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FULL PAPER

Effects of dose-escalated radiotherapy in combination with long-term androgen deprivation on prostate cancer

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Objective: We aimed to examine the effects of a dose escalation for prostate cancer patients receiving long-term androgen deprivation therapy (ADT).

Methods: A retrospective analysis of 605 patients treated with radiotherapy (RT) and long-term ADT (National Comprehensive Cancer Network criteria-defined intermediate-risk, minimum 10 months; high-risk and very-high-risk, minimum 20 months) was performed. The median ADT time was 31 months. Cox's proportional hazards models were used to compare biochemical disease-free survival (bDFS), clinical relapse-free survival (cRFS) and overall survival (OS) between the ≥ 70 , < 78 Gy group and 78 Gy group in a univariate analysis and to assess the effects of the dose escalation on bDFS in a multivariate analysis.

Results: After a median follow-up of 70 months, 5-year bDFS was significantly better in the 78 Gy group than in the ≥ 70 , < 78 Gy group [96 vs 83%; hazard ratio 3.6 (95% confidence interval 2.2–6.1); $p < 0.001$]. 5-year cRFS and OS were similar between the two groups. The multivariate analysis showed that RT dose was still an independent prognostic factor of bDFS ($p = 0.005$).

Conclusion: The results of the present study suggest that dose escalations result in significant improvements in bDFS, even when used in combination with long-term ADT. A longer follow-up is needed to clarify the effects of dose escalations on cRFS and OS.

Advances in knowledge: It remains unclear whether high-dose RT is necessary for improving the outcomes of patients receiving long-term ADT. The results suggest that dose escalations result in significant improvements in biochemical control.

INTRODUCTION

Several randomized trials and a meta-analysis reported that high-dose external beam radiotherapy (RT) improved the clinical outcomes of localized or locally advanced prostate cancer.^{1–6} Furthermore, its combination with androgen deprivation therapy (ADT) improved outcomes among patients with high-risk^{7–12} and intermediate-risk prostate cancer¹³ in the setting of conventional-dose RT of 70 Gy or less. Retrospective studies subsequently suggested that even for high-dose RT, the combination with ADT resulted in significant improvements in clinical outcomes among patients with high-risk prostate cancer.^{14–16} The DART01/05 GICOR trial demonstrated that long-term ADT (28 months) improved biochemical control and overall survival (OS) over those with short-term ADT (4 months), even with high-dose RT, particularly among patients with high-risk prostate cancer.¹⁷ However, it currently remains

unclear whether high-dose RT is necessary for improving the clinical outcomes of patients receiving long-term ADT.

Some findings suggested that there is no evidence for dose escalations to high-dose levels in combination with long-term ADT. In the European Organization for Research and Treatment of Cancer 22,991, 6 months of ADT improved biochemical and clinical disease-free survival for intermediate- and high-risk prostate cancer.¹⁸ The benefits obtained from ADT were maintained at each dose level of 70, 74 and 78 Gy, whereas multivariable analyses showed that dose escalations did not exert any significant effects when performed in combination with short-term ADT. Roach investigated the relative benefits of dose escalations vs the addition of ADT in an analysis of data provided from eight prospective randomized trials.¹⁹ The conclusion reached was that evidence supporting the use of ADT in

combination with RT was stronger than that supporting RT dose escalations. Thus, we aimed to examine the effects of a dose escalation in the setting of long-term ADT in patients with localized or locally advanced prostate cancer.

METHODS AND MATERIALS

Patient selection

This study was approved by the Institutional Review Board. Informed consent was obtained from all patients before treatment. This study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. The inclusion criteria of this retrospective study were as follows: clinical stage T1–T4N0M0 adenocarcinoma of the prostate; intermediate-risk, high-risk and very-high-risk groups according to the National Comprehensive Cancer Network criteria;²⁰ definitive RT at our institution between 2001 and 2015; combination with long-term ADT, *i.e.* a minimum of 10 months of ADT for the intermediate-risk group and a minimum of 20 months of ADT for the high-risk and very-high-risk groups. In patients with biopsy sampling <10 cores, the number of positive cores was adjusted in line with the sampling number to distinguish patients in the very-high-risk group from the high-risk group because biopsy sampling of ≥10 cores is recommended.²¹ The final cohort consisted of 605 patients: 153 (25%) in the intermediate-risk group, 253 (42%) in the high-risk group and 199 (33%) in the very-high-risk group. Patients were stratified to the ≥70, <78 Gy ($n = 205$) and 78 Gy ($n = 400$) groups in order to examine the effects of the dose escalation in combination with long-term ADT. Table 1 describes patient and treatment characteristics.

