 months)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>64 ± 7.4 years (46–86 years)</td>
<td></td>
</tr>
<tr>
<td>Prostate volume</td>
<td>34 ± 14 ml (10–75 ml)</td>
<td></td>
</tr>
</tbody>
</table>

### T-categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
<th>Prescription Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1b</td>
<td>1/174 (0.6%)</td>
<td>140 Gy 15/140 (8.6%)</td>
</tr>
<tr>
<td>T1c</td>
<td>39/174 (22.4%)</td>
<td>145 Gy 125/140 (71.8%)</td>
</tr>
<tr>
<td>T2a</td>
<td>72/174 (41.4%)</td>
<td>90 Gy 10/34 (5.8%)</td>
</tr>
<tr>
<td>T2b</td>
<td>53/174 (30.4%)</td>
<td>100 Gy 11/34 (6.3%)</td>
</tr>
<tr>
<td>T3a</td>
<td>3/174 (1.7%)</td>
<td>110 Gy 13/34 (7.5%)</td>
</tr>
<tr>
<td>Not assessed</td>
<td>6/174 (3.5%)</td>
<td></td>
</tr>
</tbody>
</table>

### PSA (initial)

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
<th>Prescription Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 ng/ml</td>
<td>114/174 (65.5%)</td>
<td></td>
</tr>
<tr>
<td>10–20 ng/ml</td>
<td>42/174 (24.2%)</td>
<td></td>
</tr>
<tr>
<td>&gt;20 ng/ml</td>
<td>18/174 (10.3%)</td>
<td></td>
</tr>
</tbody>
</table>

### Gleason score: 5 ± 1.4

### Core number (biopsy): 5 ± 2.5

### Pre-treatment

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>95/174 (54.6%)</td>
</tr>
<tr>
<td>Hormonal ablation (HA)</td>
<td>58/174 (33.3%)</td>
</tr>
<tr>
<td>TUR-P</td>
<td>10/174 (5.7%)</td>
</tr>
<tr>
<td>TUR-B</td>
<td>2/174 (1.2%)</td>
</tr>
<tr>
<td>HA + TUR-P</td>
<td>7/174 (4.0%)</td>
</tr>
<tr>
<td>HA + TUR-B</td>
<td>2/174 (1.2%)</td>
</tr>
</tbody>
</table>

According to the risk factors PSA, Gleason score and T-category, a low-risk group (T1-2, PSA < 10 ng/ml and Gleason score < 7), an intermediate-risk group (T1-2, PSA 10–20 ng/ml or Gleason score = 7), and a high-risk group (T3a or PSA > 20 ng/ml or Gleason score > 7) are defined. For the low-risk group a 125-I permanent seed implantation alone (mono-therapy) is recommended with a prescribed dose of 140–145 Gy [19], while for the high-risk group a combination of 125-I seeds with a reduced prescription dose (100–110 Gy) and external radiotherapy with a 45 Gy reference dose is preferred (combi-therapy). In the intermediate-risk group an individual treatment decision is given. A neoadjuvant hormonal treatment (pre-implantation) was prescribed in about one third of the patients, if the prostate volume in a preoperative routine transrectal ultrasound examination exceeded 40 ml.

2.2. Seed implantation

The implantation was performed in general anaesthesia with the patient in the typical dorsal lithotomy position. We used the ultrasound system Falcon 2101 with the transrectal multiplane transducer 8551 (B-K Medical, 2820 Gentofte, Denmark) adapted to the Barzell-Whitmore Micro Touch or...
the AccuSeed stepping unit. We used 125-I seeds in rapid strand technique of average activity of 0.7 mCi.

On-line planning was performed on a transverse ultrasound data set (stepping distance 0.5 cm) using the planning system VariSeed 6.7 (Varian Medical Systems, Palo Alto, California, USA). The optimisation of the dose distribution with the prescription dose 145 Gy for mono-therapy (115 Gy for combi-therapy) was based on the following objectives: minimum dose $D_{100} \geq 115$ Gy (90 Gy), $V_{100} \geq 95\%$, maximum urethra dose $\leq 230$ Gy (190 Gy), safety margin $\geq 3$ mm. After an automatic optimisation routine, an experienced user further improved the plan. However, $D_{50}$ (or $V_{150}$) was not considered. In case of combi-therapy the external standard radiotherapy was started six weeks after brachytherapy (45 Gy with a $5\times1.8$ Gy fractionation using conformal 4- or 6-field technique, rarely including the regional lymphnodes).

For post-implant analysis [15] in 66\% (114/174) of the patients a computerised scan (CT) of the prostate was available at least four weeks after implantation (in 2–3 mm slice distances according to Recommendations of the American Brachytherapy Society ABS, [9,20]). The image information was transferred in our planning system either by DICOM 3.0 interface (in our department) or by using a digitizer on hard copies (from other institutes).

