



RADIOTHERAPY OF PROSTATE CANCER: PRIMARY RADIOTHERAPY AND RADIOTHERAPY IN DISEASE RELAPSE

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SUMMARY – Radiotherapy presents one of the essential modes of treatment in patients with prostate cancer at almost any stage of the disease. It can be delivered as external beam radiotherapy, as brachytherapy or two methods combined. Higher radiation doses are proven to be more effective than low doses and moderate hypofractionation with doses up to 3.4 Gy per fraction is proven equivalent to standard fractionation using 1.8- 2 Gy per fraction. Stereotactic body radiotherapy (SBRT) with doses from 3.4 to 7.25 Gy per fraction presents valuable option in certain subgroups of patients. In case of local regional disease relapse, radiotherapy is used in curative setting.

Key words: *prostate cancer, radiotherapy, brachytherapy, hypofractionation, stereotactic body radiotherapy, salvage radiotherapy*

Introduction

Radiotherapy in prostate cancer is undoubtedly efficacious treatment. In last decades a number of clinical trials exploring different radiotherapy modalities and schedules regarding dose and fractionation have been published. Nevertheless, due to methodological limits, it can be quite difficult to compare the results of various trials. In 1985 prostate specific antigen (PSA) was introduced. That has caused a significant downward risk migration over time, which had the impact on treatment (1). In 2016 International Society of Urological Pathology (ISUP) published consensus on contemporary grading and new prostate cancer grading system was introduced as a validated alternative to the Gleason score. That led to further risk group stratification (2, 3). Heterogeneity of used endpoints also contributes to methodological limits: overall survival, cancer specific survival, clinical relapse, biochemical relapse, not to mention various definitions of biochemical relapse. All those limits make interpretation and comparison of results of reported clinical trials, as

well as their implementation in the current practice quite challenging.

The aim of this article is to present landmark trials that led to change of practice regarding the dose of radiotherapy, hypofractionation, use of stereotactic radiotherapy, brachytherapy and the role of radiotherapy in locoregional disease relapse.

Methods

A literature search of MEDLINE via PubMed was performed for the following terms: “RT”, “radiation”, “irradiation”, “prostatic neoplasms/RT”, “brachytherapy”, “dose fractionation”, “stereotactic body radiotherapy”, “salvage radiotherapy”.

Results

Dose escalation

A number of clinical trials have addressed the role of dose escalation on the disease outcome and the toxicity of higher doses.

One of the first dose escalation trials was Medical Research Council (MRC) 01 trial. It randomized 843 patients whose prostate cancer was staged as T1b- T3a N0 M0 and PSA level was less than 50 mg/mL, to

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receive either 64 Gy in 32 fractions, conformal radiotherapy, which was standard dose at the time (control group), or 74 Gy in 37 fractions (dose-escalated group). Three to six months before the beginning of irradiation, neoadjuvant androgen deprivation therapy started, and was continued until the end of radiation treatment. After a median follow up of 10 years, biochemical progression-free survival was 43% in the control group and 55% in the dose-escalated group ($p = 0.0003$). No difference was observed in overall survival; it was 71% in each group. Patients allocated to dose-escalated group had an increased rate of both acute and late toxicity (4).

GETUG06 trial randomized 306 patients with localized prostate cancer to receive 70 Gy or 80 Gy on prostate, without androgen deprivation. After 61 months of follow up, the 5-year biochemical relapse rate was 32% and 23.5%, respectively ($p = 0.09$) using Phoenix definition (nadir PSA plus 2 ng/ml). Better biochemical outcome for the higher dose group was observed in patients whose initial PSA levels were above 15 ng/ml. No difference in mortality between the two treatment approaches was noticed. Higher dose group patients had significantly more grade 2 urinary toxicity (17.5% compared to 10% at 70 Gy, $p = 0.046$) and bladder toxicity ($p = 0.039$). No significant differences in grade 2 or greater rectal toxicity nor in quality of life were reported among the patient groups (5).

