ELSEVIER

Radiotherapy and Oncology 74 (2005) 137–148

RADIOTHERAPY & ONCOLOGY
JOURNAL OF THE EUROPEAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY

www.elsevier.com/locate/radonline

GEC/ESTRO-EAU recommendations on temporary brachytherapy using stepping sources for localised prostate cancer

György Kovács[a,*], Richard Pötter[b], Tillmann Loch[c], Josef Hammer[d], Inger-Karine Kolkman-Deurloo[e], Jean J.M.C.H. de la Rosette[f], Hagen Bertermann[g]

[a]*Interdisciplinary Brachytherapy Centre, University Hospital Schleswig-Holstein Campus Kiel, Arnold Heller Str 9, D-24105 Kiel, Germany*
[b]*University Clinic for Radiotherapy and Radiobiology, Vienna General Hospital, Vienna, Austria*
[c]*Department of Urology, University of the Saarland, Homburg, Germany*
[d]*Department of Radiotherapy, Barmherzige Schwestern Hospital and St Vincenc Clinic, Linz, Austria*
[e]*Division of Clinical Physics, Department of Radiation Oncology, Erasmus MC, Daniel Den Hoed Cancer Center, Rotterdam, The Netherlands*
[f]*Department of Urology, AMC, Amsterdam, The Netherlands*
[g]*Department of Urology, City Hospital, Kiel, Germany*

Received 3 August 2004; accepted 2 September 2004
Available online 22 October 2004

Abstract

Background and purpose: The aim of this paper is to present the GEC/ESTRO-EAU recommendations for template and transrectal ultrasound (TRUS) guided transperineal temporary interstitial prostate brachytherapy using a high dose rate iridium-192 stepping source and a remote afterloading technique. Experts in prostate brachytherapy developed these recommendations on behalf of the GEC/ESTRO and of the EAU. The paper has been approved by both GEC/ESTRO steering committee members and EAU committee members.

Patients and methods: Interstitial brachytherapy (BT) to organ confined prostate cancer can be applied as a boost treatment in combination with external beam radiation therapy (EBRT) using a proper number of BT fractions in curative intent. Temporary transperineal BT alone or in combination with EBRT are feasible as a palliative/salvage treatment modality because of local recurrence, however, without large clinical experience. The use of temporary BT as a monotherapy is subject of ongoing clinical research.

Results: Recommendations for pre-treatment investigations, patient selection, equipment and facilities, the clinical team, the implant procedure (treatment planning and needle implantation) dose and fractionation, reporting, management of side effects and follow-up are given.

Conclusions: These recommendations are intended to be technically and advisory in nature, but the ultimate responsibility for the medical decision rests with the treating physician. Although, this paper represents the consensus of an interdisciplinary group of experts, TRUS and template guided temporary transperineal interstitial implants in prostate cancer are a constantly evolving field and the recommendations are subject to modifications as new data become available.

Keywords: Prostate cancer; HDR-brachytherapy; Transrectal ultrasound; Stepping source technology; Afterloading; Recommendations

1. Introduction

The proportion of patients treated by brachytherapy is rapidly increasing over the past years, and both permanent seed implants and temporary afterloading techniques play an important role in the treatment of localised prostate cancer [2,6,19,30,56]. To achieve an appropriate quality for permanent seed implants and to synchronise activities in this multidisciplinary field GEC-ESTRO/EAU/EORTC recommendations for permanent implants were previously published [2]. The following recommendations on temporary transperineal prostate brachytherapy, contain a summary of the experience in prostate BT of a small group of brachytherapy experts and urologists on behalf of the GEC/ESTRO-EAU Prostate Brachytherapy Group (PROBATE);

* Corresponding author.

0167-8140/$ - see front matter © 2004 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.radonc.2004.09.004

they are intended to form a basis for an appropriate use of this treatment modality.

Remote temporary afterloading brachytherapy has several advantages:

accurate positioning of the source by first implanting non-active guide needles,
possibility to choose the source positions over the length of the needle,
no target movement during radiation,
stepping source technology allowing for dose and volume adaptation due to adjustment of source dwell locations and times according to 3D imaging based individual dose prescription before irradiation [68].

Temporary brachytherapy using a stepping source does not need any source preparation time and there is full radiation protection. It also allows fractionated irradiation and volume optimisation of the target dose distribution. If BT and complementary EBRT are the chosen treatment, the costs of temporary BT are low. Introducing a remote afterloading technique combined with the technological developments in sonography devices, such as transrectal ultrasound (TRUS), as well as treatment planning software developments result in an appropriate target delineation and guidance of the needles [37,52]. A high quality of the treatment planning and delivery of dose to the target can be achieved [22].

Disadvantage of temporary BT-implants:

temporary BT-implants require usually a fractionated schedule which results in more work load per patient.

Temporary transperineal implants for prostate cancer have been applied since the mid 80's in an increasing number of centres worldwide. Clinical experience has been built up progressively, and the technique appears nowadays to be safe and effective [4,9,20,23,49,50,52,53].

However, the value of temporary BT and its clinical benefit compared to low-dose rate BT have not been demonstrated in randomised clinical studies. To allow relevant comparative information on clinical results, it is essential that patient data and treatment parameters are described in a similar way for permanent and for temporary implants.

An important radiobiological issue is the evaluation of biological weighting factors to apply to compensate for the differences in dose rate and time factors. Some models have been proposed but their validity and relevance for the treatment of prostatic adenocarcinoma need to be further assessed [70]. Furthermore, as the available radiobiological data do not allow definitive conclusions about the relative efficacy of temporary BT compared to other radiation treatment modalities, comparison of clinical data is required. However, radiobiological data and considerations indicate that a low alpha/beta value (<2 Gy) might be appropriate for the relative value of temporary brachytherapy with a high fraction dose. If such values are appropriate, the relative efficacy of temporary BT with a high-dose per fraction would be pronounced [11,21,35,36]. High-dose-rate brachytherapy might be then expected to produce results comparable to or better than those from low-dose-rate implants. However, using temporary implants exclusively for treatment of localised prostate cancer has not been tested clinically in a sufficient amount of patients with appropriate follow-up. Delivering the total dose exclusively in a few very high-dose fractions (one or two) is not recommended because of radiobiological disadvantages, e.g. inadequate tumour reoxygenation and normal tissue damage [63]. In any case, the application and evaluation of biological weighting factors is recommended for comparison of results and will be guided by the increase of clinical experience with longer follow-up.

Developments in remote afterloading brachytherapy (temporary BT) devices and technology as well as in transrectal sonography resulted in highly sophisticated tools in the field of interstitial treatment of localised prostate cancer. There is a wide consensus today, that TRUS guided transperineal template implant techniques represent the standard of interstitial prostate brachytherapy with an accurate needle placement [4,7,12,27,60].

Due to the excellent dose distribution of BT implants using a stepping source and anatomy related dose optimisation (adaptation of dwell locations and dwell times to the target and no impairment from oedema, from source migration, and from prostate movement during the short time interval of the boost application) and due to the significant low costs of remote afterloading treatment, BT boosts with a stepping source in combination with EBRT seems to be challenging treatment option for a selected group of patients (Tables 1 and 2).

Long-term follow-up data confirm that temporary BT boost combined with EBRT represents a successful treatment choice and results in excellent bNED, local control and survival rates (Table 2). The treatment seems to be especially advantageous for patients in intermediate and poor prognostic groups (iPSA >10 ng/ml or Gleason >7 or Stage $>$ T2a).

