3D-conformal radiotherapy for prostate cancer – does daily image guidance with tighter margins improve patient reported outcomes compared to weekly orthogonal verified irradiation? Results from a randomized controlled trial.

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Contributors:

JÅL, AS, BA, ADW, CAJ, SK and SL planned the study initially and amended the protocol together with HT in 2012. JÅL, AS, BA and HT enrolled patients and collected data at the study centres. SL was responsible for statistical planning and data analysis in collaboration with the first and last authors. JÅL, HT and AS were responsible for data collection and drafted the manuscript. JÅL and HT has contributed equally as first authors. All authors were involved in revision and have approved the final manuscript.

Declaration of interests:

Dr Kaasa reports a patent Eir Solution AS licensed.
All other authors declare no conflicts of interests

Running head:

Randomized controlled trial of Cone Beam CT IGRT in prostate cancer

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Keywords:

3D conformal radiotherapy, prostate cancer, IGRT, Phase III trial, RCT, rectal side effects.

Abstract :

Background:

Novel cancer drugs are subject to strict scientific evaluation of safety and efficacy and usually undergo a cost effectiveness analysis before approval for use in clinical practice. For new techniques in radiotherapy (RT) such as image-guided radiotherapy (IGRT), this is often not the case. We performed a randomized controlled trial to compare daily cone beam computer tomography (CBCT) IGRT with reduced planning target volume (PTV) margins versus weekly orthogonal portal imaging with conventional PTV margins. The primary aim of the study was to investigate the effect of two different image guidance techniques on patient reported outcome (PRO) by using early side effects as proxy outcome of late rectal side effects in patients receiving curative 3D-conformal RT for prostate cancer.

Methods:

This open label, phase 3 trial conducted at two RT centers in Norway enrolled men aged 18 years or older with previously untreated histologically proven intermediate or high-risk adenocarcinoma of the prostate. Patients eligible for radical 3D-conformal RT received 3 months of total androgen blockage and were randomly assigned to 78 Gy in 39 fractions guided either by weekly offline orthogonal portal imaging (15 mm margins to PTV) or by daily online CBCT IGRT (7 mm margins to PTV). Based on previous results indicating that acute rectal side effects are a valid proxy outcome for late rectal side effects, the primary outcome was acute rectal toxicity at end of RT as evaluated by rectal bother scale (five of the items from PRO's QUFW94). The RIC-trial is registered with ClinicalTrials.gov, number NCT01550237.

Findings:

Between October 2012 and June 2015, 257 patients were randomly assigned to weekly offline portal imaging (n= 129) or daily online CBCT Image-guided 3D conformal radiotherapy (n=128). Out of 250 evaluable patients, 96 % completed PRO's at baseline and 97 % at end of RT. Baseline analyses demonstrated balance between groups for baseline characteristics as well as for PRO's. In general, patients reported small degree of side effects at end of RT, and there was no difference between groups for primary outcome (rectal bother scale of QUFW94 1.871 vs 1.884, p=0.804). In addition, there were no significant differences between groups

for any other gastrointestinal or urinary symptom as reported by QUFW94 or health related quality of life analyses (EORTC QLQ 30).

Interpretation:

In radical 3D conformal RT for prostate cancer, daily CBCT IGRT with reduced PTV margins demonstrated no advantage with respect to patient reported side effects at end of RT as compared to weekly orthogonal offline portal imaging with standard PTV margins.

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Introduction:

Rectal bleeding, increased urinary frequency and loss of erection constitute common side effects of curative external beam radiotherapy (EBRT) for prostate cancer [1, 2]. Previous studies have demonstrated that acute urinary and rectal side effects independently predict corresponding late radiotherapy-induced toxicity[3, 4]. Stereotactic- Body- Radiation -Therapy (SBRT), Intensity-Modulated Radiation- Therapy (IMRT) and Volumetric-Modulated Arc-Therapy (VMAT) are examples of new techniques implemented in RT presumably to reduce such unwanted effects. However, such technological progress is rarely subject to empirical prospective testing in well-designed clinical trials. IMRT/VMAT is now considered standard therapy for prostate cancer according to guidelines from the European Association of Urology (EAU) even though there is a lack of scientific reports providing level one evidence of clinical benefits in patients[5].

