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Review

Hypofractionated Radiotherapy for Localized Prostate Cancer: A Challenging Accelerated Hypofractionated Radiotherapy

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Abstract. *Conventionally fractionated (CF) external-beam radiation therapy (1.8-2.0 Gy/fraction) is an established treatment modality for localized prostate cancer. Emerging evidence suggests that the α/β ratio for prostate cancer is as low as 1.5, which has prompted investigators to explore hypofractionated (HF) radiation therapy. We reviewed the current status of hypofractionation and found that the accumulated outcomes reveal that dose escalation by moderate (2.5-4 Gy/fraction) hypofractionation (mHF) results in a better early biochemical outcome with acceptable complication rates, although there exist no marked advantages, other than the convenience of short treatment periods. Recently, hypofractionated external-beam radiotherapy has been challenged by accelerated hypofractionation (AHF), i.e., stereotactic body irradiation, particle therapy, and a high-dose-rate brachytherapy, using 5-10 Gy/fraction with a precise dose distribution and shorter treatment periods. Five-year biochemical control rates improved to >90%, even for high-risk groups, with a higher dose delivery using a safer technology. The overall survival rate reached nearly 100% at 5 years and was unaffected by prostate cancer, particularly in patients aged >80 years. Therefore, if maintaining the quality of life is the main purpose, short-term treatment is an attractive option from the socioeconomic perspective. Furthermore, CF and mHF regimens use equivalent doses at 2 Gy per fraction (EQD2) of 62-84 Gy, whereas AHF uses a higher EQD2 of 85 to 135 Gy if an α/β ratio of 1.5 is applied. In the preliminary phase, AHF has theoretical advantages that not only reduce the treatment period but also potentially improve BC, particularly in high-risk groups using a higher EQD2.*

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Several publications have suggested that the α/β ratio (recognized as the ratio of 'intrinsic radiosensitivity' to the 'repair capability') of prostate adenocarcinoma is low (around 1.5 Gy) compared with that of late-responding normal tissues (*e.g.* rectal damage: 3 Gy) (1-3). Therefore, hypofractionation can offer an improved therapeutic ratio because of a presumed higher sensitivity of prostate cancer tissues to higher fraction doses compared with the sensitivity of normal tissue damage. Randomized and prospective trials of hypofractionation treatment schedules for prostate cancer have presented good biochemical control (BC) rates with acceptable toxicities (4-12). These clinical studies used external beam hypofractionated regimens with a dose/fraction ranging from 2.54 Gy delivered daily for 4 to 6 weeks, termed as moderate hypofractionation (mHF), which reduces the treatment period by 2-3 weeks compared to conventional fractionation (CF). Today, using new technologies, such as stereotactic body irradiation (SBRT), image-guided radiotherapy (IGRT), intensity-modulated radiotherapy (IMRT), high-dose-rate brachytherapy (HDR-BT), and particle therapy, it is possible to irradiate the target more accurately, reducing the volume of normal tissue irradiated compared with conformal CF (3D-CRT) techniques, allowing the delivery of higher doses (5-10 Gy/fraction) to the clinical target. Therefore, mHF can be challenged by accelerated (13-15), or so-called extreme (16), profoundly (17) hypofractionated (AHF) radiotherapy, *i.e.* SBRT, particle therapy, and HDR-BT.

These modalities have several merits in the treatment of prostate cancer, including precise and shorter treatment periods with an advanced dose distribution. However, patients and physicians encounter difficulty in selecting an appropriate treatment regimen because numerous options are available. Therefore, we conducted a literature review to examine the role of hypofractionation treatment. The PubMed database was searched for relevant articles published after 1990 to 2014. We only included studies assessing hypofractionated radiotherapy that comparing different schedule and had a median follow-up ≥50 months, with a large sample size (≥100 patients), important findings and which were published in English. The nominal dose was converted to equivalent dose in 2 Gy per fraction (EQD2) using a linear-quadratic model, where α/β=1.5 for prostate cancer (EQD2=prescription dose×(α/β + dose/fraction)/(α/β + 2)).

Moderate Hypofractionated Radiotherapy Using External-beam Radiotherapy (EBRT): from Two-Dimensional Planning Radiotherapy to Three-Dimensional Planning Radiotherapy and IMRT

There are five randomized controlled trials (RCT) available for comparison between hypofractionation and CF (Table I), using either prostate-specific antigen (PSA) control or biochemical control (BC). Furthermore, several reviews and meta-analyses for mHF were published recently (16, 18-20). There were two randomized trials from Australia and Canada (4-6) using a lower prescribed dosage with a classical radiotherapy technique, which does not fit any present clinical situation but provides considerable evidence.

An Italian RCT showed superiority of hypofractionation (7). The 3-year BC rates in patients at a very high risk (*i.e.* initial PSA >20 ng/ml, Gleason score ≥8, or T ≥2c) were 88% and 76% (p=0.014) in the former and latter arms, respectively. They updated their data with a median follow-up of 70 months (8) and reported that biochemical failure occurred in 35 out of the 168 patients (21%) in the study. Among these 35 patients, local failure was detected only in 11 (31%), distant failure only in 16 (46%), and both types of failure in six (17%). In two patients (6%), biochemical failure had not been clinically detected. The risk reduction by hypofractionation was significant in biochemical failure (10.3%) but not in local and distant failure. Their results confirm the isoeffectiveness of the two fractionation schedules used in this study, although a benefit in favor of hypofractionation cannot be excluded in the sub-group of patients with an iPSA level of 20 ng/ml or less. A hypofractionation schedule using higher EQD2 with long-term follow-up yielded a good 8-year actuarial BC rate of 92% without grade >3 toxicity (21). Comparison with similar EQD2 (771 Gy and 78 Gy) between CF and hypofractionation showed equivalent results (22).