Table 1
Patient selection criteria for a curative combined TEMPORARY BT and EBRT treatment

Inclusion criteria	Stages T1b–T3b
	Any Gleason score
	Any iPSA without distant metastases
Exclusion criteria	Volume >60 cm^3
	TURP within 6 months
	Infiltration of the external sphincter of the bladder neck
	Significant urinary obstructive symptoms
	Pubic arch interference
	Rectum-prostate distance on TRUS <5 mm
	Lithotomy position or anaesthesia not possible

Table 2
Results of temporary BT boost in the treatment of localised prostate cancer

	n/*n*T3	mPSA	mFU	mG	bNED (%)	PSA def.	G3 GU/GI
Borghede et al. [9]	50/13	n.d.	45	7	78	<1–2 ng/ml	8%
Dinges et al. [20]	82/61	14	24	n.d.	53	<1 ng/ml	7%
Kovács et al. [39]	189/63	16	78	7	78	<1 ng/ml	2.7/2.9%
Martinez et al. [50]	161/21	9.9	34	7	67	ASTRO cons.	5%
Mate et al. [53]	104/11	8.1	46	6	60	ASTRO cons.	n.d.

Temporary BT, transperineal TRUS guided prostate brachytherapy with a stepping source; *n*/*n*T3, total number of patients/number of T3 patients; mPSA, mean initial PSA (ng/ml); mFU, mean follow-up (months); mG, mean Gleason score; bNED, biochemical freedom of recurrence; PSA def., PSA definition of biochemical freedom of recurrence; G3 GU/GI, EORTC/RTOG scale G3 side effect genitourinary/gastrointestinal; n.d., no data available.

Some of following paragraphs (in chapter 1 and 2) refer to issues not different for permanent or interstitial implants. If appropriate, recommendations as published previously for permanent implants were taken, they are particularly indicated and referred to [2].

1.1. Pre-treatment investigations

For comparison of treatment outcome, it is essential that pre-treatment investigations be identical for patients treated with permanent implants and temporary BT for prostatic carcinoma. Therefore, the recommendations for temporary BT should be identical to those for permanent seed implantations [2].

'All patients should have a history and general physical examination to assess their suitability to the treatment. Local and if needed (initial PSA > 10 ng/ml) systemic staging should be completed' [2].

1.2. PSA

'Initial PSA should be recorded in all patients' [2].

1.3. Transrectal ultrasound (TRUS)

TRUS of the prostate should be performed on all patients by an expert (usually the urologist) to more accurately assess the local extent of disease. In the hand of experienced users, TRUS is still one of the most sensitive imaging methods to determine local extent of prostate cancer [5,17, 33,42,45,62], especially if the histologic biopsy information is present. Imaging of the zonal anatomy of the prostate gland is an important factor in defining different target areas within the gland [5,10,22,25,53]. Also the knowledge of extra-capsular disease and its localisation are extremely useful for treatment planning [4,10,22,25,39,53]. Additionally, TRUS may serve as a substitute for CT in most patients regarding the detection of pubic arch interference [71].

1.4. Prostate biopsy

'All patients should have TRUS guided biopsy proven adenocarcinoma It is usual to take six to 12 biopsy cores with ultrasound guidance' [2]. The use of TRUS improves the biopsy results and can utilise valuable information for treatment planning. The percentage of positive biopsies seems to be a strong prognostic factor [41,47,64].

1.5. Bone scan

If the probability of bone metastases is < 5% according to the Partin tables, bone scan is not obligatory [58].

1.6. CT scan/conventional MRI of the pelvis (not mandatory)

These imaging methods have a moderate value in assessing the local extent of prostate tumours. PSA values according to the Partin tables give more information on micrometastatic disease. MRI is useful in detecting nodal enlargement.

1.7. Pelvic MRI with endorectal coil (not mandatory)

This is one of the most sensitive imaging investigation to assess local extent of prostate cancer [2]. The knowledge of extra-capsular disease and its localisation is extremely important for further treatment decisions; however, TRUS is the general practice in local staging.

1.8. Surgical lymph node staging (not mandatory)

There is controversy about the benefit of surgical lymph node sampling, in particular, in patients with poor prognostic factors [20,23]. Temporary BT may be used in combination with external beam radiation therapy (EBRT) and regional lymph nodes then represent a potential target of radiation treatment. However, there is no clear evidence from clinical trials, showing advantage or disadvantage of surgical lymph node sampling with regard to therapeutic outcome.

1.9. Urodynamic studies

Lower urinary tract symptoms (LUTS) have to be evaluated before therapy and the patient has to complete an International Prostate Symptom Score (IPSS) or AUA symptom-scoring sheet. 'Maximum urinary flow rate

and post voidal residual urine should be measured and reported in patients with significant symptoms' [2]. The IPSS score should be below 12.

2. Patient selection

The most important prognostic factors with the highest impact on disease free survival are initial PSA, Gleason score (or WHO grade) and stage. For functional outcome, the initial prostate volume and lower urinary tract symptoms, best characterised by the IPSS score, provide the best guide. Indication for treatment is histologically proven localised or locally advanced prostate adenocarcinoma with a volume of the gland smaller than 60 cm^3 and with a distance to the rectal mucosa greater than 5 mm. An interval from the last surgical intervention (like TURP) longer than 6 months is advisory to reduce the chance of incontinence as severe late normal tissue injury. Furthermore, TRUS or MRI should exclude infiltration of the external sphincter or bladder neck. Patients with $>50\%$ positive probes of sextant biopsy seem to be associated with higher rates of 5-year PSA failure following permanent implant monotherapy [41]. Combined EBRT and temporary BT boost is effective in low-risk patients (T2a, initial PSA $<$ 10 ng/ml, Gleason score $= <6$) but these patients do also well with permanent brachytherapy alone, so for this patient cohort seed treatment may represent an adequate option. If low-risk patients are treated with a combined EBRT and interstitial brachytherapy boost schedule, dose and treatment time usually do not vary from other prognostic groups, however, total treatment time is longer than using permanent implants. So far there is no prospective randomised study available comparing these different types of radiation treatment. The highest advantage of EBRT + temporary BT seems to be given in intermediate- and high-risk patients ($>$T2a or PSA >10 ng/ml or Gleason >6). According to retrospective evaluations of treatment results in different prognostic groups (two factors) in high/intermediate risk cases, the long-term treatment results of combined EBRT and permanent (LDR) brachytherapy or temporary BT as a local boost seem to be favourable [9,23,49,50,53,59,65,66]. Temporary BT alone is not yet a standard treatment, but subject to clinical investigations [51,73].

2.1. The role of PSA

Prostate specific antigen (PSA) is a strong prognostic factor and initial PSA (iPSA) correlates with outcome [74]. There is consensus in literature ('ASTRO consensus'), that the use of three consecutive values reduces the risk of falsely declaring biochemical failure due to 'bouncing' PSAs. This phenomenon results when sequential PSA determinations show one or two rises followed by a fall and a subsequent rise again [1]. Many authors [16,59,69] have shown, that in patients treated with conventional EBRT with iPSA >10 ng/ml, the PSA failure rate was 50% or higher. Patients with iPSA >10 ng/ml have a higher probability in both, in extra-capsular invasion as well as in the treatment failure rate and, therefore, they are not suitable for interstitial treatment alone. In these cases, it is advisory to combine brachytherapy treatment with external beam radiotherapy [59,60]. PSA values for selection of patients for temporary brachytherapy may vary from <10 to >20 ng/ml, in any case they should be <50 ng/ml because of high risk of distant spread in this subgroup.