The introduction of 3-dimensional imaging techniques such as ultrasound, Computer Tomography (CT) and Magnetic Resonance Imaging (MRI) have increased understanding of internal organs motion during RT planning and delivery [6]. Moreover, IGRT using fiducial gold markers implanted in the prostate gland and 3-dimensional Cone Beam CT (CBCT) as well as the use of continuous electromagnetic monitors (e.g. Calypso®System, Seattle, Wash., USA) improves accuracy [7].

Such modern prostatic IGRT reduces the magnitude of systematic errors effectively but not random errors such as day-to-day variations in set-up positioning [8].

More exact patient positioning combined with daily CBCT of the target volume, enables safety margin reductions, radiation dose escalation and enhanced local tumor control, although at a higher cost compared to weekly CBCT-verification [9].

Several non-randomized studies have reported that modern IGRT may reduce radiation-induced toxicity in prostate cancer patiens[10, 11]. However, to our knowledge no randomized controlled trials (RCTs) have compared clinical outcomes following daily IGRT online versus weekly offline orthogonal portal imaging [12-15].

A survey conducted among physician members of the American Society for Radiation Oncology (ASTRO) has recently called for consensus guidelines and further evidence-based approaches for planning target volume (PTV) margin selection to ensure safe and cost-effective use of IGRT [16].

To explore the effect of different image guidance techniques on acute rectal side effects in curative 3D-conformal EBRT for prostate cancer, we have performed a RCT comparing daily

online CBCT-IGRT with reduced (PTV) margins vs weekly offline orthogonal portal imaging with conventional PTV-margins. Herein we report the results of the first analysis of Patient Reported Outcomes (PRO) on acute gastrointestinal (GI) side effects. The RIC-trial is registered with ClinicalTrials.gov, number NCT01550237.

Methods and Patients:

The RIC-trial included men younger than 80 years with histologically proven intermediate or high risk non-metastatic prostate cancer [17]. Patients with metallic hip joint replacements, previous cancer treatment the last 5 years, previous RT except for kilovolt (kV) treatment outside the pelvis, patients unable to perform a magnetic resonance imaging (MRI) or patients with abnormal kidney or liver function were excluded. Patients were enrolled at two centers in Mid-Norway; Department of Oncology, Ålesund Hospital, and The Cancer Clinic, St. Olav's Hospital, Trondheim University Hospital. Randomization was computer based, stratified by center and risk (high vs. intermediate) group. All patients received 6 months of total androgen blockage (TAB) with Gosereline acetate and Bicalutamide started 3 months neo-adjuvant prior to prostatic irradiation with 78 Gy in 2 Gy's fractions. High-risk patients received Bicalutamide for an additional 2.5 years. Four prostatic gold fiducial markers were implanted during the neo-adjuvant period. Approximately one week before RT, patients giving their written informed consent were randomly assigned to receive 0-70 Gy RT in which position control was done by weekly offline orthogonal portal imaging (standard treatment, arm A) or with daily CBCT verification (experimental treatment, arm B). An IGRT boost from 70-78 Gy with daily verification was applied in both arms. Elective pelvic nodal irradiation was not applied.

Radiotherapy planning:

CT and MRI for dose planning was performed no more than 24 hours apart and less than one week prior to start of RT with the same instructions for rectal and bladder filling. There were no routinely rectal emptying and participant were encouraged to urinate one hour prior to examination and drink 300 ml of water during the last hour before examination. Prescription and reporting of RT-volumes and doses were based on International Commission on Radiation Units & Measurements (ICRU) recommendations [18]. Target volume delineation

was based on clinical findings; CT-scans eventually fused with T1+T2 MRI-scans at the doctor's discretion. The following target volumes were defined:

Clinical target volume (CTV) prostate: the prostate including any suspected extra capsular tumor growth or infiltration into the seminal vesicles (SV) as described by clinical findings, trans-rectal ultrasound and/or pelvic MRI. The CTV-prostate/SV included the basal 1 or 2 cm of the SV in intermediate and high-risk patients, respectively.

In patients receiving standard treatment (arm A), the planning target volume (PTV2) receiving 0-70 Gy included the CTV-prostate/SV with an additional 15 mm margin in all directions. In arm B the corresponding PTV2 (0-70 Gy) included the CTV-prostate/ SV with an additional 7 mm margin in all directions.

The PTV 1 (70-78 Gy) was equal to the CTV-prostate with an additional 3 mm margin in both study arms. The following organs at risk (OARs) were delineated: Rectum, defined as the outer contour of the rectal wall from the recto-sigmoid junction to the anal canal, the corresponding rectal mucosa, defined as a 2 mm thick layer limited by air on the inside. Additionally, the urinary bladder, testicles, femoral heads, anal canal and penile bulb were delineated.

