Effect on prostate volume following neoadjuvant treatment with an androgen receptor inhibitor monotherapy versus castration plus an androgen receptor inhibitor in prostate cancer patients intended for curative radiation therapy: A randomised study

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Abstract. To avoid pubic arch interference, prostate cancer patients are treated with neoadjuvant androgen deprivation therapy (ADT) to achieve prostate volume (PV) reduction prior to radiation treatment. The aim of the present randomised study was to compare the effects on PV of two regimens of ADT, an androgen receptor inhibitor monotherapy vs. castration plus an androgen receptor inhibitor. Consecutive patients with non-metastatic prostate cancer were included in a randomised neoadjuvant study, comparing an androgen receptor inhibitor monotherapy vs. castration plus an androgen receptor inhibitor. PV was assessed prior to the start of endocrine neoadjuvant treatment and prior to the start of radiation therapy (RT). PV assessment was performed by transrectal ultrasound. A total of 110 patients were included. Final sample constituted 88 (80%) patients due to lack of PV information. Castration plus an androgen receptor inhibitor was more effective in PV reduction compared with an androgen receptor inhibitor alone (P<0.001). Planning target volume decreased in the combination arm. There was no significant difference in clinical or demographic or length of neoadjuvant hormonal treatment between the groups. Overall, a significantly larger PV reduction was achieved by castration plus androgen receptor inhibitor, as compared with androgen receptor inhibitor monotherapy. The PV reduction, however, appeared not to translate into better health associated quality of life during the subsequently given curative intended combined EBRT and HDR-brachytherapy. Potential differences between these two treatments regarding anti-tumor effects on micro metastatic disease and radiation potentiating effect remains to be addressed in future prospective trials.

Introduction

Prostate volume (PV) plays an important role in planning for radiation therapy (RT). Smaller PV implies smaller areas of organs-at-risk in Planning Target Volume (PTV) before start of RT, thus minimizing side effects from normal surrounding tissues. Larger PV, on the other hand, demands radiation of larger areas, thus increasing the risk of side effects. One theoretical rationale for offering endocrine therapy in the neoadjuvant setting before RT is to reduce the PV. There is convincing evidence from several previous studies that a short period of ADT prior to the radiation therapy may reduce PV by 25-40% (1-6). ADT used in these studies varied among luteinizing hormone release hormone (LHRH)-analogue alone, or in combination with anti-androgen or surgical castration only, or a combination of anti-androgen and 5-alfa reductase inhibitor. Whittington et al (7) showed, by using LHRH-analogue, that the greatest decrease of PV occurred in those with the largest PV at baseline. Thus, it remains as physicians' options to use ADT to get maximum volume reduction.

There are different methods for volume measurement of prostate gland. Minimally invasive surgery has shown that ultrasound is the ideal imaging system for targeting treatments because of its ease of use and the absence of adverse effects (8). Computed tomography (CT) derived estimations of PVs are generally larger than PV assessed by Magnetic Resonance, especially towards the seminal vesicles and the apex of the prostate (9). In addition, a PV evaluation in ten patients before prostate brachytherapy showed that the CT-based prostate volumes ranged from 31.1 cubic centimetres (cc) to 48.1 cc, whereas corresponding figures for transrectally ultrasound (TRUS)-based volumes were 26.6 to 46.4 cc (10). Furuya et al (11) showed prospectively, by using TRUS, that ADT significantly decreased prostate- and seminal vesicles...
volumes. Thus, TRUS assessed PV is expected to generate PTVs including minimum volumes of organs-at-risk.

There is, to our knowledge, no published randomised study addressing differences in PV reduction following treatment with an androgen receptor inhibitor monotherapy vs castration plus an androgen receptor inhibitor. Thus, the aim of the present study was to compare changes in PV in the randomised ADT study (12). The hypothesis was that PV reduction would be larger in the combined group compared to androgen receptor inhibitor monotherapy, and that PTV subsequently would be smaller in the castration plus androgen receptor inhibitor group.

**Patients and methods**

**Patients.** Consecutive patients with localised prostate cancer intended for curative treatment with radiotherapy were included in the randomised ADT study (12). The primary aim of the ADT study was to compare health-related quality-of-life (HRQoL) between the two groups over time. All patients were treated at a single institution, the Department of Oncology, Karolinska University Hospital, Sweden. Included patients signed an informed consent form before randomisation to an androgen receptor inhibitor monotherapy or to castration plus an androgen receptor inhibitor.