2.2. The role of Gleason score

The most common used grading systems are the Gleason Score System and the WHO System. Grading has been shown to be predictive of the metastatic potential and of the prognosis of the patient. Patients with Gleason score of 6 or less have a favourable prognosis, and do well with brachytherapy alone (usually permanent implants), patients with Gleason score of 7 have an intermediate prognosis, and patients with Gleason score 8–10 a poor prognosis. Temporary brachytherapy in combination with external beam therapy is often considered for patients with intermediate or poor prognosis as indicated by Gleason score. It has been also found that tumour grade may not be an accurate predictor of the overall clinical course. This may be due to sampling error as well as to importance of other prognostic factors, such as volume, stage and PSA level [14,15,34,65].

2.3. The role of clinical stage

In the pre-PSA era, clinical stage determined by digital rectal examination (DRE) was found to be a strong predictor of local control. It is now generally accepted, that DRE is associated with a high rate of underestimating true extent of prostate tumours. The incidence of unsuspected capsular penetration ranges from 25 to 65%. PSA and Gleason/WHO score are more important in defining prognostic groups than clinical stage.

There is a considerable degree of uncertainty regarding the value of imaging modalities for clinical staging. Several studies showed that transrectal ultrasound (TRUS) is helpful in detecting extra-prostatic extension with an accuracy of 50–60% [5,14,17,33,45,62]. The guidelines of the AJCC 1998 Staging System for Prostate Cancer [72] imply that palpable T2 lesions should be classified as T3-stage in case of TRUS or MRI indicating extra-capsular or seminal vesicle invasion. Patients presenting with clinical stage T2a–c or T3 are regarded as candidates for temporary brachytherapy.

2.4. The role of urinary outflow, IPSS

The patient symptom score before treatment seems to be one of the most important predictors of urinary morbidity

after treatment. Patients with residual urine volume > 50 cm^3, IPSS > 12 and Q_{max} < 15 cm^3/s are high risk candidates for treatment related impairment.

2.5. The role of prostate volume

In general, interstitial implants in prostate volumes larger than 60 cm^3 are associated with a higher risk of side effects A prostate volume > 60 cm^3 is usually not eligible for implantation. Pre-implant TUR is certainly not indicated for downsizing, as TUR represents one of the most important predictive factors contributing to serious urinary morbidity. Hormonal treatment for downsizing (due to reducing benign prostate hyperplasia volume) is indicated before brachytherapy in case of large volume prostate. Prostate volume reduction of 30% can be achieved after 3 months of hormonal cytoreduction treatment [7]. Patients with prostate larger than 60 cm^3 have also a high probability of pubic arch interference, complicating needle implantation.

3. Contra-indications

Combined EBRT and temporary BT is not indicated (a) in patients with a life expectancy shorter than 5 years, (b) in patients with regional and/or distant metastatic disease, (c) in patients with < 6 months interval to TURP, (d) in patients with a large prostatic volume defect after a previous TURP, (e) if distance between tumour and rectal mucosa < 5 mm, (f) if patient has general contraindications for appropriate anaesthesia and/or operative treatment, (g) if it is to be expected, that treatment cannot be completed because of technical problems due to anatomical abnormalities, (h) if there are contraindications for complementary external beam treatment in case of combined EBRT + temporary BT was indicated.

4. Potential indications and investigational treatments

4.1. HDR-brachytherapy alone

In patients with localised prostate cancer (T1b, T2a) presenting with favourable prognostic factors (iPSA < 10 ng/ml, Gleason max. 6) who have an 80% or greater probability of localised disease, temporary BT alone may be performed using appropriate fractionation to reach the optimal therapeutic ratio (investigational treatment) [51,73]. For patients with higher Gleason scores and higher PSA values, the risk of disease outside the prostate capsule increases. In these situations, temporary BT alone is not indicated.

4.2. HDR-BT for salvage after failure of surgery, primary hormonal treatment or EBRT

Salvage implantation in locally progressive prostate cancer after radical prostatectomy, with or without adjuvant EBRT, represents a feasible method. In locally recurrent disease EBRT has been shown to have some impact on the course of disease [13,55]. Very limited experiences are published regarding salvage permanent BT [3,48,67]. Early reports claim the feasibility of salvage temporary BT with or without complementary EBRT [46,57], however, such procedure should be applied only within prospective clinical trials. In case of implantation local disease has to be proven by biopsy and has to be visible by TRUS for target definition.

Biopsy proven local failure after EBRT in principle is suitable for salvage implantation. However, the risk of side effects is significantly higher than for brachytherapy as first line treatment and for brachytherapy as salvage treatment after radical prostatectomy (RPE). Furthermore, there is hardly any experience reported. Therefore, such procedure is not recommended in general and should be restricted to experienced hands and prospective protocols.

In the case of failures after primary hormonal monotherapy in localised prostate cancer, temporary implants with complementary EBRT is feasible, however, clinical results are not yet analysed.

4.3. Neo- and adjuvant hormone therapy (HT)

Hormonal treatment has a significant role in reducing prostate volume before treatment ('down-sizing') due to reducing BPH (benign prostate hyperplasia) volume of the gland.

The role of short course neo-adjuvant hormonal therapy combined with EBRT and temporary BT (dose escalation protocol) is under investigation. So far there is no significant advantage of short hormonal treatment observed in dose escalation studies (total biologic effective dose > 70 Gy) with regard to long-term results [24,50]. On the other hand, some groups using EBRT combined with HT and applying much lower total radiation doses showed a significant benefit for such combination [8,28,40].

5. Preconditions for temporary (HDR) brachytherapy

5.1. Equipment

Equipment for temporary BT for prostate is in some part similar to the equipment needed for permanent seed implants. The most common technique to perform prostate implants is the transperineal technique, guided by transrectal ultrasound. Minimum requirements are: (a) adequate TRUS unit with template and an adequate treatment planning software, (b) a TRUS fixation and stepping unit

with adequate fixation avoiding movements (c) an implantation room and brachytherapy suite with adequate shielding to perform the HDR treatment, according to national radiation protection rules, (d) an afterloading unit with a high-dose-rate stepping source, (e) a fluoroscopy device to perform images in treatment position for radiographic control of needle (f) a monitor system for patient observation during the performance of brachytherapy.

CT or MRI after implantation may be additionally used for treatment planning using other implantation techniques (flexible templates and/or the use of flexible needles), which are also described in literature. However, these techniques have only been reported with brief follow-up and incomplete outcome data for patients [18,29].

5.2. Facilities

Brachytherapy has to be performed in a centre, which is licensed for high-dose-rate stepping source BT treatments. The treatment room has to fulfil national regulations in radiation protection for performance of temporary BT. There has to be access to anaesthesia and sterilisation facilities.

5.3. Radiation protection

For temporary BT of prostate cancer the general radiation protection rules concerning operation theatre, patient handling and performance of temporary BT are in principal the same as for other types of remote afterloading (e.g. in gynaecology). Depending on local facilities, treatment is performed in a dedicated room for temporary BT or in a shielded operating theatre. However, it is recommended to perform the active phase of brachytherapy treatment without additional patient transportation.

The average photon energy of the iridium-192 source is over 300 keV and makes the situation with regard to radiation protection completely different from permanent implants where iodine-125 and palladium-103 seeds are used with a photon energy less than 30 kV. From the nursing point of view the main difference is, that seeds remain in the body of the patient, while temporary BT patients do not carry any activity outside the treatment room.

