Three-dimensional (3d) real-time conformal brachytherapy – a novel solution for prostate cancer treatment
Part II. A feasibility clinical pilot study

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Objectives. The pilot feasibility clinical study was designed to test the tolerance and early efficacy of the 3D-real time conformal brachytherapy combined with external irradiation of patients with prostate cancer.

Material and methods. Seventy six consecutive patients with prostate cancer in stage T1-2N0M0 entered the study. Median pretreatment PSA level was 13.6 ng/ml and Gleason score was 8 or lower. All patients received conformal external irradiation of 54 Gy in 27 fractions followed by a 10 Gy boost given using 3D-real-time CBRT.

Results. All patients tolerated the CBRT implant procedure and prior external irradiation very well, with no discomfort, and no protocol violation was noted. Acute urinary bladder toxicity grade III was noted in 1% of patients. There were no grade III gastrointestinal acute toxicity. Mild, grade I or II toxicity, was observed in 62% of patients and it did not significantly influence patient comfort. Early actuarial 1-year BNED was 97.3%. Dosimetric analysis has shown that the mean value of D100PTV was 91.7%, D90 was 97.6% and D10 for the urethra was 126.3%. All dosimetric parameters were within the limits recommended by the American Brachytherapy Society (ABS).

Conclusions. 3D-real time conformal brachytherapy using a single boost dose of 10 Gy combined with 54 Gy in 27 fractions of conformal irradiation is a safe and well tolerated treatment in case of patients with T1-2N0M0 prostate cancer. From the radiobiological point of view there is still room to intensify treatment towards fractionated 3D-real time CBRT interdigitated with external irradiation.

Trójwymiarowa brachyterapia w „czasie rzeczywistym” – nowa metoda leczenia chorych na raka gruczołu krokowego
Część II. Pilotowe badanie kliniczne

Założenia. Zaplanowano i przeprowadzono pilotowe badanie klinicne w grupie chorych na raka gruczołu krokowego w celu oceny tolerancji i skuteczności konformalnej brachyterapii 3D – w czasie rzeczywistym, skojarzonej z konformalną radioterapią przy użyciu zewnętrznych wiązek promieniowania.

Materiał i metodyka. Grupę pilotową stanowiło 76 kolejnych chorych na raka gruczołu krokowego w stopniu zaawansowania T1-2N0M0. Średnia wartość stężenia PSA przed rozpoczęciem leczenia wynosiła 13,6 ng/ml, a stopień Gleasona nie przekraczał 8. Wszyscy chory byli napromieniani dawką 54 Gy w 27 frakcjach, po której podawano dawkę uzupełniającą 10 Gy przy użyciu 3D-CBRT w czasie rzeczywistym.

Wyniki. Wszystkich chorych tolerancja była bardzo dobra. Ostry odczyn popromienny w III stopniu ze strony układu moczowego wystąpił u 1% pacjentów. U jednego chorego nie stwierdzono III stopnia nasilenia ostrego odczynu w odbytnicy. Słabe i miernie nasilone odczyny I i II stopnia wystąpiły u 62% chorych i nie wpływały istotnie na komfort leczenia. Wczesne, zaktualizowane 1-rocze prógicz bez wznowy biochemicznej wynosiło 97,3%. Wyniki analizy dozimetrycznej wykazały średni wartość parametrów D100PTV 91,7%, D90=97,6%, D10=126,3% i mieściły się w przedziałach odpowiednich wartości, rekomentowanych przez Amerykańskie Towarzystwo Brachyterapii.

Wybierz. Konformalna brachyterapia 3D w czasie rzeczywistym, zastosowana w formie dawki 10 Gy, uzupełniającej konformalne napromienianie dawką 54 Gy w 27 frakcjach, jest bezpieczną i dobrze tolerowaną metodą skojarzonego leczenia chorych na raka gruczołu krokowego w stopniu zaawansowania T1-2N0M0. Przesłanki radiobiologiczne wskazują

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Introduction

Patients with early stage of prostate cancer (T1-T2) without nodal involvement (N0) and distant metastases (M0) and with the PSA level of less of or equal to 10 ng/ml and Gleason scores of ≤ 7 are considered as a low risk subgroup of patients and have variety of treatment options, e.g. radical prostatectomy, conformal external beam radiotherapy, or brachytherapy. Brachytherapy is usually applied as a boost dose treatment. This subgroup has been chosen for the pilot “feasibility” study to evaluate the practical applicability of 3D- conformal “real time” brachytherapy (3D-CBRT) and its tolerance. The method is presented in details in part I of this paper [1].

