Reduced Rectal Toxicity with Ultrasound-Based Image Guided Radiotherapy Using BAT™ (B-Mode Acquisition and Targeting System) for Prostate Cancer

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Purpose: To evaluate the effect of image guided radiotherapy with stereotactic ultrasound BAT (B-mode acquisition and targeting system) on rectal toxicity in conformal radiotherapy of prostate cancer.

Patients and Methods: 42 sequential patients with prostate cancer undergoing radiotherapy before and after the introduction of BAT were included. Planning computed tomography (CT) was performed with empty rectum and moderately filled bladder. The planning target volume (PTV) included the prostate and seminal vesicles with a safety margin of 1.5 cm in anterior and lateral direction. In posterior direction the anterior 1/3 of the rectum circumference were included. Total dose was 66 Gy and a boost of 4 Gy excluding the seminal vesicles.

22 patients (BAT group) were treated with daily stereotactic ultrasound positioning, for the other 20 patients (NoBAT group) an EPID (electronic portal imaging device) was performed once a week. Acute and late genito-urinary (GU) and rectal toxicity and PSA values were evaluated after 1.5, 3, 6, 9 and 12 months. The total median follow up of toxicity was 3 years in the BAT group and 4 years in the NoBAT group.

Results: In the NoBAT group significant more rectal toxicity occurred, while in GU toxicity no difference was seen. Two patients in the NoBAT group showed late rectal toxicity grade 3, no toxicity > grade 2 occurred in the BAT group. There was no significant difference in PSA reduction between the groups.

Conclusion: Without BAT significant more acute and a trend to more late rectal toxicity was found. With regard to dose escalation this aspect is currently evaluated with a larger number of patients using intensity-modulated radiotherapy (IMRT).

Key Words: Image guided radiotherapy · Stereotactic ultrasound BAT · Rectal toxicity · Prostate cancer

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Reduzierte Rektumtoxizität mit bildgestützter Radiotherapie mittels BAT™ (B-Mode Acquisition and Targeting-System) beim Prostatakarzinom

Hintergrund: Ziel dieser Auswertung war es, den Effekt der bildgebungsgestützen Strahlentherapie mittels stereotaktischem Ultraschall-BAT (B-mode Acqusition and Targeting-System) auf die Akut- und Spättoxizität am Rektum sowie auf den Verlauf der PSA-Werte zu ermitteln.

Patienten und Methodik: 42 Patienten mit Prostatakarzinom wurden in die Auswertung eingeschlossen (Tabelle 1). Die Planung erfolgte standardisiert mit entleertem Rektum und moderat gefüllter Blase. Es wurde ein Planungszielvolumen (PTV) unter Einschluss der Prostata und Samenblasen mit einem Sicherheitsabstand lateral und anterior von 1,5 cm definiert. Posterior wurde maximal das vordere Rektumdrittel eingeschlossen. Die Gesamtdosis betrug 66 Gy mit einem Boost unter Ausschluss der Samenblasen mit nochmals 4 Gy.

Bei 22 Patienten erfolgte die tägliche Lagerungskontrolle mit stereotaktischem Ultraschall (BAT-Gruppe), bei den restlichen 20 (NoBAT-Gruppe) wurde einmal wöchentlich eine Verifikationsaufnahme (EPID) zur Lagerungskontrolle durchgeführt. Die Akuttoxizität und Spättoxizität an der Blase und am Rektum sowie der Verlauf der PSA-Werte nach 1,5, 3, 6, 9 und 12 Monaten wurden ermittelt. Der Beobachtungszeitraum der Patienten ohne BAT war 3–4 Jahre und mit BAT 2–3 Jahre.

Ergebnisse: In der NoBAT-Gruppe trat signifikant häufiger eine höhergradige Rektumtoxizität auf (Abbildungen 1 und 2), während sich bei der Blasentoxizität kein wesentlicher Unterschied in beiden Gruppen zeigte. Zwei Patienten aus der NoBAT-Gruppe hatten als Spättoxizität eine persistierende rektale Blutung. In der BAT-Gruppe fand sich keine Spättoxizität > Grad 2. Der Verlauf der PSA-Werte zeigte keinen relevanten Unterschied (Abbildung 3).

