Brachytherapy focal dose escalation using ultrasound based tissue characterization by patients with non-metastatic prostate cancer: Five-year results from single-center phase 2 trial

Vratislav Strnad*, Michael Lotter, Stephan Kreppner, Rainer Fietkau

Department of Radiation Oncology, University Hospital Erlangen, Erlangen, Germany

ABSTRACT

PURPOSE: This prospective trial investigates side effects and efficacy of focal dose escalation with brachytherapy for patients with prostate cancer.

METHODS AND MATERIALS: In the Phase II, monocentric prospective trial 101 patients with low-/intermediate- and high-risk prostate cancer were enrolled between 2011 and 2013. Patients received either PDR-/HDR-brachytherapy alone with 86–90 Gy (EQD2, α/β = 3 Gy) or PDR-/HDR-brachytherapy as boost after external beam radiation therapy up to a total dose of 91–96 Gy (EQD2, α/β = 3 Gy). Taking place brachytherapy all patients received the simultaneous integrated focal boost to the intra-prostatic tumor lesions visible in computer-aided ultrasonography (HistoScanning™) - up to a total dose of 108–119 Gy (EQD2, α/β = 3 Gy). The primary endpoint was toxicity. Secondary endpoints were cumulative freedom from local recurrence, PSA-free survival, distant metastases-free survival, and overall survival. This trial is registered with ClinicalTrials.gov, number NCT01409876.

RESULTS: Median follow-up was 65 months. Late toxicity was generally low with only four patients scoring urinary grade 3 toxicity (4/101, 4%). Occurrence of any grade of late rectal toxicities was very low. We did not register any grade ≥2 of late rectal toxicities. The cumulative 5 years local recurrence rate (LRR) for all patients was 1%. Five years- biochemical disease-free survival estimates according Kaplan-Meier were 98,1% and 81,3% for low-/intermediate-risk and high-risk patients, respectively. Five years metastases-free survival estimates according Kaplan-Meier were 98,0% and 83,3% for all patients, low-/intermediate-risk and high-risk patients, respectively.

CONCLUSIONS: The 5 years-results from this Phase II Trial show that focal dose escalation with computer-aided ultrasonography and brachytherapy for patients with non-metastatic prostate cancer is safe and effective. © 2022 The Authors. Published by Elsevier Inc. on behalf of American Brachytherapy Society.

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Keywords: Prostate cancer; Brachytherapy; Focal dose escalation

Introduction

Patients with non-metastatic prostate cancer can be treated with brachytherapy, external beam radiation therapy or radical prostatectomy. For low- and low-intermediate risk prostate cancer the results of external beam radiation therapy (EBRT) and sole brachytherapy treatment are comparable to radical prostatectomy with freedom from biochemical failure rates of approximately 95% after 5–10-years follow-up (1—9). For high-intermediate and high risk patients, EBRT followed by brachytherapy as boost is probably the best treatment approach with freedom from
biochemical failure ranging between 70% and 86% after 5–10-years follow-up (10–14).

Several randomized controlled trials and reports have demonstrated that dose escalation of up to 80Gy using EBRT techniques significantly improves the biochemical disease free survival (2,15–20). Further increase in dose is considered to improve the treatment results even further (2,12,16,21). Interestingly, some dose response analyses suggest that local recurrences after radiation therapy preferably occur at the site of the primary macroscopic tumor (22,23). Moreover, it is evident that the improvement of local control is associated with an improvement in terms of a reduction in the rate of distant metastases and of survival. Local failure is associated with an increase of distant metastases and mortality (1,11–13,24–26). As a consequence, a radiation dose escalation selectively to the intra-prostatic macroscopic tumor hold at least a potential to increase local control and survival while at the same time being able to respect normal tissue constraints. However, an appropriate visualization / appropriate imaging method should be considered a prerequisite for such a kind of microboost allowing a dose escalation to intra-prostatic tumor lesions. A number of recent studies have demonstrated the capability and high efficacy of multiparametric MRI to identify intra-prostatic tumor lesions and its consistency and reproducibility (27–31). On the other hand, image guidance with modern transrectal ultrasound (TRUS) provides a cost-effective and efficient method to delineate prostate boundaries particularly when using brachytherapy techniques. Unfortunately, current TRUS technology does not reliably differentiate between benign and malignant prostate tissue (32,33). Efforts to increase TRUS diagnostic performance include contrast-enhanced ultrasound, computer-assisted TRUS (C-TRUS), elastography, and computer-aided ultrasonography studies (HistoScanning™, Advanced Medical Diagnostics, Waterloo, Belgium) (34,35). Based on early HistoScanning studies, that reported sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) of up to 100%, 82%, and up to 100%, respectively (36–38), in 2011 we initiated a prospective Phase 2 trial (NCT01409876) to assess the value of HistoScanning-based “Image-guided dose-painting for localized prostate cancer”. In this paper we report the long-term results of this Phase 2 trial.