Kupellian *et al*. compared IMRT delivering 70 Gy in 28 fractions (2.5 Gy/fraction) and 3D-CRT delivering 78 Gy in 39 fractions (2.0 Gy/fraction) (23). They recently updated the outcomes of the IMRT arm with a median follow-up of 45 months (maximum 86 months) (24). The late rectal toxicity scores were 0 in 89.6% of cases, 1 in 5.9%, 2 in 3.1%, 3 in 1.3%, and 4 in 0.1% of cases (one patient). The late urinary toxicity scores were 0 in 90.5% of cases, 1 in 4.3%, 2 in 5.1%, and 3 in 0.1% of cases (one patient).

In an RCT performed at the MD Anderson Cancer Center from 2001-2010, 204 patients were treated in a randomized dose-escalation trial using IMRT and ultrasound-guided prostate localization (9). Twenty patients treated using conventional IMRT and 23 using hypofractionated IMRT received 4 months of androgen deprivation therapy (ADT) neoadjuvant/concomitantly. Four patients on the conventional IMRT arm had grade 2 gastrointestinal (GI) toxicity and one had grade 3, for 5-year actuarial rates of 5% and 1%, respectively. On the hypofractionated IMRT arm, there were nine patients with grade 2 GI toxicity and two with grade 3 toxicity, 11% and 3%, respectively. Differences between arms were not statistically significant for grade 2 and 3 toxicities, although there was a trend toward higher toxicity for patients in the hypofractionated IMRT arm for all toxicities combined (grades 1-4, p=0.058). There were 15 patients with grade 2 GU (genitourinary) toxicities on each arm and one with grade 3 GU toxicity with conventional IMRT, giving a 5-year grade 2/3 toxicity rate of 19% for both arms. They updated the toxicity data in 2014 (10). The actuarial 5-year grade ≥2 GU toxicity was 16.5% after conventional IMRT and 15.8% after hypofractionated IMRT (p=0.97). There was a non-significant numeric increase in late GI toxicity in men treated with hypofractionated IMRT compared with that in men treated with conventional IMRT. The actuarial 5-year grade ≥2 GI toxicity was 5.1% after conventional IMRT and 10.0% after hypofractionated IMRT (p=0.11).

Dearnaley *et al*. conducted a multicenter randomized controlled trial at 11 UK centers (CHHip study) (11). Patients were randomly assigned in a 1:1:1 ratio to receive CF or one of two types of high-dose hypofractionated IMRT. The primary endpoint was a toxicity of grade 2 or more after 2 years on the Radiation Therapy Oncology Group (RTOG) scale. Six [4.3%; 95% confidence interval (CI)=1.6-9.2%] out of 138 men in the 74-Gy group had GI toxicity of grade 2 or more after 2 years, as well as five (3.6%; 95% CI=1.2-8.3%) out of 137 men in the 60 Gy group and two (1.4%; 95% CI=0.2-5.0%) out of 143 men in the 57 Gy group. For GU toxicity, three (2.2%; 95% CI=0.5-6.2%) out of 138 men, three (2.2%; 95% CI=0.5-6.3%) out of 137, and none (0.0%; 97.5% CI=0.0-2.6%) out of 143 men had a toxicity of grade 2 or more after 2 years. In conclusion, high-dose hypofractionated radiotherapy appeared to be as well tolerated as CF treatment 2 years later.

