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Clinical Investigation

Daily Versus Weekly Prostate Cancer Image Guided Radiation Therapy: Phase 3 Multicenter Randomized Trial

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Summary

The optimal frequency of prostate cancer image guided radiation therapy has not yet been clearly identified. This phase 3 trial compared the efficacy of daily versus weekly image guided radiation therapy. Compared with weekly control, daily control, by improving prostate targeting, decreases the risks of recurrences and rectal toxicity.

Purpose: The optimal frequency of prostate cancer image guided radiation therapy (IGRT) has not yet been clearly identified. This study sought to compare the safety and efficacy of daily versus weekly IGRT.

Materials and Methods: This phase 3 randomized trial recruited patients with N0 localized prostate cancer. The total IGRT doses in the prostate ranged from 70 Gy to 80 Gy, sparing the lymph nodes. Patients were randomly assigned (1:1) to 2 prostate IGRT frequency groups: daily and weekly (ie, on days 1, 2, and 3 and then weekly). The primary outcome was 5-year recurrence-free survival. Secondary outcomes included overall survival and toxicity. Post hoc analyses included biochemical progression-free interval, clinical progression-free interval, and other cancer-free interval.

Results: Between June 2007 and November 2012, 470 men from 21 centers were randomized into the 2 groups. Median follow-up was 4.1 years. There was no statistically significant difference in recurrence-free survival between the groups (hazard ratio [HR] = 0.81; $P = .330$). Overall survival was worse in the daily group than in the weekly group (HR = 2.12 [95% confidence interval (CI), 1.03-4.37]; $P = .042$). Acute rectal bleeding (grade $\geq$1) was significantly lower in the daily group (6%) (n = 14) than in the weekly group (11%) (n = 26) ($P = .014$). Late rectal toxicity (grade $\geq$1) was significantly lower in the daily group (HR = 0.71 [95% CI, 0.53-0.96]; $P = .027$). Biochemical progression-free interval (HR = 0.45 [95% CI, 0.25 − 0.80]; $P = .007$) and clinical progression-free interval (HR = 0.50 [95% CI, 0.24-1.02]; $P = .057$) were better in the daily group, whereas other cancer-free interval was worse in the daily group (HR = 2.21 [95% CI, 1.10-4.44]; $P = .026$).

Conclusions: Compared with weekly control, daily IGRT control in prostate cancer significantly improves biochemical progression-free and clinical progression-free interval, and rectal toxicity.

Introduction

Prostate intrapelvic interfraction displacement can be as large as 2 cm, typically in the anteroposterior direction, exposing the patient to an increased risk of both recurrence and toxicity if not corrected using bone anatomy alignment.[1,2] Image guided radiation therapy (IGRT) includes various recently developed techniques, allowing direct or indirect prostate visualization at treatment fractions. The most commonly used IGRT modalities are intraprostatic fiducials visualized on 2 orthogonal planes (kV or portal imaging) and cone beam computed tomography (CBCT).[3] The clinical benefit of prostate IGRT has been demonstrated primarily by nonrandomized studies retrospectively comparing non-IGRT and IGRT techniques.[4-11] IGRT has been found to decrease the risk of genitourinary and gastrointestinal (GI) toxicities. However, the role of IGRT in decreasing the risk of recurrence has not been demonstrated because of the short follow-up in these studies.[4-9] Moreover, the optimal frequency of prostate cancer IGRT has not been identified.

Whereas daily control corrects both systematic and random prostate displacement, weekly control solely corrects systematic displacement, with the advantage of being faster and less expensive.[12] Systematic errors occur if the mean irradiation geometry in the fractionated treatment differs from the geometry of the treatment plan. Fraction-to-fraction variations around the mean deviation are called random errors.[13] The dosimetric consequences of systematic and random geometrical uncertainties differ, with significantly less deleterious effects (increased local failure and toxicity) caused by random deviations.[14]

This study sought to assess the benefit of daily prostate control compared with weekly control in a prospective multicenter randomized study.

Materials and Methods

Inclusion criteria and pretreatment workup

In this phase 3 multicenter open randomized trial, we included patients with localized histologically proven prostate adenocarcinoma—N0 or pN-stage—without metastasis. Pretreatment workup imaging included systematic abdominopelvic computed tomography (CT) and bone scans. Prostate magnetic resonance imaging was not required for all patients and was performed in 62% of patients. Patients with hip prostheses, pacemakers, or target volume including the pelvic lymph nodes were excluded.

Study design

The study plan comprised 2 stages. The first stage was a feasibility study aiming to standardize the imaging procedure and to compare 3-dimensional (3D) imaging and

2-dimensional imaging with regard to precision and cost. This first stage was not randomized and included the first 5 patients receiving daily IGRT recruited in each center. The second stage was the reported randomized study comparing the daily and weekly IGRT. In each recruiting center, randomization started with the enrollment of the sixth patient.

All patients provided informed consent. The trial was approved by the French Institutional Review Board in February 2007. This study is registered with ClinicalTrials.gov (NCT00433706). Only the randomized study results are reported herein.