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Schlussfolgerung: Ohne BAT trat signifikant mehr Akuttoxizität und tendenziell mehr Spättoxizität am Rektum auf. Dieser Aspekt wird insbesondere im Hinblick auf eine Dosiseskalation an einer größeren Patientengruppe mit intensitätsmodulierter Strahlentherapie (IMRT) evaluiert.

Schlüsselwörter: Bildgebungsgestützte Strahlentherapie · Stereotaktischer Ultraschall BAT · Rektumtoxizität · Prostatakarzinom

Introduction

According to the American Cancer Society there will be more than 200,000 new cases of prostate cancer in the United States per year [13]. High-dose conformal radiotherapy, as seen in several dose escalation studies for external beam radiotherapy, improves clinical and biochemical outcome of patients with cancer of the prostate [10, 22, 24, 33, 34] .

Because of higher doses, margins needed to compensate prostate motion [2, 14] and other treatment uncertainties, there is an increased risk of dose limiting side effects [9, 32] or underdosing the target. To minimize toxicity while delivering high doses to the target, a possible solution would be to localize the prostate position daily before treatment. First data about the use of transabdominal ultrasound imaging to assess and correct patient setup according to the planning target volume was published from Troccaz et al. [29].

A transabdominal ultrasound-based targeting system that allows quick use and accuracy was therefore developed (BAT™: B-Mode Acquisition and Targeting system, NOMOS Corp, Sewickley, PA, USA).

Typical magnitude of shift can be from 0–1.5 cm in every direction. This movement is usually accounted for in treatment planning by adding margins around prostate clinical target volume (CTV) to achieve the planning target volume (PTV).

As shown in randomized radiotherapy dose escalation trials [2, 25, 33], there is a steep dose-effect relationship above 65 Gy where an increase of 10 Gy results in about 10% more PSA relapse free survival or increase the rate of freedom from failure from 43–62% for 70 Gy vs. 78 Gy.

However, increasing the dose to the prostate without limiting the dose to normal tissue, especially rectum and bladder, may result in unacceptable high rates of normal tissue damage. It has been shown that reducing the treatment volume by 3-D conformal radiotherapy results in less toxicity [24] and it may be expected that these rates can be lowered even more by using external fixation devices, electronic portal imaging or daily, direct visualization of the prostate in treatment position [23]. The pro's and contra's of the technique of stereotactic ultrasound are well described in the literature [1, 3, 5, 8, 16–19, 22, 27, 28]. An analysis of dosimetric consequences using stereotactic ultrasound with BAT in a theoretical model showed that a reduction of the rectal dose up to 23% is achievable [30, 31]. So far only few clinical data about the influence of stereotactic ultrasound on acute and late toxicity exist [11, 12, 21]. Therefore, the purpose of this study was, to evaluate the clinical effect of BAT on toxicity, especially late rectal toxicity, and on effectivity (e.g. PSA) in radiotherapy of prostate cancer.

Patients and Methods

In 2001 BAT was introduced at the Department of Radiation Oncology of the University Medical Center Mannheim for optimisation of daily patient positioning in radiotherapy of prostate cancer. We analyzed sequential patient groups before and after introduction of the method into clinical practice. During this time span no change in patient preparation, treatment planning, target volume definition or irradiation practice was performed. We included a total of 42 patients undergoing external beam radiotherapy for localized prostate cancer between 2001–2002 (NoBAT) and 2003–2004 (BAT). No patient received hormonal therapy at any time and all patients received 70 Gy conformal radiotherapy without irradiation of the pelvic lymph nodes. Exclusion criteria were therefore antihormonal therapy at any time doses below 70 Gy conformal radiotherapy and additional radiation of pelvic lymphnodes.

Planning computed tomography (CT) scans were performed with empty rectum (enema 30 min before) and moderately filled bladder using a slice thickness of 3–5 mm. PTV included the prostate and seminal vesicles with a safety margin of 1.5 cm in anterior and lateral direction. In posterior direction the anterior 1/3 of the rectum circumference was included. Using a four-field box the PTV was treated with a total dose of 66 Gy. In addition a boost-PTV excluding the seminal vesicles was treated with 4 Gy in single dose fractions of 2 Gy. Besides the standard contours of PTV and organs at risk, it is necessary to contour the prostate, seminal vesicles, bladder and rectum anatomically. The treatment plan isocenter and the anatomical contours are exported as RTOG (radiotherapy oncology group) data to the BAT system. There was no difference in dose volume histograms (DVH) in both groups.