5.4. The clinical team

HDR brachytherapy needs an experienced team to perform treatment planning and delivery, and to control all issues necessary for a successful clinical treatment The interdisciplinary team should be experienced in prostate interventional procedures, in TRUS (urologist, radiologist, or radiation oncologist), and in interstitial HDR brachytherapy and should in principle consist of a radiotherapist, a urologist, and a medical physicist. The urologist should evaluate the urological status (clinical tumour stage, prostate volume, IPSS, urinary flow and residual urine volume) and exclude together with the radiation oncologist contraindications for transperineal TRUS guided brachytherapy. These findings need to be discussed within the interdisciplinary team. Documentation of the brachytherapy treatment must be performed according to national standards. It is helpful, by starting with this special treatment modality to have a radiotherapist experienced in prostate temporary brachytherapy, on-site during the first 3–5 implant procedures. In addition, a centre or courses on TRUS and/or brachytherapy should have been visited.

6. Implant procedure

6.1. Treatment planning

Temporary BT by using a stepping source offers the possibility to deliver a high boost dose to a well defined volume with high precision and a rapid decrease of dose to nearby critical structures, which are transprostatic urethra, rectal wall and bladder base/bladder outlet. Transprostatic urethra is visible (for example, with a Foley catheter placed into the bladder) on TRUS images, rectal wall will be defined as the muscle layer outside the mucosa. Since there are different both critical structures (urethra) and target areas within the prostate, it seems to be advisory to define different planning target volumes (PTV) within this organ [10,25,53]. The detectable tumour and the peripheral zone represent the regions with the highest tumour load, whereas the transitional zone and the central zone usually have a much lower tumour infiltration rate.

The prostate clinical target volume (prostate CTV 1) will be represented by the whole prostate gland visible on 5 mm separated TRUS images, often without safety margins, ‘prostate surface’ (Figs. 1–4). There are different target and treatment philosophies in literature: for the whole gland (CTV 1) some groups apply a homogenous needle distribution using inter needle spacing of 10–15 and 5 mm space from the prostate circumference followed by planned hot-spots in visible tumour infiltration areas (tumor CTV 3), as well as well-placed low-dose areas according to critical structures [10,53]. Other groups use the same homogenous needle distribution within the prostate gland and a homogenous dose distribution [20] and CT based post-implant planning containing ‘hot’ areas [22,29] without relation to a specific intraprostatatic CTV (Figs. 2 and 3). Finally, some groups use a low number of needles (mean 8) placed into the peripheral zone, which is the most frequent place of tumour origin and indicate beside the whole prostate CTV 1 a CTV related to the peripheral zone (CTV 2) [25] (Fig. 1). Independent from the geometry and number of inserted needles the fraction dose on the prostate surface (CTV 1) is very similar in the majority of groups: 6–10 Gy (range 3–10). Due to the planned inhomogenities, the isodose encompassing visible tumour infiltration areas (CTV 3) and the peripheral zone (CTV 2) may differ

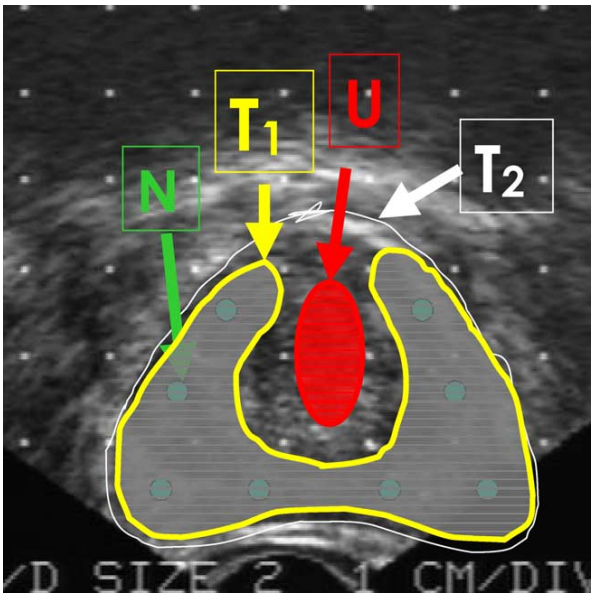

Fig. 1. Needle (source) positioning (A)—low number of needles; target is the peripheral zone. U, course of the transprostatic urethra (critical organ); CTV2, peripheral zone, representing the border of the anatomical region in the prostate with highest tumour load; *N*, planned needle positions; CTV1, capsule of the prostate, representing the border of the prostate as clinical target.

considerably depending on the technique applied: it is, e.g. 15–20 Gy per fraction in Fig.4 (∼200% of the dose in CTV 1) and <125% in Fig. 3.

Since no remarkable differences in both reported outcome and side effects have been reported so far between different treatment planning philosophies if similar risk groups are compared, the importance of these target dose

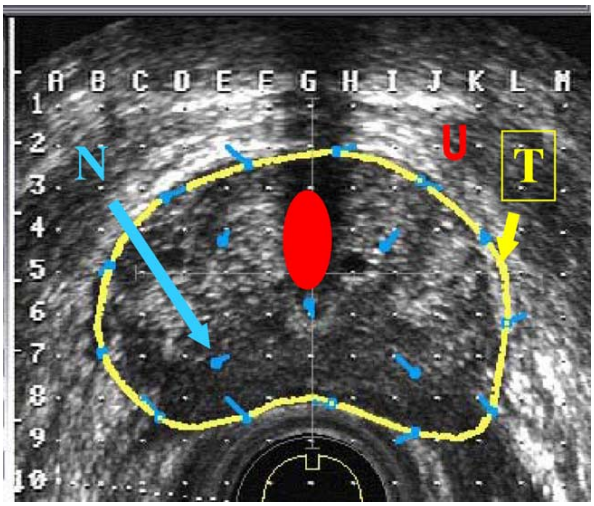

Fig. 2. Needle (source) positioning (b)—high number of needles; target is the prostate capsule. U, course of the transprostatic urethra (critical organ); CTV1, (whole prostate gland as clinical target; *N*, planned needle positions; (Courtesy of G. Edmundson, William Beaumont Hospital, Royal Oak, Michigan, USA).

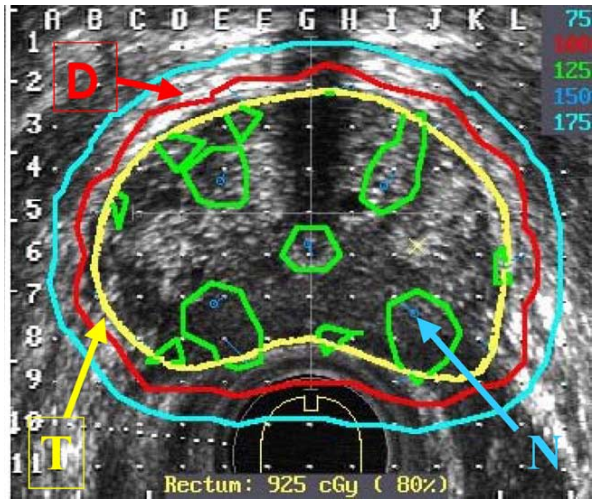

Fig. 3. Typical dose distribution using high number of needles (see Fig. 2). D, prescribed dose for CTV 1 (100%); CTV1, prostate gland as target; *N*, needles; (Courtesy of G. Edmundson, William Beaumont Hospital, Royal Oak, Michigan, USA).

inhomogeneities is not yet well understood. Regarding fraction size in a dedicated target recent radiobiological findings (low alpha/beta for prostate cancer) suggest that hypofractionation in HDR may have its opportunities for widening the therapeutic window, but also has its limits [63].