Treatment and follow-up

Three-dimensional conformal radiotherapy (3DCRT) was used until 2006 and image-guided intensity-modulated radiation therapy (IG-IMRT) thereafter. Treatment was provided definitively in daily 2 Gy fractions. Elective pelvic RT was not used for any patients. Details of RT methods were described in our previous studies.^{22,23} Most patients in the ≥70, <78 Gy group were treated with 3DCRT at 70 or 74 Gy between 2001 and 2006 irrespective of the risk groups. Some patients (14%) in the ≥70, <78 Gy group were treated with IG-IMRT at a slightly reduced dose for various reasons such as failure in dose constraints for organs at risk. All patients in the 78 Gy group were treated with IG-IMRT at 78 Gy. The ADT regimen was consistent throughout the duration of the present study. All patients received neoadjuvant ADT with a luteinizing hormone-releasing hormone analog and anti-androgen therapy. Patients continued with the same luteinizing hormone-releasing hormone analog every 3 months after RT. Median total ADT times were 31 months [interquartile range (IQR) 25–35] in all patients, 22 months (IQR 19–25) in the intermediate-risk group, 33 months (IQR 30–36) in the high-risk group and 34 months (IQR 31–36) in the very-high-risk group. A total of 59% of patients ($n = 354$) received very long-term ADT of >30 months. Patients began to receive salvage ADT after the documentation of biochemical relapse. Follow-up and serum PSA measurements were performed at intervals of 3–6 months for 5 years and 6–12 months thereafter.

Table 1. Patient and treatment characteristics

Characteristics	≥70, <78 Gy	78 Gy	<i>p</i> -value
	($n = 205$)	($n = 400$)	
Age (years)	72 (50–85)	71 (50–85)	0.027
Risk group			0.93
Intermediate	50 (24%)	103 (26%)	
High	90 (44%)	163 (41%)	
Very high	65 (32%)	134 (34%)	
Tumour stage			0.059
T1–2	76 (37%)	158 (40%)	
T3a	83 (40%)	195 (49%)	
T3b, T4	46 (22%)	47 (12%)	
PSA level (ng ml ⁻¹)	18.00	12.90	0.002
<10	48 (23%)	141 (35%)	
10–20	64 (31%)	124 (31%)	
>20	93 (45%)	135 (34%)	
Gleason score			0.002
≤6	51 (25%)	58 (15%)	
7	93 (45%)	183 (46%)	
8–10	61 (30%)	159 (40%)	
Positive score (%)	50 (8–100)	50 (2–100)	0.72
Total ADT (month)	32 (12–134)	31 (10–151)	0.38
Use of IG-IMRT	28 (14%)	400 (100%)	<0.001

ADT, androgen deprivation therapy; IG-IMRT, image-guided intensity-modulated radiotherapy; PSA, prostate-specific antigen.

Statistical analysis

The categorical variables in Table 1 were compared with the Mann–Whitney *U* test. The primary objective was to assess the effects of the dose escalation from ≥70, <78 Gy to 78 Gy on biochemical disease-free survival (bDFS), defined as the time from the start of RT to biochemical failure followed by the Phoenix definition.²⁴ Secondary objectives were clinical relapse-free survival (cRFS), OS and toxicity. cRFS was defined as the time from the start of RT to clinical relapse including local relapse, lymph node metastasis and distant metastasis detected by imaging tests. OS was defined as the time from the start of RT to death from any cause. Toxicity was scored according to the Radiation Therapy Oncology Group morbidity grading scale.²⁵ The distributions of bDFS, cRFS and OS were calculated in accordance with the Kaplan–Meier method and the Log-rank test was used to compare outcomes between groups. Cox's proportional hazards models were used in the univariate analysis to calculate the hazard ratio (HR) between two RT dose groups with bDFS, cRFS and OS. A subgroup analysis was performed for each risk group. A multivariate analysis was conducted with Cox's proportional hazards models to assess the relationship between potential prognostic factors with bDFS. An exploratory multivariate analysis was also performed for the ADT ≤30 months group

and ADT >30 months group. All factors were considered in the multivariate analysis. Variables included in the multivariate analysis were age (continuous variable), RT dose (≥ 70 , <78 vs 78 Gy), ADT time (continuous variable), stage (T3b, T4 vs T1–T3a), PSA (>20 vs ≤ 20 ng ml⁻¹), the Gleason score (>7 vs ≤ 7), rate of positive biopsies (>50 vs $\leq 50\%$) and RT method (3DCRT vs IG-IMRT). Statistical analyses were performed with EZR (Kanda 2013),²⁶ which is a graphical user interface for R (The R Foundation for Statistical Computing). A *p* value of <0.05 was considered significant.

RESULTS

The rate of risk groups, positive cores and ADT times were similar between the ≥ 70 , <78 Gy and 78 Gy groups. PSA levels were significantly higher in the ≥ 70 , <78 Gy group than in the 78 Gy group, whereas the Gleason score and rate of IG-IMRT use were significantly higher in the 78 Gy group than in the ≥ 70 , <78 Gy group. Median follow-up times were 70 months (IQR 45–98) for all patients, 88 months (IQR 55–122) for the ≥ 70 , <78 Gy group and 63 months (IQR 42–87) for the 78 Gy group.

Outcomes

The 5-year bDFS rates for the ≥ 70 , <78 and 78 Gy groups were 83% [95% confidence interval (CI) (77–88)] and 96% [95% CI (93–98)], respectively ($p < 0.001$, Figure 1a). Figure 2 shows the number of events, 5-year rates and unadjusted HRs of biochemical control, clinical relapse and OS in the subgroup analysis by recurrence risk. The benefit obtained in biochemical control from the dose escalation was the most prominent in the high-risk group.