Randomization and masking

Patients were randomly assigned (1:1) to 1 of 2 prostate IGRT control frequency groups: a daily group and a weekly control group. Computer-generated randomization was used with the minimization technique to stratify the patients by center: D'Amico prognostic risk group (low, intermediate, or high)[15]; total planned radiation dose (70 Gy or >70 Gy); and planned androgen deprivation (≤6 months or >6 months). Patients were enrolled by the investigators, who were informed of their allocated treatment groups by the registration office via fax or email.

Radiation technique

Patients underwent standard 3D radiation therapy, with or without intensity modulated radiation therapy (IMRT) and with or without androgen deprivation therapy (ADT), depending on the risk level.[15] The total prescribed radiation dose was 70 to 80 Gy in the prostate and 46 Gy in the seminal vesicles. The dose per fraction was 2 Gy (5 fractions per week). The target delineation and dose distribution were performed according to the French Study Group on Urogenital Tumors guidelines.[16,17]

Patients underwent simulation and treatment in the supine position. Intravenous iodine contrast was required. At the time of simulation, there were no recommendations concerning bowel or bladder filling. During treatment, patients had to keep a full bladder. The target volume and organs at risk (bladder, rectum, penile bulb, and femoral heads) were delineated on CT slices, with spacing of 2 mm or 3 mm. The planning target volume (PTV) margins were defined as 1 cm around the prostate and seminal vesicles, except in the posterior direction, where the margin was limited to 5 mm. The rectal wall was generated with a thickness of 5 mm from the external manually delineated rectal contour. The rectal length was defined as 1 cm below the PTV. The bladder wall was generated with a thickness of 7 mm from the external manually delineated bladder contour. The dose-volume histogram had to respect the French Study Group on Urogenital Tumors recommendations: for the rectum, V72 <25% with a maximum dose of 76 Gy; for the bladder, V70 <50% with a maximum dose of 80 Gy; and for the femoral heads, V55 <5%. Patients were treated with 6 to 23 MV x-rays. In the case of 3D conformal radiation therapy, a 4-field technique was used to treat the prostate and seminal vesicles up to 46 Gy. The boost in the prostate was then performed using either a 6-field technique with 4 opposing obliques and A/P or opposing lateral fields. In the case of IMRT, 5 beams were used (4 obliques and a posterior field).

IGRT procedures

Our IGRT modalities consisted of either direct visualization of the prostate using CBCT or ultrasound, or indirect prostate localization using 3 to 4 fiducials visualized using an orthogonal electronic portal imaging device or kV imaging, according to the standard practice of each center. The prostate registration was always performed online, manually, or automatically. In the case of automatic registration on CBCT, the first step was to manually define a box around the prostate, excluding the pelvic bone. A radiation oncologist was required to approve the prostate position for each CBCT (after prostate visualization in transversal, sagittal, and coronal views) and ultrasound, but not for fiducials. The treatment table was displaced according to the prostate registration, and the patient was treated. When the prostate displacements exceeded 1 cm, a second control was performed before the fraction to verify the correct prostate position after patient motion. The dose delivered by the CBCT was not subtracted from the therapeutic dose delivered that day. However, when the total prescribed therapeutic dose to the prostate reached 80 Gy, this prescribed dose was reduced to 78 Gy. The portal imaging radiation dose was considered and cumulated with the therapeutic dose.

For the daily IGRT group, the prostate position of each patient was analyzed and corrected before each radiation session. For the weekly IGRT group, the prostate position was analyzed and corrected on days 1, 2, and 3 and then weekly. For the fractions without IGRT control, the prostate position was based on the average of the previous recorded positions.

Protocol deviations were defined as more than 3 fractions without prostate positioning verification in the daily IGRT arm and as more than 5 supplementary fractions with prostate positioning in the weekly IGRT arm.

Follow-up

Follow-up included measurement of the prostate-specific antigen (PSA) level and digital rectal examination when the PSA level increased. The PSA level was measured 3 times: (1) before treatment initiation, (2) 6 weeks and 3 months after the treatment end, and then (3) every 6 months for 5 years. Any biochemical relapse that occurred was confirmed via 2 further PSA measurements 1 month apart, and imaging was performed to detect locoregional

recurrence or metastatic relapse. Imaging (bone scan, CT, or magnetic resonance imaging) was performed in the case of biochemical recurrence only. During the treatment, weekly clinical evaluations were performed to assess treatment toxicity. Clinical evaluations were also performed 6 weeks and 3 months after treatment end. Further clinical monitoring was performed every 6 months for 5 years to evaluate biochemical recurrence, clinical recurrence, survival status, occurrence of other primary cancers (than prostate cancer), and toxicity.

