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Original Research Article

Dose to penile bulb is not associated with erectile dysfunction 18 months post radiotherapy: A secondary analysis of a randomized trial

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ABSTRACT

Background: Erectile dysfunction is a common side effect of prostate cancer (PC) therapy. In this randomized study (The RIC-study) we used patient reported outcomes to evaluate sexual function 18 months after combined endocrine therapy and radical radiotherapy (RT) given with either wide or tight planning target volume (PTV) margins. We also analyzed the impact of radiation dose to penile bulb on sexual function.

Methods: The RIC-study included 257 men with intermediate and high-risk PC. All patients received 6 months of total androgen blockage started 3 months prior to randomization. In high-risk patients, an oral anti-androgen (Bicalutamide) was administered for an additional 2.5 years. Patients were randomized to receive 78 Gy in 39 fractions guided either by weekly offline orthogonal portal imaging or by daily online cone beam computed tomography image-guided RT. Sexual function was evaluated at 18 months after start of RT using the Questionnaire Umeå Fransson Widmark 1994. Ability to have an erection was assessed on an 11-point scale numerical rating scale (0 = no and 10 = very much) as the primary outcome. In addition, the association between penile bulb (PB) radiation dose and erectile function was analyzed.

Findings: Of 250 evaluable patients, 228 (mean age 71.8 years) returned the questionnaires. The patients reported a high degree of sexual related problems with mean scores to the primary outcome question (221 respondents) of 7.44 and 7.39 in the 2D weekly IGRT-arm and 3D daily IGRT-arm ($p = 0.93$) respectively. For four additional questions (scale 0–10) regarding sexual function resulted in mean scores >6.5 with no difference between study arms. The mean dose to PB was substantially larger in the 2D weekly IGRT-arm vs the 3D daily IGRT-arm (mean 59.8 Gy vs mean 35.1 Gy).

We found no effect of mean PB-dose on the primary outcome adjusted for study-site, risk-group and age. When adjusting for serum-testosterone level at 18 months in addition, the effect of mean PB-dose remained insignificant.

Interpretation: IGRT protocol or PB dose had no effect on ED 18 months after RT in this study population. The low potency rates can partly be explained by the prolonged use of anti-androgen in high risk patients. Longer follow-up is needed to confirm the results from the RIC-study.

1. Introduction

The prevalence of prostate cancer (PC) in Norway is doubled from 2005 to 2015, leading to an increased focus on late side effects after cancer treatment [1]. This includes reduced sexual

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function among both younger individuals and still sexually active elderly men in good health.

The European Association of Urology (EAU) guidelines define erectile dysfunction (ED) as "the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance" [2]. ED increases with age with a reported prevalence of >70% in men by the age of 70 [3]. Furthermore, ED may be the first sign of Diabetes Mellitus (DM) type 2 and is strongly associated with other conditions such as cardiovascular disease (CVD), sleep disorders, pulmonary disease and smoking, as well as alcohol abuse and a sedentary lifestyle [3,4].

ED is common after PC treatment including prostatectomy, endocrine therapy (ET) and radiotherapy (RT). The risk is increased when ET is given in addition to RT [5–8]. Furthermore, several studies have reported that the ED risk increases with radiation dose to the erectile apparatus such as the corpora cavernosa including the penile bulb (PB) [9–12].

We have previously reported acute rectal and genitourinary side effects after radical RT for PC in patients randomized to either weekly orthogonal portal imaging with conventional PTV margins or daily cone beam computed tomography (CBCT) image-guided radiotherapy (IGRT) and reduced planning target volume (PTV) margins (the RIC-study) [13]. In the present analysis, we compared patient reported sexual function in the two groups 18 months after RT using the Questionnaire Umeå Fransson Widmark 1994 (QUFW94) questionnaire single item "can you get an erection?" as primary outcome. In addition, we evaluated the impact of radiation dose to the PB on sexual function.