In the Dutch trial, in 664 patients with T1b-T4N0 prostate cancer doses of 78 Gy and 68 Gy were compared. Use of androgen deprivation therapy was allowed. Biochemical and/or clinical failure (BCF) was trial's primary endpoint. Both ASTRO (American Society for Therapeutic Radiology and Oncology) guidelines (3 consecutive PSA rises) and Phoenix definition (nadir PSA plus 2 ng/ml) were used to define it. After 110 months of follow up, BCF and local failure (LF) rates were significantly lower in the group of patients receiving 78 Gy ($p < 0.05$). However, no differences in clinical failure (CF), death from prostate cancer (PCD), and overall survival (OS) were observed (6, 7).

In the trial published by Kuban et al., 301 T1b-T3 prostate cancer patients were randomized to receive 70 Gy or 78 Gy. Median follow up was 9 years. Higher biochemical and clinical failure rates, as well as higher risk of dying of prostate cancer, were observed in patients with high-risk disease or with pre-treatment

PSA level > 10 ng/ml, if irradiated to 70 Gy. If treated with 70 Gy, patients that were less than 70 years old at treatment died three times more frequently of prostate cancer than of other causes. In this age group, patients were more likely to die from other causes if irradiated with 78 Gy. Patients that were 70 or older died of both prostate cancer and of other causes equally, if treated with 70 Gy. In this age group, not a single patient receiving 78 Gy died of prostate cancer. In conclusion, in patients with high-risk disease moderate dose escalation using radiation dose of 78 Gy offers better biochemical and clinical control and decreases death from prostate cancer. That also applies to patients whose pre-treatment PSA levels were above 10 ng/ml (8).

Total of 1532 prostate cancer patients were enrolled in NRG Oncology RTOG 0126 Randomized Clinical Trial. Patients' characteristics were the following: clinical stage T1b to T2b, Gleason score (GS) 2 to 6 with prostate specific antigen (PSA) values between 10- 20 ng/ml; or GS 7 with PSA levels less than 15 ng/ml. Patients were randomized to receive 79.2 Gy in 44 daily fractions of 1.8 Gy or 70.2 Gy in 39 daily fractions of 1.8 Gy. Three-dimensional conformal radiation therapy (3D CRT) or intensity-modulated radiation therapy (IMRT) were used as radiation techniques. Study endpoints were overall survival (OS), biochemical failure (BF, Phoenix or ASTRO definition) and frequency of acute and late radiation treatment toxic effects. Acute side effects were those occurring less than 90 days of the start of the treatment. In case side effects occurred more than 90 days from the start of the treatment, they were defined as late side effects.

After a median follow up of 8.4 years, there was no difference in OS between the groups; OS rates were 76% in group of patients receiving 79.2 Gy and 75% in the group of patients receiving 70.2 Gy ($p = 0.98$). Distant metastases occurred in 4% and 6%, respectively ($p = 0.05$). Biochemical failure, as per ASTRO definition, after 5 and 8 years of follow up, occurred in 40% and 47% of patients allocated to 70.2-Gy arm. In patients receiving 79.2 Gy, those figures were 25% and 31%, respectively ($p < 0.001$). Salvage therapy, namely androgen deprivation, cryosurgery or brachytherapy, was significantly more often used in patients in the 70.2-Gy arm ($p < 0.001$). Frequency of acute gastrointestinal (GI) and genitourinary (GU) toxicity was not significantly different between the arms. However, af-

ter 5 years of follow up, late grade 2 or greater GI and/or GU toxicity was significantly more often in 79.2-Gy group (9).

Two meta-analyses tried to determine the difference in outcomes of patients with localized prostate cancer regarding radiotherapy dose; namely is high-dose radiotherapy (HDRT) more efficient than conventional-dose radiotherapy (CDRT).

Meta-analysis by Viani et al. quantified if the total radiotherapy dose has an impact on biochemical control of the disease. It analyzed the data from 2812 patients enrolled in seven randomized controlled trials. If patients were treated with high doses, biochemical failure incidences were significantly reduced ($p < 0.0001$). That benefit was consistent across the risk groups. No difference has been observed between the treatment groups regarding mortality rate ($p = 0.38$) and specific prostate cancer mortality rate ($p = 0.45$). Late grade >2 gastrointestinal toxicity was more frequent after HDRT. According to the authors, these results suggest that HDRT provides a better therapeutic option for patients in all risk groups - low, intermediate and high (10).

