

A randomized trial comparing hypofractionated and conventionally fractionated three-dimensional conformal external-beam radiotherapy for localized prostate adenocarcinoma: a report on the first-year biochemical response

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Key words: prostate cancer; radiotherapy; hypofractionation; biochemical response.

Summary. *Objective.* This paper describes the first-year biochemical (prostate-specific antigen [PSA]) response of 91 irradiated patients enrolled in a single-institution randomized trial comparing hypofractionated (HFRT) and conventionally fractionated (CFRT) external beam radiotherapy.

Material and methods. Forty-four patients in the CFRT treatment arm were irradiated with 74 Gy in 37 fractions (2 Gy per fraction), and 47 in the HFRT arm were treated with 57 Gy, given in 13 fractions of 3 Gy plus 4 fractions of 4.5 Gy. The clinical target volume includes the prostate and a base of seminal vesicles. The proportions of patients who reached PSA nadir (nPSA) lower than or equal to 1.0 ng/mL (nPSA1) and 0.5 ng/mL (nPSA05) were compared.

Results. There were 2 non-cancer-related deaths (1 in the CFRT and 1 in the HFRT treatment arms). Biochemical relapse after irradiation was defined in five cases (3 in the CFRT and 2 in the HFRT treatment arms) during a 12-month follow-up. The remaining 84 patients were analyzed. The proportions of patients reaching nPSA1 were 50% and 54.5% in the CFRT and HFRT treatment arms, respectively (chi-square $P=0.843$). The percentages of patients reaching nPSA05 were 25% and 18.2%, respectively (chi-square $P=0.621$). The trends toward increasing proportions of biochemical responders (both nPSA1 and nPSA05) during 12 months after radiotherapy were observed, but the difference between trends for treatment arms did not reach a statistical significance.

Conclusion. The preliminary results presented here demonstrate that HFRT schedule induces biochemical response rates comparable to those in the CFRT schedule during the first-year follow-up.

Introduction

The randomized dose-escalation trials demonstrate a significant improvement in freedom from biochemical failure (FFBF) for intermediate and high-risk prostate cancer with the increase of conventionally fractionated radiotherapy dose (1–3). Even for low-risk patients, the 10-Gy dose escalation results in about 5–7% gain in 5-year FFBF (4). Conventionally fractionated dose escalation, however, results in treatment protraction, which negatively impacts patient's lifestyle and possibly lowers biological benefit.

Hypofractionation in the treatment of prostate cancer offers a shorter treatment course and increased convenience for patients. Shorter waiting lists are be-

neficial to department's productivity. Potentially hypofractionation in the treatment of prostate cancer also offers an improved therapeutic ratio due to a presumed higher sensitivity of prostate cancer tissues to higher fraction dose. Recent publications suggested that the α/β ratio (the ratio of "intrinsic radiosensitivity" to the "repair capability" of a specified tissue) of prostate adenocarcinoma was comparable to that for late-responding normal tissue or even lower because of the slow natural turnover rates in a high proportion of these tumors (5). The estimated value for α/β is 1.5 Gy (6–8). If the α/β value for prostate is reliably lower than that for late-responding rectal damage (3 Gy), hypofractionated regimens could be designed with

fewer but larger doses, which maintain equivalent late toxicity while yielding improved tumor control. Up to date, several nonrandomized and 3 randomized trials have addressed this issue, but the data about benefit of hypofractionation in the treatment of prostate cancer are still scarce.

In 2004, the Institute of Oncology of Vilnius University initiated a prospective randomized clinical trial comparing hypofractionated (HFRT) and conventionally fractionated (CFRT) external-beam radiotherapy for localized prostate cancer. The Lithuanian Bioethics Committee (LBEC) approved the study protocol and written informed consent.

The study has five endpoints: overall survival, freedom from biochemical failure, biochemical response to treatment, acute and late toxicity. Up to date, the collection of data for the first-year biochemical response to radiotherapy was completed for evaluation. The accrued 84 patients, with a minimum follow-up of 12 months, were analyzed for biochemical response to differently fractionated radiotherapy.