2. Methods

The RIC-study has been described in detail previously [13]. In short, the study included 257 men younger than 80 years treated at two Norwegian Hospitals (Ålesund Hospital and St. Olavs Hospital) with histologically proven intermediate- or high risk PC suitable for radical external beam radiotherapy (EBRT) to a total dose of 78 Gy. All patients received ET with 6 months of total androgen blockage (TAB) with a luteinizing hormone-releasing hormone (LHRH)-agonist (Gosereline acetate 10·8 mg, two injections with three months interval) and an antiandrogen (Bicalutamide 50 mg/day orally). The ET started 3 months prior to prostatic irradiation. Whereas all ET was discontinued after six months (three months after start of RT) in the intermediate risk patients, all high-risk patients received Bicalutamide (150 mg/day) for an additional 2·5 years. At start of RT, patients were randomized in two arms receiving 0–70 Gy RT in 2 Gy fractions in which position control was done by weekly offline orthogonal portal imaging (2D weekly IGRT-arm) or with daily CBCT-verification (3D daily IGRT-arm). Randomization was computer based and stratified by center and risk group. All patients received a 2 Gy × 4 boost to 78 Gy with daily CBCT-verification.

A CT-based dose-planning system was applied, and the clinical target volume (CTV) 1 included the prostate and 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 CTV2 included the prostate and basal 1 or 2 cm of the SV in intermediate and high-risk patients, respectively. In patients given standard treatment (2D weekly IGRT-arm), the planning target volume (PTV) 2 receiving 70 Gy included the CTV2 with an additional 15 mm margin in all directions. In the 3D daily IGRT-arm the corresponding PTV2 included the CTV2 with an additional 7 mm margin in all directions. The 4 Gy boost volume (PTV1) included the CTV1 with an additional 3 mm margin in both study arms.

The PB was outlined as an organ at risk (OAR) on the planning CT-scan according to the study protocol and defined as the posterior thick part of the spongious body of the penis. No dose constraint regarding the penile structures was defined. Treatment planning was performed in Oncentra v4·3 (Elekta AB, Sweden) and patients were treated on Elekta Synergy® or Elekta Precise® platforms. Volumes (cm^3) and mean dose (Gy) for the PB were estimated.

Patients met a clinical oncologist at inclusion, at end of RT and every 6 months thereafter. At inclusion, the end of RT, and at 5, 12 and 18 months follow up, the patients returned the European Organization for Research and Treatment of Cancer questionnaire regarding health-related quality of life (EORTC QLQ-C30) and organ specific questions (urinary, bowel and sexual symptoms) by use of the Questionnaire Umeå Fransson Widmark 1994 (QUFW94), also called Prostate Cancer Symptom Scale [14]. Both questionnaires evaluate symptoms during the previous week and have been developed to assess the quality of life in cancer patients and to evaluate side effects experienced by PC patients following pelvic RT [14,15].

The following items in the QUFW94 questionnaire regarding sexual function were graded on an 11-point scale: Ability to have an erection, ability to have an erection with and without assistance (0 = normal and 10 = not at all), problems with sex life (0 = no and 10 = very much), sexual desire (0 = very much and 10 = not at all). Moreover, the patients were requested to record whether the erection was sufficient to carry out sexual intercourse and if the erection was sufficient with and without medication (yes/no). The use (always/seldom/not at all) as well as type of medication (alprostadil, sildenafil, apomorphine or others) to carry out sexual intercourse was recorded.

2.1. Statistics

The statistical analysis was performed according to a preplanned strategy using the QUFW94 questionnaire item "can you get an erection?" as primary outcome. The main analysis were linear regression for scale outcome variables, logistic regression for dichotomous outcome variables, and ordinal logistic regression for the question with three ordered alternatives. Treatment group was the covariate of primary interest, and was adjusted for site (Ålesund Hospital versus St Olavs Hospital) and risk group (high versus intermediate), since randomization was stratified on these. We also adjusted for age which is an important prognostic factor as recommended by Vittinghoff et al. 2012, page 417 [16].