Outcomes

The primary outcome was recurrence-free survival (RFS). RFS was defined as the time from randomization to biochemical PSA recurrence, clinical recurrence, or death from any cause, whichever occurred first, or to the date of last follow-up. The biochemical PSA recurrence was defined according to the American Society for Radiation Oncology 2006 conference criteria (PSA $>$ nadir $+$ 2 ng/mL).[18] The date of the biochemical PSA recurrence corresponded to the date of the first PSA measurement, revealing a PSA level exceeding nadir $+$ 2 ng/mL. The clinical recurrence, which was defined as recurrence detected via clinical examination or imaging, included both local and distant recurrences. Any initiation of salvage therapy was considered recurrence, even if relapse was not proven according to the American Society for Radiation Oncology 2006 conference criteria.

The secondary outcomes included overall survival (OS) and safety. OS was defined as the time from randomization to the date of death from any cause or last follow-up. Safety included acute toxicity and late toxicity. Any toxicity corresponding to the Common Terminology Criteria for Adverse Events, version 3, occurring during the treatment or within 3 months of treatment end was considered acute toxicity. Any toxicity defined by the Common Terminology Criteria for Adverse Events, version 3, that occurred 3 months after treatment end was considered late toxicity. The incidence of late toxicities was calculated from randomization onward.

Post hoc efficacy analyses included the following outcomes: biochemical recurrence incidence, clinical recurrence incidence, and other cancer incidence. The biochemical progression-free interval was defined as the time from randomization to the date of biochemical PSA recurrence or the last follow-up (deaths were censored). The clinical progression-free interval was defined as the time from randomization to the date of clinical recurrence or the last follow-up (deaths were censored). Other cancer occurrence was defined as the occurrence of primary cancers (other than prostate cancer) occurring after the randomization. The other cancer free−interval was defined as the time from randomization to other cancer manifestation or the last follow-up (deaths were censored). Five patients exhibited another cancer before randomization, 3 in the daily IGRT arm and 2 in the weekly IGRT arm. They were not excluded from the analysis but were considered failures at the time of randomization for the other cancer free−interval.

Statistical analysis

The expected 5-year RFS rate was 75%. The study was designed to detect a minimum 12% absolute difference in the 5-year RFS between the groups, achieving a statistical power of 80% and type I error of 5% for 2-sided log-rank tests. To achieve these criteria, 91 events needed to be observed and 202 patients recruited per group. We expected to include 210 patients per group. In January 2012, because of a protocol deviation regarding the control frequency (daily control in the weekly arm) in 1 center, the number of patients to be included and randomized in the trial was increased to 235 per group. Therefore, 470 patients were included in the randomized trial. The primary efficacy and safety analysis was conducted on an intention-to-treat basis, according to the protocol. Post hoc sensitivity analyses were performed, excluding patients who had experienced major treatment deviation (per protocol analysis).

The hazard ratios (HRs) were defined as the risk of an event in the daily IGRT group compared with the same risk in the weekly IGRT group. For RFS, the 2 groups were compared using a Cox model adjusted on the basis of stratification factors. For all other survival analyses and late toxicity analyses, the HRs and their 95% confidence intervals (CIs) were estimated using Cox models without adjustment. P values were computed using the Wald test. Survival rates and incidence rates were calculated with 95% CIs, using the Rothman formula. A subgroup analysis for the primary outcome (RFS) based on stratification factors was performed using a multivariate Cox regression model. We also checked for heterogeneity in treatment effect on both RFS and OS according to ADT, using a Cox model with interaction test between the treatment arm and ADT. The impact of the IGRT modality on the OS and other cancer−free survival was assessed using the Cox model. We assessed first the effect of the use of CBCT (yes or no) on OS and other cancer−free survival. We then assessed the interaction between the use of CBCT (yes or no) and the treatment arm on both survivals.

The median follow-up (years) was computed using the reverse Kaplan−Meier method for deaths.[19] Patients were considered *lost to follow-up* if the last follow-up was before January 2014 (1 year before the study cut-off date). Occurrences of acute toxicity were compared using Fisher's exact test.

A competing risk analysis was performed (post hoc analyses) to assess the extent of variability in the relative risk reductions across the different components of the primary outcome, with the added inclusion of other cancer (see Appendix E1; available online at https://dx.doi.org/10.