Before daily treatment patients were requested to empty the bladder 0.5 h before treatment and to drink half a litre of water. Also the rectum should be empty. In the treatment room the first step is the positioning relative to skin markers and in-room lasers. Then the ultrasound probe, which is connected via a position sensing robotic arm, is referenced to the gantry by a docking cradle mounted at the Linac head. Sagittal and axial transabdominal ultrasound images of the pelvic anatomy are acquired. A well filled bladder provides the appropriate acoustic window. It is important to visualize the position of the prostate itself as compared to the seminal vesicles because of their higher relative mobility. The reference structures from treatment planning CT relative to the treatment isocenter are virtually overlaid on the acquired ultrasound images. If appropriate, the CT based contours can be virtually shifted on the touch screen in three dimensions to get a perfect match. If the virtual shifts are > 1 mm couch correction is necessary,

then the ultrasound probe is docked into a cradle connected to the treatment table. The table must be moved according to the shift vectors in three dimensions. After correcting the patient's positioning, another set of sagittal and axial ultrasound images are acquired. When a perfect match of the acquired ultrasound images (relative to the treatment isocenter) and the contour set from treatment planning (relative to planning isocenter) is achieved, radiation treatment can be started. If the recommended couch shifts were > 1 cm in antero-posterior/postero-anterior (ap/pa) direction, patients were requested to empty their rectum (e.g. using an enema).

In this way for 20 patients (NoBAT group, treated between 2001 and 2002) an EPID was acquired once a week as usual before introduction of the BAT method. Verification based on bone landmarks. If there was > 0.5 cm difference next day positioning was corrected based on the verification data. In a sequential, non-randomized fashion, 22 patients (BAT group) were treated with daily stereotactic ultrasound positioning (BAT group).

Acute toxicity e.g. of the rectum and bladder (GU) was prospectively scored weekly during radiotherapy according to RTOG scale. Late toxicity was scored according to the LENT-SOMA scale with a median follow-up of 3 years in the BAT group and 4 years in the NoBAT group. In addition PSA values were evaluated after 6 weeks, 3, 6, 9 and 12 months.

Statistical analysis was performed using SPSS, version 14.0.1 (SPSS, Chicago, IL, USA). Patient characteristics were analyzed using unpaired t-tests or chi-square tests. Toxicity parameters were analyzed using chi-square tests.

Results

Patient Characteristics

The mean pre-treatment PSA values were 10.1 ng/ml in the BAT group and 15.8 ng/ml in the NoBAT group. Most patients had T1 or T2 stage prostate cancer. About 70% of the patients had a Gleason score of 6 or 7. There were no statistically significant differences between the BAT and NoBAT treatment groups in terms of the distribution of patients by pre-treatment PSA level, stage, Gleason score, T category or age (Table 1).

In the BAT group a total of 524 BAT alignments were performed. The mean recommended couch shifts in lateral, longitudinal and ap/pa direction were 2 mm (max 2.03 cm, SD 3 mm), 3 mm (max 2.09 cm, SD 3.6 mm) and 5 mm (max 2.63 cm, SD 5.9 mm). Couch shifts more than our safety margins were < 10% (lateral: 0.5%, longitudinal 0.7% and ap/pa 6.6%).

Toxicity

There was no difference in acute GU toxicity (miction frequency, dysuria) between the two groups. Only one patient in the BAT group suffered from > grade 2 toxicity (pollacisuria grade 3 in week 6 and 7). Also in late GU toxicity there was no differences to observe (≥ grade 3: BAT group 3 patients, NoBAT group 2 patients).

Overall acute rectal toxicity was moderate, no patient suffered from toxicity > grade 2. There was a significant difference in proctitis especially in the 5th, 6th and 7th week of radiotherapy favouring the BAT group (week 5: p = 0.007; week 6: p = 0.010; week 7: p = 0.018) (Figure 1). Also diarrhoea > grade 2 occurred less frequent in the BAT group not reaching statistical significance (Figure 2).

Table 1. Patient characteristics. BAT: B-mode acquisition and targeting system.