### Methods

**Study design and participants**

We analyzed the long-term results from this monocentric, phase 2, non-randomized prospective trial. The trial was undertaken at University Hospital Erlangen. The corresponding ethics committee approved the protocol.

Patients treated from 2011 were considered eligible for the trial if they were aged 18 years or older, had cT1–3 prostate cancer, no distant metastases and a prostate volume smaller 70 cm³. All eligible patients were included in our analyses. Patients were excluded if they had T4 prostate cancer, metastatic disease, or if International Prostate Symptom Score (IPSS) was higher than 20, general or regional anesthesia was not possible or if there were pathological blood coagulation parameters. We obtained written informed consent according to Good Clinical Practice guidelines and the local rules of our institute. All eligible patients were stratified into low-risk, intermediate-risk, and high-risk groups according to pretreatment PSA level, Gleason score, and clinical cancer stage (39,40). The most important patient characteristics are listed in Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>63 (41 – 76y.)</td>
</tr>
<tr>
<td>T stage</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>34/101 (33.7%)</td>
</tr>
<tr>
<td>T2</td>
<td>59/101 (58.4%)</td>
</tr>
<tr>
<td>T3</td>
<td>8/101 (7.9%)</td>
</tr>
<tr>
<td>Gleason</td>
<td></td>
</tr>
<tr>
<td>≤6</td>
<td>44/101 (43.6%)</td>
</tr>
<tr>
<td>7</td>
<td>35/101 (34.7%)</td>
</tr>
<tr>
<td>&gt;7</td>
<td>22/101 (21.8%)</td>
</tr>
<tr>
<td>Pretreatment PSA level (ng/mL)</td>
<td></td>
</tr>
<tr>
<td>≤10</td>
<td>59/101 (58.4%)</td>
</tr>
<tr>
<td>10–20</td>
<td>25/101 (24.8%)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>17/101 (16.8%)</td>
</tr>
<tr>
<td>DÁmico risk group</td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>22/101 (21.8%)</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>31/101 (30.7%)</td>
</tr>
<tr>
<td>High risk</td>
<td>48/101 (47.5%)</td>
</tr>
<tr>
<td>Treatment modality</td>
<td></td>
</tr>
<tr>
<td>Brachytherapy alone</td>
<td>22/22 pts.</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>(2/22 HDR-BT, 20/22 PDR-BT)</td>
</tr>
<tr>
<td>High risk</td>
<td>5/31 (PDR-BT)</td>
</tr>
<tr>
<td>EBRT+Brachytherapy Low risk</td>
<td>0/48</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>26/31</td>
</tr>
<tr>
<td>High risk</td>
<td>5/31 (PDR-BT, 21/31 PDR-BT)</td>
</tr>
</tbody>
</table>

| EBRT = external beam radiation therapy, HDR-BT = high-dose rate brachytherapy, PDR-BT = pulsed-dose rate brachytherapy. |

### Procedures

Before the start of the radiation therapy, all patients received a transrectal ultrasound sonography (TRUS) examination. As a special part of this examination additional 3-D ultrasound raw data was acquired performing a standardized three-dimensional (3D) examination of the prostate using motorized TRUS in the sagittal plane of a dedicated ultrasound device (B-K Medical, Copenhagen, Denmark; equipped with an 8658 probe) (36,37). The data was subsequently analyzed, possible suspicious foci of prostate cancer visualized and tumor foci volumes (cut-off threshold
volume of >0.5 cm³, the typical threshold used for attribution of significant foci of prostate cancer) calculated (41). With the Histoscan algorithm of the special use software, each labelled unit was categorized as suspicious or non-suspicious, generating a red overlay for areas suspicious for prostate cancer (42).