We used available case analysis. That is, each analysis included the patients with complete data on the relevant variable(s). In addition, regression analysis with mean dose to PB as covariate instead of treatment group was carried out for the primary outcome. We also performed the analysis with testosterone level at 18 months as covariate.

3. Results

In total, 250 out of 257 included patients were analyzed in the previous published RIC-study [13]. At 18 months after start of RT, 228 (91%) out of 250 patients returned the questionnaires (Fig. 1). Out of these, 119 patients were included at St. Olavs Hospital and 109 at Ålesund Hospital. Three patients died before 18 months of follow-up due to other causes than PC (pancreatic cancer, lung cancer and malignant melanoma) diagnosed after finishing prostatic irradiation. One patient died of unknown reason, one patient withdrew from the study, one patient was unable to fill out the questionnaire due to a cerebral insult, and 16 patients did not give any reason for not returning the questionnaires.

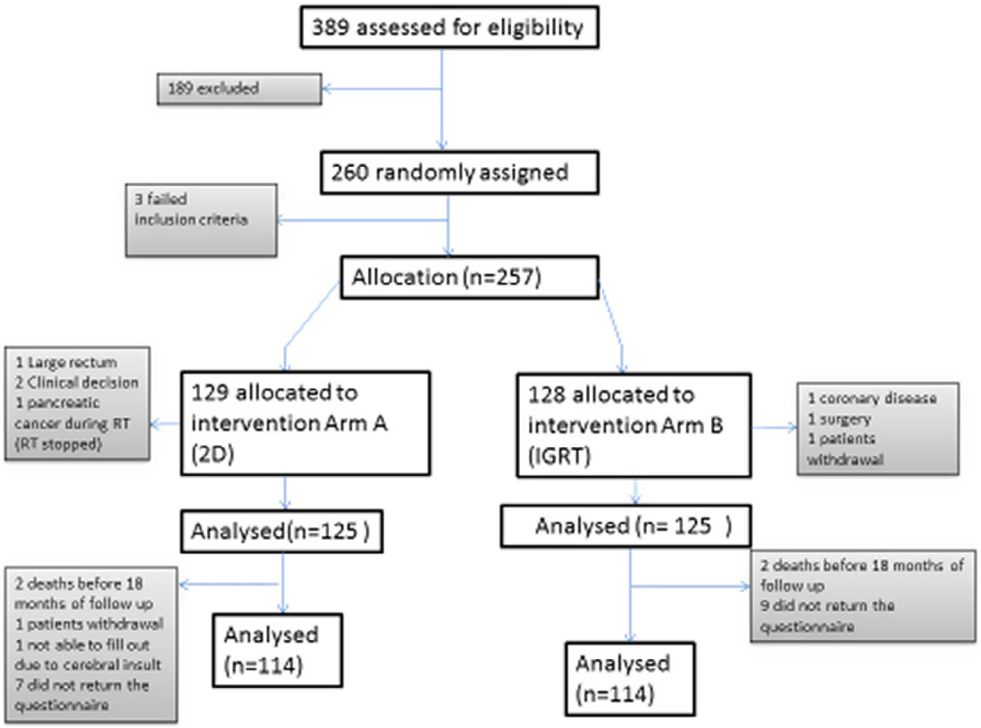

Fig. 1. Consort diagram.

Baseline characteristics were balanced between treatment arms (Table 1). The mean age was 71·8 years. A total of 143 (63%) patients had cardiovascular disease (CVD) according to WHO (World Health Organization) definition or associated risk factors such as hypertension and hypercholesterolemia and 31 (13·5%) had diabetes mellitus.