We contoured the prostate and rectum carefully claiming at agreement between the prostate volume achieved during real-time planning with the volume based on the CT scan (no safety margins included). No contrast media or catheterisation were routinely used, and therefore the urethra could not be precisely delineated. Every contour was performed by the same person (D.B.) under supervision of a radiologist (P.W.). The number of implanted seeds (minus eventual lost seeds) were also given, and either reproduced by the SeedFinder module of VariSeed or by manual specification via digitizer.

After retrospective calculation of the dose distribution, we extracted the index doses $D_{100}$,... and volumes $V_{100}$,... for the prostate and the rectum. Furthermore, we included two parameters describing the homogeneity such as $(D_{10}−D_{50})/D_{50}$ and $V_{150}/V_{100}$. We found the location of the urethra too uncertain in the CT-scans with respect to the steep dose gradients, and did not consider this structure in the postimplant analysis. However, we included the urethra dose from the real-time plans.

### 2.3. Toxicity evaluation

Every patient was asked to answer retrospectively a questionnaire for scoring acute and chronic toxicity sent to the patients during 2002 (resulting in a minimum follow-up time of 3 months) [21,22]. Our assessment is focussed on score changes of symptoms describing an increase or deterioration over time (and not on their absolute strength) according to Table 2.

For every key side effect a score of grade 0–4 was offered for selection at three timings, i.e. before the implantation, at the maximum of acute toxicity (at 4th–6th week) and with respect to a longer follow-up (present state, i.e. >3 months after implantation). We added three items to evaluate the influence upon quality of life (QoL) and the acceptance of the brachytherapy. This is not a validated score, but

<table>
<thead>
<tr>
<th>Key symptom</th>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urinary toxicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>Normal</td>
<td>3–4 h</td>
<td>2–3 h</td>
<td>1–2 h</td>
<td>&lt;1 h</td>
<td></td>
</tr>
<tr>
<td>Nocturia</td>
<td>Never</td>
<td>1×</td>
<td>2×</td>
<td>3×</td>
<td>more than 3×</td>
<td></td>
</tr>
<tr>
<td>Dysuria</td>
<td>Never</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily</td>
<td>Permanent</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>No</td>
<td>Minor</td>
<td>Moderate</td>
<td>Strong</td>
<td>Intolerable</td>
<td></td>
</tr>
<tr>
<td>Urgency</td>
<td>Never</td>
<td>Weekly</td>
<td>1× daily</td>
<td>&gt;2× daily</td>
<td>Permanent</td>
<td></td>
</tr>
<tr>
<td>Pads</td>
<td>Never</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily</td>
<td>Permanent</td>
<td></td>
</tr>
<tr>
<td>Decreased stream</td>
<td>Normal</td>
<td>Sometimes</td>
<td>Often</td>
<td>Weak</td>
<td>Obstruction</td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td>Never</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily</td>
<td>Permanent</td>
<td></td>
</tr>
<tr>
<td>Medication&lt;sup&gt;a&lt;/sup&gt; (0–3)</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Permanent</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rectal toxicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>Normal</td>
<td>2–4/d</td>
<td>4–8/d</td>
<td>&gt;8/d</td>
<td>Uncontrolled</td>
<td></td>
</tr>
<tr>
<td>Urgency/Tenesmus</td>
<td>Never</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily</td>
<td>Permanent</td>
<td></td>
</tr>
<tr>
<td>Pain at defecation</td>
<td>Never</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily</td>
<td>Permanent</td>
<td></td>
</tr>
<tr>
<td>Incontinence</td>
<td>Never</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily</td>
<td>Permanent</td>
<td></td>
</tr>
<tr>
<td>Mucus production</td>
<td>Never</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily</td>
<td>Permanent</td>
<td></td>
</tr>
<tr>
<td>Blood apposition</td>
<td>Never</td>
<td>Monthly</td>
<td>Weekly</td>
<td>Daily</td>
<td>Permanent</td>
<td></td>
</tr>
<tr>
<td>Medication&lt;sup&gt;b&lt;/sup&gt; (0–3)</td>
<td>Never</td>
<td>Weekly</td>
<td>2× weekly</td>
<td>Daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sexual dysfunction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>Never</td>
<td>Sometimes</td>
<td>Often</td>
<td>Always</td>
<td>Not possible</td>
<td></td>
</tr>
<tr>
<td>Libido</td>
<td>Normal</td>
<td>Slightly reduced</td>
<td>Moderately reduced</td>
<td>Strongly reduced</td>
<td>Not existing</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> $\alpha$-blocking agents, sometimes analgesics.
<sup>b</sup> Laxatives, rarely corticosteroid-containing ointments.
nevertheless useful to find a dependency of QoL changes on certain treatment factors.

We designed the questionnaire and the score as simple as possible to enhance response (achieving a return of 145/174, i.e. 83%). The items were answered by the patients in 90–99%. These percentages are listed in Tables 4–6 for every side effect (in brackets). A univariate analysis of the toxicity parameters was performed in the statistical package SPSS 10.0. For every factor we specified two groups of equal size using the distribution-free Mann–Whitney test. We differentiated three level ranges of significance: \( P=0.05\)–0.1 indicates a trend and is at least mentioned and discussed, \( P=0.01\)–0.05 indicates evidence (but the number of factors requires some doubt), and finally \( P<0.01\) gives strong evidence (even after correction according to Bonferoni) with an error probability of the first kind of \( \alpha<5\%\).