Urethral doses < 10 Gy/fraction and rectal doses < 6 Gy/-fraction are well tolerable at a certain point or in a limited volume, which should be precisely stated. They have to be kept within the accepted overall tolerance levels of these organs [10,20,25,50,53]. It is advisory to keep the maximal

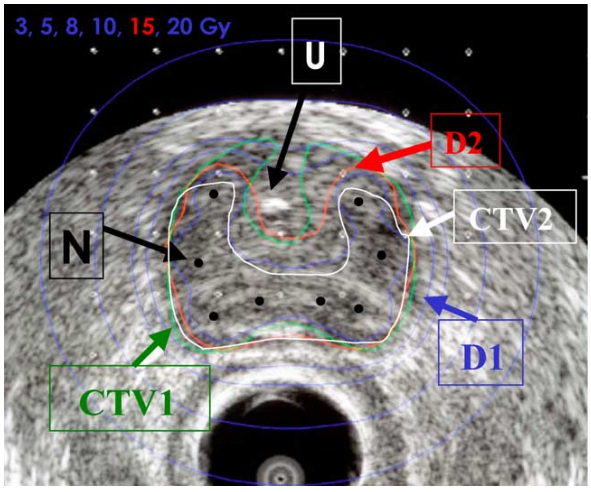

Fig. 4. Typical dose distribution using low number of needles (see Fig. 1). D, reference isodose (15 Gy); CTV1, capsule of the prostate, representing the border of the prostate as clinical target; CTV2, peripheral zone, representing the border of the anatomical region in the prostate with highest tumour load; D1, prescribed dose for CTV1 (10 Gy); D2, prescribed dose for CTV2 (15 Gy); U, marked urethra; *N*, needles.

urethral dose per fraction under 120% of the MTD [53]. There are no literature data on temporary BT-induced erectal dysfunction, but in permanent brachytherapy the radiation dose delivered to 50% to the bulb of the penis is recommended to be <50 Gy to minimise post-treatment potency impairment [54]. Evaluation of potency rate related to bulb dose in combined EBRT + temporary BT is necessary in cohorts with long follow-up (min. 10 years).

Treatment planning can be performed as pre-planning some days before implantation or as intra-operative on-line planning in the operation theatre or as a CT—based post-implant procedure. However, on-line planning seems to be advantageous in terms of patient comfort. A treatment planning system has to be available, which has been appropriately tested before first application. As mentioned above, there are different methods of applied needle geometry and target dose homogeneity, as well as differences in target definition [4,10,20,38,39,49,53]. Beside the prostate capsule (CTV 1) the peripheral zone should be delineated (CTV 2) and, if possible, regions infiltrated by macroscopic tumour (CTV 3) as these seem to be the most important boost target volumes inside the prostate. For pre-treatment planning purposes, the patient has to be in a lithotomy position identical to that used for the implant procedure. Axial TRUS images in steps of 5 mm distance from base to apex of prostate using the stepping unit are necessary, nowadays supplemented by coronal and sagittal views. The co-ordinates of the template appear on each section and this can be used as imaging basis for the 3D pre-treatment planning procedure defining the coordinates of the needles and the source dwell times and source positions. In treatment situation, identical position of patient and prostate has to be achieved. In case of relevant deviations (on-line) corrections can be performed. The use of a stepping source and inactive guide needles in afterloading technique allow for planning needle positions and dwell times dependent on the specific demands with the needles in place. If there is, for example, macroscopic infiltration of the latero-posterior capsule left a higher dose may be applied in this area by prolonging dwell times or increasing dwell locations. This will result in a higher dose in this area (CTV 3 for GTV) by increasing the high-dose volume around one or more needles ('boost-in-boost strategy').

The physicist/dosimetrist and radiation therapist calculate the dwell times and dwell positions for each needle to provide an appropriate dose distribution for the CTV(s) with lower doses to the urethra, bladder base and rectal wall.

Placement of needles first to peripheral locations is advocated. The use of on-line treatment planning and later placement of further needles according to the actualised dosimetry data was introduced by some of the temporary BT groups. Consequent use of intra-operative on-line treatment planning resulted in a significant reduction of the operator dependence and led to a higher uniformity of treatment plans [22].

6.2. Needle application

For the application of needles, general or spinal anaesthesia is needed. The patient is placed in lithotomy position and a Foley catheter is placed into the urinary bladder. If a pre-planning method is used, the position of the patient and the template position should reproduce the positioning identical to the pre-plan images. Contrast medium gives visualisation of the bladder on fluoroscopy. The sonography unit with its first plane at the base of the prostate is in the planned position of the needle tips. The needles are inserted transperineally under direct sonographic control. If the needle tip position deviates more than 3 mm compared to the pre-planning coordinates on the template, on-site planning has to be performed according to the new needle coordinates. After completing the implant, if in vivo dosimetry is to be performed, positioning of the in vivo dosimetry catheters into the transprostatic urethra and the rectum follows under fluoroscopy control. Orthogonal radiographs of the implant are recommended for documentation purposes. In the procedure of needle placement it is important to know, that usually the first source position is 2.5 mm backwards from the tip of the needle. With deflating the water balloon of the probe, or extraction of the motor unit of the TURS device one can achieve additional distance between the basal needle line and the rectal mucosa resulting in a lower rectal dose as seen on US. Performing the active phase of the treatment not immediately after the implantation procedure, regular control of needle geometry (e.g. X-rays) and, if necessary, modifications in dosimetry is recommended before each fraction. After completing the treatment, the needles and the dosimetry devices can be removed, followed by tamponation/compression of the perineal region. After 6–8 h, the Foley catheter can be removed.

6.3. Brachytherapy dose and fractionation

It is recommended that adequate information be recorded to give a consistent description of dose and fractionation in the implant. Different fractionation schemes with different target volumes (prostate capsule, peripheral zone, TRUS visible tumour volume) are reported in literature (Table 3). The most common prescribed temporary BT fraction doses covering the whole prostate are 6–10 Gy per fraction (range 3–10) to the prostate surface with a total brachytherapy dose of 12–20 Gy in 2–4 fractions combined with a conventional fractionated EBRT of 45–54 Gy, applied in 6–7 weeks. For the peripheral zone prescribed doses go up to 15–20 Gy per fraction. Due to different application techniques, e.g., a new implantation procedure for each fraction or one implant and fractionated loading of needles, the reported inter-fraction times vary from a few hours to 14 days in literature. This interfraction time and the overall treatment time should be clearly stated although the clinical relevance of this differences is unknown due to lack of prospective trials

Table 3
Prostate target dose variations in temporary BT of localised prostate cancer

	EBRT	#BT fx	Gy/fx	Target
Borghede et al. [9]	50	2	15	Tumor volume (CTV3)
Dinges et al. [20]	45	2	10	Prostate capsule (CTV1)
Kovács et al. [39]	40/50	2	15	Peripheral zone (CTV2)
Martinez et al. [49]	45	3	5.5–10.5	Prostate capsule (CTV1)
Mate et al. [53]	50.4	4	3–4	Prostate capsule (CTV1)

Temporary BT, transperineal TRUS guided prostate brachytherapy with a stepping source; EBRT, external beam radiation dose (Gy); # BT fx, number of brachytherapy fractions; Gy/fx, dose of one brachytherapy fraction.

and to the fact that retrospective studies have not yet shown any significant differences in outcome. For assessment of the total biological effect of dose and fractionation the use of a biological model is recommended [11].

6.4. Recording and reporting EBRT + stepping source temporary brachytherapy

The ICRU recommendations for recording and reporting brachytherapy applications should be followed as much as possible [32]: GTV, CTV, total reference air kerma (TRAK); description of implantation technique and loading pattern; prescribed dose (PD) per fraction and total dose, treated volume (TV), minimum target dose (MTD), mean central dose (MCD), high-dose volumes (HDV), homogeneity index (HI); time dose pattern.