The 5-year cRFS rates for the ≥ 70 , <78 and 78 Gy groups were 98% [95% CI (94–99)] and 98% [95% CI (96–99)], respectively ($p = 0.80$, Figure 1b). The 5-year OS rates for the ≥ 70 , <78 and 78 Gy groups were 98% [95% CI (95–99)] and 99% [95% CI (97–100)], respectively ($p = 0.16$, Figure 1c). A subgroup analysis by recurrence risk was not performed for the intermediate-risk and high-risk groups because of the small number of events for clinical relapse and death from any cause.

Table 2 shows the results of univariate and multivariate analyses for biochemical control in all patients. The independent prognostic factors of biochemical control were age, RT dose and the Gleason score. An exploratory multivariate analysis showed that the RT dose was one of the independent prognostic factors of biochemical control in the ADT ≤ 30 months group {HR 18 [95% CI (2.8–113)]; $p = 0.002$ }, but not in the ADT >30 months group {HR 4.1 [95% CI (0.88–19)]; $p = 0.071$ }. Tables 3–5 show the results of univariate and multivariate analyses for biochemical control in each risk group. Table 6 shows the results of univariate and multivariate analyses for biochemical control in the high-risk group treated with 20–36 months of ADT ($n = 204$).

Toxicity

Late Grade 2 or higher gastrointestinal (GI) toxicities occurred in 12 patients (6%) in the ≥ 70 , <78 Gy group and 34 patients (9%) in the 78 Gy group. Late Grade 3 GI toxicities occurred in 9 patients (2%) in the 78 Gy group and no Grade 3 GI toxicity

Figure 1. (a) Biochemical disease-free survival, (b) clinical relapse-free survival and (c) overall survival for the ≥ 70 , <78 Gy and 78 Gy groups.

was observed in the ≥ 70 , <78 Gy group. Grade 4 GI toxicity was not observed in either group. The 5-year cumulative incidence of late Grade 2 or higher GI toxicities was 6% in the ≥ 70 , <78 Gy group and 9% in the 78 Gy group ($p = 0.24$). Late Grade 2 or higher genitourinary (GU) toxicities occurred in 7 patients (3%) in the ≥ 70 , <78 Gy group and 39 patients (10%) in the 78 Gy group. Late Grade 3 GU toxicities occurred in 1 patient (0.5%) in

Figure 2. Effects of radiation doses in combination with long-term androgen deprivation. 95% CI, 95% confidence interval; NA, not applicable.

the ≥70, <78 Gy group and 4 patients (1%) in the ≥70, <78 Gy group. Grade 4 GU toxicity was not observed in either group. The 5-year cumulative incidence of late Grade 2 or higher GI toxicities was 4% in the ≥70, <78 Gy group and 10% in the 78 Gy group ($p = 0.004$).

DISCUSSION

The results of the present study showed that the dose escalation from 70 to 78 Gy resulted in significant improvements in biochemical control, even in combination with long-term ADT, particularly for patients with high-risk and very-high-risk

disease. The benefit obtained from the dose escalation was not observed in clinical relapse and OS because of the small number of these events. A longer follow-up is needed in order to evaluate the effects of dose escalations on clinical relapse and OS. It currently remains unclear whether high-dose RT is necessary to improve the clinical outcomes of prostate cancer patients when used in combination with long-term ADT because randomized trials have not yet been conducted to examine RT dose effects in combination with long-term ADT. "The balance between the use of ADT and radiation dose is a topic of much interest".²⁷ In addition to the two studies

Table 2. Univariate and multivariate analyses of biochemical disease-free survival (bDFS) in all patients

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (continuous)	0.96 (0.92–0.99)	0.021	0.92 (0.88–0.97)	0.001
Dose (≥70, <78 vs 78)	3.6 (2.2–6.1)	<0.001	4.8 (1.6–15)	0.005
ADT (continuous)	0.99 (0.99–1.0)	0.97	0.99 (0.97–1.0)	0.49
Tumour stage (T3b, T4 vs T1–T3a)	1.9 (1.1–3.2)	0.016	1.4 (0.72–2.6)	0.34
PSA (>20 vs ≤20)	2.0 (1.2–3.2)	0.005	1.1 (0.57–2.0)	0.82
Gleason score (>7 vs ≤7)	2.3 (1.4–3.6)	<0.001	2.4 (1.3–4.3)	0.003
Positive biopsy rate (>50 vs ≤50)	2.5 (1.4–4.7)	0.003	1.8 (0.94–3.5)	0.076
RT method (3DCRT vs IG-IMRT)	3.2 (1.9–5.2)	<0.001	0.61 (0.21–1.8)	0.37

3DCRT, three-dimensional conformal radiotherapy; 95% CI, 95% confidence interval; ADT, androgen deprivation therapy; bDFS, biochemical disease-free survival; HR, hazard ratio; IG-IMRT, image-guided intensity-modulated radiotherapy; PSA, prostate-specific antigen; RT, radiotherapy.