Material and methods

Eligibility criteria

We chose the following eligibility criteria for the 3D- real time CBRT: (1) clinical T1-T2 without pelvic nodal disease and other distant metastases (N0M0); (2) biopsy-confirmed adenocarcinoma with pretreatment PSA level and Gleason score; (3) no contraindication for spinal anesthesia; (4) signed informed consent. All patients have been previously seen and qualified by the Prostate Cancer Team at the Institute.

Material

Between January 1, 2003 and June 30, 2004, 76 patients with prostate cancer in stage T1-T2N0M0 have been qualified for the 3D- real time CBRT given as a boost dose at the beginning or at the end of conformal external irradiation. The median age of patients was 65 years (range 57-81). A majority of patients were between 50 and 70 years old. Of the 76 patients two had Gleason score 8, nine had Gleason score 7, and the remaining 65 patients (86%) had Gleason score below 7.

PSA level prior to the treatment was equal to, or lower than 10 ng/ml in 30 cases (40%). There were 5 patients with PSA level above 50 ng/ml (Table I A). Median pretreatment PSA was 13.6 ng/ml (Figure 1A). There were 11 patients (14%) with two poor prognostic factors (PSA>10 ng/ml, GS>7). Sixty six of the 76 patients (87%) received hormonotherapy (mainly Zoladex or Flutomid, or both) prior to radiation therapy. None of the patients underwent surgery.

Radiotherapy

All patients received conformal external irradiation (3D-CERT) of 44 Gy in 22 fractions given once-a-day to a large pelvic PTV and followed by a 10 Gy boost in 5 fractions targeted to the prostate using 3D-conformal technique.

Table I. PSA level (A) before and (B) after ERT-BRT

<table>
<thead>
<tr>
<th>PSA LEVEL</th>
<th>No pts</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6.0</td>
<td>12</td>
<td>15.5%</td>
</tr>
<tr>
<td>6.01-10.0</td>
<td>18</td>
<td>24.0%</td>
</tr>
<tr>
<td>10.01-20.0</td>
<td>27</td>
<td>36.0%</td>
</tr>
<tr>
<td>20.01-50.0</td>
<td>14</td>
<td>18.0%</td>
</tr>
<tr>
<td>&gt;50.0</td>
<td>5</td>
<td>6.5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PSA LEVEL</th>
<th>No pts</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.5</td>
<td>54</td>
<td>71%</td>
</tr>
<tr>
<td>0.51-1.0</td>
<td>10</td>
<td>13%</td>
</tr>
<tr>
<td>1.01-1.5</td>
<td>3</td>
<td>4%</td>
</tr>
<tr>
<td>1.51-2.0</td>
<td>2</td>
<td>3%</td>
</tr>
<tr>
<td>&gt;2.0*</td>
<td>7</td>
<td>9%</td>
</tr>
</tbody>
</table>

* for one patient PSA increased from 68.4 ng/ml to 82 ng/ml

Figure 1. Cumulative rate of the PSA levels (A) before and (B) after 3D-CERT + 3D-CBRT
Brachytherapy

Basing on the TRUS images the prostate volume (pV) was estimated (Table II). In 66 patients (87%) the pV was within the range of 18-40 cc. A single dose of 10 Gy was delivered one or two days after completing CERT, using the technique described in part I of this paper. The implant consisted of 12-18 needles (in the majority of cases – 17 or 18 needles had been inserted). The prescribed dose was measured on the surface (contour) of the prostate capsule.

Table II. Prostate volume at the time of 3D-CBRT

<table>
<thead>
<tr>
<th>Prostate volume</th>
<th>No. pts</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20 cc</td>
<td>18</td>
<td>24%</td>
</tr>
<tr>
<td>20.5-30 cc</td>
<td>33</td>
<td>43%</td>
</tr>
<tr>
<td>30.5-40 cc</td>
<td>15</td>
<td>20%</td>
</tr>
<tr>
<td>40.5-50 cc</td>
<td>8</td>
<td>10%</td>
</tr>
<tr>
<td>50.5-55 cc</td>
<td>2</td>
<td>3%</td>
</tr>
</tbody>
</table>

Dosimetric analysis

According to the American Brachytherapy Society Recommendations (ABS), values of D100PTV (percentage of the PTV volume covered by 100% isodose) and D90 (dose delivered to 90% of the target volume) were measured and recorded to evaluate the quality of the treatment. To evaluate the level and range of doses delivered to the urethra the D10 (dose delivered to 10% volume of the urethra) was measured. The rectal dose was estimated in the rectal reference point, as described by Martinez et al [2].