3. Results

3.1. Descriptive statistics and dose distributions

The dose and volume parameters for the prostate and rectum comparing the real-time dose plan and the postimplantation analysis are given in Table 3 (mono-brachytherapy).

A reasonable agreement is achieved on average between real-time and postimplantation data. The difference is quite high for the minimum dose in the target volume \( D_{100}\) (Section 2.2). The agreement is higher for the index doses \( D_{90}, D_{80}, D_{70}, \ldots \) where the mean deviations are falling from 12% to a few %. Note that Table 3 is averaging over a learning curve: As consequence of the earliest experiences the prescription dose was increased from 140 to 145 Gy (Table 1), and after the first 100 patients the claimed standard for \( V_{100}\) during real-time planning was elevated from 95 to 98%. In consequence, the quality as well as the agreement between real-time performance and postimplantation analysis have improved with time.

3.2. Description of toxicity

The most significant acute side effect is urinary obstruction or even retention requiring intervention. In the mono-brachytherapy group, 14% (16 patients) of the patients required a catheter, 6% prophylactically (7 patients) and 8% (9 patients) because of manifest retention. Of these 2% (2 patients) needed an intervention such as stent insertion or incision of the urethra to re-establish the urinary passage. In the long-term, still 6% (7 patients) required a catheter for the acute period of 4–6 weeks. Of these, 3% (3 patients) required an additional intervention to remove the obstruction. This is more than in the combined-bi Brachytherapy group where only 7% (2 patients) received a catheter over the whole postimplantation period (with no other intervention).

The urinary toxicity (Table 4) is considerable with grades up to 3 (nocturia) during the acute phase. However, the base status is not 0 for all symptoms in this elder patient group. Especially, nocturia and obstruction problems exist before implantation for a number of patients, e.g. nearly 40% had nocturia scored \( \geq 2\) and about 20% obstruction symptoms scored \( \geq 2\). Therefore, the highest deterioration of the condition in the acute phase is found for urinary dysfunction (score difference of \( \Delta =2.3\) ) followed by urinary frequency, nocturia and medication on average.

A clear decline of urinary symptoms in frequency and intensity is documented comparing the acute phase (6 weeks post-implantation) with the time of assessment (mean follow-up time 9 months). Dysuria is still on a level of 1.2 above the pre-treatment state, followed by urinary frequency (0.8) and nocturia (0.7), and medication was still needed (1.0). After all, one third of the patients have had an increase of dysuria with a score 2 or more. For the combined brachytherapy, the urinary toxicity is less (see below). Obviously, the urinary toxicity is the dominant side effect for this treatment, but further decrease with follow-up time is expected from our data (Section 3.3).

The rectal toxicity (Table 5) is relatively low with long-term score changes of 0.1–0.3. Only for one symptom (pain) is the chronic increase of the score at 0.5 for the combined-brachytherapy. Here, a trend for a slightly higher toxicity in the combination brachytherapy arm is indicated (see below). The induced sexual dysfunction is in the medium range. Again, the pre-treatment status with disturbances on average...
near grade 1 must be considered. In the chronic phase, an
impairment of grade 1 for mono-brachytherapy and grade 1.5 for combined-brachytherapy with respect to the pre-
treatment status is found. In the acute phase, the difference
is about 0.5 grade higher. About 30% of the patients
with brachytherapy alone have a deterioration of potency of
$D_Z^{2–4}$ grade, this percentage is higher (40–50%) for the
patients with combined-brachytherapy.

### 3.3. Univariate analysis of side effects

The univariate analyses for the score differences of
urinary/rectal toxicity and impairment of sexual function
(mono-brachytherapy) are summarised in Tables 6 and 7
describing the dependency on the actual descriptors of the
dose distribution (derived from the postimplant analysis). A
corresponding, but much less impressive, correlation is seen
for the dose descriptors from the real-time plans. This
reflects the difference between the planned (i.e. desired) and
actual dose distributions.

The urinary toxicity (Table 6) increases in the acute
phase with higher doses applied to a considerable
percentage of the prostate such as $D_{50}$ (or $D_{80}$) as well
as the corresponding volumes ($V_{150}, V_{200}$ in %). Note
that because of the approximately constant activity per
seed (0.7 mCi, see Section 2.2) these parameters are
 correlated with the number of seeds (or total activity), or
number of needles (even though differential loading was
used), and finally with the prostate volume. The same
parameters are predictive for the remaining long-term
urinary toxicity. The typical symptoms are dysuria,
urinary frequency and nocturia. Interestingly, age was
found as a protective factor with respect to some urinary
symptoms, in particular obstruction. Preceding TUR-P is
associated with long-term side effects, however, of a
different nature (obstruction, hematuria). Doses at the
urethra in the on-line plan were not correlated with any
urinary symptom.