Data on testosterone level (normal range 6·73–31·8 nmol/l at St. Olavs Hospital and 4·5–26·6 nmol/l at Ålesund Hospital, respectively) were obtained in 190 (83%) of the 228 study patients. Of these, 135 (71%) had testosterone level within normal range at 18 months, with mean levels (SD) of 8·9 (6·1) and 9·4 (6·6) nmol/l in the 2D weekly IGRT-arm and 3D daily IGRT-arm, respectively ($p = 0·496$). Seven patients in the 2D weekly IGRT-arm and six patients in the 3D daily IGRT-arm who were given prolonged LHRH-agonist treatment due to side effects from Bicalutamide or metastatic disease, still had castrate levels (<1·7 nmol/l) of testosterone at 18 months.

Of the 228 patients who returned the questionnaires 18 months after start of RT, 221 (97%) responded to the primary outcome question, "Can you get an erection". We found no difference between the arms for this outcome at 18 months follow up: The mean score was 7·44 in 2D weekly IGRT-arm and 7·39 in the 3D daily IGRT-arm, regression coefficient 0·04 (CI −0·81 to 0·89, $p = 0·93$) when adjusting for site, risk group and age, see Table 2. Only 16% (n = 15 in the 2D weekly IGRT-arm and n = 16 in the 3D daily IGRT-arm) of the patients reported a sufficient erection to carry out sexual intercourse at 18 months (Table 3). Baseline characteristics in the 31 potent patients are described in table 4. The majority of potent patients had CVD (10 in the 2D weekly IGRT-arm and 11 in the 3D daily IGRT-arm). Five patients in each study arm reported need of medication to carry out sexual intercourse. Patients reported a high degree of sexual related problems for all five questions scaled from 0 to 10 with mean scores from 6·52 to 8·04 (Table 2).

Table 1
Baseline characteristics in 228 RIC-study patients who returned the EORTC QLQ-C30 and QUFW94 questionnaires at 18 months.

	2D weekly IGRT (n = 114) (SD)	3D daily IGRT (n = 114) (SD)
Age (years) at inclusion, mean (SD)	72·2 (4·3)	71·4 (4·6)
Risk group		
High, n (%)	70 (61·4)	69 (60·5)
Intermediate, n (%)	44 (38·6)	45 (39·5)
PSA[1] at treatment start, mean (SD)	16·5 (15·1)	16·2 (12·1)
Tumor stage, n (%)		
T1	20 (17·6)	25 (21·9)
T2	42 (36·8)	36 (31·6)
T3	52 (45·6)	52 (45·6)
T4	0 (0)	1 (0·9)
Gleason score, n (%)		
Gleason score 6	8 (7·0)	11 (9·7)
Gleason score 7	64 (56·1)	67 (58·8)
Gleason score 8	24 (21·1)	17 (14·9)
Gleason score 9	15 (13·2)	16 (14·0)
Gleason score 10	3 (2·6)	3 (2·6)
Diabetes Mellitus, n (%)	18 (15·8)	13 (11·4)
Cardiovascular disease and risk factors[2], n (%)	69 (60·5)	74 (64·9)
Other disease[3], n (%)	9 (7·9)	6 (5·3)
PB volume[4,5], mean (SD)	3·5 (1·8)	3·9 (2·1)
PB dose[5,6], mean (SD)	59·8 (14·8)	35·0 (21·4)

Abbreviations: EORTC QLQ-C30: European Organization for Research and Treatment of Cancer questionnaire regarding health-related quality of life, QUFW94: Questionnaire Umeå Fransson Widmark 1994, 2D: Two-dimensional, IGRT: image-guided radiotherapy, 3D: three-dimensional, SD: standard deviation, PSA: prostate specific antigen, PB: penile bulb.

[1] nmol/l.
[2] According to WHO (World Health Organization) definition including risk factors (hypertension and hypercholesterolemia).
[3] Include gastrointestinal and kidney disease.
[4] cm^3.
[5] Evaluable in 219 patients.
[6] Gy.

Table 2
Response to the QUFW94 questionnaire graded on an 11-point (0–10) scale. Ten denotes the worst outcome.