Results

Treatment compliance

After signing informed consent all patients underwent 3D-CERT and 3D-CBRT implants as initially prescribed. No patient was excluded from the analysis.

PSA outcome

Figure 1B shows the cumulative pattern of PSA after treatment compared with the pretreatment PSA levels. Prior to treatment 60% of patients had PSA at a level ≥10 ng/ml, and after therapy in 84% of patients PSA decreased to a level of less than 1 ng/ml (Table 1B). The mean post-treatment PSA value was 0.13 ng/ml. This gives, on average, a 100-fold magnitude of the decrease in the PSA level as compared with the mean pretreatment value. Nevertheless, in 34 cases (45%) even 200-1000 fold differences between pre- and post-treatment PSA levels have been noted, especially in those cases where the pretreatment PSA was high (>15 ng/ml). Only in two patients did the PSA level increase after treatment, as compared with the pretreatment values.

Analyzing the impact of prognostic factors on the PSA level (Table III), among the 48 patients with one or two poor prognostic factors (PSA ≥10 ng/ml, GS ≥7), PSA after treatment of more than 1 ng/ml has been noted in 17% of patients with one poor prognostic factor, and in 27% of patients with two poor prognostic factors, as compared to only 9% of patients in the “favourable” group. Among 76 patients one patient developed distant bone and lung metastases 3 months after completing the treatment (GS=7, PSA=54.3 ng/ml).

Table III. Biochemical remission depending on the number of poor prognostic factors prior to treatment

<table>
<thead>
<tr>
<th>Patient category: (poor prognostic factors)</th>
<th>No pts. with higher PSA level than 1ng/ml after ERT-BRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>3/28 – 9%</td>
</tr>
<tr>
<td>one: Gleason ≥7</td>
<td>0/2 – 0%</td>
</tr>
<tr>
<td>PSA &gt; 10 ng/ml</td>
<td>6/35 – 17%</td>
</tr>
<tr>
<td>two: both Gl and PSA</td>
<td>3/11 – 27%</td>
</tr>
</tbody>
</table>

Because follow-up is still relatively short, within the range of 3-18 months, it does not allow to estimate long term results, but early results show 97.3% of 1-year BNED (biochemical no evidence of disease).

Acute toxicity

All patients tolerated the implant procedure very well, without discomfort. Generally, the entire treatment course of combined conformal ERT and BRT was well tolerated and we observed no acute effects requiring treatment modification. The treatment-related acute toxicities were primarily gastrointestinal and urinary. Acute grade III urinary toxicity was observed in 1% of patients. No severe acute effects (grade IV) have been noted (Table IV). Mild perineal pain occurred in 11% of patients, but it was transient. In the group of patients with a minimum follow-up of 12 months, no chronic gastrointestinal and urinary toxicities have been observed. All other mild toxicities were of grade I or II (62%) and could be expected to occur in patients with pelvic external irradiation. For the combined treatment tested it is difficult to separate the toxicities related to the 3D-CBRT from those caused by external irradiation, however it was observed that an extra boost of 10 Gy of 3D-CBRT did not significantly increase the severity of the already observed CERT-related acute effects.

Table IV. Acute toxicity scored using EORTC system during and directly after completing 3D-ERT + 3D-CBRT for prostate cancer

<table>
<thead>
<tr>
<th>CRITICAL ORGAN</th>
<th>0°</th>
<th>I°</th>
<th>II°</th>
<th>III°</th>
<th>IV°</th>
</tr>
</thead>
<tbody>
<tr>
<td>bladder</td>
<td>50.5%</td>
<td>42%</td>
<td>6.5%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>rectum</td>
<td>76%</td>
<td>20%</td>
<td>4%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Dosimetric results

The parameter D100\textsubscript{PTV} (percentage of PTV volume covered by 100\% isodose) was 91.7\% (80.3-95.8\%). The row measurements scattergram show that for 72\% of cases D100\textsubscript{PTV} was \geq 90\% (Figure 2a). The mean D90 (dose delivered to at least 90\% of the target volume) was 97.6\% (86.4-109.1\%). The D90 scattergram (Figure 2b) shows that for 82\% of cases D90 was \geq 95\%. The urethral D10 (dose delivered to 10\% volume of the urethra) for 95\% of cases was in the range of 120\% and 130\% (Figure 2c) and the mean value was 126.3\% (120.5-170.1\%). The rectal doses were not higher than 65\% of the prescribed dose.