Table 3. Univariate and multivariate analyses of biochemical disease-free survival (bDFS) in the very-high-risk group

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Age (continuous)	0.91 (0.86–0.96)	<0.001	0.89 (0.84–0.95)	<0.001
Dose (≥ 70 , <78 vs 78)	2.2 (1.1–4.5)	0.021	6.4 (1.3–31)	0.022
ADT (continuous)	1.0 (0.98–1.0)	0.84	0.99 (0.98–1.0)	0.80
Tumour stage (T3b, T4 vs T1–T3a)	1.4 (0.70–2.8)	0.34	2.0 (0.91–4.3)	0.085
PSA (>20 vs ≤ 20)	1.6 (0.76–3.4)	0.22	0.84 (0.34–2.1)	0.70
Gleason score (>7 vs ≤ 7)	3.4 (1.0–11)	0.045	5.5 (0.69–44)	0.11
Positive biopsy rate (>50 vs ≤ 50)	NA	<0.001	NA	<0.001
RT method (3DCRT vs IG-IMRT)	2.0 (1.0–4.1)	0.041	0.30 (0.06–1.5)	0.15

3DCRT, three-dimensional conformal radiotherapy; 95% CI, 95% confidence interval; ADT, androgen deprivation therapy; HR, hazard ratio; IG-IMRT, image-guided intensity-modulated radiotherapy; NA, not applicable; PSA, prostate-specific antigen; RT, radiotherapy.

HRs of positive biopsy rate were too high to measure.

described in the Introduction,^{18,19} further findings suggest that dose escalations to high-dose levels are not beneficial when used in combination with long-term ADT. Information obtained from 2012 patients with localized prostate cancer who received RT with or without ADT indicated that the gains from increasing the RT dose from 70 to 80 Gy were markedly less than those from adding ≥ 3 months of ADT.²⁸ The findings of recent retrospective studies have suggested the lack of benefits of dose escalations from 74 Gy up to 78 Gy for high-risk and intermediate-risk prostate cancer patients receiving long-term ADT.^{29,30} On the other hand, there is evidence to support the benefits of dose escalations, even when used with ADT. In the MRC RT01 trial, the benefit of dose escalations between 64 Gy and 74 Gy was observed in the setting of short-term ADT, particularly for the high-risk group.² The findings of the TROG 03.04 RADAR trial showed a significant effect of dose escalations for high-risk and intermediate-risk prostate cancer patients given short- or intermediate-term ADT.³¹ ASCENDE-RT was a randomized comparison of two methods of dose escalation in the context of combined modality therapy

for high- and intermediate-risk prostate cancer that included 12 months of ADT and whole pelvic irradiation to 46 Gy. Compared with a ¹²⁵I brachytherapy boost, males randomized to an external beam RT boost to a total of 78 Gy were twice as likely to have experienced biochemical failure at a median follow-up of 6.5 years.³² PCS-VI Phase III trial³³ is designed to compare the safety of a standard pelvic external beam RT combined with a high-dose rate brachytherapy boost to a shorter course of hypofractionated dose escalation RT in patients with high-risk prostate cancer. All the patients are also treated with ADT for a total duration of 28 months. This trial is currently underway. To the best of our knowledge, the present study is the first to show that high-dose RT is superior to moderate-dose RT in patients given long-term ADT in terms of biochemical control.

In the present study, the benefit from dose escalations was more prominent in the high-risk group than in the very high-risk group. This result suggests that the optimal therapeutic strategy, not only RT dose escalations, but also systemic therapy, for patients

Table 4. Univariate and multivariate analyses of bDFS in the high-risk group

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Age (continuous)	1.0 (0.97–1.1)	0.31	1.0 (0.91–1.1)	0.92
Dose (≥ 70 , <78 vs 78)	15 (3.6–66)	<0.001	13 (1.7–100)	0.013
ADT (continuous)	0.99 (0.95–1.0)	0.73	0.95 (0.85–1.1)	0.42
Tumour stage (T3b, T4 vs T1–T3a)	NA	NA	NA	NA
PSA (>20 vs ≤ 20)	2.3 (0.99–5.4)	0.052	2.0 (0.60–6.8)	0.25
Gleason score (>7 vs ≤ 7)	1.5 (0.60–3.5)	0.41	1.4 (0.21–9.4)	0.73
Positive biopsy rate (>50 vs ≤ 50)	1.9 (0.65–5.8)	0.24	1.5 (0.37–6.3)	0.55
RT method (3DCRT vs IG-IMRT)	8.1 (2.7–24)	<0.001	0.63 (0.13–3.2)	0.57

3DCRT, three-dimensional conformal radiotherapy; 95% CI, 95% confidence interval; ADT, androgen deprivation therapy; bDFS, biochemical disease-free survival; HR, hazard ratio; IG-IMRT, image-guided intensity-modulated radiotherapy; NA, not applicable; PSA, prostate-specific antigen; RT, radiotherapy.