Zan et al. in their meta-analysis evaluated 6 randomized controlled trials of long-term follow-ups to assess efficacy and toxicity of HDRT and CDRT. Trials included 2,822 patients. In terms of 10-year efficacy, HDRT was associated with a significant reduction of biochemical failure rates: 34.0 % vs. 24.7 %, $p < 0.00001$, but no difference was observed in overall survival (73.4 % vs. 74.3 % $p = 0.64$) and prostate cancer specific survival (PCSS; 90.7 % vs. 91.6 %, $p = 0.47$). Decrease of biochemical failure at 10 years was consistent in all trials, regardless of androgen deprivation therapy. Patients treated with HDRT had a significantly later grade 2 or higher ($G \geq 2$) GI (28.0 % vs. 18.6 %, $p < 0.00001$) and GU toxicity (22.6 % vs. 19.5 %, $p = 0.04$). There was no significant difference in quality of life between HDRT and CDRT ($p > 0.05$). Since the advantage in biochemical control did not translate into an improvement in OS and PCSS and HDRT was connected with worse late toxicity outcomes, these authors are more cautious and suggest that HDRT should be discreetly used in the treatment of patients with prostate cancer (11).

Kalbasi and al. analyzed the data of 42,481 prostate cancer patients from National Cancer Data Base (NCDB). 12 229 patients had a low risk, 16,714 inter-

mediate risk and 13 538 high risk disease. They underwent radiotherapy in the period between 2004 and 2006. Threshold for distinction between the groups was 75.6 Gy; therefore, doses between 68.4 and 75.6 Gy were referred as standard dose and those between 75.6 and 90 Gy as escalated dose.

Patients with intermediate and high-risk prostate cancer had a better OS if treated with higher doses ($p < 0.001$). However, this benefit has not been shown for low risk prostate cancer patients ($p = 0.54$). In intermediate risk group a 7.8% reduction of death risk has been observed with every 2 Gy dose increment. In high risk group death risk reduction per every 2 Gy dose increment was 6.3% (12).

Trials are summarized in Table 1. (13)

Hypofractionated radiation therapy- hypofractionation

Term standard fractionation stands for the delivery of radiotherapy in daily doses (fractions) of 1.8 -2 Gy. In case daily doses higher than 2 Gy are being used, that kind of radiation treatment is referred to as hypofractionated radiation therapy or hypofractionation. The α/β ratio is a radiobiological parameter explaining how normal and cancer tissues would respond to different radiation schedules. According to literature data, α/β ratio of prostate cancer is assumed to be about 1.5; therefore, sensitivity of prostate cancer on fraction size is to be expected. Hypofractionation could be moderate with daily fractions between 2.1 and 3.4 Gy or extreme, in case daily fractions higher than 3.4 Gy are used.

Besides expected clinical benefit, hypofractionated radiation treatment is given in lower number of radiation sessions. That makes overall treatment time shorter, which is more convenient for both patient and staff.

Moderate hypofractionation

A number of randomized clinical trials evaluated use of moderate hypofractionation (MH) in prostate cancer patients. Basically, short biochemical disease control between treatment arms was similar. However, due to short follow up, long-term effects on organs at risk, namely bowel and bladder, are not yet completely recognized.