An important factor for long-term urinary toxicity is the
follow-up time leading to a significant decrease comparing
the groups with shorter (<8.5 months) and longer follow-up
times (>8.5 months) (Table 6 below). Probably, this trend
continues with this time constant, expecting a return near to
the initial level after years.

### Table 4

Urinary toxicity with respect to the key symptoms showing the scores 0–4 (according Table 2) before treatment, in the acute phase (6 weeks after implantation), in the later phase (3–21 months thereafter), and their changes. Differences of the base status between mono- and combi-brachytherapy are separately indicated. A differentiation with respect to the follow-up time is given later (Table 7)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Base status</th>
<th>Acute status (6 weeks)</th>
<th>Chronic status (3–21 months)</th>
<th>Long-term score increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary frequency (97%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mono</td>
<td>0.7 (58/19/17/6/1)</td>
<td>2.5 (5/11/26/46/12)</td>
<td>1.5 (16/37/30/13/3)</td>
<td>0.8 (43/34/17/3/3)</td>
</tr>
<tr>
<td>Combi</td>
<td>2.2 (4/30/26/22/18)</td>
<td>1.4 (22/37/26/11/4)</td>
<td>0.6 (41/29/19/11/0)</td>
<td></td>
</tr>
<tr>
<td>Nocturia (98%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mono</td>
<td>1.2 (34/31/20/10/5)</td>
<td>3.0 (2/1/17/34/37)</td>
<td>1.9 (6/38/30/17/9)</td>
<td>0.7 (43/37/17/3/0)</td>
</tr>
<tr>
<td>Combi</td>
<td>1.8 (11/36/21/25/7)</td>
<td>3.0 (4/7/30/7/52)</td>
<td>2.0 (4/43/2/21/11)</td>
<td>0.1 (57/29/7/7/0)</td>
</tr>
<tr>
<td>Dysuria (99%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mono</td>
<td>0.1 (91/5/3/0/1)</td>
<td>2.4 (20/13/10/26/32)</td>
<td>1.3 (46/17/9/13/15)</td>
<td>1.2 (49/16/10/13/12)</td>
</tr>
<tr>
<td>Combi</td>
<td>1.8 (32/4/32/18/14)</td>
<td>0.9 (57/14/18/4/7)</td>
<td>0.8 (61/18/11/3/7)</td>
<td></td>
</tr>
<tr>
<td>Pain at urination (99%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mono</td>
<td>0.0 (94/5/1/0/0)</td>
<td>1.9 (21/14/24/36/5)</td>
<td>1.0 (46/24/20/9/1)</td>
<td>0.9 (48/24/20/7/1)</td>
</tr>
<tr>
<td>Combi</td>
<td>1.7 (30/0/41/22/7)</td>
<td>0.7 (59/19/18/4/0)</td>
<td>0.6 (62/15/19/4/0)</td>
<td></td>
</tr>
<tr>
<td>Urgency (95%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mono</td>
<td>0.1 (96/20/2/0/0)</td>
<td>0.8 (65/11/0/13/2)</td>
<td>0.4 (77/10/7/4/2)</td>
<td>0.4 (80/9/6/4/1)</td>
</tr>
<tr>
<td>Combi</td>
<td>0.3 (86/70/3/0/4)</td>
<td>0.5 (78/7/41/11/0)</td>
<td>0.3 (89/4/4/0/3)</td>
<td>0.1 (93/0/4/0/3)</td>
</tr>
<tr>
<td>Pads (94%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mono</td>
<td>0.0 (98/00/0/1/1)</td>
<td>0.6 (78/6/0/11/5)</td>
<td>0.4 (85/5/0/6/4)</td>
<td>0.3 (87/5/0/5/3)</td>
</tr>
<tr>
<td>Combi</td>
<td>0.2 (93/0/0/7/0)</td>
<td>0.2 (92/4/0/0/4)</td>
<td>0.2 (92/4/0/0/4)</td>
<td></td>
</tr>
<tr>
<td>Decreased stream (obstruction) (96%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mono</td>
<td>0.7 (60/21/13/6/0)</td>
<td>2.0 (10/24/36/22/8)</td>
<td>1.3 (30/37/29/9/4)</td>
<td>0.6 (50/31/14/3/2)</td>
</tr>
<tr>
<td>Combi</td>
<td>1.1 (52/11/11/26/0)</td>
<td>1.9 (26/7/6/41/0)</td>
<td>1.3 (36/25/18/18/3)</td>
<td>0.1 (63/26/11/8/0)</td>
</tr>
<tr>
<td>Hematuria (98%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mono</td>
<td>0.0 (97/30/0/0/0)</td>
<td>0.6 (65/20/13/2/0)</td>
<td>0.1 (92/6/2/0/0)</td>
<td>0.1 (92/7/1/0/0)</td>
</tr>
<tr>
<td>Combi</td>
<td>0.4 (71/25/0/4/0)</td>
<td>0.0 (100/0/0/0/0)</td>
<td>0.1 (100/0/0/0/0)</td>
<td></td>
</tr>
<tr>
<td>Medication (alpha-blocker) (90%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mono</td>
<td>0.2 (90/2/2/6/0)</td>
<td>1.6 (39/6/11/13/0)</td>
<td>1.2 (53/3/15/29/0)</td>
<td>1.0 (59/5/13/23/0)</td>
</tr>
<tr>
<td>Combi</td>
<td>1.6 (40/4/8/48/0)</td>
<td>1.1 (54/4/17/25/0)</td>
<td>0.8 (63/4/8/25/0)</td>
<td></td>
</tr>
</tbody>
</table>