	2D weekly IGRT (n = 114)		3D daily IGRT (n = 114)		Coefficient (β) 2D weekly IGRT versus 3D daily IGRT	
Question Scale: 0–10	Number of respondents	Mean (SD)	Number of respondents	Mean (SD)	Estimate [2] (95% CI)	p-value
[1]Can you get an erection?	108	7·44 (3·3)	113	7·39 (3·1)	0·04 (−0·81 to 0·89)	0·93
Do you have a problem with your sex life?	98	7·00 (3·8)	101	6·67 (3·6)	0·35 (−0·70 to 1·40)	0·51
Do you feel like sexual activity?	109	6·74 (3·1)	111	6·52 (3·1)	0·19 (−0·62 to 1·0)	0·65
Are you able to have an erection without medication?	103	7·75 (3·2)	108	7·55 (3·2)	0·18 (−0·68 to 1·04)	0·68
Can you get an erection (with assistance)?	32	7·22 (3·6)	25	8·04 (2·9)	−1·03 (−2·87 to 0·80)	0·26

Abbreviations: QUFW94: Questionnaire Umeå Fransson Widmark 1994, 2D:Two-dimensional, IGRT: image-guided radiotherapy, 3D: three-dimensional, SD: standard deviation. CI: confidence interval.
[1] Primary outcome.
[2] Coefficient for 2D weekly IGRT versus 3D daily IGRT in linear regression, adjusted for site, risk group, and age.

Table 3
Response to the QUFW94 questionnaire with scale yes/no and always/seldom/often.

	2D weekly IGRT (n = 114)		3D daily IGRT (n = 114)			
Question Scale: Yes/no	Number of respondents		Number of respondents		Odds Ratio (95%CI)[1]	p
Is the erection sufficient to carry out sexual intercourse?	95	yes: 15·8%	100	yes: 16·0%	1·06 (0·48 to 2·32)	0·89
Is the erection sufficient (without assistance) to carry out sexual intercourse?	91	yes: 13·2%	94	yes: 16%	0·87 (0·375 to 2·03)	0·75
Is the erection sufficient (with assistance) to carry out sexual intercourse?	37	yes: 24·3%	23	yes: 17·4%	1·69 (0·432 to 6·56)	0·45
Question Scale: always/seldom/not at all	Number of respondents		Number of respondents		Odds Ratio (95% CI)[2]	p
Have you used assistance to carry out sexual intercourse?	89	always: 5·6% seldom: 9·0% not at all: 85·4%	101	always: 5% seldom: 5·9% not at all: 89·1%	0·71 (0·30 to 1·68)	0·43

Abbreviations: QUFW94: Questionnaire Umeå Fransson Widmark 1994, 2D: Two-dimensional, IGRT: image-guided radiotherapy, 3D: three-dimensional, CI: confidence interval.
[1] Odds ratio (OR) for 2D weekly IGRT versus 3D daily IGRT in logistic regression, adjusted for site, risk group, and age.
[2] Odds ratio (OR) for the 3D daily IGRT arm (versus the 2D weekly IGRT arm) in ordinal logistic regression, adjusted for site, risk group, and age.

The mean PB volumes (SD) were 3·5 (1·8) and 3·9 (2·1) cm^3 in 2D weekly IGRT-arm (108 evaluable patients) and the 3D daily IGRT-arm (111 evaluable patients), respectively (Table 1). The mean dose to PB was substantially larger in the 2D weekly IGRT-arm vs the 3D daily IGRT-arm (mean 59·8 Gy vs mean 35·1 Gy). We found no effect of mean dose to PB in regression analysis for the primary outcome ("can you get an erection?") adjusted for site, risk group and age (Regression coefficient $-0{\cdot}01$ Gy^{-1}, CI $-0{\cdot}03$ to 0·01, $p = 0{\cdot}34$). When adjusting for testosterone level at 18 months in addition, the effect of mean dose to PB remained insignificant (regression coefficient $-0{\cdot}006$ Gy^{-1}, CI $-0{\cdot}03$ to 0·02, $p = 0{\cdot}61$).