Table 5. Univariate and multivariate analyses of bDFS in the intermediate-risk group

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Age (continuous)	0.97 (0.89–1.1)	0.55	0.91 (0.81–1.0)	0.12
Dose (≥ 70 , <78 vs 78)	3.0 (0.90–10)	0.073	NA	<0.001
ADT (continuous)	0.92 (0.81–1.0)	0.13	0.94 (0.84–1.1)	0.31
Tumour stage (T3b, T4 vs T1–T3a)	NA	NA	NA	NA
PSA (>20 vs ≤ 20)	NA	NA	NA	NA
Gleason score (>7 vs ≤ 7)	NA	NA	NA	NA
Positive biopsy rate (>50 vs ≤ 50)	0.31 (0.04–2.4)	0.26	0.22 (0.03–1.9)	0.17
RT method (3DCRT vs IG-IMRT)	3.1 (0.94–11)	0.063	NA	<0.001

3DCRT, three-dimensional conformal radiotherapy; 95% CI, 95% confidence interval; ADT, androgen deprivation therapy; HR, hazard ratio; IG-IMRT, image-guided intensity-modulated radiotherapy; NA, not applicable; PSA, prostate-specific antigen; RT, radiotherapy.

with very-high-risk disease need to be reconsidered. In the Phase III RTOG 0521 trial, patients classified as high-risk or very-high-risk received RT and long-term ADT vs RT and long-term ADT with docetaxel and prednisone.³⁴ The findings obtained showed that these adjuvant systemic therapies improved OS at 4 years. An exploratory analysis revealed that the effects of dose escalations on biochemical control were markedly stronger in the long-term ADT (≤ 30 months) group {HR 18 [95% (CI 2.8–113)]} than in the very long-term ADT (>30 months) group {HR 4.1 [95% (CI 0.88–19)]}. This finding suggests that the outcomes of patients receiving shorter ADT were more dependent on the RT dose. It may now be standard for the high-risk group treated with high-dose RT to be administered 18–36 months of ADT. The results of Table 6 showed that the dose escalation resulted in significant improvements in biochemical control in combination with a standard duration of ADT for patients with high-risk disease.

There is controversy regarding whole pelvic RT (WPRT) for localized prostate cancer except for patients in the low-risk group. In the 2017 National Comprehensive Cancer Network® (NCCN) guidelines, WPRT can be considered

for high-risk and very-high-risk cancer, and patients with intermediate-risk cancer may be considered for WPRT. To the best of our knowledge, WPRT has not been associated with the expected improvement of clinical outcome in randomized Phase 3 trials.^{35,36} Thus, we have not used WPRT for localized prostate cancer, and we use long-term ADT instead. Accordingly, the ongoing RTOG 0924 trial,³⁷ investigating the benefit of WPRT in addition to high-dose RT and ADT in the radiation treatment of unfavourable intermediate-risk and favourable high-risk prostate cancer. Prostate-specific membrane antigen (PSMA) has considerable overexpression on most prostate cancer cells, and has gained increasing interest as a target molecule for imaging.³⁸ PSMA-positron emission tomography might enable more precise localization of prostate cancer. PSMA-positron emission tomography may clarify the role of elective nodal irradiation (*i.e.* WPRT) or dose escalation.

Although it is recommended for patients with high-risk and very-high-risk prostate cancer to receive long-term ADT,^{17,20} the role or optimal duration of ADT in the management of intermediate-risk disease remains controversial in the setting of high-dose RT.³⁹ Several randomized trials examined the effects of

Table 6. Univariate and multivariate analyses of bDFS in the high-risk group treated with 20–36 months of ADT ($n = 204$)

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Age (continuous)	1.1 (0.98–1.2)	0.17	0.98 (0.89–1.1)	0.69
Dose (≥ 70 , <78 vs 78)	11 (2.4–47)	<0.001	16 (1.8–145)	0.013
ADT (continuous)	0.98 (0.88–1.1)	0.70	0.91 (0.77–1.1)	0.27
Tumour stage (T3b, T4 vs T1–T3a)	NA	NA	NA	NA
PSA (>20 vs ≤ 20)	1.8 (0.72–4.4)	0.21	1.6 (0.40–6.0)	0.52
Gleason score (>7 vs ≤ 7)	1.9 (0.73–4.8)	0.19	0.99 (0.14–7.1)	0.99
Positive biopsy rate (>50 vs ≤ 50)	1.5 (0.48–4.8)	0.48	1.0 (0.22–4.7)	0.99
RT method (3DCRT vs IG-IMRT)	5.5 (1.8–17)	0.003	0.39 (0.07–2.3)	0.29

3DCRT, three-dimensional conformal radiotherapy; 95% CI, 95% confidence interval; ADT, androgen deprivation therapy; HR, hazard ratio; IG-IMRT, image-guided intensity-modulated radiotherapy; NA, not applicable; PSA, prostate-specific antigen; RT, radiotherapy.

short-term ADT combined with high-dose RT in patients with intermediate-risk disease.^{2,18,40} In the GETUG 14 trial including 377 males with intermediate-risk disease treated with high-dose RT of 80 Gy, the cumulative incidence of biochemical failure was 21% in RT alone vs 10% in RT with 4 months of ADT ($p < 0.01$). Short-term ADT improved biochemical control more than the lack of ADT; however, a longer follow-up is needed in order to demonstrate any impact on OS.⁴⁰ Thus, it may now be standard for patients with intermediate-risk prostate cancer to be administered 4–6 months of ADT in combination with high-dose RT.²⁰ The minimum duration of long-term ADT was set at 10 months for the intermediate-risk group and 20 months for the high-risk and very-high-risk groups. Median total ADT times were 22 months for the intermediate-risk group, 33 months for the high-risk group, and 34 months for the very-high-risk group. Therefore, the duration of ADT in the present study was very long-term, particularly for the intermediate-risk group. Nevertheless, the results obtained showed that the dose escalation from 70 Gy to 78 Gy resulted in a significant improvement in biochemical control. Thus, a high-dose of more than 78 Gy may be necessary in terms of curative RT for intermediate-risk disease even in combination with long-term ADT.