The percentages in brackets give the portion of evaluable answers for the particular item in the returned questionnaires.
The rectal toxicity (Table 7) depends in the acute phase on
the doses and seed numbers (activities) in the target volume,
even though on a low level. Long-term effects are, as expected,
correlated with dose or volume parameters of the rectum.
Finally, some statistical relationships for incontinence (urgency
and/or sphincter function) remain in the long-term analysis.
However, they result in only minor handicaps for a few patients.
Interestingly, an affected continence is also associated with
a higher number of cores during biopsy. No relevant dependence
on the follow-up time is found for the rectal toxicity.

Impairment of sexual function is in the acute phase mainly
connected with the dose distribution in the prostate (Table 7).
The most relevant correlation is found for D<sub>50</sub> (P<0.01)
suggesting that exposure of a high portion of the prostate
above 240 Gy might promote erectile dysfunction. The
responsible neurovascular structures are very close to the
laterodorsal prostate and probably more or less involved in
the high dose regions. Altogether, these correlations are
weaker than in case of the other toxicities (urinary, rectal).
Interestingly, no correlation has been found with the fact
whether or not neoadjuvant hormonal (i.e. restricted to a few
months) treatment is given. Sexual impairment slightly
increases with follow-up time (in particular erectile dysfunc-
tion, see Table 7 below).

For the smaller group of patients with combi-brachytherapy
(N=34) similar statistical correlations are seen (but statistically
less valid). Comparison of the toxicity spectrum of mono- and
combi-brachytherapy elucidates characteristic but not signifi-
cant differences (because of the small patient number). While
urinary symptoms are increased in the mono-brachytherapy
group (Table 6), chronic rectal toxicity as well as the erectile
dysfunction might be slightly increased in the combined-
brachytherapy group (but not statistically significant).

The scores evaluating acceptance and quality of life were
favourable with an acceptance or positive assessment of
85–88%, however on a subjective basis. About one third of
the patients report on a reduced quality of life (most of them
slightly). We found correlations with treatment-related
factors. In correspondence to the urinary toxicity, larger
prostate volumes and in consequence high activities, seed
and needle numbers result in a suppressed acceptance and/or
reduced quality of life (Table 6). Accordingly, the combi-
brachytherapy has the tendency to be better accepted by the
patients than the mono-brachytherapy.

Table 5
Rectal toxicity and impairment of sexual function with respect to the key symptoms (score 0–4 according Table 2). Supportiva such as Sildenafil (Viagra) are increasingly used by the patients and improve the function in about one half. The percentages in brackets give the portion of evaluable answers for the particular item in the returned questionnaires. Base status for Mono and Combi is equal, if not otherwise stated.