Material and methods

The protocol was designed to randomize patients with clinically localized prostate cancer to 74 Gy in 37 fractions at 2 Gy per fraction over 7.5 weeks (conventionally fractionated radiation therapy [CFRT]) vs. 57 Gy in 17 fractions over 3.5 weeks giving 13 fractions of 3 Gy plus 4 fractions of 4.5 Gy (hypofractionated radiation therapy [HFRT]). The HFRT regimen was hypothesized to be equivalent to 81 Gy in 2-Gy fractions assuming an α/β ratio of 1.5 Gy. This regimen was also designed to maintain predicted late toxicity equivalent to about 74 Gy in 37 fractions if α/β ratio for late-responding tissues is 3 Gy and predicted acute toxicity equivalent corresponding to about 64 Gy in 32 fractions if α/β ratio for early responding tissues is 10 Gy (9). The rationale for using 13 fractions of 3 Gy plus 4 fractions of 4.5 Gy in the study arm instead of constant fraction larger than 3 Gy was to detect an excess of acute toxicity and eliminate systematic patient setup error during the first 2 weeks of moderately hypofractionated irradiation.

The main inclusion criteria were as follows: prostate adenocarcinoma of low- and intermediate-risk group, with risk of seminal vesicle and/or pelvic lymph node involvement of less than 15% regarding Partin's nomograms and Roach formula, no hormonal therapy or surgical castration before radiotherapy. Only three patients with stage T3A cancer of the prostate were included in study, because they all had refused the advised hormonal therapy. Forty-four patients were

Table 1. Patient initial PSA and tumor characteristics

Parameter	CFRT	HFRT
Initial PSA ≤ 10	44	47
Initial PSA 11–20	0	0
Initial PSA > 20	0	0
T1	16	20
T2	26	26
T3	2	1
Gleason score ≤ 6	44	45
Gleason score 7	0	2
Gleason score 8–10	0	0

treated with CFRT and 47 with HFRT. The distribution of the patients by clinical T stage, by biopsy Gleason score, and initial PSA level is shown in Table 1.

The clinical target volume (CTV) included the entire prostate and the base of seminal vesicles. The planning target volume (PTV) margin of 8–10 mm was added to CTV in all directions. Conventional patient positioning using skin marks and lasers was used followed by weekly portal imaging and/or repeated simulations matched with digitally reconstructed radiographs (DRRs). Three-dimensional conformal radiotherapy with five-field technique (antero-posterior, 2 lateral and 2 posterior oblique fields) with the 15 or 25 MV MLC collimated photon beams were used for treatment planning and delivery. The prescribed dose was specified to the isocenter. The minimal dose (D_{min}) aimed to deliver to the PTV was 95%. The maximum dose (D_{max}) within the plan was 107%. For the rectum and bladder, $D_{max} \leq 95\%$ and $D_{max} \leq 100\%$, respectively, were allowed. For the rectum, the following rules were considered appropriate: V90 (i.e. the rectal volume receiving 90% of the prescription dose) and V75 (i.e. the rectal volume receiving 75% of the prescription dose) should be $\leq 30\%$ and $\leq 50\%$, respectively. The same constraints were used for bladder – V90 and V75.

Patients were evaluated weekly for 12 weeks starting from the beginning of irradiation. PSA tests were performed every 3 months during the first year after irradiation and every 6 months later.

Descriptive statistics were used to characterize the patient age, disease stage, initial PSA, Gleason score. The same methods were used to report patient proportions with PSA nadir of ≤ 1.0 ng/mL (nPSA1) and ≤ 0.5 ng/mL (nPSA05). The chi-square test was used to assess differences in nPSA1 and nPSA05 prevalence ratio.

Table 2. Numbers of patients who reached nPSA1 and nPSA05

Arm	Break of cutoff value	1 month	3 months	6 months	9 months	12 months
nPSA ≤1.0						
CFRT	Yes	4	9	17	18	20
	No	36	31	23	22	20
HFRT	Yes	0	7	11	14	24
	No	44	37	33	30	20
	chi-square test <i>P</i> value	0.1017	0.624	0.089	0.214	0.843
nPSA ≤0.5						
CFRT	Yes	1	2	5	7	10
	No	39	38	35	33	30
HFRT	Yes	0	1	2	5	8
	No	44	43	42	39	36
	chi-square test <i>P</i> value	0.291	0.501	0.187	0.64	0.621

CFRT – conventionally fractionated external-beam radiotherapy,
 HFRT – hypofractionated external beam radiotherapy.