The radiation therapy concept was either brachytherapy alone or a combination of external beam radiation therapy (EBRT) and brachytherapy as boost. Patients with low risk prostate cancer (cT1 or cT2, Gleason score ≤6 and PSA value ≤10) got sole brachytherapy. Patients with intermediate- and high-risk prostate cancer were treated with EBRT followed by interstitial brachytherapy as boost.

External beam radiation therapy
External beam radiation therapy (EBRT) was performed to prostate and seminal vesicles only with an additional safety margin in the range of 5–10mm in all directions for patients with a risk of lymph node metastasis below 20%, calculated according the Yale formula (43). In patients with a probability of lymph node affection of more than 20%, the internal and common iliac nodes were also included up to the level of the lower border of L5 with safety margins of 10–15mm in all directions. The EBRT was administered using the IMRT-technique in single daily fractions of 1.8Gy at the reference point in line with ICRU 50 recommendations five times per week up to a total reference dose of 50.4Gy.

Brachytherapy
The brachytherapy technique we used is already described in detail elsewhere (44). In brief: under transrectal ultrasound guidance, stainless steel or titanium needles (length 20cm) were placed through a transperineal approach in the entire prostate. For this special therapy PDR-brachytherapy was preferred, although HDR-brachytherapy was also performed. For sole PDR-brachytherapy a total dose of 70Gy was administered in two sessions of 35Gy with a pulse dose of 0.7Gy given every hour for 24 h per day. On average, there was a time gap of 3–4 weeks between sessions. Assuming a value of 3Gy for the fractionation sensitivity α/β and a repair half-time of 1.9 h, the biologically equivalent dose (EQD2) for this PDR schedule is calculated to be 90.2Gy (44). For PDR-brachytherapy as boost after EBRT, the total dose of 35Gy was administered in one session – 35Gy / 0.7Gy/h, 24h (EQD2= 45.1Gy, α/β= 3Gy, T½= 1.9h). As an alternative to PDR-brachytherapy, part of the patients were treated with a HDR regime. For sole HDR-brachytherapy the dose was 4 × 9Gy in two sessions (EQD2=86.4Gy, α/β= 3Gy). In case of HDR-brachytherapy as boost after EBRT, the dose was given in one session with two fractions of 9 or 9.5Gy (EQD2=43.2–47.5Gy, α/β= 3Gy) (Table 2 and 3). For brachytherapy procedures, the clinical target volume (CTV) consisted of the entire prostate gland without any added safety margins. In addition, all intra-prostatic tumor areas, as detected with Histoscan-based analysis, were demarcated as HR-CTV (high-risk CTV) without any added safety margin. Furthermore, we delineated the urethra and rectal mucosa as organs at risk. Because of the fact that it is impossible to perform Histoscan imaging during brachytherapy and to the inability to perform an exact fusion of Histoscan-images with online-images of brachytherapy, we manually converted as accurately as possible the size, shape and volume of tumor foci visible by the Histoscan-examination into TRUS sets of images made during brachytherapy and in cases of discrepancy between Histoscan- and brachytherapy-images of the prostate we delineated the tumor foci in the brachytherapy-images stretched. As a consequence of this the final size, shape and volume of tumor foci in the brachytherapy TRUS imaging data set was nearly always slightly overestimated, as compared to the one generated by Histoscan-based analysis. The dose specification was done based on DVH values with V100≥95% and D90≥100% as the optimum while keeping the doses to OAR below the tolerance doses (see below). Furthermore the final dose optimization for all intra-prostatic tumor areas detected with Histoscan (high-risk clinical target volume, HR-CTV) was adapted in such way, that for HR-CTV the value of VHR-CTV120 was more than 90% and DHR-CTV90 > 120%. Beyond that for HR-CTV we documented also values of VHR-CTV130, VHR-CTV140, VHR-CTV150, and DHR-CTV100. Simultaneously we payed attention to the dose constraints for the organs at-risk - D2cc < 85Gy for bladder and D2cc < 75Gy for rectum (these doses are total doses, i.e., brachytherapy doses and the sum of EBRT, if applicable) and D0.1cc < 130% for the urethra. Using the radiobiological values (T½ and α/β) mentioned above, we reached EQD2-dose values in the HR-CTV of around 119Gy for brachytherapy alone and in the range of 108–114Gy if brachytherapy was applied as boost after 50.4Gy of EBRT. The corresponding details are summarized in Table 3.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate (CTV) ultrasound volume</td>
<td>23.8 cc (11.4–59.1)</td>
</tr>
<tr>
<td>CTV: D90 (% prescription dose)</td>
<td>111.3 (99.8–111.9)</td>
</tr>
<tr>
<td>CTV: V100 (%)</td>
<td>97.4 (89.7–99.9)</td>
</tr>
<tr>
<td>Intra-prostatic tumor areas (HR-CTV) volume</td>
<td>1.39 cc (0.4–7.1)</td>
</tr>
<tr>
<td>HR-CTV: D90 (% prescription dose)</td>
<td>125.0 (101.3–149.9)</td>
</tr>
<tr>
<td>HR-CTV: V120 (%)</td>
<td>94.3 (64.2–99.9)</td>
</tr>
<tr>
<td>HR-CTV: V130 (%)</td>
<td>85.4 (50.6–99.9)</td>
</tr>
<tr>
<td>HR-CTV: V140 (%)</td>
<td>74.5 (39.6–99.9)</td>
</tr>
<tr>
<td>HR-CTV: V150 (%)</td>
<td>60.2 (28.1–98.4)</td>
</tr>
<tr>
<td>Organ at risk</td>
<td></td>
</tr>
<tr>
<td>Rectum: D2cc (% prescription dose)</td>
<td>70.5 (29.0–86.4)</td>
</tr>
<tr>
<td>Urethra: D0.1cc (% prescription dose)</td>
<td>125.9 (94.4–144.0)</td>
</tr>
</tbody>
</table>