Tabelle 1. Patientencharakteristik. BAT: B-mode Acquisition and Targeting-System.

	BAT	No BAT
Age median (range)	72.5 (60–82)	75.5 (65–84)
Gleason score		
2–5	2	2
6–7	17	13
8–10	3	5
Low risk	6	4
Intermediate risk	10	8
High risk	6	8
T Stage		
T1c	6	9
T2a	10	4
T2b	4	5
T2c	1	0
T3	1	2
Median PSA (ng/ml)	9.15 (1.7–37.0)	11.25 (5.0–46.0)

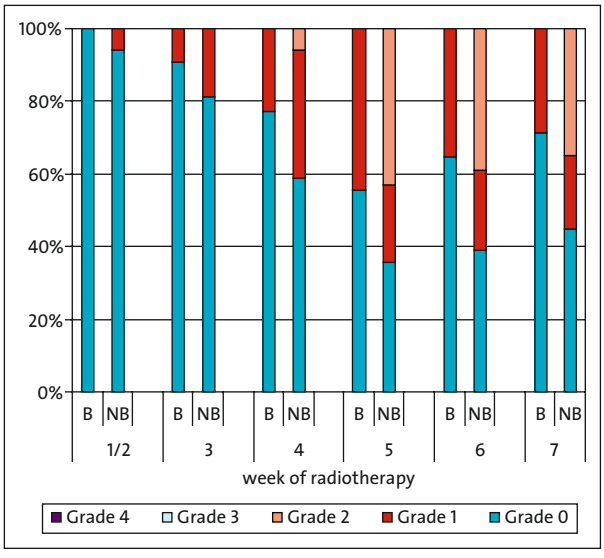

Figure 1. Acute proctitis during radiotherapy according to the RTOG (radiotherapy oncology group) scale. B: B-mode acquisition and targeting system (BAT); NB: no BAT.

Abbildung 1. Akute Proktitis während Radiatio nach den Toxizitätskriterien der RTOG (radiotherapy oncology group). B: B-mode Acquisition and Targeting-System (BAT); NB: kein BAT.

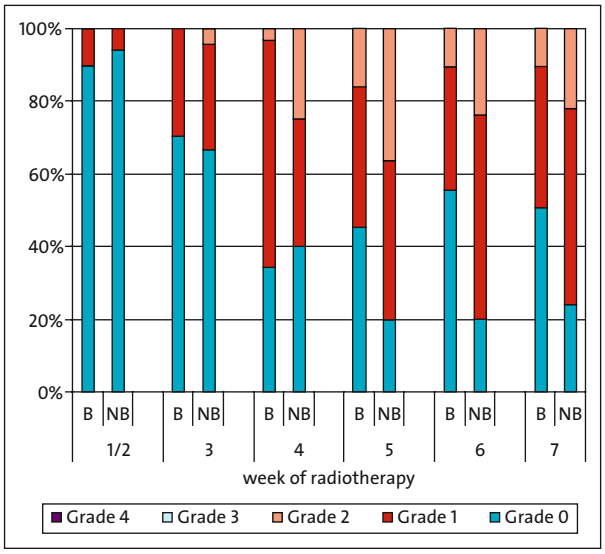

Figure 2. Acute diarrhoea during radiotherapy according to the RTOG (radiotherapy oncology group) scale. B: B-mode acquisition and targeting system (BAT); NB: no BAT.

Abbildung 2. Akute Diarrhö während Radiatio nach den Toxizitätskriterien der RTOG (radiotherapy oncology group). B: B-mode Acquisition and Targeting-System (BAT); NB: kein BAT.

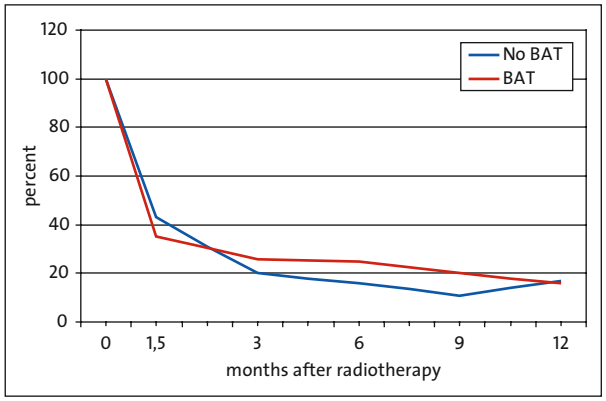

Figure 3. Percental decline of PSA values after therapy. BAT: B-mode acquisition and targeting system.