Results

All 91 patients received radiotherapy according to the protocol. The median age of the patients at the beginning of treatment was 63 years (range, 53–75) in the HFRT and 65 years (range, 50–78) in the CFRT treatment arm. There were 2 deaths due to non-cancer disease (1 in the CFRT and 1 in the HFRT treatment arms). Biochemical relapse after irradiation was defined in five cases (3 in the CFRT and 2 in the HFRT treatment arms) during a 12-month follow-up. The American Society for Therapeutic Radiology and Oncology (ASTRO) definition of biochemical progression was used to report the PSA relapse (10). The remaining 84 patients had at least 12 months of follow-up after the completion of irradiation and were analyzed for PSA response to the treatment (Table 2).

The nPSA1 and nPSA05 prevalence ratio was calculated monthly in both treatment arms and plotted in separate diagrams (Figs. 1 and 2). There was no significant difference in proportions of patients between CFRT and HFRT treatment arms, who achieved either nPSA1 or nPSA05. At 12 months after the completion of the irradiation, the proportions of patients reaching nPSA1 were 50% and 54.5% in the CFRT and HFRT treatments arms, respectively (chi-square $P=0.843$). The percentages of patients reaching nPSA05 were 25% and 18.2%, respectively (chi-square $P=0.621$). The trends toward increasing proportions of biochemical responders (both nPSA1

and nPSA05) during 12 months after radiotherapy were observed, but the difference between trends for CFRT and HFRT treatment arms did not reach statistical significance.

Discussion

The low α/β values have been proposed for prostate cancer in recent years. However, several investigators have questioned the low α/β value, and clinical data on hypofractionation in prostate cancer are sparse. Several reports on hypofractionation for prostate radiotherapy from nonrandomized and randomized trials have been published to date. The available data are summarized in Table 3. Despite marked differences in dose prescription, treatment planning, delivery, verification and result interpretation methods, one may conclude from these (11–14, 16–20) nonrandomized trials that the results compare favorably with those achieved in conventionally fractionated radiotherapy series.

Three further series including two randomized trials used low radiation doses considered inappropriate today (21, 22). Only the results regarding acute toxicity from ongoing randomized trial have been reported recently (23). No results of efficacy from this study will be available for 2 to 4 years.

It is well established that pretreatment PSA, PSA doubling time (PSADT), stage, grade, dose, and post-treatment nPSA are all predictors of biochemical relapse in selected groups of men treated with radiothe-

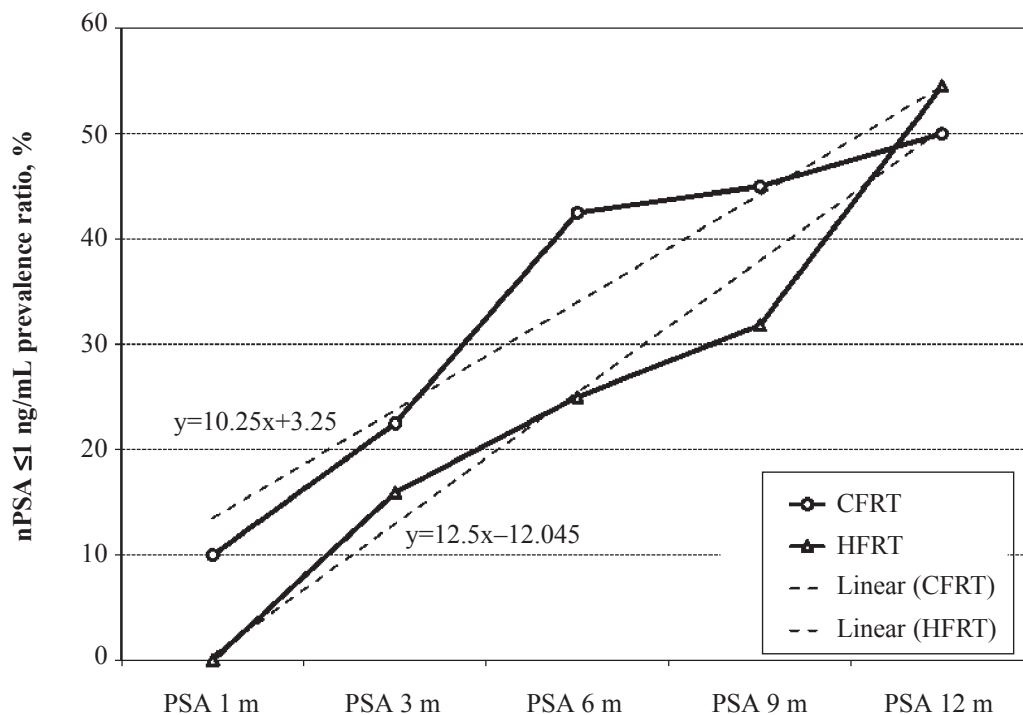


Fig. 1. Change of nPSA ≤1.0 ng/mL prevalence ratio in patient groups during 12 months after irradiation