CT-based, 3D-conformal treatment planning was mandatory, as were multi- leaf collimators (MLC). Using a four-field box technique with necessary supplemental field segments, 15 megavolt (MV) photon beams from 0 to 70 Gy were applied. For the 70-78 Gy boost, a 5 field (1 anterior, 2 oblique anterior and 2 lateral) technique was applied. Isocenter was placed in the fiducial gold marker located closest to the base of the prostate. The target volume doses should be within 95-107% of the prescribed dose. However, the rectal dose constraint was defined as 60 Gy to no more than half of the circumference in both study arms. If necessary, posterior blocking with MLC was accepted.

Dose-volume histograms were retrieved from the treatment planning system for rectal volumes receiving 50 Gy or more (V50 Gy) and 60 Gy or more (V60 Gy). Treatment planning was performed in Oncentra v4.3 (Elekta AB, Sweden) and patients were treated on Elekta Synergy® or Elekta Precise platforms.

Verification procedures:

Study arm A: After alignment by skin markers, position was controlled by 2-D MV portal imaging of fiducial markers on treatment days 1-3 and then weekly. All systematic errors were corrected after the third fraction, and an action level of 10 mm were used for the weekly controls. Shifts >10 mm required two consecutive controls the next days and the overall systematic errors were corrected for all subsequent fractions. On treatments 36-39, daily online corrections of position were performed based on orthogonal MV-imaging of fiducial markers and errors > 2 mm were corrected, as only the CTV with a small margin was treated from 70-78Gy.

Study arm B: After alignment by skin markers, 3D kV imaging with CBCT of prostate with fiducial markers were performed and all localization errors corrected prior to each fraction (treatment 1-39).

Measures:

Bowel symptoms (primary endpoint) and urinary symptoms (secondary endpoint) were measured using the validated self-assessment questionnaire QUFW94, aka Prostate Cancer Symptom Scale [19, 20] The questionnaire utilizes a modified linear analogue scale with response boxes containing numerical values between 0 and 10, where 0= "no problem/very good function" and 10= "many problems/very bad function". Five items from the questionnaire represents the rectal bother scale (overall bother from all bowel symptoms, stool frequency, stool leakage, planning of toilet visits and limitations in daily activity caused by bowel symptoms).The average estimate of each item is added and then divided by five. The resulting score constitute the primary outcome measure in the present study.

The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire was used to evaluate health-related quality of life (HRQOL) [21]. This questionnaire consists of five functional scales: physical, role, emotional, cognitive, and social functioning. It also includes a global health status/QOL scale. Higher score on the functional scales means higher function/higher HRQOL. Three symptom scales and six symptom single items are also included. Higher score on the symptom scales/items means worse symptoms/reduced HRQOL. All calculations based on the EORTC QLQ-C30 were performed according to the EORTC guidelines [21]. The patients were asked to evaluate their symptoms during the previous week.

Statistics:

The primary endpoint was acute gastrointestinal side effects at end of RT as measured by the rectal bother scale from the QUFW94 questionnaire [1, 22]. Secondary endpoints included freedom from biochemical progression at 3 years from randomization defined according to ASTRO guidelines (nadir + 2 ng/ml) [23], cancer specific- and overall survival at 5 and 10 years, acute genitourinary side effects as well as late (5 + 10 years) genitourinary and rectal side effects as measured by QUFW94 and CTCv4.0.
For evaluation of the efficacy of IGRT in reducing rectal side effects, a minor clinical absolute difference between groups of 0.75 reduction in mean score of the rectal bother scale in QUFW94 in favor of study arm B patients was anticipated. Based on previous results, a mean symptom score on single item "frequency" of 3.5 with a standard deviation of 2.0 were anticipated at end of RT in the standard arm [19]. In order to detect a difference of 0.75 in symptom score with 80% power (α=0.05), 113 patients in each arm would need to be included. As approximately 15% (34 patients) were assumed non-evaluable, the study aimed to include 260 patients.