<table>
<thead>
<tr>
<th>Mean (% score 0/1/2/3/4)</th>
<th>Base status</th>
<th>Acute status (6 weeks)</th>
<th>Chronic status (3–21 months)</th>
<th>Long-term score increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (97%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mono</td>
<td>0.3 (71/27/1/1/0)</td>
<td>0.9 (41/42/9/2/6)</td>
<td>0.6 (55/37/4/2/2)</td>
<td>0.3 (78/17/1/3/1)</td>
</tr>
<tr>
<td>Combi</td>
<td>0.9 (36/46/11/7/0)</td>
<td>0.6 (50/43/40/0/3)</td>
<td>0.3 (72/21/7/0/0)</td>
<td></td>
</tr>
<tr>
<td>Urgency (96%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mono</td>
<td>0.0 (95/5/0/0/0)</td>
<td>0.2 (90/3/3/5/1)</td>
<td>0.1 (91/5/3/0/1)</td>
<td>0.1 (93/4/2/0/1)</td>
</tr>
<tr>
<td>Combi</td>
<td>0.4 (74/18/40/4/0)</td>
<td>0.2 (82/14/0/4/0)</td>
<td>0.1 (93/4/3/0/0)</td>
<td></td>
</tr>
<tr>
<td>Pain at defecation (97%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mono</td>
<td>0.1 (92/7/1/0/0)</td>
<td>0.5 (73/13/7/5/2)</td>
<td>0.3 (82/14/1/3/0)</td>
<td>0.2 (88/7/3/2/0)</td>
</tr>
<tr>
<td>Combi</td>
<td>0.8 (61/11/18/10/0)</td>
<td>0.6 (71/11/11/4/3)</td>
<td>0.5 (79/7/11/3/0)</td>
<td></td>
</tr>
<tr>
<td>Incontinence (sphincter weakness) (96%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mono</td>
<td>0.0 (100/0/0/0/0)</td>
<td>0.4 (75/14/6/3/2)</td>
<td>0.2 (84/11/2/2/1)</td>
<td>0.2 (84/11/2/2/1)</td>
</tr>
<tr>
<td>Combi</td>
<td>0.5 (71/18/47/0/0)</td>
<td>0.3 (89/4/40/3/3)</td>
<td>0.3 (89/4/40/3/3)</td>
<td></td>
</tr>
<tr>
<td>Mucus production (96%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mono</td>
<td>0.0 (95/4/1/0/0)</td>
<td>0.4 (77/13/7/3/0)</td>
<td>0.2 (83/13/2/1/1)</td>
<td>0.1 (89/9/1/1/1)</td>
</tr>
<tr>
<td>Combi</td>
<td>0.8 (65/14/7/7/7)</td>
<td>0.4 (75/14/4/7/0)</td>
<td>0.4 (78/11/4/7/0)</td>
<td></td>
</tr>
<tr>
<td>Blood apposition (93%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mono</td>
<td>0.0 (97/2/1/0/0)</td>
<td>0.1 (95/1/3/0/1)</td>
<td>0.1 (95/2/1/1/1)</td>
<td>0.1 (95/2/1/1/1)</td>
</tr>
<tr>
<td>Combi</td>
<td>0.3 (89/0/7/0/4)</td>
<td>0.0 (100/0/0/0/0)</td>
<td>0.0 (100/0/0/0/0)</td>
<td></td>
</tr>
<tr>
<td>Medication (laxatives) (94%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mono</td>
<td>0.0 (98/1/1/0/0)</td>
<td>0.1 (96/2/2/0/0)</td>
<td>0.0 (97/3/0/0/0)</td>
<td>0.0 (98/2/0/0/0)</td>
</tr>
<tr>
<td>Combi</td>
<td>0.0 (97/0/3/0/0)</td>
<td>0.2 (89/4/7/0/0)</td>
<td>0.2 (89/4/7/0/0)</td>
<td></td>
</tr>
<tr>
<td>Erectile function (93%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mono</td>
<td>0.8 (52/28/86/6/6)</td>
<td>2.3 (11/27/15/20/7)</td>
<td>1.9 (22/26/16/16/20)</td>
<td>1.0 (45/26/15/10/4)</td>
</tr>
<tr>
<td>Combi</td>
<td>1.0 (50/27/84/11)</td>
<td>2.8 (71/19/11/52)</td>
<td>2.6 (15/11/22/7/45)</td>
<td>1.5 (35/11/31/15/8)</td>
</tr>
<tr>
<td>Libido (90%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mono</td>
<td>0.7 (68/13/10/4/5)</td>
<td>2.3 (13/18/23/22/24)</td>
<td>1.7 (24/23/17/13)</td>
<td>1.0 (39/28/22/9/2)</td>
</tr>
<tr>
<td>Combi</td>
<td>0.9 (65/8/12/4/11)</td>
<td>2.7 (11/11/15/26/37)</td>
<td>2.2 (20/16/12/32/20)</td>
<td>1.2 (40/20/16/24/0)</td>
</tr>
</tbody>
</table>
Discussion

4.1. Toxicity of permanent seed implantation in comparison to the other options

Our study contributes to a clinical data pool to assess the acute and chronic side effects and discomfort after permanent prostate seed implantation. The largest burden to the patients is acute urinary retention requiring a catheter for a longer period (15% for the mono-brachytherapy) or even an invasive and risky procedure (~5% for the monotherapy). In comparison, Crook et al. [5] and Salem et al. [27] found similar rates of 13% for acute urinary retention after permanent prostate seed implantation. The other side effects are less severe and focussed on urinary symptoms.

A careful evaluation of this toxicity spectrum compared to the other treatment modalities such as radical retropubic prostatectomy (RRP) or external beam radiotherapy (EBRT) is a difficult task. Valid data for the toxicity of RRP on average are found in Begg et al. (11,522 men) [2].