Table I. *Hypofractionated external beam radiation therapy from 2D to IMRT.*

Author (Institute)	Year (Total Pt No.)	Study Pt No. follow-up period (median)	ADT Risk group (L/I/H) (Risk classification system)	Radiotherapy (daily Fx) [EQD2: α/β 1.5]	5y- PSA control rate*(1) (L/I/H)	Adverse reaction Late G2 or more if otherwise cited [criteria]	
Two-dimensional radiotherapy (2D)							
Lukka (4) (Canada)	2005 (n=936)	RCT: HF *vs*. CF n=466 *vs*. 470 (5.7Y)	ADT (-) T1-2, PSA<40 60%GS-6, 31% GS7, 9% GS8-	52.5Gy/20fr *vs*. 66Gy/33fr (2.625Gy *vs*. 2Gy) [62Gy *vs*. 66Gy]	53% *vs*. 60% (A)* -7% 90%CI:- 12.6--1.6%	GI 1.9% *vs*. 1.9%, GU 1.3% *vs*. 1.3% [RTOG]	HF <CF but Low dose study Acute toxicity 11.4% (HF) > 7% (CF)
2D and three-dimensional conformal radiotherapy (3D-CRT)							
Yeoh (5, 6) (Australia)	2011 (n=217) (156 2D, 61 3D-CRT)	RCT: HF *vs*. CF n=108 *vs*. 109 (90M)	ADT (-) T1-2, PSA<80	55Gy/20fr (4 in wk) vs. 64Gy/32fr (2.75Gy *vs*. 2Gy) [66.8Gy *vs*. 64Gy]	53% *vs*. 34% (90M) $p<0.05$	GI 20% *vs*. 14% GU HR:1.58 (1.01-2.47) at 4Y [LENT/ SOMA]	HF > CF but Low dose study HF worse than CF in GU
3D-CRT							
Arcangeli (7, 8) (Italy)	2010 (n=168)	RCT: HF *vs*. CF n=83 *vs*. 85 (32M *vs*. 35M)	9 M ADT (+) 74% GS -6, 24% GS7-	80 Gy/ 40 Fr *vs*. 62 Gy/ 20 Fr (4 in wk) (2Gy *vs*. 3.1Gy) [80Gy *vs*. 81.4Gy]	87% *vs*. 79% $p=0.035$	GI 17% *vs*. 16% GU 14% *vs*. 11% [LENT-SOMA]	HF > CF PSA control (70M update) GU GI equivocal
Patel (21) (McGill, Canada)	2013 (n=129)	US IGRT (90M)	ADT (-) L-I T1-2c, PSA≤20, GS≤7	66Gy /22fr (3Gy) [84.9Gy]	97%	GI 27%, GU 33% [CTCAE v3.0]	Long term follow-up T1-2c, PSA≤20 ng/mL, GS≤7 HF=CF
Leborgne (22) (Wisconsin)	2012 (n=274)	HF *vs*. CF n=114 *vs*. 160 (66M *vs*. 63M)	31 *vs*. 40 ADT L/I/H=36%/48%/18% vs. 66%/50%/6% (NCCN)	57-64 (median 60) Gy/20fr *vs*. 72-80 (78)/39fr (3Gy -4 in wk *vs*. 2Gy) [77.1Gy *vs*. 78Gy]	89% *vs*. 89%	GI 4.3% *vs*. 5%, GU 4.3% *vs*. 2.5% [RTOG]	
3D-CRT and IMRT							
Kupellian (23) (Cleveland)	2002 (n=282) **SCIMRT *vs*. 3D CRT	HF *vs*. CF n=166 *vs*. 116 (21M *vs*. 32M)	65% ADT 49% GS -6, 51% GS 7-	70 Gy/28fr *vs*. 78 Gy/39fr (2.5Gy *vs*. 2Gy) [80Gy *vs*. 78Gy]	94% *vs*. 88% (30M)	GI 5% *vs*. 12%, GU 1.2% *vs*. 1.7% [RTOG]	HF=CF
IMRT							
Kupelian (24) (Cleveland)	2007 (n=770)	70Gy/28fr IMRT (45M)	ADT (+) (34%/ 28%/38%) (D'Amico)	70Gy/28fr (2.5Gy) [80Gy]	83% (94% / 83%/ 72%)	GI 4.5% GU 5.2% [RTOG]	High-dose HF feasible
Kuban (9, 10) (MDACC)	2011 (n=204) IMRT	RCT: HF *vs*. CF n=102 *vs*. 102 (4.8Y *vs*. 4.6Y)	21% ADT L/I/H = 28%/ 71%/ 1% (NCCN)	72Gy /30fr *vs*. 75.6Gy/42fr (2.4Gy *vs*. 1.8Gy) [80.2Gy *vs*. 81.4Gy]	96% *vs*. 92% (A)	GI 14% *vs*. 6% GU 19% *vs*. 19% [modified RTOG]	HF=CF
Dearnaley (11) (UK)	2012 (n=457) CHHiP IMRT	RCT: HF *vs*. CF n=153 *vs*. 153 *vs*. 151 (50.5M)	3-6 M ADT(+) T1-3, PSA<30 ng/ml 3D-CRT/IMRT	74Gy/37fr *vs*. 60Gy/20fr vs. 57Gy/19fr (2Gy *vs*. 3Gy) [74Gy *vs*. 77Gy vs. 73.4Gy]	NA	GI 4.3% *vs*. 3.6% *vs*. 1.4% GU 2.2% *vs*. 2.2% *vs*. 0% [RTOG]	HF=CF in toxicity HF feasible
Pollack (12) (Fox Chase)	2013 (n=303)	RCT: HF *vs*. CF n=151 *vs*. 152 (68.4M)	H and part of I ADT(+) 34% GS- 6, 47% GS7, 19% GS 8-	70.2Gy/26Fr (4 in wk) vs. 76 Gy/38Fr (2.7Gy *vs*. 2Gy) [84Gy *vs*. 76Gy]	76.7% *vs*. 78.6%	GI 22.5%, *vs*. 18.1% GU 21.5% *vs*. 13.4% [modified LENT/RTOG]	HF=CF Poor IPSS predict GU

ADT; Androgen deprivation therapy, L; low risk, I; intermediate risk, H; high risk, EQD2; Equivalent dose in 2 Gy fractions, *1PSA failure is defined according to Phoenix criteria if otherwise stated, G2; grade 2, RCT; randomized control trial. HF; hypofractionated, CF; conventional fraction, GI; gastrointestinal, GU; genitourinary, RTOG; Radiation Therapy Oncology Group, LENT/SOMA; Late Effect Normal Tissues/ Subjective, Objective, Management, and Analytic, CTCAE: Common Terminology Criteria for Adverse Events. NCCN; The National Comprehensive Cancer Network, IPSS; International Prostate Symptom Score, (A)ASTRO definition, (A)* ASTRO definition + any clinical failure, GS; Gleason scores, NA; not available, MDACC; MD Anderson cancer center, US IGRT; ultrasound-guided image guided radiothrerapy, **SCIMRT; short-course intensity-modulated RT using iamge guided RT.

Pollack *et al*. obtained similar outcomes both for hypofractionation and CF in an RCT between 2002 and 2006 (12). High-risk patients received long-term ADT, and some intermediate-risk patients received short-term ADT. The 5-year BC rates were 78.6% (95% CI=85.2-71.3%) for conventional IMRT and 76.7% (95% CI=83.6-69.0%) for hypofractionated IMRT (p=0.745). There were no statistically significant differences in late toxicity between the arms. Patients with compromised urinary function before enrollment had markedly worse urinary function after hypofractionated IMRT.