The statistical analysis was performed according to a pre-planned strategy:
The main analysis was regression analysis with the mean rectal bother scale at end of RT as dependent variable, and treatment group, pre-treatment mean rectal bother scale, site (Ålesund Hospital versus St. Olav's Hospital), and dichotomized risk group as covariates. [24, 25]. Site and risk group were included because they were used as stratification variables in the randomization [25].
Normality of residuals was checked by visual inspection of Q-Q plots. For some of the single item measures, the residuals were slightly skewed. Hence, alternative analyses with log-transformed data were carried out.
Missing data on the five rectal bother items were singly imputed using the Expectation-Maximation algorithm with the scores on these items as predictors. Analyses were carried out blinded to treatment group. For single-item measures in QUFW94 and for health related quality of life measures (EORTC QLQ C-30) the regression analysis was performed on available cases, data not imputed.
For primary outcome (rectal bother scale), significance level was set at 0.05, for all other HRQOL scales and symptoms, the level was 0.01 due to multiple outcomes measuring similar constructs.

Irradiated volumes (V50 Gy and V60 Gy) were compared between treatment groups using Student's t-test assuming unequal variances.

Results:

From October 2012 to June 2015, 260 (St. Olavs Hospital 131 and Ålesund Hospital 129) patients were included. Two patients were erroneously included and one patient withdrew from the study before randomization. Additionally seven patients did not complete EBRT and did not report side effects at the end of RT. Consequently, these patients could not be included in the analysis. The reason for interrupting EBRT were pancreatic cancer, AMI, patients withdrawal and clinical decision (1, 1, 2, 3 patients, respectively). (Fig 1, consort diagram). Baseline characteristics were balanced between treatment arms (Table 1). The patients were balanced regarding height, weight, and comorbidities (diabetes mellitus, gastrointestinal, kidney and liver disease), data not shown.

Out of 250 evaluable patients, 239 (96%) and 241 (97%) returned the QUFW94 and EORTC-QLQ C30 at baseline and at end of RT, respectively. The patients reported low degree of gastrointestinal side effects. There was no significant difference between groups for primary outcome (rectal bother scale 1.871 vs. 1.884, p=0.804) (Table 2). Although there was a trend towards increased nocturia in arm B (mean 3.73 in arm A vs mean 4.37 in arm B, p=0.020), and hematuria in arm A (mean 0.36 in arm A vs mean 0.10 in arm B, (p=0.040), the differenced did not reach the pre specified level of statistical significance ($p<0.01$). In addition, there were no differences between groups for any other urinary or gastrointestinal symptoms as measured by QUFW94.

HRQOL analyses demonstrated no differences between groups (Table 3).

Secondary analysis with log transformed data were carried out for the single-item measures with slightly skewed residuals. These secondary analyses gave essentially the same results as for untransformed data (data not shown).

The volume (cm^3) of CTV2 (0-70 Gy) did not differ between the two treatment groups (Table 4).

Analyses of dose volume histograms (DVHs) demonstrated that the volume (cm^3) of PTV2 (0-70 Gy) was, as expected, significantly larger in patients in arm A receiving EBRT with standard PTV2 margins of 15 mm in all directions compared to patients in arm B with reduced PTV2 margins (7 mm in all directions) (Table 4). Posterior shielding with MLC

because of the 60 Gy rectal dose constraint to no more than half of the rectal circumference was applied frequently in arm A. Still, V50 Gy. V60 Gy and V70 Gy to the rectal volume and V66.5 Gy to PTV2 (0-70 Gy) were significantly larger in arm A (mean PTV2 270.1 cm^3 in arm A vs mean PTV2 131.0 cm^3 in arm B, $p< 0.001$, Table 4). The mean doses to the PTV 2 in arms A and B were 74.5 and 76.2 Gy, respectively ($p< 0.001$).

Discussion:

As compared to weekly orthogonal portal imaging in patients with intermediate and high-risk prostate cancer, IGRT with daily CBCT verification and reduced margins from CTV to PTV significantly reduced the volume receiving 70 Gy (PTV 2) and rectal volumes receiving 50, 60 and 70 Gy. Contrary to what was hypothesized in the trial, this did not translate into a reduction of patient reported acute side effects from the gastrointestinal tract or higher HRQOL scores at end of RT. For blood in urine, we found very low symptom burden in both study arms and the trend towards a difference did not reach the pre-specified level of statistical significance ($p=0.01$).Given the very low symptom burden in both arms, we consider the possible difference clinically insignificant. For nocturi the mean score was lower in arm A vs arm B (3.73 vs 4.37, $p=0.020$) nor this statistically significant and of minor clinical significance.

