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Original article

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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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 vs 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) using early side effects as proxy outcome of late rectal side effects in patients receiving curative 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 RT received it after 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 IGRT ($n = 128$). Out of 250 evaluable patients, 96% completed PROs at baseline and 97% at end of RT. Baseline analyses demonstrated balance between groups for baseline characteristics as well as for PROs. In general, patients reported a 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. Health related quality of life analyses (EORTC QLQ 30) demonstrated no differences between groups.

Interpretation: In radical 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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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

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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 radiotherapy (RT) presumably to reduce such unwanted effects. However, such technological progress is rarely subjected 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) has 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 patients [10,11]. However, to our knowledge no randomized controlled trials (RCTs) have compared clinical outcomes following daily IGRT online vs 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 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 radiotherapy, 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 to 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 h 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, transrectal 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, 3-D 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. Errors smaller than 10 mm were not corrected until treatment day 4, when a summed vector calculation of the errors on days 1–3 guided total correction. After correction, position was controlled by orthogonal MV-imaging of fiducial markers once weekly and only errors exceeding 10 mm were corrected. On treatments 36–39, daily online corrections of position were performed

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