Abbildung 3. Prozentualer PSA-Abfall nach Therapie. BAT: B-mode Acquisition and Targeting-System.

No patient in the BAT group showed late rectal toxicity ≥ grade 3, while two patients in the NoBAT group showed grade 3 rectal late toxicity (rectal bleeding). Because of retrospective character of the examination there is no consistent documentation of late rectal toxicity, only bleeding or no bleeding was documented.

PSA

Starting with a pre-treatment PSA score of 10.1 ng/ml (SD 6.687) in the BAT group and 15.8 ng/ml (SD 11.907) in the NoBAT group, there was no difference in mean percental PSA reduction between the two groups (Figure 3).

Discussion

Ultrasound is a non-invasive, relatively easy and fast real-time image acquisition technique for targeting the prostate for radiotherapy. The technique of the BAT system is well described in the literature. Several studies evaluated the accuracy of stereotactic ultrasound in comparison with CT or fiducal markers [15, 17, 20, 26]. Also image quality, inter-/intra-user variability and the influence of probe pressure has been investigated in detail [1, 3, 5, 8, 27]. Only few studies reported the influence of daily image guidance using stereotactic ultrasound on acute and late rectal toxicity [11, 12, 21]. The current investigation analyzes the use of BAT system compared with a sequentially treated group in which no ultrasound was used.

There was no difference in post treatment PSA reduction between the two groups. The PSA values from 6 weeks up to 12 months after radiation therapy showed an equal percental decrease. There was no PSA follow-up more than 12 months in the BAT group, so we reported no further data in the NoBAT group.

Because of the institutional policy for treatment planning with empty rectum and filled bladder, the prostate can only move towards the symphysis (anteriorly in relation to the bony anatomy). Because of safety margins of 1.5 cm in this direction, without image guidance there is no loss of dose at the prostate, only the potential for increased rectal toxicity.

In addition, the current results suggest that use of the BAT system did not affect the rate of acute GU problems like dysuria or frequency of during day or night. One reason for these findings might be the identical dose to the prostatic urethra, which seems to be one factor for GU symptoms. The dose in this area was similar in the BAT and NoBAT group.

The main finding, however, a reduced incidence of acute gastrointestinal toxicity in the BAT group is in line with the literature. Mohan et al. also found encouraging low acute rectal toxicity using BAT in combination with IMRT [21]. The explanation for this finding is also in the preparation of patiens: When treatment planning is performed on an empty rectum, any difference in rectal filling during actual treatment will inevitably increase rectal wall exposure over the plan DVH which provides an estimate of both minimal tumor and rectum dose. We opted for this paradigm to avoid the experience of de Crevoisier et al [4], who planned on CT with full rectum, thus getting DVH that represent estimates of maximum tumor- and rectal doses. In their case, the systematic error introduced by planning on a full rectum led to effective underdosing of the tumor. We chose planning on an empty rectum to avoid underdosing the tumor, accepting an effectively systematically higher dose to the rectum over a fractionated treatment. Image guidance corrects this systematic difference between planned and treated rectum DVH while not changing dose to the tumor, thus reducing rectal toxicity but not further improving PSA control. Especially dose to the posterior rectal wall is reduced,

which is similarly reported when endorectal balloons are used [6, 7]. Wertz et al. analyzed in a theoretic model the dosimetric consequences of positioning correction with BAT. They found, that with correction the mean rectal dose can be significantly reduced [31], especially when radiotherapy is performed as IMRT [30]. In our clinical evaluation late rectal toxicity grade 3 (rectal bleeding) occurred in two patients of the NoBAT group (10%), no patient of the image guided radiotherapy (IGRT) group showed rectal toxicity grade 3 or higher. Even with this small number of patients a trend towards lesser acute and late rectal toxicity with stereotactic ultrasound was seen.

Conclusion

Image guided radiotherapy using stereotactic ultrasound in 3-D conformal radiotherapy of prostate cancer reduces acute and late rectal toxicity. This is currently evaluated with a larger number of patients and with further dose escalation using IMRT.

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