4. Discussion

The key finding in this study was that the ability to have an erection 18 months after local 78 Gy EBRT for prostate cancer was not different in patients treated with a reduced PTV margin and daily CBCT as compared to those who received the same treatment with wider margins and weekly verification. Moreover, there was no identified association between radiation dose to the PB and erectile function.

Although controversial, RT has been considered to yield less ED than radical prostatectomy [11]. The degree of ED increases gradually after RT, and there is some evidence that the functional decline is stabilized after approximately 2 years. Thereafter few patients with ED will regain their sexual function [17–19]. In the ProtecT-trial (Prostate Testing for Cancer and treatment), 67% of the patients (mean age 62 years) reported erection firm enough for intercourse prior to treatment for PC. By 6 months, the proportion fell to 22% in patients given RT, increasing to 37% at 12 months and thereafter declining to 34% at 24 months and 27% at 6 years. The corresponding figures following prostatectomy at 6 months and 6 years were 12% and 17%, respectively. The active monitoring group scored best with 52% after 6 months and 30% at year 6, demonstrating that other factors than cancer therapy, such as aging and comorbidity, are involved in ED development [20].

The estimated prevalence of ED in the general population range between 50 and 100% in men older than 70 years [3]. Shiri et al. reported a prevalence of 89% in Finnish men aged 75, and 76·5% in men aged 50–75 years [4]. However, other studies report lower prevalence (20–40% in men aged 60–69 and 50% in men >70 years) [21]. The discrepancy may be due to different questionnaires and diagnostic criteria. Moreover, CVD and DM are strongly associated with ED [3]. The mean age in our study population was 71·8 years. More than 60% of the patients reported CVD or associated risk factors according to WHO and 14% reported DM (Table 1). The mean age of patients operated with radical prostatectomy in Norway is

Table 4
Baseline characteristics in 31 potent RIC-study patients at 18 months.

	2D weekly IGRT (n = 15)	3D daily IGRT (n = 15)
Age (years) at inclusion, mean (SD)	72.9 (3.6)	68.3 (5.1)
St. Olavs hospital (n)	10	9
Ålesund hospital (n)	5	7
Risk group		
High-risk (n)	8	7
Intermediate risk (n)	7	9
PSA[1] (nmol/l) at treatment start, mean (SD)	20.3 (SD 17.6)	15.9 (SD 10.4)
Tumor stage (n)		
T1	1	5
T2	10	5
T3	4	6
Gleason score (n)		
Gleason score 6	0	1
Gleason score 7	12	13
Gleason score 8	2	1
Gleason score 10	1	1
PB volume[2], mean (SD)	3.4 (SD 2.0)	4.2 (SD1.7)
PB dose[3], mean (SD)	63.8 (SD 8.0)	33.0 (SD 25)
Cardiovascular disease and risk factors[4] (n)	10	11
Gastrointestinal disease	1	0
Testosterone recovery[5] at 18 mnd (n)		
Yes	12	15
No	3	1

[1] nmol/l.
[2] $cm^{3.}$
[3] Gy.
[4] According to WHO (World Health Organization) definition including risk factors (hypertension and hypercholesterolemia).
[5] Within normal range: 6.73–31.8 nmol/l (St. Olavs hospital) and 4.5–26.6 nmol/l (Ålesund hospital).

63 years, while patients treated with RT are older with a mean age of 69 years [22]. The RIC study patients were even older. It is thus still possible that the younger patients with lesser comorbidity (who are currently selected for surgical treatment) could have benefited from a reduced PB-dose if treated with radical RT. This is important to bear in mind since the evidence in support of selecting younger men for surgery is poor.