Table 6
Factors for urinary toxicity. For the acute phase, the specific symptoms are listed. For the subacute phase, details of the grading are given in the groups if \( P < 0.05 \) (Mann–Whitney test)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Acute score increase (group differences with ( P &lt; 0.05 ))</th>
<th>Long-term score increase</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( D_{50} (D_{80}) )</td>
<td>( \leq 240 \text{ Gy}: ) less frequency, nocturia</td>
<td>Frequency ( (83/14/30) \leq 240 \text{ Gy} ) ( (71/20/63) &gt; 240 \text{ Gy} )</td>
<td>0.002</td>
</tr>
<tr>
<td>( V_{200} (V_{150}+V_{100}) )</td>
<td>( \leq 31%: ) less frequency, nocturia increased acceptance</td>
<td>Frequency ( (81/16/63) \leq 31% ) ( (74/17/63) &gt; 31% )</td>
<td>0.010</td>
</tr>
<tr>
<td>Number of seeds ( (\text{prostate volume, total activity}) )</td>
<td>( \leq 43: ) less dysuria, pain, hematuria increased acceptance increased positive opinion</td>
<td>Dysuria ( (76/5/11/9) \leq 43 ) ( (52/15/16/16) &gt; 43 )</td>
<td>0.035</td>
</tr>
<tr>
<td>Number of needles</td>
<td>( \leq 16: ) less nocturia, dysuria, pain increased acceptance</td>
<td>Pain ( (80/16/2/2) \leq 43 ) ( (63/24/13/0) &gt; 43 )</td>
<td>0.010</td>
</tr>
<tr>
<td>Age</td>
<td>( &gt; 63 \text{ years}: ) less obstruction, dysuria, pain</td>
<td>Obstruction ( (82/12/4/0) \leq 63 \text{ y} ) ( (79/16/3/2) &gt; 63 \text{ y} )</td>
<td>0.031</td>
</tr>
<tr>
<td>TUR-P</td>
<td>–</td>
<td>Hematuria ( (100/0/0/0) ) no TUR-P ( (92/8/0/0) ) TUR-P</td>
<td>0.001</td>
</tr>
<tr>
<td>Mono/combi</td>
<td>Combi: less dysuria, urgency, obstruction, increased acceptance</td>
<td>Urgency ( (97/0/0/3) ) combi ( (88/64/2) ) mono</td>
<td>0.047</td>
</tr>
<tr>
<td>Follow-up time</td>
<td></td>
<td>Dysuria ( (59/8/13/20) \leq 8.5 \text{ m} ) ( (72/11/13/4) &gt; 8.5 \text{ m} )</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pain ( (66/23/8/2) \leq 8.5 \text{ m} ) ( (81/14/60/8) &gt; 8.5 \text{ m} )</td>
<td>0.034</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medication ( (56/14/31/0) \leq 8.5 \text{ m} ) ( (73/12/15/0) &gt; 8.5 \text{ m} )</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Table 7
Factors for rectal toxicity and sexual dysfunction. See Table 6 for further explanation

<table>
<thead>
<tr>
<th>Factor</th>
<th>Acute score increase (group differences with ( P &lt; 0.05 ))</th>
<th>Long-term score increase</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( D_{140} ) (rectum) ( V_{100}, V_{80} ) of rectum</td>
<td>–</td>
<td>Incontinence ( (100/0/0/0) \leq 140 \text{ Gy} ) ( (91/6/30) &gt; 140 \text{ Gy} )</td>
<td>0.012</td>
</tr>
<tr>
<td>Number of biopsies</td>
<td>( \leq 5: ) less rectal incontinence</td>
<td>Incontinence ( (100/0/0/0) \leq 5 ) ( (94/2/2/2) &gt; 5 )</td>
<td>0.038</td>
</tr>
<tr>
<td>Number of seeds ( (\text{total activity}) )</td>
<td>( \leq 43: ) less rectal frequency</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>( &gt; 63 \text{ years}: ) less rectal incontinence, pain</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>( D_{50} )</td>
<td>( \leq 240 \text{ Gy}: ) less erectile dysfunction</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Follow-up time</td>
<td>–</td>
<td>Erectile dysfunction ( (78/16/5/2) \leq 8.5 \text{ m} ) ( (64/14/16/6) &gt; 8.5 \text{ m} )</td>
<td>0.042</td>
</tr>
</tbody>
</table>
and Steineck et al. (326 men) [32], which found considerable toxicity such as post-/perioperative morbidity (around 30%) and even mortality (0.5%), late urinary complications (20–30%) requiring interventions (mostly bladder neck obstruction or urethral strictures), and in particular long-term incontinence (20–30%). The latter must be distinguished from using protective aids because of urgency, which amounts to 4–8% in our group (Table 4), but is less affecting quality of life.

Dysuria is a typical side effect of permanent seed implantation as demonstrated in our analysis with a frequency of 10–30% [3,18]. However, the impact on QoL is moderate even in the case of dysuria scored at 3–4. Our data indicate that further temporal resolution of the symptoms is to be expected in agreement with [18], where even a time interval up to 45 months has been documented. Urinary toxicity is less often described in EBRT [10,28]. Late dysuria might be increased in dose escalation schedules with IMRT (intensity-modulated radiotherapy), e.g. Zelefsky et al. [36] describe a late ≥grade 2 urinary toxicity of 15%.

Late rectal morbidity is the dominant side effect of EBRT with variable frequency of 10–40% for ≥grade 2 toxicity after radiation doses > 70 Gy [4,10,28]. The rate of adverse effects depends crucially on total dose and irradiation technique. A steep increase of rectal toxicity is found if relevant parts of the rectal wall achieve 75 Gy [12]. Advanced radiation techniques such as intensity-modulated radiotherapy (IMRT) reduce late rectal toxicity probably below 5–10% [4]. However, these data were accumulated in monocentric studies at prominent centres, probably associated with uncommon patient selection and effort. Late rectal toxicity is not described after RRP, and moderate after brachytherapy. Grade 2 proctitis in approximately 10% [31,35] or less [16] is described until the third year after implantation. In our analysis, a chronic toxicity score ≥2 was found only in about 5% after mono-brachytherapy. Symptoms typical for EBRT (e.g. rectal bleeding) are especially rare in case of brachytherapy (here 0–3%). Our data do not indicate that late rectal toxicity increases with follow-up time, but the observation time might be still too short (requiring several years).