Several reviews and meta-analyses have concluded that hypofractionated radiotherapy in localized prostate cancer was not superior to CF radiotherapy with current schedules (18, 19). The incidence of acute adverse GI events was higher in the hypofractionated group (risk ratio=2.02, 95% CI=1.45-2.81; p=0.0001) (18). Moderate hypofractionated schedules should only be used in the context of clinical trials (19).

Accelerated Hypofractionation

Hypofractionation using higher single doses of 5 Gy or more is termed 'accelerated' (13-15), 'extreme' (16), or 'profoundly' (17) AHF. In the AHF scheme, several modalities are challenging, including SBRT, particle therapy, and HDR-BT. Each has merits and disadvantages.

Stereotactic body radiotherapy. SBRT is one of the attractive alternative approaches to hypofractionation. SBRT using an image-guided approach enables physicians to deliver a precise dose in a short-term AHF treatment regimen.

A pooled analysis of 1,100 patients treated with CyberKnife who enrolled in prospective phase II clinical trials during 2003-2011 from eight Institutions showed the feasibility of SBRT (25). There were 49 patients with PSA failure (4.5%), nine of whom were subsequently determined to exhibit benign PSA bounces. The 5-year BC rate was 93% for patients overall; 95%, 83%, and 78% for those with Gleason score ≤6, 7, and ≥8, respectively (p=0.001). A PSA bounce of >0.2 ng/ml was noted among 16% of patients. For 135 patients with a follow-up of minimum 5 years, the 5-year BC rate for low- and intermediate-risk patients was 99% and 93%, respectively.

A 6-year outcome in 304 patients who received CyberKnife SBRT with AHF revealed that late grade 2 urinary complications were observed in 4% of patients treated with 35 Gy and 9% of patients treated with 36.25 Gy (26). There were five cases (2%) of late grade 3 urinary toxicity among patients who were treated with 36.25 Gy. Late grade 2 rectal complications were observed in 2% of patients treated with 35 Gy and 5% of patients treated with 36.25 Gy. An overall decrease of 20% in the sexual quality of life score was observed. Among patients sexually functional prior to treatment, 75% stated that they remained sexually functional.

A phase I/II Canadian study confirmed feasibility and efficacy of SBRT 35 Gy in five fractions (27), once weekly on standard linear accelerators, which revealed that 96% were biopsy-negative post-treatment.

High dose rate brachytherapy. Brachytherapy can achieve excellent dose distribution by easily following organ motion (Table II); therefore, a high BC rate is generally expected, but with increased toxicity mainly in the urological area. Major brachytherapy sources are classified as low-dose-rate (LDR; a dose of 0.4-2 Gy/h,) and high-dose-rate (HDR; a dose of >12 Gy/h). In the present study, we selected only HDR-BT because this review aimed to explore hypofractionation.

A randomized phase III trial was performed comparing EBRT alone with EBRT combined with HDR-BT boost in patients with unfavorable prostate cancer from 1997 to 2005 (28). Treatment arm, risk category, and ADT were significant covariates for risk of relapse in the multivariate analysis. Differences in overall survival were not significant (88% and 89%, respectively). EBRT with HDR-BT resulted in a significant improvement in BC/clinical relapse-free survival compared with EBRT alone, with a 31% reduction in the risk of recurrence (p=0.01) and similar incidences of severe late urinary and rectal morbidity. This is expected because the HDR-BT plus EBRT group received a higher BED of 159 Gy than did the EBRT group with a BED of 62.9 Gy (α/β ratio of 1.5). However, it should be noted that these results imply that such escalated EQD2 do not improve overall survival. Using an HDR boost over CF has the advantage of reducing the overall treatment time; the treatment time usually exceeds 9 weeks at some institutions and can be a huge burden to patients. The 2012 National Comprehensive Cancer Network Clinical Practice Guidelines recommend brachytherapy in combination with EBRT as a treatment option for patients with high-risk localized tumors or locally advanced disease (29).

High-dose-rate Monotherapy

HDR monotherapy was also assessed at several institutions with BC rates ranging from 79% to 100% and local control rates from 97% to 100% (29). The toxicity rates were low, although some authors have reported grade 3 toxicities. The frequency of late GU toxicity grade 2 or more ranges from 0 to 59.0% and the rate for late GI toxicity is 0-13.0% (31).

Between 1996 and 2005, HDR monotherapy was explored in patients with low- and intermediate-risk prostate cancer at California Endocurietherapy and the William Beaumont Hospital (32). At California Endocurietherapy, the dose was 42 Gy in six fractions (two implantations 1 week apart) delivered using a computed tomography-defined planning

treatment volume. At the William Beaumont Hospital, the dose was 38 Gy in four fractions (one implantation) based on intraoperative transrectal ultrasound real-time treatment planning. The 8-year results were 99% local control, 97% BC (nadir +2), 99% distant metastasis-free survival, 99% cause-specific survival, and 95% overall survival. GU toxicity consisted of 10% transient grade 2 urinary frequency or urgency and of 3% grade 3 episode of urinary retention. A total of 206 LDR and 248 HDR brachytherapy-treated patients at were compared (15). HDR and LDR monotherapy had the same 5-year BC rates, but HDR brachytherapy was associated with less acute and chronic GI and GU toxicities. The LDR dose at the William Beaumont Hospital was 120 Gy (LDR-^{103}Pd). The 5-year BC rates were 89%, 91%, and 88% for LDR and HDR at theWilliam Beaumont Hospital, and HDR at California Endocurietherapy, respectively. The majority of complications were of grade 1. HDR was associated with less acute grade 1-3 dysuria: 60% *vs*. 39% (p=0.001); urinary frequency/urgency: 90% *vs*. 58% (p=0.001); and rectal pain: 17% *vs*. 6.5% (p<0.001). Long-term urinary frequency/urgency (54% *vs*. 43%; p=0.03) and dysuria (22% *vs*. 15%) were less frequent with HDR. The 5-year actuarial impotence rate was 30% for LDR and 20% for HDR (p=0.23).