Table 1 Characteristics of patients, tumors, radiation, and imaging modalities

Characteristics	Daily IGRT group (n = 236)	Weekly IGRT group (n = 234)
Age (y)*	70 (7)	70 (7)
Diabetes mellitus (type I and II)	24 (10%)	27 (12%)
Anticoagulant treatment/antiplatelet drug	67 (29%)	69 (30%)
cT		
1-2a	103 (44%)	102 (44%)
2b	55 (23%)	57 (24%)
2c-4	78 (33%)	75 (32%)
cN		
0	236 (100%)	234 (100%)
pN-	36 (15%)	29 (12%)
Gleason score		
4-6	67 (28%)	57 (24%)
7	149 (63%)	154 (66%)
8-10	20 (9%)	23 (10%)
Serum PSA level (ng/mL)*	11 (9.22)	11 (9.92)
Prognostic group (D'Amico)[15]		
Low risk	3 (1%)	0 (0%)
Intermediate risk	161 (68%)	164 (70%)
High risk	72 (31%)	70 (30%)
Total dose to the prostate (Gy)†	78 (44%-80%)	78 (62%-80%)
Radiation technique		
3DCRT	73 (31%)	76 (32%)
IMRT	163 (69%)	158 (68%)
Imaging modalities		
EPID + fiducials	24 (10%)	26 (11%)
2D kV images + fiducials	31 (13%)	24 (10%)
Cone beam CT	180 (77%)	184 (79%)
Ultrasounds	1 (<1%)	0 (0%)
Second imaging at the fraction (prostate displacement ≥1 cm)	507 (6%)	159 (2%)
Hormonotherapy		
No	127 (54%)	124 (53%)
≤6 months	50 (21%)	52 (22%)
>6 months	59 (25%)	58 (25%)
Hormone therapy in intermediate risk group		
No	114 (71%)	111 (68%)
≤6 months	31 (19%)	39 (24%)
>6 months	16 (10%)	14 (9%)
Hormone therapy in high-risk group		
No	10 (14%)	13 (19%)
≤6 months	19 (26%)	13 (19%)
>6 months	43 (60%)	44 (63%)

Abbreviations: cN = clinical nodal status; cT = clinical tumor stage; EPID = electronic portal imaging devices; IMRT = intensity modulated radiation therapy; pN = pathological nodal status; PSA = prostate-specific antigen; 3DCRT = 3-dimensional conformal radiation therapy; 2D = 2-dimensional.

* Mean (standard deviation).

† Median (range), or n (%).

1016/j.ijrobp.2018.07.2006). SAS 9.3 software was used for all statistical analyses.

Results

Between June 20, 2007, and November 16, 2012, 470 patients were included in the randomized stage: 236 patients in the daily IGRT group and 234 patients in the weekly IGRT group. Two patients (1 from each group) withdrew consent, although both patients allowed their data to be used (Fig. E1; available online at https://dx.doi.org/10.1016/j.ijrobp.2018.07.2006). The baseline patient and tumor characteristics are presented in Table 1. Table E1 (available online at https://dx.doi.org/10.1016/j.ijrobp.2018.07.2006) describes the doses to the volumes of interest (target volume and organs at risk) by treatment arm. Long-duration ADT was received by the majority of high-risk prostate cancer (mostly for the locally advanced T3-T4 stage) (Table 1). Patients with the T2c stage as the only high-risk criteria may not have received ADT.

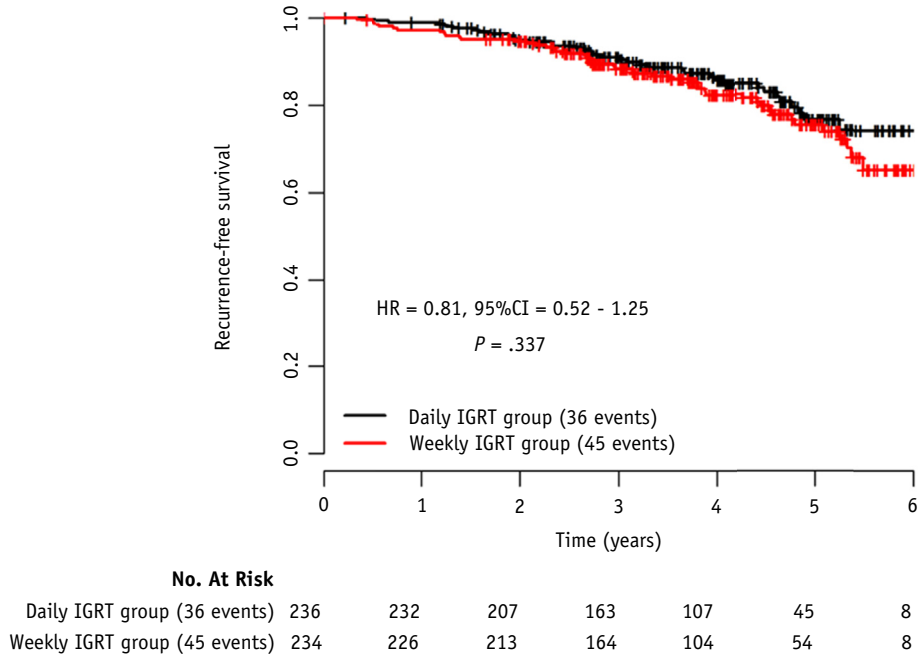

Fig. 1. Recurrence-free survival in daily IGRT group and weekly IGRT group. *Abbreviations:* CI = confidence interval; HR = hazard ratio; IGRT = image guided radiation therapy.

IGRT modalities are presented in Table 1. Protocol deviations occurred for 7% of patients (n = 17) in the daily IGRT group and 24% of patients (n = 56) in the weekly IGRT group.

At the cut-off date of January 22, 2015, the median follow-up was 4.1 years (Q1-Q3 = 3.1-5.1). The lost-to-follow-up patients was 8 % of patients (n = 19) in the daily IGRT group and 6% of patients (n = 14) in the weekly IGRT group.