CTV = clinical target volume, HR-CTV = high-risk clinical target volume, cc = cubic centimeter, V = volume, D = dose.
Antihormonal therapy

A total of 69 of 101 patients (68%) did not receive any additional antihormonal treatment. At the time of brachytherapy 4 of 31 patients (13%) with intermediate risk prostate cancer and 26 of 48 patients (54%) with high risk cancer disease received adjuvant antihormonal therapy of different duration – mostly for 1–2 years. No patient with low risk prostate cancer received any antihormonal treatment.

Outcomes

The primary aim of the study was to evaluate the feasibility and safety of HistoScanning-based focal dose escalation with image-guided dose-painting brachytherapy for localized prostate cancer by recording serious adverse events. Urinary and rectal toxicities were assessed according to the Common Toxicity Criteria Adverse Events Versions 4 (45). Adverse events were scored during weekly treatment every 3 months for the first 2 years and half-yearly thereafter. Against this background, as well as for pragmatic reasons, we considered that the total number of 100 patients was sufficient (dropout included). A secondary objective was to analyze the effectiveness of our treatment in terms of cumulative 5 year local recurrence-free rate (LRR), biochemical disease-free survival, distant metastases-free survival (DMFS) and overall survival rates. Biochemical recurrence was defined as the lowest prostate-specific antigen (PSA) value after treatment (PSA nadir) plus 2 ng/mL, according to the Phoenix criteria (46). Local recurrence and distant metastases-free survival were defined as evidence of recurrent disease on imaging and time to clinically evident local recurrence or to the first distant metastasis. Patients treated at our institution between 2011 and 2014 were included in the study. The study had approval from the ethics committee of the Erlangen University hospital and prior to enrollment we obtained informed consent from all patients. This trial is registered with ClinicalTrials.gov, number NCT01409876.

Statistical analysis

For statistical analysis, the IBM SPSS Statistics 24 software package was used. We used the Kaplan-Meier method to calculate the probability of local control and survival, and a log rank test to compare the subgroups. All events (cumulative local recurrence rate, biochemical disease-free (biochemical no evidence of disease) survival, overall survival) were defined for the time period from the beginning of radiation therapy to the time of the event or death. The biochemical disease-free survival was defined for the period from the start of salvage brachytherapy to a PSA increase of > 2 ng/mL above nadir (Phoenix definition).