**Methods.** Between 2005 and 2011 a total of 110 patients were included in the ADT study (12). Before 2008, the referring urologist measured PV (Volume 1) before referral to the Department of Oncology. Between 2008 and 2011 PV measurement were routinely performed at the Department of Oncology to ensure homogeneity. Second PV measurement (Volume 2) was performed before start of HDR brachytherapy, about three months after randomization. Planning target volume was calculated on the basis of clinical imaging techniques and MRI (if available). The cut-off was set to 10% for increase, based on one study done by Henderson and co-workers (5) where 8% increase in PV was noted in patients without hormonal therapy. The between group comparison of PTV was performed by unpaired t-test. The cut-off 20% for decrease in PV was set as minimum reduction would be larger in the combined group compared to androgen receptor inhibitor monotherapy, and that PTV subsequently would be smaller in the castration plus androgen receptor inhibitor group.

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**PV assessment.** TRUS (BK Medical endocavity biplane Transducer 8848.12-4 MHz) was used to measure PV at the Department of Oncology. The procedure was performed in an operating room with the patient in the dorsal lithotomy position. The TRUS transducer was positioned in a stepping device that allowed the prostate to be scanned systematically in both axial and sagittal planes. The ultrasound system permitted very accurate volume and surface outline calculations of the prostate and seminal vesicles. The height and width were measured in the transverse plane and length in the sagittal plane. Ultrasound apparatus then generated the volume automatically. The results were recorded in the patients’ medical chart, providing the physicians access to individual results during patient consultations.

**Assessment of HRQoL.** The patients completed HRQoL questionnaires after informed consent and before randomisation, and again before start of RT, about three months after randomisation. The European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) and the EORTC Prostate Cancer Specific Module (EORTC PR-25) were used (13,14).

**Statistical methods.** Absolute differences in PV between the baseline and the follow-up assessment were tested for each group by the paired t-test. The mean paired change is presented together with 95% confidence intervals. Differences between the study groups at baseline and at follow-up were estimated and tested using linear regression models. At the follow-up visit differences were estimated both by not including Volume 1 in the model (univariate analysis), and by including the Volume 1 in the model (multivariate analysis). P-values from these models refer to Wald tests. All statistical analyses were based on the ‘intention-to-treat’ principle.

The cut-off 20% for decrease in PV was set as minimum decrease, based on the observation from similar studies (1-5). The cut-off was set to 10% for increase, based on one study done by Henderson and co-workers (5) where 8% increase in PV was noted in patients without hormonal therapy. The between group comparison of PTV was performed by unpaired t-test.

The HRQoL results are presented as mean differences and 95% confidence intervals (CIs). The reported P-values are two-sided and refer to Wald tests. A P-value of ≤0.05 was considered statistically significant.
Results

The baseline clinical characteristics by randomisation groups are presented in Table I. A total of 110 patients were included in the neoadjuvant study (12). Eleven patients were, however, not included in the present analyses as information of PV at baseline was lacking. Another 11 patients were excluded because they were treated with EBRT only, where volume measurement was not performed routinely at RT start. Reasons for not being subjected for combined EBRT-brachytherapy (11 patients) were the following: ‘No decrease in PV after AA’ (1 patient), ‘PV>65 cc’ (3 patients), ‘Earlier transurethral resection of prostate’ (3 patients), ‘Co-morbidity’ (3 patients), ‘Lobus tertius’ (1 patient). Thus, 88 patients (80%) remained to be analysed, 45 patients (51%) in Group A and 43 patients (49%) in Group B. Two patients switched over from Group A to the Group B (however treated with LHRH analogue only) due to liver toxicity, but were included per the intention-to-treat principle.

Castration plus an androgen receptor inhibitor was more effective in PV reduction as compared to androgen receptor inhibitor monotherapy (P<0.001) (Table II). Mean volume reduction was 28% (30 to 21.6 cc) and 17.5% (33 to 27.2 cc) respectively. In Group A, PV was reduced by ≥20% in 23 patients (51%). Corresponding fig. for Group B was 34 patients (79%). PV was increased by ≥10% in 4 patients (8%) in Group A and in 1 patient (2%) in Group B. The time between the assessments was similar in both groups. There was no statistically significant difference in duration of neoadjuvant treatment or in clinical and demographic variables between the two groups.