Discussion

For years, locally advanced prostate cancer has been posing a therapeutic challenge. Quite a number of definitive therapeutic options have been tested over the last 2-3 decades, i.e. external ± interstitial irradiation, mixed beam treatment with protons or neutrons, particle beam alone, prostatectomy with or without hormonal and radiotherapy. Traditional treatment planning is more or less hampered by the difficulty in differential delivery of a higher dose to the prostate and sparing surrounding sensitive normal tissue. Hormonal therapy is combined with local treatment, with the belief of an additive or synergistic effect improving local control. Unfavourable geometrical conditions, target volume inaccuracy, the risk of set-up systemic and random errors and internal organ motion occurring during external beam irradiation are important limitations for dose escalation. Technological progress and development of three-dimensional treatment planning systems has permitted an accurate confirmation of the prescribed dose to the prostate target volume and to modulate dose intensity (conformal and dose intensity modulated radiotherapy – CERT, IMRT). These developments have provided an opportunity to escalate highly conformal doses, which can be translated into a significant benefit in “no biochemical evidence of disease” survival and in “cause-specific” survival [3-5].

The next important step forward was the development of a new conformal 3D-real time brachytherapy system using ultrasound–guided interstitial prostate implantations and on-line dosimetry (3D-CBRT). Among the many advantages specified in part I of this paper [1] two of them seem to be the most important.

First of all, this allows to combine both conformal techniques of external and interstitial irradiation to increase dose intensity within the accurately defined target. The second advantage is the shortening of the overall treatment time.

Martinez and his group from the W. Beaumont Center, USA have gained the largest experience in testing the applicability, tolerance and effectiveness of the 3D-CBRT as a monotherapy, interdigitated or boost treatment of prostate cancer [2, 4-7]. They have been the first team to suggest the use of 3D-CBRT in two or three fractions, combined interdigitally with external beam irradiation (Table V). Their study [5] was performed on both favourable and unfavourable cases. The authors have noted a 30\% gain in 5-year BNED for the group treated with two fractions of either 8.25 Gy, 8.75 Gy, 9.50 Gy, 10.50 Gy or 11.5 Gy given in day 5 and 19 during the course of external irradiation (ERT), as compared to a combination of 3 fractions of 5.5Gy, 6.0 Gy or 6.5 Gy on day 5, 12, 19 of the ERT (87\% vs. 57\% in Table V, A1-A2). Compared with the

Figure 2. Dose measurements scattergrams for (a) D100\textsubscript{PTV}, (b) D90, and (c) D10
<table>
<thead>
<tr>
<th>Study group</th>
<th>SCHEDULE</th>
<th>TD in Gy</th>
<th>OTT in days</th>
<th>No. pts</th>
<th>α/β = 10 Gy</th>
<th>α/β = 3 Gy</th>
<th>α/β = 1.5 Gy</th>
<th>NBED</th>
<th>TOXICITY</th>
<th>ACUTE</th>
<th>LATE</th>
<th>EFFICACY</th>
<th>5 yr. BNED</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-1. Beaumont, A-1 (low) (5)</td>
<td>46 Gy/23 fx – ERT + (5.5-6.5 Gy) x 3 – 3D-CBRT</td>
<td>62.5 – 65.5</td>
<td>33</td>
<td>58</td>
<td>67.3 – 72.8</td>
<td>74.1 – 83.1</td>
<td>79.0 – 90.6</td>
<td></td>
<td>III° – 12%</td>
<td>urinary</td>
<td>IIP° – 8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A-2. Beaumont, A-2 (high) (5)</td>
<td>46 Gy/23 fx – ERT + (8.25-11.5) x 2 – 3D-CBRT</td>
<td>62.5 – 69.0</td>
<td>33</td>
<td>149</td>
<td>71.1 – 105.3</td>
<td>83.1 – 112.7</td>
<td>91.9 – 131.4</td>
<td></td>
<td>III° – 2%</td>
<td>urinary</td>
<td>IIP° – 0.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. Beaumont (2)</td>
<td>45.6 Gy/24 fx – ERT + 5.5 Gy x 3 – 3D-CBRT</td>
<td>62.1</td>
<td>39</td>
<td>33</td>
<td>68.7</td>
<td>72.5</td>
<td>77.4</td>
<td></td>
<td>III° – 9%</td>
<td>hematopasmia – 15% perineal pain – 12%</td>
<td>*</td>
<td>92%</td>
<td>(risk of subsegment increase – 3%)</td>
</tr>
<tr>
<td>C. Beaumont (6)</td>
<td>9.5 x 4 – 3D-CBRT</td>
<td>38.0</td>
<td>2</td>
<td>41</td>
<td>61.5</td>
<td>95.03</td>
<td>119.4</td>
<td></td>
<td>II° – 17%</td>
<td>III-IV° – 0%</td>
<td>*</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>D. Gliwice</td>
<td>54 Gy/27 fx – CERT + 10 Gy x 1 – 3D-CBRT</td>
<td>64.0</td>
<td>38</td>
<td>76</td>
<td>70.7</td>
<td>80.02</td>
<td>86.8</td>
<td></td>
<td>III° – 1% bladder II° – 0% rectal IV° – 0% (both)</td>
<td>*</td>
<td>71%</td>
<td>(PSA &lt; 2ng/ml - 95%)</td>
<td></td>
</tr>
</tbody>
</table>