Hoskin *et al*. evaluated a total of 197 patients treated with 34 Gy in four fractions, 36 Gy in four fractions, 31.5 Gy in three fractions, or 26 Gy in two fractions (33-34). The incidence of early grade 3 or more GU morbidity was 3-7%, and grade 4 was 0-4%. During the first 12 weeks, the highest mean International Prostate Symptom Score (IPSS) value was 14 and between 6 months and 5 years, it was 8. Grade 3 or 4 early GI morbidity was not observed. The 3-year actuarial rate of grade 3 GU toxicity was 3%-16% and for strictures requiring surgery, it was 3-7% (4-year rate). An incidence of 1% of grade 3 GI events was seen at 3 years. Late grade 4 GU or GI events were not observed. At 3 years, 99% BC was obtained in patients with intermediate-risk and 91% BC in patients with high-risk disease (p=0.02). They updated the outcome of patients treated with 3×10.5 Gy (n=109) and 2 × 13 Gy (n=118) HDR brachytherapy alone (34). Urinary, bowel symptoms, and IPSS were higher after 31.5 Gy than after 26 Gy; however, differences were significant only for grade 1 and 2 urinary toxicity. At 3 years, 93% and 97% of patients treated with 26 and 31.5 Gy, respectively, were free from biochemical relapse (p=0.5) and 91% for the latter regimen at 5 years.

A German group presented outcomes of the largest series of transrectal ultrasound-guided HDR monotherapy which included 718 patients (35). Three treatment protocols were applied: 141 patients received 38.0 Gy using one implant in four fractions of 9.5 Gy with computed tomography-based treatment planning; 351 patients received 38.0 Gy in four fractions of 9.5 Gy, using two implants (2 weeks apart) and intraoperative transrectal ultrasound real-time treatment planning; and 226 patients received 34.5 Gy, using three single-fraction implants of 11.5 Gy (3 weeks apart). The 60-month BC and metastasis-free survival rates for the entire cohort were 94% and 98%, respectively. Late grade 3 GU and GI toxicities were 3.5% and 1.6%, respectively. Two patients developed grade 4 incontinence.

The Osaka group initiated HDR brachytherapy monotherapy in the 1990s and was the first to report the use of HDR brachytherapy without EBRT (36). The 5-year PSA failure-free, local control, disease-free survival, and overall survival rates were 83%, 97%, 87%, and 96%, respectively. Late grade 2 toxicity was observed in 13 patients. Following those experiences, Yoshida *et al*. implemented MRI image-guided HDR brachytherapy for dose optimization (37, 38). They updated their data, focusing on a group of 48 high-risk patients (39). Neoadjuvant ADT was administered to all 48 patients; 12 patients also received adjuvant ADT. The planned prescribed dose was 54 Gy in nine fractions over 5 days for the first 13 patients and 49 Gy in seven fractions over 4 days for 34 patients. Only one patient who was over 80 years old received 38 Gy in four fractions over 3 days. The 5-year overall survival and BC rates were 98% and 87%, respectively. Grade 2 or more late GU and GI complications occurred in seven patients (14%) and two patients (4%), respectively.

Ultimate single-fraction HDR brachytherapy was performed with transperineal hyaluronic acid injection into the perirectal fat to displace the rectal wall away (40). Between 2008 and 2010, 40 consecutive patients were treated for clinically favorable localized prostate cancer; the median follow-up was 19 months (range=8-32 months); 35% received ADT before brachytherapy. All patients received one implant and one fraction of HDR with a fraction dose of 19 Gy. No chronic toxicity was observed after treatment up to the time of analysis. The 32-month actuarial BC was 100% and 88% (p=0.06) for low- and intermediate-risk groups, respectively.

For HDT brachytherapy monotherapy, the longest follow-up for outcomes is reported for mHF (4-9 fractions); however, excellent preliminary results are being reported with ultrahypofractionation (1-3 fractions) (33, 34, 40, 41). The emergence of ultrahypofractionation with only 1-2 treatments makes HDR logistically comparable to seed implant and adds a high degree of dosimetry control and accuracy in brachytherapy. Single-fraction HDR monotherapy is now being investigated, and if the data are confirmed with longer follow-up, it may well become the treatment-of-choice for many men with localized prostate cancer.

HDR brachytherapy, alone or given as a boost combined with moderate-dose EBRT, gave a preliminary but impressively high BC rate. However, brachytherapy (and some types of SBRT) inevitably uses invasive procedures to

Table II. *Moderate to accelerated hypofractionation using stereotactic body radiotherapy (SBRT), high dose rate brachytherapy (HDR-BT) and particle therapy.*