The rates of late Grade 2 or higher GI toxicity were not significantly different between the ≥ 70 , < 78 Gy and 78 Gy groups (6 vs 9%; $p = 0.24$). This was attributed to the use of IG-IMRT sparing the dose to the rectum in the 78 Gy group. On the other hand, the rate of late Grade 2 or higher GU toxicity was significantly higher in the 78 Gy group than in the ≥ 70 , < 78 Gy group (10 vs 4%; $p = 0.004$). This result may be due to the irradiated dose to the urethra inside the prostate being higher in the 78 Gy group than in the ≥ 70 , < 78 Gy group. Our results indicate that late toxicity profiles were acceptable based on the incidence of late Grade 2 or higher GI and GU toxicity, which reportedly ranged between 3 and 20% and between 3 and 18%, respectively, in recent studies with the use of high-dose conventionally fractionated RT with no

ADT or short-term ADT.^{1,17,41} Thus, the administration of long-term ADT was not considered to be associated with the development of late RT toxicity.

Some factors limit the interpretation of this single institutional retrospective review. This study had an insufficient follow-up time and only a small number of events, particularly clinical relapse and deaths from any cause. A longer follow-up is required to assess the effects of dose escalations on clinical relapse and OS. The interpretations of Tables 3–6 should be cautious because there were small patients in each risk group, and those results seemed to be statistically less powerful. Furthermore, there were bias in patients and treatment characteristics between the ≥ 70 , < 78 Gy and 78 Gy groups. RT methods differed between the two dose groups such as the use of image guidance in the 78 Gy group; however, the multivariate analysis showed that the RT method (3DCRT vs IG-IMRT) was not associated with biochemical control.

CONCLUSION

The results of the present study suggest that the dose escalation from 70 to 78 Gy resulted in significant improvements in biochemical control in the setting of long-term ADT, particularly for patients with high-risk and very-high-risk prostate cancer. A longer follow-up is needed in order to assess the effects of dose escalations on clinical relapse and OS.

DISCLOSURE

Takeshi Kodaira has received payment for consulting and educational presentations from Hitachi Co. and Elekta Co.

ETHICAL APPROVAL

This study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or similar ethical standards. Informed consent was obtained from all patients included in the study.

REFERENCES

1. Beckendorf V, Guerif S, Le Pris E, Cosset JM, Bougnoux A, Chauvet B, et al. 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. *Int J Radiat Oncol Biol Phys* 2011; **80**: 1056–63. doi: <https://doi.org/10.1016/j.ijrobp.2010.03.049>
2. Dearnaley DP, Jovic G, Syndikus I, Khoo V, Cowan RA, Graham JD, et al. Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2014; **15**: 464–73. doi: [https://doi.org/10.1016/S1470-2045\(14\)70040-3](https://doi.org/10.1016/S1470-2045(14)70040-3)
3. Kuban DA, Levy LB, Cheung MR, Lee AK, Choi S, Frank S, et al. Long-term failure patterns and survival in a randomized dose-escalation trial for prostate cancer. Who dies of disease? *Int J Radiat Oncol Biol Phys* 2011; **79**: 1310–7. doi: <https://doi.org/10.1016/j.ijrobp.2010.01.006>
4. Peeters ST, Heemsbergen WD, Koper PC, van Putten WL, Slot A, Dielwart MF, et al. Dose-response in radiotherapy for localized prostate cancer: results of the dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. *J Clin Oncol* 2006; **24**: 1990–6. doi: <https://doi.org/10.1200/JCO.2005.05.2530>
5. Viani GA, Stefano EJ, Afonso SL. Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials. *Int J Radiat Oncol Biol Phys* 2009; **74**: 1405–18. doi: <https://doi.org/10.1016/j.ijrobp.2008.10.091>
6. Zietman AL, Bae K, Slater JD, Shipley WU, Efstathiou JA, Coen JJ, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95-09. *J Clin Oncol* 2010; **28**: 1106–11. doi: <https://doi.org/10.1200/JCO.2009.25.8475>
7. Bolla M, de Rijke TM, Van Tienhoven G, Van den Bergh AC, Oddens J, Poortmans PM, et al. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med* 2009; **360**: 2516–27. doi: <https://doi.org/10.1056/NEJMoa0810095>
8. Bolla M, Van Tienhoven G, Warde P, Dubois JB, Mirimanoff RO, Storme G,