The addition of ET to RT has improved survival in PC patients significantly although at cost of increased acute and late side effects, especially ED [8,23,24]. The reported median time to normalization of testosterone level after medical castration range between 18·3 and 25 months dependent on duration and substance used [25,26]. In our study, 71% of the patients had testosterone recovery 18 months after the last Gosereline acetate injection. In potent patients, 87% had testosterone recovery at 18 months. Even though recovery of a normal testosterone level is achieved in the majority following medical castration, a large proportion still report impotency. Wilke et al. found that only 10% regained potency after 2 years of ET treatment combined with RT, despite the return to supracastrate levels [27]. We evaluated erectile function 18 months after inclusion when 71% of the study population had regained testosterone level within normal range. Most likely, the proportion was higher at 24 months with a possible favorable effect on potency. On the other hand, the gradual decline of erectile function caused by irradiation and age contribute in the opposite direction [20]. We believe that the possible difference between ED figures at 24 months and those obtained at 18 months in this study would be marginal.

Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) recommends to keep the mean dose to 95% of the PB volume to <50 Gy [11]. Damage to small vessels, nerves and tissue fibrosis are considered to be of major importance in ED development [28]. A review by Rivin del Campo et al. on ED 2 years or more after RT in PC included 8 studies which examined the relationship between PB dose and ED [29]. An association was found in 4 of these studies. A reliability score with five items (potency before RT, questionnaire used for potency evaluation, dose range to PTV, threshold effect and PB definition) was used. The studies with the highest scores, support the PB dose-volume constraint recommended by QUANTEC. Evidence from randomized studies of a favorable effect on erectile function from modern RT-techniques with reduced PB-dose has, however, been missing. In our study, the dose to PB was significantly higher in the 2D weekly IGRT-arm due to larger PTV-margins (mean 59·8 Gy vs mean 35·1 Gy). Notably, the percentage of ED was high in both study arms, and few patients (16%) were able to complete sexual intercourse 18 months after RT. The mean dose to PB in potent patients was 63.8 Gy in the 2D weekly IGRT-arm and 33.0 Gy in the 3D daily IGRT-arm. Our study did not provide evidence that a radiation dose to the PB higher than the levels recommended by QUANTEC increased ED.

This study has some limitations. The RIC-study patients were included after 3 months neo-adjuvant TAB at a time when erectile dysfunction is expected to be total. We do not have data on sexual function at the start of neo-adjuvant ET. It is, however likely that a high proportion of these elderly and relatively comorbid men already had ED at treatment start, although evenly distributed in the two treatment groups due to the randomized study design. Moreover, 60% of the patients still used Bicalutamide at 18 months due to high-risk disease. It is thus highly likely that Bicalutamide in addition to high age, comorbidity and incomplete testosterone recovery in 29% contributed to the high incidence of ED found in this study. The exact distribution of cardiovascular disease, hypertension, hyperlipidemia and other diseases such as neurological, endocrine or pulmonary conditions, medication, smoking or alcohol abuse in the RIC study population is unknown. Notwithstanding the adverse effect on erectile function, we expect that these ED risk-factors were evenly distributed with similar effects in both groups in this randomized study.

The Radiation Therapy Oncology Group (RTOG) defines PB as the part of the bulbus spongiosum immediately inferior to the genitourinary diaphragm with rounded shape, best identified with Magnetic Resonance Imaging (MRI) (T2) or Computed Tomography (CT)-scan with urethra contrast [30]. In the RIC-study, the PB was defined as the posterior thick part of the spongious body of the penis and was delineated on CT-scans without intravenous or urethral contrast. This anatomic definition differs to some extend from the definition by RTOG in the study reported by Gay et al. [30]. Even though MRI is superior to CT imaging of pelvic soft tissue, and the penile bulb appears best on T2-weighted MR images [31], CT-based dose-planning with narrow slice thickness such as the 2 mm applied in this study is still commonly used in daily practice.