Sexual function is diminished after all treatment options [4,32], whereby brachytherapy is associated with the best preservation of potency (70% for mono-brachytherapy, but only <50% for combined-brachytherapy). After 2 years, 60% preserved sexual function has been found by Stock et al [33], in a 6-year interval >50% for mono-brachytherapy by Merrick et al. [17]. Our data indicate, that further decrease of potency with follow-up time cannot be excluded.

The toxicity spectrum of brachytherapy appears quite attractive, in particular if we consider that the survival curves for all three options are comparable. Potential for improvement exists for every option to reduce the toxicity further. While nerve-sparing techniques for the surgical option are limited to a particular group of patients (to improve the sexual function), improved radiation techniques such as intensity modulated radiotherapy are becoming more and more in use. Strategies to improve the seed implantation technique are outlined below.

4.2. Factors affecting the toxicity of permanent seed implantation

For the intensity of long-term urinary symptoms, the doses in large portions of the prostate volume (D30, D50, but not the maximum doses D10) or correspondingly the percentage of volumes exposed to a high dose (V150, V200) are predictive (Table 6) and are influenced by the number of seeds (for a fixed activity per seed, here 0.7 mCi) and needles. In other studies, increased urinary morbidity after seed implantation was seen in patients with large prostatic glands [29], but this connection was only marginal in our analysis. The disturbance of sexual function appears to follow similar rules (Table 7). Therefore, the high-dose part of the dose–volume histogram, in particular the gradient between D80 and D50, influences the level of urinary toxicity and impairment of potency. The urinary toxicity and potency are also influenced by age and previous TUR of the prostate. While younger men appear more sensitive with respect to urinary symptoms, they can better compensate impaired potency.

Combined-brachytherapy is associated with less urinary toxicity, especially in terms of urgency, nocturia and hematuria, clearly due to the lower mean doses in comparison to the mono-brachytherapy. On the other hand, potency is more compromised in the combined-group. This indicates that the influence of the external radiotherapy is more important with respect to the erectile function (obviously because of the higher dose exposition to the surrounding tissue, e.g. the supplying vessels of the penis). We note that in both groups about half of the patients with disturbed potency respond to Sildenafil or comparable agents.

Positive assessment of the brachytherapy and QoL is correlated with factors influencing the urinary toxicity. Basically, all factors increasing the volume of the prostate exposed to a high radiation dose will reduce the acceptance, such as prostate volume (>30 ml), number of seeds (>43), number of needles (>16), total activity (>30 mCi), and V200. In particular, the combined patient group considers the treatment more positive than the mono-group.

We conclude that a shift of the dose–volume histogram to the left is desirable. First, one should minimise the number of seeds by inclusion of D50 (or other index doses) into the optimisation process. However, there are mathematical limitations. Second, decreasing the activity per seed (and increasing the seed number accordingly) might result in a more homogeneous dose distribution, which reduces the percentage of the prostate volume with excessively high
doses. Note that other groups achieve typical values for $V_{150}$ of 50–60% (instead of 60–75% according to Table 2) with lower seed activities. However, the ‘optimal’ activity per seed is a matter of discussion. On one hand, this step increases the costs of the brachytherapy [14]. On the other hand, there is also a trade-off between homogeneity, target coverage and protection of the central parts (urethra). In an optimisation model, D’Souza and Meyer [6] found the best activity choice between 0.4 and 0.5 mCi per seed. However, in another recent analysis the range was 0.4–0.6 mCi per seed in order to spare the urethra and to cover the target volume [30].

For late rectal toxicity (Table 7), we found as predictive factors the maximum dose in the rectum ($D_{1\text{ ml}} < 140\text{ Gy}$) or the rectal volume exposed to the prescription dose (should be $<0.14\text{ ml}$). Interestingly, the number of biopsy cores has some influence, probably because biopsies are performed transrectally and might leave a pre-injury, which adds to the consecutive radiation effects. The rectal toxicity is slightly higher in the combined-group. However, the influence on QoL is minor, and further optimisation with respect to the rectum load appears not of high priority.

In summary, the toxicity, acute as well as long-term, of the present study is quite acceptable in comparison to the other treatment options (RRP, EBRT). Our analysis suggests that the tolerance might be further improved in terms of urinary morbidity, potency and quality of life by taking into account $D_{30}$ and, maybe, by slightly decreasing the mean activity per seed, e.g. down to $\sim 0.6\text{ mCi/seed}$, in order to reduce the high-dose parts ($>240\text{ Gy}$) of the prostate. The late morbidity of the rectum is minor, but can be independently reduced by considering the high-dose parts of the rectum ($>140\text{ Gy}$). Combined-brachytherapy is even better accepted than mono-brachytherapy.

**Acknowledgements**

The authors acknowledge the generous support by the Liselotte Beutel Foundation.

**References**