RFS (primary endpoint)

At the last follow-up, 15% of patients (n = 36) in the daily IGRT group and 19% of patients (n = 45) in the weekly IGRT group had experienced an RFS-defined event. First events in the daily and weekly groups were biochemical failure (16 and 36 patients, respectively), clinical failure (2 patients and 1 patient, respectively), and death from causes unrelated to prostate cancer (18 and 8 patients, respectively). There was no statistically significant difference in RFS between the 2 groups (HR = 0.81 [95% CI, 0.52-1.25]; *P* = .330) (Fig. 1). The 5-year RFS values were 77% (95% CI, 68-83) in the daily IGRT group and 75% (95% CI, 68-82) in the weekly IGRT group. Subgroup analysis suggested no significant interaction between the stratification factors and RFS (Fig. E4; available online at https://dx.doi.org/10.1016/j.ijrobp.2018.07.2006).

Table 2 Maximum grade of acute toxicity, according to Common Terminology for Criteria of Adverse Events, version 3.0

	Daily IGRT group (n = 236)			Weekly IGRT group (n = 234)			
Toxicity	Grade 1	Grade 2	Grade 3-4	Grade 1	Grade 2	Grade 3-4	*P*
Rectal	105 (44%)	33 (14%)	2 (1%)	114 (49%)	33 (14%)	0 (0%)	.484
Diarrhea	62 (26%)	15 (6%)	1 (<1%)	67 (29%)	12 (5%)	0 (0%)	.750
Flatulence	41 (17%)	5 (2%)	0 (0%)	43 (18%)	2 (1%)	0 (0%)	.602
Hemorrhoids	19 (8%)	2 (1%)	1 (<1%)	20 (9%)	5 (2%)	0 (0%)	.569
Fecal incontinence	5 (2%)	1 (<1%)	0 (0%)	4 (2%)	1 (<1%)	0 (0%)	1.000
Proctitis	64 (27%)	14 (6%)	0 (0%)	59 (25%)	16 (7%)	0 (0%)	.859
Rectal bleeding	12 (5%)	2 (1%)	0 (0%)	26 (11%)	0 (0%)	0 (0%)	.014
Bladder	128 (54%)	74 (31%)	3 (1%)	124 (53%)	65 (28%)	8 (3%)	.359
Hematuria	6 (3%)	0 (0%)	0 (0%)	8 (3%)	0 (0%)	0 (0%)	.600
Urinary tract infection	7 (3%)	3 (1%)	0 (0%)	3 (1%)	4 (2%)	1 (<1%)	.452
Cystitis	114 (48%)	24 (10%)	0 (0%)	98 (42%)	29 (12%)	3 (1%)	.204
Urinary incontinence	13 (6%)	4 (2%)	0 (0%)	12 (5%)	3 (1%)	0 (0%)	1.000
Pollakiuria	122 (52%)	57 (24%)	3 (1%)	110 (47%)	52 (22%)	5 (2%)	.470

Abbreviation: IGRT = image guided radiation therapy.

Table 3 Incidence of any grade late toxicity at 5 years among patients in this study*

Toxicity	Daily IGRT group (n = 236)	Weekly IGRT group (n = 234)	HR	*P*
Rectal, % (range)	37% (30%-45%)	46% (39-53)	0.71 (0.53-0.96)	.027
Diarrhea	9% (6-14)	9% (5-13)	1.18 (0.64-2.19)	.592
Flatulence	6% (4 -11)	7% (4-11)	0.81 (0.39-1.68)	.567
Hemorrhoids	11% (7-17)	7% (4-11)	1.71 (0.86-3.42)	.128
Fecal incontinence	7% (4-12)	4% (2-7)	1.41 (0.57-3.51)	.456
Proctitis	11% (7-16)	21% (16-27)	0.51 (0.31-0.84)	.008
Rectal bleeding	23% (17-31)	31% (25-38)	0.62 (0.42-0.92)	.016
Bladder	65% (58-71)	63% (56-70)	1.06 (0.84-1.34)	.640
Hematuria	8% (5-13)	12% (9-18)	0.60 (0.32-1.12)	.107
Urinary tract infection	4% (2-10)	3% (1-6)	0.90 (0.30-2.68)	.849
Cystitis	27% (21-34)	24% (18-30)	1.19 (0.81- 1.73)	.382
Urinary incontinence	15% (10-22)	13% (9-18)	0.95 (0.55-1.66)	.867
Pollakiuria	52% (45-59)	57% (49-64)	0.97 (0.75-1.26)	.818

Abbreviations: HR = hazard ratio; IGRT = image guided radiation therapy.
* Values are 5-year incidence rate (95% confidence interval), hazard ratio (95% confidence interval), and Cox model *P* value.