A comparison of prostate target volume (PTV) for the planning of radiotherapy revealed a statistically significant difference (P>0.001) between the two groups in mean volume, 47.4 cc (SD=12.8) in Group A vs. 37.9 cc (SD=7.6) in Group B.

At the assessment after the first 3 months statistically significant differences between the groups in ‘overall quality of life’, ‘fatigue’, and ‘sexual interest’, favouring Group A (Table III). No other between group differences was found for HRQoL.

Discussion

PV plays an important role when planning irradiation with curative intention in prostate cancer, since large PTV may affect organs at risk and subsequent radiation related
side effects. PV reduction is one of the rationales for using neo-adjuvant ADT to minimize the radiation field, and thus the side effects. In the present, prospective study, castration plus an androgen receptor inhibitor significantly decreased PV more than androgen receptor inhibitor monotherapy and subsequently PTV was smaller in Group B than in Group A. One retrospective study showed, in 22 patients, that the median percentage of volume reduction after combination group was 25% (4). Another non-randomised prospective study showed an 8% volume reduction in the bicalutamide group compared to a 26% reduction in the goserelin group after final analysis of 81 patients (5). Thus, our hypothesis was in concordance with results from other studies.

In the present study PV was increased by ≥10% in 4 patients (8%) in Group A and in 1 patient (2%) in Group B. This finding is surprising, as no other study has, to our knowledge, reported similar findings. The increase in PV during ADT treatment might be explained by the fact that the same physician did not assess PV at the first point of assessment and at the second measurement three months later. Thus, the absolute figures for PV should be considered with caution. Ideally, the same physician should have performed both assessments. Kuczynski et al (15) mentioned in their study that one of the sources of error in measurement of PV was inter-physician variability, and pointed out that variability in PV measurement is unavoidable. Patients in both randomised groups in our study suffered this variability to the same extent. Thus, we do not consider this to hamper our results.

RT has many side effects that are expected to negatively influence patients' quality of life. A cross sectional study of 989 prostate cancer patients treated with RT showed that defecation urgency was the most common symptom among survivors after 2-14 years' follow-up, followed by faecal leakage and loose stools (16). Similar results have been presented in patients treated with pelvic irradiation, both men and women, where defecation urgency and faecal leakage has been identified as the most disturbing of all radiation-induced symptoms (17-21).

In the neoadjuvant study (12), differences between the groups at the three months' assessment, before the start of RT, were found for ‘overall quality of life’, ‘fatigue’ and ‘sexual interest’, all in favour of monotherapy. These differences were expected, as castration obtained in Group B might cause these problems. About 18 months after randomization (around nine months after termination of RT), statistically significant differences were found for ‘cognitive functioning’ and ‘sexual interest’ (12). There were, however, no differences in urinary or bowel symptoms at this assessment point. These findings were surprising, as the smaller volumes irradiated in the combination group were expected to result in lower levels of urinary and bowel symptoms. One possible explanation may be that combined EBRT BT irradiated both groups, and that the small putative differences in side-effects caused by volume differences of the external RT were outweighed by side effects from the brachytherapy.

The randomized prospective single-centre design is the strength of our study. In addition, TRUS was used to perform assessment of PV, which is one of the most reliable methods for this kind of assessment. Two urologic-oncologists, knowledgeable of radiation planning in prostate cancer, screened all patients' medical charts carefully. One weakness of the study is that the results would be more reliable if PV measurement...
had been confined to the same physician at both points of assessment. Sample size is another weakness of the study.

In summary, a significantly less prominent PV reduction was achieved following neoadjuvant ADT using an androgen receptor inhibitor monotherapy compared to castration plus an androgen receptor inhibitor. This PTV reduction, however, appeared not to translate into a more favourable quality of life profile during the subsequently given curative combined EBRT-brachytherapy. Potential differences regarding anti-tumoral effects on micro metastatic disease and radiation potentiating remains to be addressed in future prospective trials.

References