Author (Institute or Country)	Year (Total Pt No.)	Study Pt No. follow-up period (median)	ADT Risk group* (L/I/H) (Risk classification)	Radiotherapy (daily Fx) [EQD2: α/β 1.5]	5y- PSA control rate*(1) (L/I/H)	Adverse reaction Late G2 or more if otherwise cited [criteria]	
SBRT							
King (25) (USA)	2013 (n=1100) CyberKnife Pooled study	35Gy → 36.25Gy→ 38-40Gy n=385 → 589 → 126 (3Y)	14% ADT (60%/ 30%/ 10%) (D'Amico)	35Gy → 36.25Gy → 38-40Gy (7Gy →7.25Gy →9.06Gy) [90.6Gy →109.3Gy]	(95%/84%/81%) 35Gy →36.25Gy →38-40Gy 92.5%→ 90.7% →95.8%	Not Available	SBRT feasible
Katz (26) (Winthrop Univ.)	2013 (n=304) CyberKnife	35 Gy /5fr → 36.25 Gy/5fr n=50 → 254 (60M)	57 ADT T1-2a (211/ 81/ 12) (NCCN)	35 Gy /5fr → 36.25 Gy /5fr (7Gy →7.25Gy) [85 →90.6Gy]	(97% / 90.7% / 74.1%) 35 Gy /5fr → 36.25 Gy /5fr 98% → 97%	GI 2% → 5%, GU 4% →11% [RTOG]	SBRT feasible Dose escalation study
Loblaw (27) (Canada)	2013 (n=84) IGRT: fiducial + MVCT	35 Gy /5fr (55M)	ADT (-) L (NA)	35 Gy /5fr (7Gy) [85 Gy]	98%	GI 8% GU 5% [RTOG]	
HDR-BT (EBRT+HDR-BT)							
Hoskin (28) (UK)	2012 (n=215)	RCT: EBRT *vs.* EBRT+BT n=106 *vs.* 110 (85M)	75-77% ADT (7/ 43 / 56) *vs.* (2/ 48/ 60) (NCCN)	55Gy/22fr *vs.* 35.75Gy/ 13fr+17Gy/2fr [62.9Gy *vs.* 159Gy]	61% *vs.* 75% (p=0.04)	Severe GI: 6% *vs.* 7% severe GU: 26% *vs.* 26% [Dische score]	EBRT+BT>EBRT OS equivocal
HDR-BT (HDR-BT monotherapy)							
Demanes (32) (CET,WBH)	2011 (n=298)	157 CET and 141 WBH (5.2Y)	24% ADT L-I (D'Amico)	42Gy/6fr (CET) and 38Gy/4fr (WBH) [102Gy, 119Gy]	97% (8Y)	GI <1.0%, GU 13% [CTCAE v3]	
Martines (15) (CET, WBH)	2010 (n=454)	HDR 38Gy/4fr (WBH) *vs.* 42Gy/6fr (CET) *vs.* LDR 120Gy n=171 *vs.* 77 *vs.* 206 (4.8Y)	ADT (47 *vs.* 20 *vs.* 64 PT) (171/ 50/ 44) (T1c–T2a, GS 7, PSA ≤12)	38Gy/4fr *vs.* 42Gy/6fr *vs.* 120Gy [119Gy, 102Gy, NA]	89% *vs.* 91% *vs.* 88%	GI: HDR *vs.* LDR: rectal bleeding 1.5% *vs.* 1% GU: HDR *vs.* LDR: frequency/ urgency 14% *vs.* 14% [CTCAE v3]	
Hoskin (33, 34) (UK)	2012 (n=197)	34Gy/4fr, 36Gy/4fr, 31.5Gy/3Fr, 26Gy/2fr n=30, 25, 109, 33 (54M, 60M 34M, 6M)	157 ADT (8/ 103/ 86) (NCCN)	34Gy/4fr, 36Gy/4fr, 31.5Gy/ 3Fr, 26Gy/2fr (8.5 Gy, 9Gy, 10.5Gy, 13Gy) [97.1Gy, 86.9Gy, 108.0Gy, 107.7Gy]	(I/ H=99%/ 91% 3Y)	GI 3-7% GU 33-40% [RTOG]	HDR-BT good results
Zamboglow (35) (Germany)	2013 (n=718)	(A)38Gy/4fr *vs.* (B) 38Gy/4fr *vs.* (C) 34.5Gy/3fr n=141 *vs.* 351 *vs.* 226 (4.4Y) (91.9M *vs.* 59.3 M *vs.* 25.4M)	30 *vs.* 70 *vs.* 55 ADT (14/351/226) (Memorial Sloan-Kettering)	(A) *vs.* (B) *vs.* (C) (9.5Gy, 9.5Gy, 11.5Gy) [119.4Gy, 119.4Gy, 128.1Gy]	(95% /93%/93%) (A) *vs.* (B) *vs.* (C): 98% *vs.* 95% *vs.* 95% (3Y)	GI : Rectal mucositis (A) *vs.* (B) *vs.* (C) 4% *vs.* 2% *vs.* 0.4% GU: frequency/urgency (A) *vs.* (B) *vs.* (C) 11.3% *vs.* 5.4% *vs.* 7.5% [CTCAE v3]	