OS (secondary endpoint)

In the daily IGRT group, 9% of patients (n = 22) died, compared with 4% of patients (n = 11) in the weekly IGRT group. The OS was worse in the daily IGRT group (HR = 2.12 [95% CI, 1.03-4.37]; *P* = .042) (Fig. E2; available online at https://dx.doi.org/10.1016/j.ijrobp.2018.07.2006). The 5-year OS rates were 83% (95% CI, 75%-89%) in the daily IGRT group and 95% (95% CI, 90%-97%) in the weekly IGRT group. In the daily IGRT group, deaths were attributed to the following causes: cardiovascular disease in 27% of patients (n = 6), prostate cancer in 4% (n = 1), other cancers in 55% (n = 12), and other causes in 14% (n = 3). In the weekly IGRT group, the causes were cardiovascular disease in 9% of patients (n = 1), prostate cancer in 27% of patients (n = 3), other cancers in 46% of patients (n = 5), and other causes in 18% of patients (n = 2). The IGRT modality had no impact on OS. There were no statistically significant interactions between OS and the treatment arm and ADT.

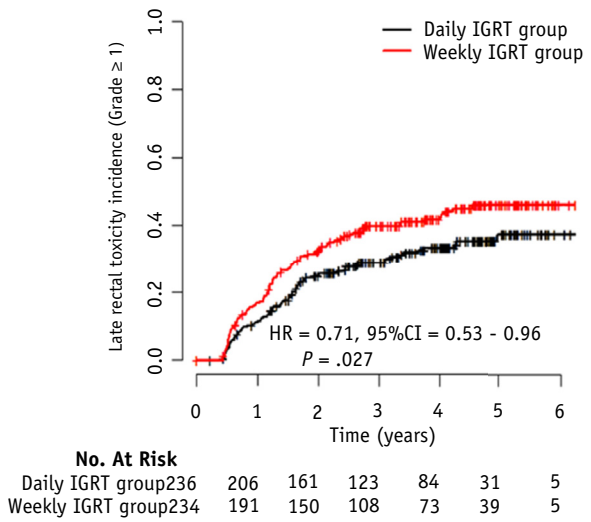

Fig. 2. Risk of late rectal toxicity in daily IGRT group and weekly IGRT group patients. Late rectal toxicity incidence with grade ≥1 according to Common Terminology for Criteria of Adverse Events, version 3.0, in the daily IGRT group and the weekly IGRT group. *Abbreviations:* CI = confidence interval; HR = hazard ratio; IGRT = image guided radiation therapy.

Acute and late toxicities (secondary endpoint)

There was no statistically significant difference between the groups in terms of the incidence of acute rectal and bladder toxicities (Table 2), except for grade ≥1 rectal bleeding, which was significantly less frequent in the daily IGRT group (6%) compared with the weekly IGRT group (11%) (*P* = .014). There was a statistically significant difference between the groups in terms of the incidence of late rectal toxicity (grade ≥1, HR = 0.71 [95% CI, 0.53-0.96]; *P* = .027) (Table 3; Fig. 2). The 5-year rectal toxicity incidence rates were 37% (95% CI, 30%-45%) in the daily IGRT group and 46% (95% CI, 39%-53%) in the weekly IGRT group. The difference primarily applied to proctitis and rectal bleeding. The 5-year rectal bleeding incidence rates were 23% (95% CI, 17%-31%) in the daily IGRT group and 31% (95% CI, 25%-38%) in the weekly IGRT group (*P* = .016). The 5-year rectal toxicity incidence rates (grade ≥2) were 10% (95% CI, 7%-16%) in the daily IGRT group and 13% (95% CI, 9%-18%) in the weekly IGRT group (*P* = .261). The 5-year bladder toxicity incidence rates (grade ≥2) were 14% (95% CI, 9%-19%) in the daily IGRT group and 18% (95% CI, 13%-24%) in the weekly IGRT group (*P* = .345). The 5-year rectal and bladder toxicity rates (grade ≥2) by symptom and treatment arm are reported in Table E2 (available online at https://dx.doi.org/10.1016/j.ijrobp.2018.07.2006). These rates were not significantly different between the 2 arms. The 5-year rectal