- et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. *Lancet Oncol* 2010; **11**: 1066–73. doi: [https://doi.org/10.1016/S1470-2045\(10\)70223-0](https://doi.org/10.1016/S1470-2045(10)70223-0)
9. Bria E, Cuppone F, Giannarelli D, Milella M, Ruggeri EM, Sperduti I, et al. Does hormone treatment added to radiotherapy improve outcome in locally advanced prostate cancer?: meta-analysis of randomized trials. *Cancer* 2009; **115**: 3446–56. doi: <https://doi.org/10.1002/cncr.24392>
 10. D'Amico AV, Chen MH, Renshaw AA, Loffredo M, Kantoff PW. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. *JAMA* 2008; **299**: 289–95. doi: <https://doi.org/10.1001/jama.299.3.289>
 11. Horwitz EM, Bae K, Hanks GE, Porter A, Grignon DJ, Brereton HD, et al. Ten-year follow-up of radiation therapy oncology group protocol 92-02: a phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. *J Clin Oncol* 2008; **26**: 2497–504. doi: <https://doi.org/10.1200/JCO.2007.14.9021>
 12. Roach M, Bae K, Speight J, Wolkov HB, Rubin P, Lee RJ, et al. Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. *J Clin Oncol* 2008; **26**: 585–91. doi: <https://doi.org/10.1200/JCO.2007.13.9881>
 13. Jones CU, Hunt D, McGowan DG, Amin MB, Chetner MP, Bruner DW, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. *N Engl J Med* 2011; **365**: 107–18. doi: <https://doi.org/10.1056/NEJMoa1012348>
 14. Feng FY, Blas K, Olson K, Stenmark M, Sandler H, Hamstra DA. Retrospective evaluation reveals that long-term androgen deprivation therapy improves cause-specific and overall survival in the setting of dose-escalated radiation for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2013; **86**: 64–71. doi: <https://doi.org/10.1016/j.ijrobp.2012.11.024>
 15. Nguyen QN, Levy LB, Lee AK, Choi SS, Frank SJ, Pugh TJ, et al. Long-term outcomes for men with high-risk prostate cancer treated definitively with external beam radiotherapy with or without androgen deprivation. *Cancer* 2013; **119**: 3265–71. doi: <https://doi.org/10.1002/cncr.28213>
 16. Zapatero A, García-Vicente F, Martín de Vidales C, Cruz Conde A, Ibáñez Y, Fernández I, et al. Long-term results after high-dose radiotherapy and adjuvant hormones in prostate cancer: how curable is high-risk disease? *Int J Radiat Oncol Biol Phys* 2011; **81**: 1279–85. doi: <https://doi.org/10.1016/j.ijrobp.2010.07.1975>
 17. Zapatero A, Guerrero A, Maldonado X, Alvarez A, Gonzalez San Segundo C, Cabeza Rodríguez MA, et al. High-dose radiotherapy with short-term or long-term androgen deprivation in localised prostate cancer (DART01/05 GICOR): a randomised, controlled, phase 3 trial. *Lancet Oncol* 2015; **16**: 320–7. doi: [https://doi.org/10.1016/S1470-2045\(15\)70045-8](https://doi.org/10.1016/S1470-2045(15)70045-8)
 18. Bolla M, Maingon P, Carrie C, Villa S, Kitsios P, Poortmans PM, et al. Short androgen suppression and radiation dose escalation for intermediate- and high-risk localized prostate cancer: results of EORTC trial 22991. *J Clin Oncol* 2016; **34**: 1748–56. doi: <https://doi.org/10.1200/JCO.2015.64.8055>
 19. Roach M. Dose escalated external beam radiotherapy versus neoadjuvant androgen deprivation therapy and conventional dose external beam radiotherapy for clinically localized prostate cancer: do we need both? *Strahlenther Onkol* 2007; **183**: 26–8. doi: <https://doi.org/10.1007/s00066-007-2011-8>
 20. Mohler JL, Armstrong AJ, Bahnson RR, D'Amico AV, Davis BJ, Eastham JA, et al. Prostate cancer, version 1.2016. *J Natl Compr Canc Netw* 2016; **14**: 19–30. doi: <https://doi.org/10.6004/jnccn.2016.0004>
 21. Eichler K, Hempel S, Wilby J, Myers L, Bachmann LM, Kleijnen J. Diagnostic value of systematic biopsy methods in the investigation of prostate cancer: a systematic review. *J Urol* 2006; **175**: 1605–12. doi: [https://doi.org/10.1016/S0022-5347\(05\)00957-2](https://doi.org/10.1016/S0022-5347(05)00957-2)
 22. Tomita N, Kodaira T, Tachibana H, Nakamura T, Tomoda T, Nakahara R, et al. Dynamic conformal arc radiotherapy with rectum hollow-out technique for localized prostate cancer. *Radiother Oncol* 2009; **90**: 346–52. doi: <https://doi.org/10.1016/j.radonc.2008.09.020>
 23. Tomita N, Soga N, Ogura Y, Hayashi N, Kageyama T, Ito M, et al. High-dose radiotherapy with helical tomotherapy and long-term androgen deprivation therapy for prostate cancer: 5-year outcomes. *J Cancer Res Clin Oncol* 2016; **142**: 1609–19. doi: <https://doi.org/10.1007/s00432-016-2173-9>
 24. Roach M, Hanks G, Thames H, 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**: 965–74. doi: <https://doi.org/10.1016/j.ijrobp.2006.04.029>
 25. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995; **31**: 1341–6. doi: [https://doi.org/10.1016/0360-3016\(95\)00060-C](https://doi.org/10.1016/0360-3016(95)00060-C)
 26. Kanda Y. Investigation of the freely available easy-to-use software 'EZ' for medical statistics. *Bone Marrow Transplant* 2013; **48**: 452–8. doi: <https://doi.org/10.1038/bmt.2012.244>
 27. Pollack A, Abramowitz MC. Weighing the addition of androgen suppression therapy to radiotherapy dose escalation for intermediate-risk prostate cancer. *J Clin Oncol* 2016; **34**: 1715–7. doi: <https://doi.org/10.1200/JCO.2015.66.2320>
 28. Stoyanova R, Pahlajani NH, Egleston BL, Buyyounouski MK, Chen DY, Horwitz EM, et al. The impact of dose-escalated radiotherapy plus androgen deprivation for prostate cancer using 2 linked nomograms. *Cancer* 2013; **119**: 1080–8. doi: <https://doi.org/10.1002/cncr.27857>
 29. Shakespeare TP, Wilcox SW, Aherne NJ. Can we avoid dose escalation for intermediate-risk prostate cancer in the setting of short-course neoadjuvant androgen deprivation? *Onco Targets Ther* 2016; **9**: 1635–9. doi: <https://doi.org/10.2147/OTT.S102327>
 30. Shakespeare TP, Wilcox SW, Aherne NJ. Can we avoid high levels of dose escalation for high-risk prostate cancer in the setting of androgen deprivation? *Onco Targets Ther* 2016; **9**: 2819–24. doi: <https://doi.org/10.2147/OTT.S105174>
 31. Denham JW, Steigler A, Joseph D, Lamb DS, Spry NA, Duchesne G, et al. Radiation dose escalation or longer androgen suppression for locally advanced prostate cancer? Data from the TROG 03.04 RADAR trial. *Radiother Oncol* 2015; **115**: 301–7. doi: <https://doi.org/10.1016/j.radonc.2015.05.016>
 32. Morris WJ, Tyldesley S, Rodda S, Halperin R, Pai H, McKenzie M, et al. Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (the ASCENDE-RT Trial): an analysis of survival endpoints for a randomized trial comparing a low-dose-rate brachytherapy boost to a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2017; **98**: 275–85. doi: <https://doi.org/10.1016/j.ijrobp.2016.11.026>