Legend:
ERT – standard external beam irradiation; • dose per fraction (fx) of 2.0 Gy and 1.8 Gy was in proportion of “half and half”; CERT – conformal external beam irradiation; 3D-CBRT – three-dimensional conformal, real-time brachytherapy; TD – total physical dose, OTT – overall treatment time, NBED – Normalized Biologically Equivalent Dose (equation see in text); BNED – Biochemical No Evidence of Disease; * – too short follow-up, no data; •3D-CBRT given interdigitally with external irradiation – 3 fractions in day 5, 12, 19, and 2 fractions in day 5 and 19; ▲ – 5 year actuarial rate
conventional 7 weeks of external radiotherapy, the overall treatment time has been shortened by 16 days (i.e. from 49 to 33 days). Both external and 3D-CBRT were well tolerated by the patients and the incidence of late 5-year actuarial moderate urinary complications (grade III) was about 8%; with only 0.5% of gastrointestinal grade III complications. An interesting suggestion is to use 3D-CBRT as monotherapy, consisting of 4 fractions (twice-a-day) of 9.5 Gy in 2 days [6]. Preliminary results look very encouraging, with 17% of acute effects and without grade III-IV acute complications (Table V.C).

To test a new technique of 3D-CBRT we have started a detailed pilot clinical study using 10 Gy as a single boost dose (Table V.D). The advantage of our schedule as compared with the studies of Martinez is that both external and interstitial irradiation were conformal. We found this schedule feasible and very well tolerated by patients. The low incidence of grade III effects in our series is similar to that reported by Martinez et al [2, 5, 6]. Although it is almost impossible to distinguish between the acute effects related to external and interstitial irradiation, the 3D-CBRT did not cause any increase in the severity of acute effects. Mild perineal pain in 11% of patients was transient, and did not influence the level of good tolerance.

Dosimetric results showed that the parameters of D100, D90 and D10 were within the acceptable limits recommended by the American Brachytherapy Society and similar to those reported by Martinez. It may suggest that 3D-CBRT is a precise conformal technique of treatment. Prostate motion may influence dose dosimetry and it is likely to be a serious problem in external beam radiotherapy. It calls the use of larger PTV. However, for the single dose of 3D-CBRT used in our study this problem can be ignored. Martinez et al, [2] have pointed out that the prostate motion is predominantly in the superior portion of the gland and in the anterior-posterior direction and it may occur between fractions with the potential to change the dose received by the target. However, the authors did not detect significant anteroposterior motion. Using real-time TRUS imaging with on-line dosimetry they have been able to make corrections for minor prostate displacement and to contour any changes prior to each conformal CBRT fraction.