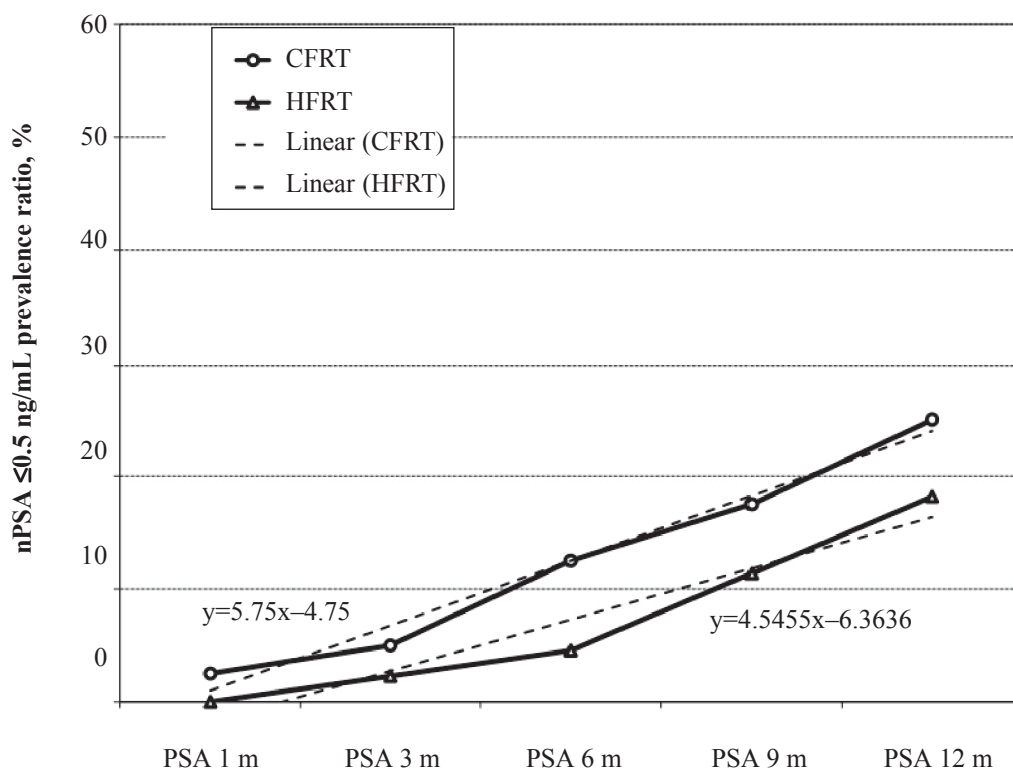


Fig. 2. Change of nPSA ≤0.5 ng/mL prevalence ratio in patient groups during 12 months after irradiation

Table 3. Long-term results from nonrandomized and randomized hypofractionation on prostate cancer trials

Author	Total dose (Gy)/ Number of fractions/ Fraction size (Gy)	EQD _{2Gy} if α/β 1.5/3/10 Gy (Gy)	FFBF (%) [Follow-up years]
Nonrandomized trials			
Kupelian et al. (11, 12)	70/28/2.5	80/77/73	85 [‡] , 88 ^{**} [5]
Tsuji et al. (13)	66/20/3.3		83.2 [5]
Kitamura et al. (14)	65/26/2.5	74/71.5/68	91.7 [2.5]
	70/28/2.5	80/77/73	89.4 [1.5]
Soete et al. (15)	56/16/3.5	80/73/63	ND
Ritter et al. (16)	64.7/22/2.94	82/77/70	96 ^{**} [2]
	58.08/16/3.36	85/77/66	
	51.6/12/4.3	85.5/75/61	
Junius et al. (17)	66/25/2.64	78/74/69.5	92 [‡] , 100 ^{**} [1]
Martin et al. (18, 19)	60/20/3	77/72/65	76 [‡] [2]
			97 ^{**} [3]
Madsen et al. (20)	33.5/5/6.7	78/65/47	70 [‡] , 90 ^{**} [2]
Leborgne et al. (21)	80/40/2	80/80/80	ND
	60/20/3	77/72/65	
	63/20/3.15	84/77.5/69	
Randomized trials			
Lukka et al. (22)	66/33/2	66/66/66	48.6 ^ˆ
	52.5/20/2.625	62/59/55	55.6 ^ˆ
Yeoh et al. (23)	64/32/2	64/64/64	56 [5]
	55/20/2.75	67/63/58	56 [5]
Pollack et al. (24)	76/38/2	76/76/76	ND
	70.2/26/2.7	84/80/74	

EQD_{2Gy} – total biologically equivalent dose in 2 Gy fractions (if α/β 1.5 Gy, 3 Gy, and 10 Gy).