There is evidence that patient reported acute side effects predict urinary as well as rectal long term RT-toxicity and such constitute a clinically important proxy outcome [3, 4].
The RIC-study is to our knowledge the first RCT that compares side effects following curative 3D conformal EBRT for prostate with either daily IGRT or verification by weekly orthogonal portal imaging. However, several non-randomized studies have previously compared IGRT to non-IGRT. While Chung et al found reduced acute rectal and urinary side effects when comparing image guided IMRT (IG-IMRT) to IMRT without image guiding for high risk prostate cancer in a small patient series (n=25), Zhong et al found no such benefit[12, 26]. Engels et al. reported increased biochemical failure in a group of patients with distended rectum receiving IGRT with reduced safety margins[13]. Several other non-randomized trials have compared IG-IMRT to IMRT in prostate cancer treatment [11, 15]. In accordance with the RIC-study, none of these studies demonstrated that IGRT reduce acute toxicity.

Wortel and co-workers compared two cohorts of prostate cancer patients given 78 Gy in 2 Gy's fractions in two separate RCT's [14, 27]. Patients who received IG-IMRT (5-8 mm margins from CTV to PTV) in the standard arm of a hypofractionation trial performed during 2007-2011 were compared with patients treated with 3-field 3D-conformal RT (10 mm margins from CTV to PTV) in the high dose arm of a dose escalation trial performed during 1997-2003. Acute toxicity score based on the RTOG scoring system were derived directly from patient reported outcome measures. Even though the margin differences from CTV to PTV in these two cohorts were smaller than the margin differences between the two arms in our trial, the patients in Wortels study reported significant reductions of both acute patient reported gastrointestinal and urinary symptoms following IG-IMRT. The GI symptoms were significantly reduced also at 5 years follow up, whereas urinary symptoms diminished with time. Although the discrepancy between these results and our findings may be due to the addition of IMRT or to different measures of side effects, a bias caused by the non-randomized comparison in the Wortel trial cannot be ruled out.

One might speculate that the additional irradiation derived from kV imaging may have contributed to acute side effects in the IGRT arm and thus diminish the potential difference. However, the total dose derived from daily 3-D kV pelvic imaging during 39 treatment days is less than 1 Gy, i.e. far less than the variation of 95-107% dose coverage that is commonly accepted in modern RT and considered negligible.

There is a well-known relationship between side effects and irradiated volume [28] . The RIC-study patients did not receive prophylactic pelvic lymph node irradiation, a procedure that is controversial but frequently applied in high-risk patients. Notwithstanding our findings, the daily prostatic IGRT with tight CTV-PTV margins applied in arm B of the RIC-study may still be beneficial for patients also receiving adjuvant irradiation of the pelvic lymph nodes. Reduced CTV-PTV safety margins has the potential of less side effects, but it is of major importance not to reduce the margins excessively due to the risk of geographical miss and lack of target volume coverage. This applies especially for patients with rectal distension at the time of the planning CT [13, 29, 30].

Moreover, the RIC study evaluated the effect of reduced irradiated volume in arm B, and in our opinion, sufficient precision with such tight margins cannot be achieved without daily image guiding.

The rectal dose constraint was 60 Gy to no more than half of the circumference in both study arms which frequently resulted in some degree of posterior blocking of the PTV2 (0-70 Gy) in patients given EBRT with weekly verification (arm A). The difference in irradiated rectal volume between arms was 15 cm^3 and the liberal use of rectal blocking may have reduced patient reported rectal toxicity in arm A. Although within the 95-107% requirement, the mean PTV-dose was significantly lower in arm A as could be expected due to the posterior blocking (Table 4). The mean CTV-dose was however identical in both arms, and, in our opinion, the probability of local control should be equal in both treatment groups.

On the other hand, the analyses of the DVHs demonstrate clearly that the V50 Gy, V60 Gy and V70 Gy delivered to the rectum were significantly smaller in arm B (IGRT arm) as compared to arm A (Table 4). Thus, although IGRT with daily CBCT verification significantly reduced normal tissue irradiation it still failed to decrease acute side effects.

The ideal study design is a blinded randomized trial. This study was open and one could expect that the open label design would result in more rather than less patient reported side effects in arm A due to patient's expectations.

CT-MRI fusion was used at the physician's discretion. Given that the CTV volumes were similar in arm A and B, it is not reason to believe that any difference MRI-use between arms have influenced on the study results. Additionally, the OARs were outlined on the CT-scans only.