It has to be taken into account that implantation of a prostate is a procedure covering different targets and applying different target doses due to zonal anatomy related differences, possible tumour locations within the prostate gland and different implantation techniques and loading patterns used. Therefore, it is advisory to define different target areas within the gland and to record and report treatment parameters as outlined above related to the overall prostate CTV (CTV 1), to the peripheral zone CTV (CTV 2), and to areas where gross disease is detectable (CTV 3).

In case of different CTVs inside the prostate the terms MCD, HI and HDV are not applicable straightforward as defined by ICRU 58 for one target volume. Reporting these parameters has then to include a detailed description of the way the dose points have been positioned to define the MCD: dose points, e.g. can be different for the different CTVs.

In addition, parameters which have been proven to be useful for reporting permanent prostate implants should be applied as they seem to be valid and reliable and also enable a better comparison between the different brachytherapy procedures: D90, D100, V100, V150, V200 [2].

The exclusive use of dose volume histogram (DVH) does not give enough information on anatomic distribution of applied dose within the prostate gland as a single target. Using one target (the prostate gland) and one minimum target dose, allows only the description of dose on the surface of the prostate, but does not take into account that there are significant differences (70–250%) in different areas of the gland with high or low tumour load.

The dose to organs at risk (bladder base, urethra, rectal wall) should be part of the report. The dose should be related to fixed points and/or fixed volumes, even if there is no general agreement on certain points or fixed volumes at present. There are, e.g. suggestions to indicate the dose D (2 cm^3) for the most exposed 2 cm^3 of rectum or bladder, and D (0.1 cm^3) for the most exposed 0.1 cm^3 of the urethra or D1 for 1% of the contoured prostatic urethra.

The time dose pattern should include:

dose rate and dose per fraction of the target dose (D100, D90) for CTV 1, CTV 2 and CTV 3,
number and duration of the fractions,
time interval between fractions and the overall time.

The physical absorbed dose should always be reported but the dose should also be expressed using weighting factors for different doses per fraction so that an overall total dose comparable to conventional fractionation can be given. This information allows intercomparison of different treatment schedules with regard to their biological efficacy.

6.5. Management of side effects

Common acute side effects after prostate brachytherapy occurring within 90 days after treatment are perineal pain, urinary retention, dysuria, cystitis or proctitis. Late side effects usually result in different grades of proctitis, cystitis, urethral strictures, incontinence and changes in potency. In reporting adverse side effects, the RTOG/EORTC score is commonly used in radiation oncology [61], the IPSS and the sexual function score in urology. After high quality treatment the rate of grade 3 late side effects should be below 5%, which is comparable with results of 3D-conformal radiotherapy [40,44]. Quality of life (QL) after transperineal TRUS and template guided prostate brachytherapy + EBRT seems not to be significantly impaired on the long term [26]. Some significant decreases have been reported in the first months after permanent brachytherapy and radical prostatectomy, but not after external beam treatment. One year after HRQOL scores were not significantly different from the baseline measurements for any group [43]. The rate of potency impairment is usually reported to be around 35–40% in conformal EBRT patients presented with stable disease, median 31 months after treatment [44]. Similar rate was observed after temporary BT + EBRT treatments, however, prospective observations are needed [26].

In case of acute low urinary symptoms, alpha-blockers and non-steroidal anti-inflammatory drugs are helpful. Temporary post-implant urinary retention is usually due to post-implant oedema and has to be treated by catheterisation. Late injury should be treated usually in a conservative way. Transurethral resection of the prostate should be avoided at least within 6 months before and in the first year after the treatment to avoid unnecessary incontinence [2,31].

6.6. Follow-up

Patients should be seen 6 weeks after completing the treatment by the radiotherapist and urologist to check the level of acute reactions. Afterwards, they have to be seen quarterly for the first year and half-yearly up to 5 years and then annually. Follow-up should include clinical examination, history, PSA and record of treatment related side effects (including status of potency and IPSS) using validated scoring systems, also a TURS is required.

7. Conclusion

Numerous groups have shown that high quality treatment planning and performance of temporary HDR brachytherapy combined with EBRT leads to good treatment results in patients with localised prostate cancer, and is particularly recommended for patients with intermediate and high risk disease. Significant professional skill and a well functioning co-operation within an experienced interdisciplinary team are mandatory. Published outcome data (5–8 years follow-up) are encouraging and increasingly provided by different groups active in this field. Due to the natural history of prostate cancer with slow growth in the majority of cases, however, even longer follow-up is recommended for final conclusions (10–15 years).

There is growing consensus on these recommendations as outlined by the GEC-ESTRO/EAU group which include patient work up with defined pre-treatment investigations, patient selection based on individual risk assessment, contra-indications and potential indications, preconditions for temporary brachytherapy, implant procedure with target volume definition, treatment planning and needle placement and a common language for recording and reporting treatment. These recommendations should be followed as closely as possible to ensure a high quality of temporary brachytherapy treatment and to further evolve this field with rapidly developing imaging, application, and software technology and clinical experience. Outcome should be continuously evaluated within prospective clinical trials and compared to other treatment modalities based on the parameters as recommended.

References

[1] American Society for Therapeutic Radiology and Oncology Consensus Panel. Consensus statement: guidelines for PSA following radiation therapy. Int J Radiat Oncol Biol Phys 1997;37:1035–41.
[2] Ash D, Flynn A, Battermann J, et al. ESTRO/EAU/EORTC recommendations on permanent seed implantation for localized prostate cancer. Radiother Oncol 2000;57:315–21.
[3] Battermannn JJ. Feasibility of permanent implants for prostate cancer after previous radiotherapy in the true pelvis. Radiother Oncol 2000; 57:297–300.
[4] Bertermann H, Brix F. Ultrasonically guided interstitial high dose rate brachytherapy with Ir-192: technique and preliminary results in locally confined prostate cancer. In: Martinez AA, Orton CF, Mould RF, editors. Brachytherapy HDR and LDR: remote afterloading state of the art. Leersum, The Netherlands: Nucletron International BV; 1990. p. 281–303.
[5] Bertermann H. Transrektale Sonographie von Prostata und Samenblasen. T-Klassifikation. Landsberg: Ecomed; 1997 p. 25–59.
[6] Blasko JC, Grimm PD, Ragde H. Brachytherapy and organ preservation in the management of carcinoma of the prostate. Semin Radiat Oncol 1993;3:240–9.
[7] Blasko JC, Ragde H, Schumacher D. Transperineal percutaneous iodine 125 implantations for prostatic carcinoma using transrectal ultrasound and template guidance. Endocurie Hypertherm Oncol 1987;3:131–9.
[8] Bolla M, Gonsales D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. N Engl J Med 1997;337:295–300.
[9] Borghede G, Hedelin H, Holmäng S, et al. Combined treatment with temporary short-term high dose rate iridium-192 brachytherapy and external beam radiotherapy for irradiation of localized prostatic carcinoma. Radiother Oncol 1997;44:237–44.
[10] Borghede G, Hedelin H, Holmäng S, Johansson KA, Sernbo G, Mercke C. Irradiation of localized prostatic carcinoma with a combination of high dose rate iridium-192 brachytherapy and external beam radiotherapy with three target definitions and dose levels inside the prostate gland. Radiother Oncol 1997;44:245–50.
[11] Brenner DJ, Martinez AA, Edmundson GK, et al. Direct evidence that prostate tumors show high sensitivity to fractionation (low alpha/beta ratio), similar to late-responding normal tissue. Int J Radiat Oncol Biol Phys 2002;52:6–13.
[12] Bruggmoser G, Nanko N, Hempel M, Heitz R, Wannenmacher M. Equipment for rapid and reliable perineal implantation of I-125 seeds in prostatic cancer with reduced radiation exposure. Strahlenther Onkol 1987;163:593–4.
[13] Cadeddu JA, Partin AW, De Wese TL, Walsh PC. Long term results of radiation therapy for prostate cancer recurrence following radical prostatectomy. J Urol 1998;159:173–8.
[14] Chodak GW, Wald V, Parmer E. Comparison of digital examination and transrectal ultrasonography for the diagnosis of prostate cancer. J Urol 1986;135:951–4.
[15] Cookson MS, Fleshner NE, Soloway SM, et al. Correlation between Gleason score of needle biopsy and radical prostatectomy specimen: accuracy and clinical implications. J Urol 1997;157:559–62.
[16] Davis JW, Kolm P, Wright GL, et al. The durability of external beam radiation therapy for prostate cancer: can it be identified? J Urol 1999; 162:758–61.
[17] De la Rosette JJMC, Aarnink RG. New developments in ultrasonography for the detection of prostate cancer. J Endourol 2001;15: 93–104.
[18] Demanes DJ, Rodrigues RR, Altieri GA. High dose rate prostate brachytherapy: the California endocurietherapy (CET) method. Radiother Oncol 2000;57:289–96.
[19] Devlin PM, Brus CR, Kazakin J, et al. First national survey on the use of high dose rate afterloading brachytherapy for carcinoma of the