[‡]ASTRO definition of biochemical progression; ^{**}“PSA + 2 ng/mL” definition of biochemical progression;

^ˆ Risk of 5-year clinical and/or biochemical progression; ND – no data.

rapy for prostate cancer. There are several studies to demonstrate the overwhelming predictive power of posttreatment nPSA for distant failure and death from prostate cancer (24, 25). We used these criteria (nPSA1 and nPSA05) to analyze and compare the efficacy of both conventionally fractionated and hypofractionated radiotherapy schedules in our study. Our early results after 12-month follow-up suggest that hypofractionation for prostate cancer could be as effective as conventionally fractionated radiotherapy.

There is some chance that the absence of daily target localization in this study could cause difficulties in comparison of biochemical tumor response between patient groups after a longer follow-up period because

of the higher probability of geographical miss with decreased number of fractions. Though, with CTV to PTV margin of 10 mm in many centers using 3D conformal radiotherapy, daily prostate movements are generally accommodated.

Conclusions

The first results of study presented here demonstrate that short-course hypofractionation schedule is feasible and induces biochemical response rates comparable to those in the conventional schedule during the first-year follow-up. Extended follow-up is needed to justify safety and efficacy of our fractionation schedule in the long term.

Hipofrakcionuota ir įprastai frakcionuota trimatė konforminė neišplitusio prostatos vėžio spindulinė terapija. Pirmųjų metų biocheminio atsako įvertinimas

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Raktažodžiai: prostatos vėžys, spindulinė terapija, hipofrakcionavimas, biocheminis atsakas.

Santrauka. *Tikslas.* Išanalizuoti vienoje institucijoje vykdyto randomizuoto klinikinio tyrimo rezultatus ir palyginti hipofrakcionuotą (HFRT) ir įprastai frakcionuotą (CFRT) neišplitusio prostatos vėžio išorinę spindulinę terapiją, įvertinti 91 ligonio biocheminį atsaką į gydymą per pirmuosius metus.

Tyrimo medžiaga ir metodai. CFRT taikyta 44 ligoniams, švitinta prostata ir sėklinių pūslelių pagrindas (CTV) 37 frakcijos po 2,0 Gy iki suminės 74 Gy dozės. HFRT taikyta 47 ligoniams, toks pat taikiny (CTV) švitintas 13 frakcijų po 3,0 Gy ir 4 frakcijos po 4,5 Gy iki suminės 57 Gy dozės. Palygintos ligonių, kuriems nustatytas PSA nadyras (nPSA) lygus arba mažesnis už 1,0 ng/ml (nPSA1) ir 0,5 ng/ml (nPSA05), proporcijos CFRT ir HFRT grupėse.

Rezultatai. Per 12 mėnesių nuo spindulinio gydymo pabaigos du ligoniai mirė nuo kitų priežasčių, nesusiėję su prostatos vėžiu (po vieną CFRT ir HFRT grupėse), užfiksuoti penki biocheminio ligos progresavimo atvejai (3 – CFRT ir 2 – HFRT grupėse). Likusiems 84 ligoniams įvertintas PSA atsakas į gydymą. CFRT grupėje nPSA1 nustatytas 50 proc. ligonių, HFRT – 54,5 proc. (chi-square $p=0,843$). nPSA05 nustatytas 25 ir 18,2 proc. ligonių CFRT ir HFRT, atitinkamai (chi-square $p=0,621$). Per 12 mėnesių abiejose grupėse pastebėta akivaizdi ligonių, kuriems nustatytas biocheminis atsakas (tiek nPSA1, tiek ir nPSA05) skaičiaus augimo tendencija, tačiau statistiškai reikšmingo skirtumo tarp grupių nenustatyta.

Išvada. Ankstyvieji šio klinikinio tyrimo duomenys HFRT ir CFRT tiriamųjų grupėse rodo panašų biocheminį atsaką per pirmuosius metus po spindulinio gydymo.

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