33. Niazi T, Davis MB. Comparative study of radiotherapy treatments to treat high risk prostate cancer patients. 2017. Available from: <https://clinicaltrials.gov/show/NCT02303327>
34. Sandler HM, Hu C, Rosenthal SA, Sartor O, Gomella LG, Amin M, et al. A phase III protocol of androgen suppression (AS) and 3DCRT/IMRT versus AS and 3DCRT/IMRT followed by chemotherapy (CT) with docetaxel and prednisone for localized, high-risk prostate cancer (RTOG 0521). *J Clin Oncol* 2015; **33**(Suppl 18): LBA5002. doi: https://doi.org/10.1200/jco.2015.33.18_suppl.lba5002
35. Pommier P, Chabaud S, Lagrange JL, Richaud P, Lesaunier F, Le Prise E, et al. Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Preliminary results of GETUG-01. *J Clin Oncol* 2007; **25**: 5366–73. doi: <https://doi.org/10.1200/JCO.2006.10.5171>
36. Lawton CA, DeSilvio M, Roach M, Uhl V, Kirsch R, Seider M, et al. An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions. *Int J Radiat Oncol Biol Phys* 2007; **69**: 646–55. doi: <https://doi.org/10.1016/j.ijrobp.2007.04.003>
37. RTOG. RTOG 0924 protocol information. 2017. Available from: <https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0924>
38. Maurer T, Eiber M, Schwaiger M, Gschwend JE. Current use of PSMA-PET in prostate cancer management. *Nat Rev Urol* 2016; **13**: 226–35. doi: <https://doi.org/10.1038/nrurol.2016.26>
39. Zumsteg ZS, Zelefsky MJ. Short-term androgen deprivation therapy for patients with intermediate-risk prostate cancer undergoing dose-escalated radiotherapy: the standard of care? *Lancet Oncol* 2012; **13**: e259–e269. doi: [https://doi.org/10.1016/S1470-2045\(12\)70084-0](https://doi.org/10.1016/S1470-2045(12)70084-0)
40. Dubray BM, Salleron J, Guerif SG, Prise EL, Reynaud-Bougnoix A, Hannoun-Levi JM. Does short-term androgen depletion add to high dose radiotherapy (80 Gy) in localized intermediate risk prostate cancer? Final analysis of GETUG 14 randomized trial (EU-20503/NCT00104741). *J Clin Oncol* 2016; **34**(sSuppl 15): 2016.
41. Alicikus ZA, Yamada Y, Zhang Z, Pei X, Hunt M, Kollmeier M, et al. Ten-year outcomes of high-dose, intensity-modulated radiotherapy for localized prostate cancer. *Cancer* 2011; **117**: 1429–37. doi: <https://doi.org/10.1002/cncr.25467>