Table II. *Continued*

Table II. *Continued*

Author (Institute or Country)	Year (Total Pt No.)	Study Pt No. follow-up period (median)	ADT Risk group* (L/I/H) (Risk classification)	Radiotherapy (daily Fx) [EQD2: α/β 1.5]	5y- PSA control rate*(1) (L/I/H)	Adverse reaction Late G2 or more if otherwise cited [criteria]	
Yoshioka (36) (Osaka Univ.)	2013 (n=112)	54 Gy/9Fr (5.4Y)	ADT (+) (15/ 29/ 68) (NCCN)	54 Gy/9Fr [115.7Gy]	(85%/ 93%/ 79%)	14% (8 GI + 7GU) [CTCAE v3]	
Yoshida (37-39) (Osaka National Hosp.)	2014 (n=100)	38 Gy/ 4 Fr, 49 Gy/ 7 Fr, 54 Gy/ 9 Fr, 40 Gy /5 Fr n=4, 69, 26, 1 (5Y)	ADT (+) (21/ 35/ 44) (NCCN)	38 Gy/ 4 Fr, 49 Gy/ 7 Fr, 54 Gy/ 9 Fr, 40 Gy /5 Fr [119.4Gy, 119Gy, 115.7Gy, 108.6Gy]	(100%/ 97%/ 88%)	GI 2% GU 12% [CTCAE v3]	MRI image guided BT
Prada (40) (Spain)	2012 (n=40)	19Gy/1fr (55M)	35% ADT L/ I=29/11 (Memorial Sloan-Kettering)	19Gy/1fr [111.3Gy]	(L/ I=100% / 88%) at 32M	GI 0% GU 0% [CTCAE v4]	Single fx HDR-BT
Particle therapy							
Kim (41) (Korea)	2013 (n=82) Proton	60CGE /20fr, 54CGE /15fr, 47CGE /10fr, 35CGE / 5fr n=19, 16, 17, 18, 12 (42M)	ADT (-) L:I:H=28, 37, 17 (NCCN)	60CGE /20fr, 54CGE / 15fr, 47CGE /10fr, 35CGE / 5fr (3Gy/fr, 3.6Gy/fr, 4.7Gy/fr, 7Gy/fr) [77.1 CGE, 78.7GyCGE, 83.3GyCGE, 85GyCGE]	(92%/ 90%/ 75%(4Y))	GI 16% GU7% [AUA, QoL, LENT-SOMA]	
Ishikawa (42) (NIRS)	2012 (n=927) Carbon	66GyE/20fr, 63GyE/20fr, 57.6GyE/16fr n=250, 246, 461 (43M)	ADT L/I/H=0%/ 100%/ 100% (159/ 278/ 490) (NCCN)	66GyE/20fr, 63GyE/ 20fr, 57.6GyE/16fr (4 in wk) (3GyE/fr, 3.15GyE/fr, 3.6GyE/fr) [77.1GyE, 83.7GyE, 83.9GyE]	(90%/ 97%/ 88%)	GI 3.2%, 2.3%, 0.5% GU 13.6%, 7%, 2% [RTOG EORTC]	51.2GyE/12fr ongoing (4.26GyE/fr→84.1GyE)

ADT; Androgen deprivation therapy, L; low risk, I; intermediate risk, H; high risk, EQD2; Equivalent dose in 2 Gy fractions, *1PSA failure is defined according to Phoenix criteria if otherwise stated, G2; grade 2, GI; gastrointestinal, GU; genitourinary. NCCN; The National Comprehensive Cancer Network, RTOG; Radiation Therapy Oncology Group, LENT/SOMA; Late Effect Normal Tissues/ Subjective, Objective, Management, and Analytic, CTCAE; Common Terminology Criteria for Adverse Events, (A) 38Gy/ 4 fr=1 implantaiton, (B) 38Gy/ 4 fr=2 implantation separated by 2 weeks, AUA; American Urological Association score, QoL; urinary quality of life score, EORTC; The European Organisation for Research and Treatment of Cancer. CET; California Endocueiethreapy Center, WBH; William Viewmont Hospital, CTCAE v.3.0 Common Terminology Criteria for Adverse Events version 3.0, NIRS; National institute of Radiological Science, CGE; cobalt gray equivalent.

insert applicators or a metal marker, which may be an obstacle to widening its application. In addition, because of the short follow-up period in most of HDR studies, very little actuarial toxicity data per patient are available. Comparison with IMRT, for example, would be difficult at present and requires more mature clinical data on HDR monotherapy (31).

Particle therapy. Particle therapy has also implemented hypofractionated regimens using a superior dose distribution, partly to overcome the disadvantage of expensive cost.

Eighty-two patients with biopsy-proven T1-3N0M0 prostate adenocarcinoma and no history of ADT were randomly assigned to five different dose schedules of proton therapy (42) (Table II): Arm 1, 60 cobalt Gray equivalent (CGE=proton dose in Gy × 1.1) per 20 fractions over 5 weeks; Arm 2, 54 CGE per 15 fractions over 5 weeks; Arm 3, 47 CGE per 10 fractions over 5 weeks; Arm 4, 35 CGE per five fractions over 2.5 weeks; or Arm 5, 35 CGE per five fractions over 5 weeks. The median follow-up duration was 42 months (range=11-52 months). The acute GI and GU grade 2 or more toxicity rates were 0 and 5%, respectively. Arm 3 had the least acute GU toxicity, while Arm 2 had the least late GI toxicity, with no grade 2 or more toxicity. The four-year BC rate was 86%. Hypofractionated proton therapy is feasible, with an acceptable toxicity profile.

Two phase I/II dose escalation studies (protocols 9402 and 9703) of AHF carbon-ion radiotherapy for patients with both early- and advance-stage prostate cancer had been performed between 1995 and 2000 (43). Subsequent phase II study (9904) was initiated in 2000 (66 Gy in 20 fractions over 5 weeks, obtained from the phase I/II studies). Approximately 1100 patients had received carbon-ion radiotherapy as of 2011. The 5-year BC rates for low-, intermediate-, and high-risk patients were 90%, 97%, and 88%, respectively (43).