The main objective of conformal 3D-ERT and 3D-CBRT is to improve locoregional control and long-term BNED. Although our early results are encouraging, the interpretation should be very careful. In contrast to Martinez’s studies, which had included a wide range of favourable and unfavourable cases, our pilot study included only T1-2N0M0 prostate cancer patients, mostly with favourable PSA level and Gleason score. Therefore the relatively high rate of 97% of 1-year BNED is not surprising. Gaining experience in the first step of clinical studies on 3D-CBRT, the combination 3D-CBRT fractions interdigitated with external conformal ERT looks very promising, especially because the dose can be further intensified by shortening the overall treatment time by another 1-2 weeks. A significant, and probably the most important advantage, is the radiobiologic benefit of 3D-CBRT. Brenner and Hall [11] have, in 1999, presented the suggestion that the sensitivity of prostate cancer to changes in dose-per-fraction might be extremely and uniquely high. Despite the criticism raised of by some authors, there is significant experimental and clinical evidence that the α/β ratio for prostate cancer could be very low (1.5 Gy with 95% CI: 0.8-2.2 Gy), and much lower than that for late responding tissues [8-10]. Using the Martinez data for 3D-CBRT [5] Brenner et al. [11] estimated an α/β ratio of 1.2 Gy (95% CI: 0.03-4.1 Gy).

Comparing α/β values estimated for various sets of data of the ERT and/or BRT, D’Souza and Thomas [9] have concluded that the uncertainties might be inherent in such comparisons (differences in dose distribution, dose rate, and type of radiation) and they imply that a broad range of α/β ratios is possible but still with the value remaining low.

If this is true, and the α/β value for prostate cancer control is low, the consequences for prostate cancer radiotherapy could be significant and leading to hypofractionation as an ideal solution. This radiobiological rationale was used by Stromberg and Martinez [7] to design hypofractionated 3D-CBRT interdigitated with external irradiation. Four daily fractions of external irradiation prior to each implant fraction at the end of week 1, 2 and 3 were assumed to depopulate tumour cells. Three CBRT fractions should prevent sublethal damage repair at the cellular level. The biologically equivalent doses (BED) calculated for two CBRT regimes (Table V, A-2 and C) are considerably high, in the range of 119-131 Gy. Such BED would be extremely difficult to achieve even with external IMRT.

Using different ERT and BRT fraction sizes it is difficult to compare the biological effectiveness of various treatment schedules. Therefore, we used the following Normalized Biologically Effective Dose (NBED) formula proposed by Fowler et al [10]:

\[
NBED = D_{\text{new}} \left(1 + \frac{d_{\text{new}}}{\alpha/\beta}\right) / (1 + 2.0/\alpha/\beta)
\]

which allows to normalize various schedules to a conventional 2.0 Gy fraction regimen. Table V shows the NBED values for three α/β ratios representing acutely responding tissue (i.e. the mucosa) (α/β=10 Gy), the rectum (α/β=3.0 Gy), and prostate cancer (α/β=1.5 Gy). For schedule “A-2” the NBED for prostate cancer is 131.4 Gy for and for rectum and normal mucosa the respective NBED are lower by 15% and 20%, respectively. It suggest that the therapeutic gain in the tumour can be achieved together with a lower risk of late rectal complications and even with lower risk of acute mucosal effects which, in fact, has been noted in the Martinez and their studies. For CBRT as monotherapy (Table V.C) the difference between biological doses for tumour and
normal tissues is even larger. In our pilot study this tendency can also be noted with NBED of 86.8 Gy\textsuperscript{1.5} for the prostate (Table V, D). It suggests that there is still room to escalate the boost dose delivered by 3D-CBRT. Fowler et al. [10] suggest to use 10 fractions of 4.77 Gy. It would overdose the prostate tumour by 15.3% BED, equivalent to a NTD of 85 Gy in 2 Gy fractions, whereas the rectal tissue would receive the equivalent of a NTD of 74 Gy. This would also cause a 10% reduction in NTD for early responding tissues. It is difficult to decide which combination of CERT and CBRT may provide the highest benefits, but there is no doubt that conformal ERT combined or interdigitated with a TRUS-guided real time conformal brachytherapy boost provides precise dose delivery. This is well tolerated and effective treatment modality for some patients with prostate cancer (especially with a large target volume). The accurate selection of patients and the choice of an optimal combination of irradiation regimes need further clinical studies and randomized trials to evaluate the real beneficial effect.

Conclusions

A pilot study on 3D-real time CBRT using a single boost dose of 10 Gy combined with 54 Gy in 27 fractions of conformal external irradiation has proven that this is a well tolerated treatment modality in case of patients with T1-2N0M0 prostate cancer. There is still radiobiological room to intensify the treatment towards factionated 3D-real time CBRT interdigited with external irradiation.

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References