First randomized studies were undertaken in Australia and Canada. The rationale of the hypofraction-

Table 1 Dose escalation trials in localized prostate cancer (13)

Trial	No of patients	Stage	Radiation dose	Follow-up	Outcome	Results
MRC RT01 Dearneley et al. Lancet Oncol 2014	843	T1b-T3a N0M0, PSA<50 ng/ml neoadj. HT	64 vs. 74Gy	median 10 years	biochemical progression free survival (BFS), overall survival (OS)	BFS 43% 64Gy, 55% 74Gy (p= 0.0003), OS 71% both groups (p= 0.96)
GETUG 06 Beckendorf et al. Int J Radiat Oncol Biol Phys 2011	306	T1b-3a, N0, M0, PSA<50 ng/ml	70 vs. 80Gy	median 61 month	ASTRO biochemical failure (BCF)	BF 39% 70Gy, 28% 80Gy
Dutch trial Heemsbergen et al. Radiother Oncol 2014	664	T1b-T4 164 patients with neoadjuvant HT	68 vs. 78Gy	median 110 months	biochemical (Phoenix definition) and clinical failure free (FFF)	FFF 43% 68Gy, 49% 78 Gy (p= 0.045)
MD Anderson Kuban et al. Int J Radiat Oncol Biol Phys, 2011	301	T1-3, N0, M0, PSA 10 ng/ml vs. PSA >10 ng/ml	70 vs. 78Gy	median 9 years	disease specific mortality (DSM) vs. other cause of death	high risk: (PSA> 10): DSM 16% 70Gy, 4% 78Gy (p=0.05) higher risk DSM 15% 70Gy, 2% 78. Gy (p=0.03)
RTOG 0126, Michalsky et al, JAMA Oncol. 2018	1,532	T1b-T2b ISUP grade 1 + PSA 10-20 ng/ml or ISUP grade 2/3 + PSA < 15 ng/ml	70.2 vs. 79.2 Gy	100 mo	overall survival (OS) distant metastases (DM) biochemical failure (BCF, ASTRO definition)	75% OS at 70.2 Gy 76% OS at 79.2 Gy 6% DM at 70.2 Gy 4% DM at 79.2 Gy (p = 0.05) 47% BCF at 70.2 Gy 31% BCF at 79.2 Gy (p < 0.001; Phoenix, p < 0.001)
retrospective NCDB trial Kabasi et al, JAMA Oncol 2015	12 229 16714 13538	low risk, 22% HT intermediate risk, 49% HT high risk, 77% HT	<75.6 vs > 75.6 Gy	median 85-86 months	overall survival (OS)	HR 0.98, for dose escalation (p= 0.54) HR 0.84 for dose escalation (p<0.001) HR 0.82 for dose escalation (p< 0.001)

ation, however, was not prostate cancer α/β ratio but the convenience of shorter overall treatment time. Due to countries' size, in both Australia and Canada patients had to travel large distances in order to get radiotherapy (14).

In NCI Canada trial with a reported median follow up of 5.7 years, 936 patients were enrolled. Pros-

tate cancer was staged as clinically T1-T2 and PSA levels had to be below 40 ng/ml. Patients were randomized to receive hypofractionated radiotherapy (52.5 Gy in daily fractions of 2.62 Gy) or conventionally fractionated radiotherapy (66 Gy in 33 daily fractions of 2 Gy). No concomitant antiandrogen therapy was used. Biochemical or clinical failure (BCF) was set

as the study's primary outcome. At 5 years, the BCF probability in the short arm was 59.95% and in the long arm 52.95%. Those data gave the advantage to the long arm approach. There was no difference between the arms regarding overall survival or 2-year post-radiotherapy biopsy. When compared to the long arm, patients in the short arm had a higher frequency of acute toxicity (11.4% vs. 7%). No difference was detected between the arms in terms of the late toxicity (3.2%). It should be stressed that doses used in both arms of the trial are lower than those being used nowadays (15).

In Australian trial 217 patients were randomized to either hypofractionated or conventionally fractionated radiation treatment. Patients in hypofractionated arm received 55 Gy during 4 weeks in 20 daily fractions and patients in the control arm received 64 Gy in 32 daily fractions; their overall treatment time was 6.5 weeks. It is to notice that 156 patients received two-dimensional radiotherapy and for RT planning two-dimensional computed tomography method was used. After a median follow up of 90 months, biochemical relapse, which was defined as nadir PSA +2 ng/ml occurred in 36 patients in the hypofractionated group and in 49 patients in the control group. Therefore, 90-month biochemical relapse free survival turned out to be significantly better with the hypofractionated schedule (53% vs. 34%). There was no difference in overall survival between the arms. Genitourinary and gastrointestinal toxicity was similar between the schedules and it persisted 60 months upon radiotherapy (16).