Results

Dosimetry

Using brachytherapy the median coverage index (V100) for prostate (CTV) was 97.4% and the corresponding median value of D90 was 111.3%. The median value of V120 for all intra-prostatic tumor areas detected (HR-CTV) was 94.3%. For intra-prostatic tumor areas detected with HistoScanning (HR-CTV) the median values of V120, V130, and V150 were 94.3%, 85.4%, and 60.2%, respectively. For detailed information on the dose parameters please see Tables 2 and 3 and an example of a typical dose distribution in Fig. 1.
Clinical outcomes

The median follow-up was 65 months. The cumulative 5 year local recurrence rate (LRR) for all patients was 1%. When subdivided by risk categories, 5 year-LRR estimates were 0%, and 2% for low-/intermediate- and high-risk patients, respectively. 5 year biochemical disease-free survival estimates according Kaplan-Meier were 98.1% and 81.3% for low-/intermediate-risk and high-risk patients (Fig. 2). Five year metastases-free survival estimates according Kaplan-Meier was 98.0% and 83.3% for low-/intermediate-risk and high-risk patients (Fig. 3), respectively. 5 year overall survival was 60.4% and 47.9% for low-/intermediate-risk and high-risk patients, respectively.

Late toxicity was generally low with only four patients scoring a grade 3 toxicity (4/101, 4%). All these patients had grade 3 urinary late side effects requiring surgical intervention such as stricture dilatation or transurethral resection. Furthermore, 5 patients (5/101, 5%) experienced grade 2 late urinary toxicity – persistent urinary symptoms such as nycturia, polakusuria requiring medication (anticholinergics, alpha antagonists, no-steroid anti-inflammatory drugs) or pads for urinary incontinence. Grade 1 urinary toxicity was observed in 35 of 101 patients (34%). We did not identify any correlation between late urinary symptoms and urethral dose. No grade 4 toxicity was seen. Occurrence of any grade of late rectal toxicities was very low – only 3 of 101 of patients (3%) experienced Grade 1 rectal toxicity. We did not register any grade ≥2 of late rectal toxicities.

Discussion

In this prospective Phase 2 trial, we report outcomes of computer-aided ultrasonography (HistoScanning)-based focal dose escalation with image-guided dose-painting...
brachytherapy for non-metastatic prostate cancer. In all patients, in the HistoScanning-positive tumor areas, an adequate coverage with doses greater than 120% ($V_{120\text{median}} = 94\%$) maintaining appropriate coverage of whole prostate gland ($V_{100\text{median}} = 97\%$) and comparatively low doses to the urethra and rectum could be achieved. As clinical justification of these parameters, we registered a high 5 years-tumor control probability (99\%) and 5-year-biochemical disease-free survival (90\%) while simultaneously finding a very low incidence of serious late side effects – in the low single-digit range.

Other authors reported results of focal dose escalation with brachytherapy or external beam radiation therapy particularly using magnetic resonance spectroscopic imaging (MRSI) (47–49), multiparametric-MRI(50–54) or combination of MRSI and MRI(55). All these authors reported a very low rate of side effects as a results of focused dose escalation without increasing dose to surrounding organs at risk for a relatively small number of patients ranging from 5 to 47 (47,48,49,50,51,52,53, 55,56,57,58,59). Typically, the authors report focal dose escalation to approximately 125%–150% of the prescribed dose to the whole prostate gland (53). In the largest study dedicated focal dose escalation to the tumor foci in prostate cancer, the multicenter randomized Focal Lesion Ablative Micro-boost in prostate cancer (FLAME) trial, patients in the dose-escalated arm received an escalated dose up to 95 Gy to the visible tumor and 77 Gy to the whole gland(54,60). Within a 5 years follow-up the authors did not observe a significant increase in GU and GI toxicity when compared to the standard treatment. The cumulative incidence of late genitourinary and GI toxicity grade ≥2 was 23\% and 12\% in the standard arm versus 28\% and 13\% in the focal boost arm, respectively (60,61). It is important to mention that the 5 years-biochemical disease-free survival was significantly higher in the focal boost arm when compared to the standard arm at 92\% and 85\% ($p < 0.001$), respectively (60). Contrary to this fact the 5 years metastasis free survival was in the range of 90\%, but did not show any statistically significant difference between treatment arms ($p = 0.27$)(60).