Modern RT applying different IGRT-techniques has led to less random errors associated with set-up and also better control with organ motion during treatment. Nevertheless, systematic errors may still be introduced due to uncertainties in delineating of different target volumes and OARs prior to the treatment. Perna et al. performed a dummy run in which 15 physicians from different institutes delineated the PB on CT-images [32]. Due to large inter-observer variation, the authors recommend MRI for RT dose-planning as well as dummy-runs prior to studies and fewer physicians involved in the target contouring. Prior to the start of the RIC-study, three dummy-runs were performed revealing some variability in the contouring of the PB from center to center. All the oncologists involved in the daily routine at the two participating RT-centers contoured the PB in our study. Arguably, adherence to

the recommendations by Perna et al. may have reduced the variability in PB contouring. On the other hand, the RIC-study reflects daily practice ensuring a higher external validity. Another strength of the study was the high compliance (97%) to the primary outcome question.

In conclusion, although the patients in the 3D daily IGRT-arm received a significantly lower PB dose, the RIC-study did not reveal an effect of IGRT with reduced margins on erectile and sexual function 18 months after radical EBRT in combination with ET in men with PC. The RIC-study results must, however, be interpreted with care. The reduction of irradiated volume may protect against a variety of late side effects, and shielding of the corpora cavernosa and the PB in particular may still be justified, especially in younger sexually active men with less comorbidity. More so since modern RT and daily imaging gives the opportunity to reduce OAR-dose including the PB without compromising dose to the tumor. Longer follow-up is needed to confirm the results from the RIC-study.

Research in context

Evidence before this study

The prevalence of prostate cancer is increasing worldwide, leading to enlarged focus on late side effects after cancer treatment, including reduced sexual function. Erectile dysfunction is a common side effect of all treatment modalities for prostate cancer (surgery, endocrine therapy and radiotherapy). Modern IGRT such as Cone Beam CT (CBCT) was introduced in the late 1990s and gave a new insight to the internal organs motion during RT planning and delivery. Theoretically, this opened doors to several clinical improvements, especially dose escalation. Results from previous non-randomized studies suggest that modern IGRT and tighter PTV margins reduce radiation-induced toxicity in radical RT treatment for prostate cancer patients. There is, however, a lack of scientific evidence from randomized studies that IGRT provides such benefits.

Added value of this study

To our knowledge, the RIC-study is the first randomized trial that compares patient reported outcomes of modern IGRT and reduced margins versus weekly portal imaging and standard margins in radical RT in prostate cancer patients.

We performed a randomized phase 3-trial including patients suitable for radical external beam prostatic irradiation (total dose 78 Gy) in two arms, either with 7 mm PTV margins and daily CBCT IGRT or 15 mm PTV margins and weekly orthogonal portal imaging. The primary aim of the study was acute rectal side effects and the results are reported previously. In the present analysis, we compared patient reported sexual function in the two groups 18 months after RT using the Questionnaire Umeå Fransson Widmark 1994 (QUFW94) questionnaire single item "can you get an erection?" as primary outcome. In addition, we evaluated the impact of radiation dose to the PB on sexual function. We found no difference between groups for these outcomes in this elderly patient population with a high degree of comorbidity.

Implications of all the available evidence

Studies have shown that the degree of erectile dysfunction gradually increases after radiotherapy, and some evidence suggest stabilization after 2 years. Increasing age, comorbidity, the use of endocrine therapy as well as radiation dose to erectile structures are risk factors for erectile dysfunction.

Results from previous non-randomized studies suggest that modern IGRT and tighter PTV margins reduce radiation-induced toxicity in radical RT treatment for prostate cancer. This randomized phase 3-trial study demonstrated, however, no benefit of daily IGRT regarding erectile function in patients receiving radical external beam RT for prostate cancer. Undoubtedly, new RT techniques are often implemented in standard clinical practice with limited evidence of benefits to patients. So far, this randomized study has not provided such evidence. The patients will, however, be followed for at least ten years regarding late side effects and cancer control. Longer follow-up is needed to confirm the results from the RIC-study.

6. 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 author. HT and AS were responsible for data collection and drafted the manuscript. All authors were involved in revision and have approved the final manuscript.

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