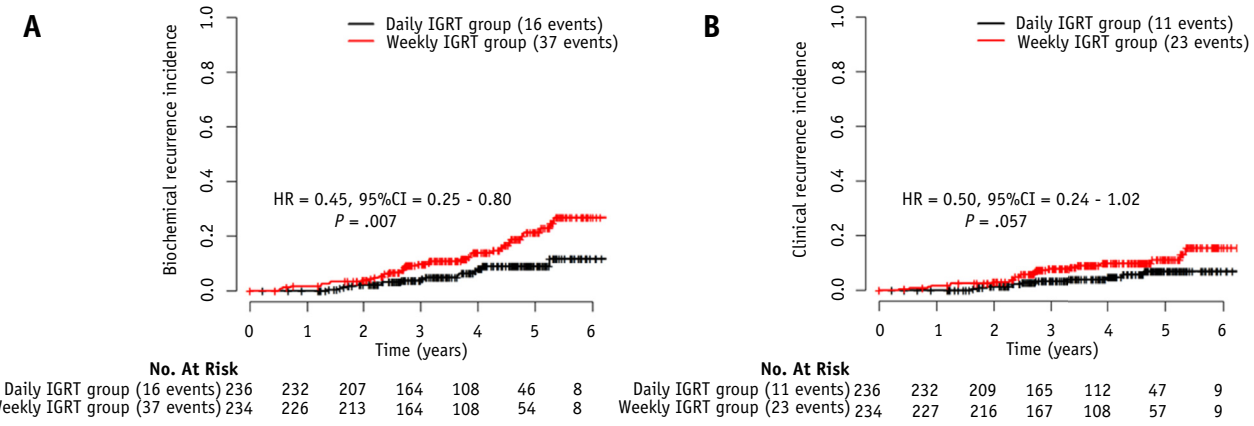

Fig. 3. (A) Biochemical recurrence incidence and (B) clinical recurrence incidence in daily IGRT group and weekly IGRT group. *Abbreviations:* CI = confidence interval; HR = hazard ratio; IGRT = image guided radiation therapy.

toxicity incidence rates (grade 3) were 1% (95% CI, 0%-2%) in the daily IGRT group and 2% (95% CI, 0%-4%) in the weekly IGRT group (P = .149). The 5-year bladder toxicity incidence rates (grade 3) were 1% (95% CI: 0%-2%) in the daily IGRT group and 3% (95% CI, 0%-6%) in the weekly IGRT group (P = .306).

Biochemical progression, clinical progression, and other cancer (post hoc analyses).

Biochemical progression was reported in 7% of the daily IGRT patients (n = 16) versus 16% of the weekly IGRT patients (n = 37). The biochemical progression-free interval was longer in the daily IGRT group (HR = 0.45 [95% CI, 0.25 0-80]; P = .007) (Fig. 3A). The 5-year biochemical progression incidence rates were 9% (95% CI, 5%-15%) in the daily IGRT group and 21% (95% CI, 15%-29%) in the weekly IGRT group.

Clinical progression was reported in 5% of daily IGRT patients (n = 11) versus 10% of weekly IGRT patients (n = 23). The clinical progression-free interval was longer in the daily IGRT group (HR = 0.50 [95% CI, 0.24-1.02]; P = .057) (Fig. 3B). The 5-year clinical progression incidence rates were 7% (95% CI, 4%-13%) in the daily IGRT group and 11% (95% CI, 7%-17%) in the weekly IGRT group. Clinical progression manifested in the prostate (35%), lymph nodes (35%), bone (59%), and other locations (12%). Five clinical progressions occurred solely in the prostate.

Other cancers manifested in 10% of daily IGRT patients (n = 24) versus 5% of weekly IGRT patients (n = 12). The other cancer free-interval was worse in the daily IGRT group (HR = 2.21 [95% CI, 1.10-4.44]; P = .026) (Fig. E3; available online at https://dx.doi.org/10.1016/j.ijrobp.2018.07.2006). The 5-year other cancer incidence rate was 16% (95% CI, 10%-23%) in the daily IGRT group and 6% (95% CI, 3%-10%) in the weekly IGRT group. Other cancers occurred within a median of 31 months (range, 2-80 months) after randomization and were located in the pelvis (18%); abdomen (33%); lung (13%); head, neck and brain (10%); blood (13%); and skin (8%), along with unknown primary locations in 5% of cases. Other pelvic cancer accounted for 15% in the daily IGRT group and 21% in the weekly IGRT group. Table E3 (available online at https://dx.doi.org/10.1016/j.ijrobp.2018.07.2006) presents the other cancer localizations and delay of occurrence for each patient by treatment group. Table E4 (available online at https://dx.doi.org/10.1016/j.ijrobp.2018.07.2006) presents the results of the intention-to-treat—based analysis versus the per-protocol—based analysis. The competing risk analysis revealed a statistically significant difference with regard to other cancer incidence (P = .024) (13% daily IGRT vs 4% weekly IGRT). There was no statistically significant difference when death was the event of interest (P = .065) (daily IGRT 7% vs weekly IGRT 1%) (Table E5; available online at https://dx.doi.org/10.1016/j.ijrobp.2018.07.2006).

Discussion

We believe that this is the first randomized phase 3 trial evaluating the benefits of IGRT in prostate cancer for toxicity and recurrence. By improving prostate targeting, daily control outperforms weekly control, significantly decreasing the risk of biochemical and clinical recurrences and rectal toxicity.