Discussion

Technological advances in radiation therapy delivery have permitted the use of high-dose-per-fraction radiation therapy for prostate cancer. At present, prospective studies support the safety of mHF; however, long-term results of non-inferiority studies are required. BC rates improved with dose escalation and hormonal therapy and reached 90-100% in low-risk groups, 80-95% in intermediate groups and 60-70% in high-risk groups at 5 years. Overall survival rates also improved and reached nearly 100% at 5 years (44). Therefore, a major concern is changing from BC to quality of life maintenance, particularly in elderly patients (45). A recent RCT of 1532 patients with 7 years of median follow-up (RTOG-0126) failed to demonstrate an increased overall survival using higher EQD2 (79.2 Gy *vs.* 70.2 Gy), even showing increased prostate cancer progression, metastasis, or initial treatment failure with escalated toxicity (46). This implies that larger patient populations and longer follow-up periods are required to confirm the superiority of higher EQD2 for overall survival using 70-80 Gy. In this respect, hypofractionation, particularly AHF has great merits in reducing the socioeconomical burden by reducing treatment periods.

The fundamental issue regarding hypofractionation is based on a hypothesis of low α/β ratio for prostate adenocarcinoma compared to that of late-responding normal tissues (*i.e.* rectal damage: 3 Gy) (1-3). Dasu *et al.* reported an α/β-value of 1-1.7 Gy based on an analysis including 14,168 patients, which is so far the most precise estimation of α/β-ratio for EBRT with the largest patient collective (3). Miralbell *et al.* recently published data on nearly 6,000 patients of different prostate cancer risk groups, all treated with EBRT, either with standard fractionation (1.8-2.0 Gy/fraction; 40% of patients) or hypofractionation (2.5-6.7 Gy/fraction; 60% of patients) (2). An α/β-value of 1.4 Gy (95% CI=0.9-2.2) was obtained using the linear-quadratic model (2). Sun *et al.* argued that compared to CF, hypofractionation only yields a consistent advantage in BC for high-risk patients (hazard ratio=0.61, 95% CI=0.46-0.82; p=0.001) (47). Similar findings were reported for HDR brachytherapy (30) and SBRT (25) when they used higher EQD2. King *et al.* reported no influence of ADT on BC rates based on data pooled from >1,000 SBRT-treated patients (p=0.71), even within the intermediate- and high-risk groups. They suspected that this was a consequence of the high EQD2 that SBRT used. The evidence for improved outcomes with the addition of ADT originates from clinical trials where the external-beam dose was 70 Gy. There is current retrospective evidence that with conventionally fractionated dose escalation to 78 Gy or higher, there may be little to gain from ADT (25). Therefore, AHF using aggressive higher EQD2 has a potential advantage, particularly for the high-risk group.

According to this notion, the risk classification system should be modified to select candidates for more aggressive treatment in the high-risk group because low- to intermediate-risk groups have recently achieved nearly 100% BC rates, which are high enough to meet the requirement particularly for elderly patients. However, for the higher risk group, some patients require more aggressive treatment schedules to improve BC rates. To meet these demands, the National Comprehensive Cancer Network has created a new category: the super-high-risk group (29). Yoshioka *et al.* have proposed a new grading system, the PRIX system (48), for perquisite separation and the determination of which high-risk patients should undergo a more aggressive treatment; the system was confirmed by Yoshida *et al.* (37, 47, 48). Although it is the preliminary phase, these experiments will be helpful for patient selection for further aggressive treatment.

Avoiding normal tissue toxicity is of paramount importance with regard to hypofractionated treatments. However, an outstanding concern is that the α/β ratio for late rectal side-effects is largely unknown and difficult to assess from the available data. The α/β ratio of the late-reacting normal tissues, such as the rectum, is usually assumed to be 3 Gy (50), but may be higher. The rectal toxicity data from the RTOG 94-06 trial were analyzed and the best α/β ratio fit for late rectal damage was 4.6 Gy, although the confidence intervals were wide (51). Brenner has reviewed data from several Centers using a dose/fraction of 1.8 to 3 Gy and derived an α/β ratio of 5.4 Gy for the rectum (52).

The α/β ratio of a normal bladder has not been well studied and is assumed to be in the region of 5-10 Gy (53). There is some evidence that the region of the bladder receiving a higher dose is more significant, with the trigonal area appearing to be most sensitive for urethral obstruction (54); mature long-term follow-up data from extreme hypofractionated trials are not yet available. Furthermore, a critique has suggested that if the α/β ratio is translated into molecular, biological, and physical terms, it would clarify the detailed mechanism for experts in other cancer fields and the general population.

There are several ongoing prospective RCTs, including proton therapy and SBRT, to test the potential of hypofractionated regimens. The Hypofractionated Radiotherapy of International Risk Localized Prostate Cancer trial (HYPO-RT-PC; ISRCTN45905321) randomized intermediate-risk patients to receive SBRT 42.7 Gy in seven fractions (6.1 Gy/fraction) *vs*. 78 Gy in 39 fractions with IMRT. The Prostate Advances in Comparative Evidence (PACE) study is an international multicenter randomized study of organ confined, low- and intermediate-risk prostate cancer and is composed of two parallel randomization schemes based on the applicability of surgery as a treatment option for the patient (NCT01584258). Patients willing to consider surgery are randomized to either laparoscopic (or da Vinci prostatectomy) or CyberKnife prostate SBRT 36.25 Gy in five fractions or 38 Gy in four fractions. The Proton Cooperative Group has randomized 192 patients into either 79.2 Gy in 44 fractions or 38 Gy in five fractions for low-risk patients. RTOG has recently completed accrual for a large prospective study of 1,115 patients randomly assigned to either 28- or 41-fraction regimens (RTOG 0415), and a randomized phase II trial comparing 5- and 12-fraction accelerated hypofractionation is nearing accrual completion (RTOG 0938). We are awaiting outcomes of these RCTs.

In conclusion, hypofractionated regimens are performed in clinical trials with a risk of higher toxicity. However, AHF is challenging considering its basis and socioeconomic advantages.

Conflicts of Interest

None.

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