In comparison to these excellent data in our phase two trial we observed very similar efficacy – both 5 years biochemical disease-free-survival rates and 5 years metastasis free survival values are in the range of 90\% in both trials. We think that these very similar efficacy results mirror similar doses in visible tumor foci used in both trials – in FLAME-trial the reported EQD2 was 108.3 Gy ($\alpha/\beta = 3\text{Gy}$) in our phase 2 trial the total EQD2-doses were in range of 108–119 Gy ($\alpha/\beta = 3\text{Gy}$). Small differences between the two trials are recognizable only in regard to late side effects. In the FLAME trial cumulative serious late GU toxicity grade ≥3 was reported in 5.6\% patients and cumulative serious late GI toxicity grade ≥3 in 1.4\% patients, respectively (60). In our present analysis, we observed serious late GU toxicity in 4\% and no GI toxicity grade ≥3. Whether these very small differences are simply by chance or a consequence of the steep dose gradient characteristic for the brachytherapy used in our trial remains speculative. In any case both trials concurly demonstrated outstanding oncological results with negligible late side effects.

A key strength of our analysis is the fact, that we report data of a prospective trial with appropriate follow-up and a rather large number of patients. To the best of our
knowledge, alongside the FLAME-trial our Phase 2 trial with 101 patients encompasses the largest patient cohort of any series involving intra-prostatic focal dose escalation. In comparison to some other reports (47), our dose escalation in tumor areas seems to be moderate – with a median $V_{2000} = 94\%$. Nevertheless, the clinical results surpass our expectations. It seems that the focal dose escalation of up to 120% of the prescribed dose, which corresponds to biologically equivalent doses EQD2 $> 100\text{ Gy} (\alpha/\beta = 3\text{ Gy})$ in identifiable tumor areas, is entirely adequate. As a consequence, our clinical results allow us to hypothesize that further significant intra-prostatic dose escalation of more than 120% of the prescription dose, corresponding to values of EQD2 $> 100\text{ Gy}$, is probably not beneficial. A definitive statement on this will, however, only be possible with an appropriate phase 3 trial.

The key limitation of our trial is in the sensitivity, specificity and spacial resolution of the HistoScanning-based analysis. In early pilot studies, authors reported a 100% sensitivity and 81% specificity of HistoScanning-based analysis (36), but in later investigations the sensitivity and specificity varied substantially and ranged from 60 to 90% and 50–94% (35,38,62–64). In conclusion, despite the fact that both the sensitivity and the specificity of HistoScanning-based analysis include some degree of uncertainty, in all our patients the whole prostate gland was treated with sufficient dose and the intra-prostatic focal dose escalation was generous concerning the size and borders of intra-prostatic lesions (see Fig. 1). We believe that the consequence of this treatment strategy – adequate dose to the whole prostate gland and generous definition of intra-prostatic tumor lesion – is the main reason reasonable clinical results reported despite all the uncertainties of the HistoScanning-based definition of intra-prostatic lesions. Unfortunately, the current standard of care – multi-parametric MRI including diffusion-weighted and dynamic contrast-enhanced MRI – was not routinely available at the time of the initiation of our trial. It stands to reason that the objective of local cancer therapy is to eradicate all local disease foci and as a consequence, the definitive evidence will be available with longer follow-up ideally including assessment of tissue biopsies (65).

Finally, we conclude that the presented prospective results confirm the results of the Phase 3 FLAME-trial (60) as well as those of numerous other investigations (49–55), suggesting that the focal tumor boost to intra-prostatic tumor lesions is effective and safe at the same time as yielding excellent oncological results. As a consequence, we are convinced that the clinical benefit of focal intra-prostatic dose escalation is already duly validated, very clearly defined and should be considered in determining the optimal treatment strategy when treating patients with non-metastatic prostate cancer with radiotherapy.

References


(EQD(2)>100Gy) dose escalation on dominant intra-prostatic lesions (DILs) by Helical Tomotherapy. *Acta Oncol* 2011;50:25–34.