The combination of IMRT and daily IGRT has become the standard of care for external-beam radiation treatment (EBRT) in prostate cancer, particularly when delivering a high dose or using a hypofractionated regimen.[20-22] For more than a decade, nonrandomized studies have proven that IMRT allows for dose escalation in the prostate while not increasing genitourinary or GI toxicities,[23,24] and a clear dose—effect relationship has been demonstrated for prostate cancer concerning local control and biochemical failure.[16,25,26] However, fewer reports explore the benefits of prostate IGRT. Indeed, the clinical benefit of prostate IGRT has been assessed by comparing the outcomes of patients with prostate cancer treated with either IGRT or non-IGRT techniques in monocentric and retrospective studies only and with short follow-up. [4-10] Altogether, these

studies have shown that IGRT significantly decreased the acute[7,9,11] and late[4-6,8,10] rectal and bladder toxicities. Only 1 study reported that the prostate IGRT decreased the risk of biochemical failure.[4]

Our prospective randomized study included a large cohort of patients (n = 470) recruited in a large number of cancer centers (n = 21), primarily treated with IMRT delivering high doses (78 Gy) to the prostate. This randomized study indirectly evidenced the clinical benefit of IGRT in its ability to reduce risks of recurrence and rectal toxicity by demonstrating that daily control was superior to weekly control and therefore to non-IGRT. The impact of the IGRT frequency on clinical outcomes appears to be large because the risk of biochemical and clinical recurrences was reduced by a factor of 2 with daily control. This impact means that random prostate displacements were extensive and frequently superior to the PTV margins, which were 5 mm in the posterior direction. These results are fully supportive of a dosimetric study that compared a daily online CBCT verification schedule with a protocol of verification on days 1 to 3, followed by weekly online imaging.[27]

In this study, 90% of patients exhibited improved target coverage with daily online imaging compared with weekly imaging. A recent phase 3 study compared daily CBCT IGRT using reduced PTV margins (7 mm) with weekly orthogonal portal imaging using conventional PTV margins (15 mm) in a series of 257 patients with localized prostate cancer treated to a total dose of 78 Gy.[28] All the patients had 4 prostatic gold fiducial markers in the prostate. The primary outcome was acute rectal toxicity at the end of the radiation therapy, as evaluated by a rectal bother scale. In contrast to the well-established relationship between rectal bleeding and rectum irradiated volume, there was no difference between groups for the primary outcome or for any acute other GI or urinary symptom. The reduced rate of rectal bleeding in the daily arm observed in our study may be related to our small posterior PTV margin (5 mm), which may not adequately cover prostatic motion without daily imaging.

The OS in our study decreased in the daily group (HR = 2.12), meaning that the decrease in biochemical and clinical failures could not translate into a benefit in our primary outcome (RFS). The increased mortality in the daily group may be due to increased occurrence of other cancers (HR = 2.28) and an increased number of deaths from cardiovascular disease (6 patients in the daily group and only 1 patient in the weekly group). No significant differences were observed for OS in the competing risk analysis, suggesting that the increased risk of death in the daily group may be due to the increased risk of other cancer in this arm.

Given the effective small sample size in the competing post hoc risk analysis (number of other cancers as first event, 11 vs 24) and the short follow-up (approximately 4 years), our results must be interpreted with great caution. Previous studies comparing prostate cancer survivors treated with EBRT with those undergoing radical prostatectomy have effectively demonstrated increased risk of second malignancies in patients treated with EBRT.[29,30] However, the latency period between radiation exposure and radiation-induced malignancy typically lasts more than 5 years, reaching 15 years in some cases, and radiation-associated malignancies are expected to occur primarily in the irradiated field. These statements for defining radiation-induced malignancies are not in agreement with the other cancers reported in our study because the minority of these cancers occurred in the irradiated pelvis (18%) or blood (13%), and the median time before occurrence was relatively short (31 months), with first other cancers occurring as early as 2 months after randomization. However, our 5-year other cancer incidence rate of 19% in daily IGRT patients appears to be superior to the 8-year rate of 11% reported by Fizazi et al in a series of 413 patients with high-risk prostate cancer treated with a 3D conformal technique without image guidance in the same centers. [31] In any case, the use of daily verification requires careful consideration of the concomitant dose from imaging.[32] Thus, simulations have shown that CBCT imaging makes a small fractional contribution to the total radiation dose received by critical organs. [33]

The main drawback of our study is the short follow-up (median, 4.1 years), which is insufficient for definitively assessing radiation-induced malignancy. Moreover, there may be a better RFS with daily control because the curves have started to diverge in Figure 1. Similarly, as shown in Figure E2 (available online at https://dx.doi.org/10.1016/j.ijrobp.2018.07.2006), the gap between the 2 treatment arms has started to narrow, which might suggest that the observed difference in OS might disappear with longer follow-up.

The large number of protocol deviations, primarily experienced in the weekly group (24%) and in 1 center, justified increasing the number of patients by 64 and performing a per-protocol analysis. Nonetheless, this analysis confirmed and even slightly increased the observed differences between the 2 arms of the study.

Another limitation of our study is that the exclusion criteria did not include invasive malignancies before cancer diagnosis. Moreover, as discussed previously, our findings are related to the choice of our PTV margins and therefore cannot be generalized. The treatment planning, bowel and bladder filling, and IGRT protocols could have been more standardized across participating centers. Finally, a central review of the prostate registrations was not performed.

Conclusions

Compared with weekly control, daily control in prostate-cancer IGRT decreases the risks of biochemical and clinical recurrences and rectal toxicity. However, longer follow-up is needed to confirm the results.

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