prostate. Proceedings of the 10th international brachytherapy conference. Madrid, Spain; 11–14 November, 2000, p. 60. [Abstract #30].

[20] Dinges S, Deger S, Koswig S, et al. High dose rate interstitial brachytherapy combined with external beam irradiation for localized prostate cancer—a prospective study. Radiother Oncol 1998;48: 197–203.

[21] D'Sousa WD, Thames HD. Is the alpha/beta ratio for prostate cancer low? Int J Radiat Oncol Biol Phys 2001;51:1–3.

[22] Edmundson GK, Di Yan RT, Martinez AA. Intraoperative optimisation of needle placement and dwell times for conformal prostate brachytherapy. Int J Radiat Oncol Biol Phys 1995;33:1257–63.

[23] Galalae RM, Kovács G, Schultze J, et al. Long term outcome after elective irradiation on the pelvic lymphatics and local dose escalation using high-dose-rate brachytherapy for locally advanced prostate cancer. Int J Radiat Oncol Biol Phys 2002;52:81–90.

[24] Galalae R, Martinez AA, Mitchell C, Gustafson GS, Kovacs G. No benefit at 5 years from a brief course of neoadjuvant androgen deprivation for prostate cancer patients treated with a conformal high dose rate brachytherapy boost (Abstract). Int J Radiat Oncol Biol Phys 2001;51:319.

[25] Galalae R, Kovács G, Loch T, et al. Anatomy-related and transrectal sonography-guided interstitial high-dose-rate brachytherapy combined with elective irradiation of the pelvic lymphatics for localized prostate cancer: the Kiel experience. In: Wiegel T, Heicapell R, Miller K, Hinkelbein W et al, editors. Controversies in uro-oncology. Front Radiat Ther Oncol, vol. 36. Basel: Karger; 2002. p. 183–90.

[26] Galalae R, Riemer B, Rzehak P, et al. Is health related quality of life status a new prognostic factor for survival in men with localized prostate cancer? Measurement following high dose rate brachytherapy and teletherapy using a prostate specific instrument (Abstract) Radiother Oncol 2000;55:47.

[27] Hammer J. Iodine-125 seed implantation in the treatment of prostatic carcinoma. Strahlenther Onkol 1991;167:63–81.

[28] Hinkelbein W. Adjuvant or therapeutic androgen suppression in locoregional advanced prostatic carcinoma (RTOG 85-31) [Article in German]. Strahlenther Onkol 1998;174:385–6.

[29] Hoskin PJ. High dose rate brachytherapy boost treatment in radical radiotherapy for prostate cancer. Radiother Oncol 2000;57:285–8.

[30] Hsu JI, Pickett B, Shinohara K, Krieg R, Roach III M, Phillips T. Normal tissue dosimetric comparison between HDR prostate implant boost and conformal external beam radiotherapy boost: potential for dose escalation. Int J Radiat Oncol Biol Phys 2000;46:851–8.

[31] Hu K, Wallner K. Rectal and urinary morbidity in patients undergoing prostate I-125 implant (Abstract). Int J Radiat Oncol Biol Phys 1997; 39:292.

[32] ICRU Report 58. Dose and volume specification for reporting interstitial brachytherapy, International Commission on Radiation Units and Measurements, ICRU, Bethesda, Maryland, USA; 1997.

[33] Ismail M, Gomella LG. Ultrasound for prostate imaging and biopsy. Curr Opin Urol 2001;11:471–7.

[34] Johnstone PA, Riffenburgh R, Saunders EL, et al. Grading inaccuracies in diagnostic biopsies revealing prostatic adenocarcinoma: implications for definitive radiation therapy. Int J Radiat Oncol Biol Phys 1995;32:479–82.

[35] King CR, DiPetrillo TA, Waser DE. Optimal radiotherapy for prostate cancer: predictions for conventional external beam IMRT, and brachytherapy from radiobiologic models. Int J Radiat Oncol Biol Phys 2000;46:165–72.

[36] King CR, Fowler J. A simple analytic derivation suggests that prostate cancer alpha/beta ratio is low. Int J Radiat Oncol Biol Phys 2001;51: 213–4.

[37] Kini VR, Edmundson GK, Vicini FA, Jaffray DA, Gustafson G, Martinez AA. Use of three-dimensional radiation therapy planning tools and intraoperative ultrasound to evaluate high dose rate prostate brachytherapy implants. Int J Radiat Oncol Biol Phys 1999;43:571–8.

[38] Kovacs G, Galalae R, Wirth B, et al. Optimisation of interstitial brachytherapy by a new implant technique in the treatment of prostate cancer (ger). Strahlenther Onkol 1995;171:685–8.

[39] Kovács G, Galalae R, Loch T, et al. Treatment outcome following high dose rate brachytherapy and external beam radiation in localized prostate cancer—the Kiel experience (ger.). In: Roth SL, Ackermann R, Bock W-J, Gabbert HE, Ganzer U, Göbel U, Häussinger D, Haas R, Röher H-D, Schulte KW, editors. Klinische Onkologie 2000/'01. Düsseldorf: Tumorzentrum Düsseldorf e.V; 2000. p. 343–7.

[40] Lawton CA, Winter K, Murray K, et al. Updated results of the phase III Radiation Therapy Oncology Group (RTOG) trial 85-31 evaluating the potential benefit of androgen suppression following standard radiation therapy for unfavourable prognosis carcinoma of the prostate. Int J Radiat Oncol Biol Phys 2001;49:937–46.

[41] Lee AK, Schultz S, Renshaw AA, Richie JP, D'Amico AV. Optimizing patient selection for prostate monotherapy. Int J Radiat Oncol Biol Phys 2001;49:673–7.

[42] Lee F, Siders DB, Torp-Pedersen ST. Prostate cancer: transrectal ultrasound and pathology comparison: a preliminary study of outer gland (peripheral and central zones) and inner gland (transition zone) cancer. Cancer 1987;67:1132–6.