The findings in this study does not apply to hypofractionation, a technique that is increasingly used based on emerging evidence of efficacy in prostatic EBRT [31, 32].

Modern technology in health care is an important driver of health care costs. IGRT increases costs because of the investments necessary as well as increased personnel time spent [9]. Although commonly recommended in international clinical guidelines, it is noteworthy that we have not been able to demonstrate any clinical benefit from extended use of IGRT and reduced PTV margins for the RIC-study patients so far. Our patients will be followed for at least 10 years from inclusion, and it remains to see whether the daily CBCT-IGRT applied in arm B will result in reduced late effects without adversely affecting disease control. In our opinion, the present results underline the need for technical medical innovations to be thoroughly evaluated in controlled clinical trials with long-term follow up.

References:

1. Fransson P, Lund JA, Damber JE, Klepp O, Wiklund F, Fossa S, et al. Quality of life in patients with locally advanced prostate cancer given endocrine treatment with or without radiotherapy: 4-year follow-up of SPCG-7/SFUO-3, an open-label, randomised, phase III trial. Lancet Oncol. 2009;10(4):370-80.
2. Lund JA. Late Effects to the Rectum and Anus in Prostate Cancer Patients Randomized to Hormonal Therapy Versus Hormonal Therapy Plus Radiotherapy. J Gastroenterol Hepatol. 2013;2(10).
3. Jereczek-Fossa BA, Zerini D, Fodor C, Santoro L, Serafini F, Cambria R, et al. Correlation between acute and late toxicity in 973 prostate cancer patients treated with three-dimensional conformal external beam radiotherapy. Int J Radiat Oncol Biol Phys. 2010;78(1):26-34.
4. Heemsbergen WD, Peeters ST, Koper PC, Hoogeman MS, Lebesque JV. Acute and late gastrointestinal toxicity after radiotherapy in prostate cancer patients: consequential late damage. Int J Radiat Oncol Biol Phys. 2006;66(1):3-10.
5. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol. 2016.
6. Langen KM, Jones DT. Organ motion and its management. Int J Radiat Oncol Biol Phys. 2001;50(1):265-78.
7. Das S, Liu T, Jani AB, Rossi P, Shelton J, Shi Z, et al. Comparison of image-guided radiotherapy technologies for prostate cancer. Am J Clin Oncol. 2014;37(6):616-23.
8. Kupelian PA, Lee C, Langen KM, Zeidan OA, Manon RR, Willoughby TR, et al. Evaluation of image-guidance strategies in the treatment of localized prostate cancer. Int J Radiat Oncol Biol Phys. 2008;70(4):1151-7.
9. Perrier L, Morelle M, Pommier P, Lagrange JL, Laplanche A, Dudouet P, et al. Cost of prostate image-guided radiation therapy: results of a randomized trial. Radiother Oncol. 2013;106(1):50-8.
10. Sveistrup J, af Rosenschold PM, Deasy JO, Oh JH, Pommer T, Petersen PM, et al. Improvement in toxicity in high risk prostate cancer patients treated with image-guided intensity-modulated radiotherapy compared to 3D conformal radiotherapy without daily image guidance. Radiat Oncol. 2014;9:44.
11. Zelefsky MJ, Kollmeier M, Cox B, Fidaleo A, Sperling D, Pei X, et al. Improved clinical outcomes with high-dose image guided radiotherapy compared with non-IGRT for the treatment of clinically localized prostate cancer. Int J Radiat Oncol Biol Phys. 2012;84(1):125-9.
12. Chung HT, Xia P, Chan LW, Park-Somers E, Roach M, 3rd. Does image-guided radiotherapy improve toxicity profile in whole pelvic-treated high-risk prostate cancer? Comparison between IG-IMRT and IMRT. Int J Radiat Oncol Biol Phys. 2009;73(1):53-60.
13. Engels B, Soete G, Verellen D, Storme G. Conformal arc radiotherapy for prostate cancer: increased biochemical failure in patients with distended rectum on the planning computed tomogram despite image guidance by implanted markers. Int J Radiat Oncol Biol Phys. 2009;74(2):388-91.
14. Wortel RC, Incrocci L, Pos FJ, Lebesque JV, Witte MG, van der Heide UA, et al. Acute toxicity after image-guided intensity modulated radiation therapy compared to 3D conformal radiation therapy in prostate cancer patients. Int J Radiat Oncol Biol Phys. 2015;91(4):737-44.
15. Yamazaki H, Nakamura S, Nishimura T, Yoshida K, Yoshioka Y, Koizumi M, et al. Transitioning from conventional radiotherapy to intensity-modulated radiotherapy for localized prostate cancer: changing focus from rectal bleeding to detailed quality of life analysis. J Radiat Res. 2014;55(6):1033-47.