[43] Lee WR, Hall C, McQuellon RP, Case LD, McCullogh DL. A prospective quality-of-life study in men with clinically localized prostate carcinoma treated with radical prostatectomy, external beam radiotherapy, or interstitial brachytherapy. Int J Radiat Oncol Biol Phys 2001;51:614–23.

[44] Lilleby W, Fossa SD, Waehre HR, Olsen DR. Long-term morbidity and quality of life in patients with localized prostate cancer undergoing definitive radiotherapy or radical prostatectomy. Int J Radiat Oncol Biol Phys 1999;43:735–43.

[45] Loch T, Bertermann H, Stöckle M. Technische und anatomische Grundlagen des transrektalen Ultraschalls (TRUS) der Prostata. Urologe B 2000;40:475–83.

[46] Loch T, Kovacs G, Nürnberg N, et al. High dose rate brachytherapy (HDR-BT) for local recurrence after radical prostatectomy: a new treatment modality. Radiother Oncol 1999;51:S10.

[47] Loch T, McNeal JE, Stamey TA. Interpretation of bilateral positive biopsies in prostate cancer. J Urol 1995;154:1078–83.

[48] Loening SA, Tuner JW. Use of percutaneous transperineal Au-198 seeds to treat recurrent prostate adenocarcinoma after failure of definitive radiotherapy. Prostate 1993;23:283–90.

[49] Martinez AA, Gonzalez J, Stromberg J, et al. Conformal prostate brachytherapy: initial experience of a phase I/II dose-escalating trial. Int J Radiat Oncol Biol Phys 1995;33:1019–27.

[50] Martinez AA, Kestin LL, Stromberg JS, et al. Internim report of image guided conformal high dose rate brachytherapy for patients with unfavourable prostate cancer: the William Beaumont phase II dose escalating trial. Int J Radiat Oncol Biol Phys 2000;47:343–52.

[51] Martinez AA, Pataki I, Edmundson G, et al. Phase II prospective study of the use of conformal high-dose-rate brachytherapy as monotherapy for the treatment of favourable stage prostate cancer: a feasibility report. Int J Radiat Oncol Biol Phys 2001;49:61–9.

[52] Martinez AA, Stitt JA, Speiser BL, et al. Conformal interstitial HDR brachytherapy. In: Perez CA, Brady LW, editors. Principles and practice of radiation oncology. 3rd ed. Philadelphia: Lippincott-Raven; 1998. p. 576–82.

[53] Mate TP, Gottesman JE, Hatton J, Gribble M, van Hollebeke L. High dose rate afterloading 192 iridium prostate brachytherapy: feasibility report. Int J Radiat Oncol Biol Phys 1998;41:525–33.

[54] Merrick GS, Wallner K, Buttler WM, Galbreath RW, Lief JH, Benson ML. A comparison of radiation dose to the bulb of the penis in men with and without prostate brachytherapy—induced erectile dysfunction. Int J Radiat Oncol Biol Phys 2001;50:597–604.

[55] Morris MM, Dallow KC, Zietmann AL, et al. Adjuvant and salvage irradiation following radical prostatectomy for prostate cancer. Int J Radiat Oncol Biol Phys 1997;38:731–6.

[56] Nag S, Beyer D, Friedland J, et al. American Brachytherapy Society (ABS) recommendations for transperineal permanent brachytherapy of prostate cancer. Int J Radiat Oncol Biol Phys 1999;44:789–99.
[57] Niehoff P, Loch T, Galalae R, et al. HDR brachytherapy treatment for local recurrence after radical prostatectomy: first results and experiences. Radiother Oncol 2000;55:44.
[58] Partin AW, Kattan MW, Subong EN, et al. Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer. A multi-institutional update. JAMA 1997;277:1445–51.
[59] Ragde H, Elgamal AA, Snow PB, et al. Ten-year disease free survival after transperineal sonography-guided iodine-125 brachytherapy with or without 45-gray external beam irradiation in the treatment of patients with clinically localized, low to high Gleason grade prostate carcinoma. Cancer 1998;83:989–1001.
[60] Riccabona M, Hammer J, Schorn A. Percutaneous, perineal, ultrasound-controlled implantation of 125iodine in prostatic cancer: technics, report of initial experiences and comparison with the retropubic method of implantation. Urologe [A] 1987;26:15–21.
[61] Rubin P, Constine LS, Fajardo LF, et al. Late effects consensus conference: RTOG/EORTC. Radiother Oncol 1995;35:5–7.
[62] Sanchez-Chapado M, Angulo JC, Ibarburen C, et al. Comparison of digital rectal examination, transrectal ultrasonography, and multicoil magnetic resonance imaging for preoperative evaluation of prostate cancer. Eur Urol 1997;32:140–9.
[63] Simina P, Schneider ChJ, Fowler J. The optimal fraction size in high dose rate brachytherapy: dependency on tissue repair kinetics and low-dose rate. Int J Radiat Oncol Biol Phys 2002;52:844–9.
[64] Steinberg DM, Sauvageot J, Piantadosi S, et al. Correlation of needle biopsy and radical prostatectomy Gleason grade in academic and community settings. Am J Surg Pathol 1997;21:566–76.
[65] Stromberg JS, Martinez A, Benson R, et al. Improved local control and survival for surgically staged patients with locally advanced prostate cancer treated with up-front low-dose rate iridium-192 prostate implantation and external beam irradiation. Int J Radiat Oncol Biol Phys 1994;28:171–7.
[66] Stromberg JS, Martinez A, Horwitz EM, et al. Conformal high dose rate iridium-192 boost brachytherapy in locally advanced prostate cancer: superior prostate specific antigen response compared with external beam treatment. Cancer J Sci Am 1997;3:346–52.
[67] Teh BS, Berner BM, Carpenter LS, et al. Permanent gold-198 implant for locally recurrent adenocarcinoma of the prostate after failing initial radiotherapy. J Brachyther Int 1998;14:233.
[68] Thomadsen BR, Houdek PV, Edmundson G, van der Laarse R, Kolkmann-Deurloo IKK, Visser AG. Treatment planning and optimisation. In: Nag S, editor. High dose rate (HDR) brachytherapy. A textbook. Future Publishing Company; 1994. p. 19–145.
[69] Vicinci FA, Vijay RK, Edmundson G, Gustavson GS, Stromberg J, Martinez AA. A comprehensive review of prostate cancer brachytherapy: defining an optimal technique. Int J Radiat Oncol Biol Phys 1999; 44:483–91.
[70] Visser AG, van der Aardweg GJMJ, Levendag PC. Pulsed dose rate and fractionated high dose rate brachytherapy: choice of brachytherapy schedules to replace low dose rate treatments. Int J Radiat Oncol Biol Phys 1996;34:497–505.
[71] Wallner K, Ellis W, Russsel K, Cavanagh W, Blasko J. Use of TRUS to predict pubic arch interference of prostate brachytherapy. Int J Radiat Oncol Biol Phys 1999;43:583–5.
[72] Yarbro JW, Page DL, Fielding LP, Partridge EE, Murphy GP. American Joint Committee on Cancer Prognostic Factors Consensus Conference. Cancer 1999;86:2436–46.
[73] Yoshioka Y, Nose T, Yoshida T, et al. High-dose-rate interstitial brachytherapy as a monotherapy for localized prostate cancer: treatment description and preliminary results of a phase I/II clinical trial. Int J Radiat Oncol Biol Phys 2000;48:675–81.
[74] Zagars GK, Pollack A, von Eschenbach AC. Prostate cancer and radiation therapy: the message covered by serum prostate specific antigen. Int J Radiat Oncol Biol Phys 1995;33:23–5.