16. Nabavizadeh N, Elliott DA, Chen Y, Kusano AS, Mitin T, Thomas CR, Jr., et al. Image Guided Radiation Therapy (IGRT) Practice Patterns and IGRT's Impact on Workflow and Treatment Planning: Results From a National Survey of American Society for Radiation Oncology Members. Int J Radiat Oncol Biol Phys. 2016;94(4):850-7.
17. D'Amico AV, Whittington R, Malkowicz S, et al. BIochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA. 1998;280(11):969-74.
18. ICRU. Prescribing, recording and Reporting Photon Beam Therapy (Supplement to ICRU Report 50). ICRU report 62. 1999:pp iX+52, 1999.
19. Reidunsdatter RJ, Lund JA, Fransson P, Widmark A, Fossa SD, Kaasa S. Validation of the intestinal part of the prostate cancer questionnaire "QUFW94": psychometric properties, responsiveness, and content validity. Int J Radiat Oncol Biol Phys. 2010;77(3):793-804.
20. Hamoen EH, De Rooij M, Witjes JA, Barentsz JO, Rovers MM. Measuring health-related quality of life in men with prostate cancer: A systematic review of the most used questionnaires and their validity. Urol Oncol. 2015;33(2):69.e19-28.
21. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.
22. Fossa SD, Wiklund F, Klepp O, Angelsen A, Solberg A, Damber JE, et al. Ten- and 15-yr Prostate Cancer-specific Mortality in Patients with Nonmetastatic Locally Advanced or Aggressive Intermediate Prostate Cancer, Randomized to Lifelong Endocrine Treatment Alone or Combined with Radiotherapy: Final Results of The Scandinavian Prostate Cancer Group-7. Eur Urol. 2016;70(4):684-91.
23. Roach M, 3rd, Hanks G, Thames H, Jr., Schellhammer P, Shipley WU, Sokol GH, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys. 2006;65(4):965-74.
24. Van Breukelen GJ. ANCOVA versus change from baseline: more power in randomized studies, more bias in nonrandomized studies [corrected]. J Clin Epidemiol. 2006;59(9):920-5.
25. Vittinghoff E. Regression Methods in Biostatistics: Linear, logistic, survival and repeated measure models, 2nd ed. 2012.
26. Zhong Q, Gao H, Li G, Xiu X, Wu Q, Li M, et al. Significance of image guidance to clinical outcomes for localized prostate cancer. BioMed research international. 2014;2014:860639.
27. Wortel RC, Incrocci L, Pos FJ, van der Heide UA, Lebesque JV, Aluwini S, et al. Late Side Effects After Image Guided Intensity Modulated Radiation Therapy Compared to 3D-Conformal Radiation Therapy for Prostate Cancer: Results From 2 Prospective Cohorts. Int J Radiat Oncol Biol Phys. 2016;95(2):680-9.
28. Nuyttens JJ, Milito S, Rust PF, Turrisi AT, 3rd. Dose-volume relationship for acute side effects during high dose conformal radiotherapy for prostate cancer. Radiother Oncol. 2002;64(2):209-14.
29. Engels B, Soete G, Gevaert T, Storme G, Michielsen D, De Ridder M. Impact of planning target volume margins and rectal distention on biochemical failure in image-guided radiotherapy of prostate cancer. Radiother Oncol. 2014;111(1):106-9.
30. de Crevoisier R, Tucker SL, Dong L, Mohan R, Cheung R, Cox JD, et al. Increased risk of biochemical and local failure in patients with distended rectum on the planning CT for prostate cancer radiotherapy. Int J Radiat Oncol Biol Phys. 2005;62(4):965-73.
31. Moon DH, Efstathiou JA, Chen RC. What is the best way to radiate the prostate in 2016? Urol Oncol. 2017;35(2):59-68.
32. Dal Pra A, Souhami L. Prostate cancer radiation therapy: A physician's perspective. Phys Med. 2016;32(3):438-45.