These first hypofractionation trials undoubtedly demonstrated feasibility of the concept, but due to applied radiotherapy techniques and doses that no longer present standard of care, their efficacy and toxicity data should be taken into consideration cautiously.

Three modern, large randomized trials evaluated non-inferiority of moderate hypofractionation to conventional fractionation: CHHiP, RTOG 0415 and PROFIT.

CHHiP study was a randomized controlled phase 3 trial that included 33 216 patients with prostate cancer, clinically staged as T1b-T3aN0M0. Study arms, according to radiation schedules, were the following: 60 Gy given in 20 3-Gy daily fractions, 57 Gy given in 19 3-Gy daily fractions and the control arm of 74 Gy in 37 2-Gy daily fractions. Intensity modulated ra-

diotherapy was used. Whole pelvis radiotherapy was not given. In 97% of patients both neoadjuvant and concomitant antiandrogen therapy was used. Image guided radiotherapy was not performed in 53% of patients, equally in each arm of the trial. Median follow up was 64 months and biochemical or clinical failure (BCF) was set up as the study outcome. At five years, the proportion of patients that were BCF free was 90.6% for 60 Gy in 20 fractions, 85.9% for 57 Gy in 19 fractions and 88.3% for standard fractionation- 74 Gy in 37 fractions. Therefore 60 Gy was proven to be non-inferior to 74 Gy. When compared to the control arm, 57 Gy could not be claimed non-inferior. Late toxicity was not significantly different between the treatment arms. Frequencies of bladder and bowel grade ≥ 2 adverse reactions were 11.7% and 11.9% respectively for 60 Gy group, 6.6% and 11.3% for 57 Gy group and 9.1% and 13.7% for the control group (17).

In RTOG 0415 trial 1115 low-risk prostate cancer patients were randomized to receive 73.8 Gy given in 41 daily fractions of 1.8 Gy during 8.2 weeks, which was conventional regimen (C-RT, CF), or 70 Gy given in 28 fractions of 2.5 Gy through 5.6 weeks (hypofractionated radiotherapy, H-RT). The trial was designed to establish if the 5-year disease-free survival (DFS) of patients who underwent hypofractionated radiotherapy would not be worse than 5-year DFS of conventionally irradiated patients by more than 7.65% (HR < 1.52). Androgen suppression was not allowed, except in case of prostate cancer recurrence as a salvage treatment. Median follow up was 5.8 years. The estimated 5-year (DFS) was 86.3% in the H-RT arm and 85.3% in the C-RT arm. The DFS HR was 0.85, therefore meeting predefined non-inferiority criterion ($p < 0.001$). No significant difference in acute toxicities was observed between the arms. Patients in H-RT arm of the trial had more often late grade 2 and 3 genitourinary and gastrointestinal adverse events (HR 1.31 to 1.59) (18).

1206 intermediate-risk prostate cancer patients were enrolled in PROFIT trial. Patients allocated in hypofractionated arm of the trial received 60 Gy in 20 daily fractions; overall treatment time was 4 weeks. Patients in the control arm (conventional RT) received 78 Gy in 39 daily fractions. Patients were not permitted to receive androgen deprivation treatment. Biochemical-clinical failure (BCF) was set up as the primary outcome. It included PSA failure (defined as

nadir PSA value + 2), hormonal treatment, clinical relapse (local or distant) or prostate cancer death. No difference has been observed between the arms in 5-year BCF after a median follow up of 6 years (85%). No significant differences have been reported in overall survival or late grade ≥ 3 genitourinary and gastrointestinal toxicity (19).

Even though these three trials enrolled different risk group patients and the use of androgen deprivation therapy among them varied, all of them met their primary aim to prove non-inferiority of moderate hypofractionation to conventional fractionation. Regarding late toxicity, no difference between the two arms was reported in CHHiP and PROFIT trial, while in RTOG trial late toxicity was more common with MF.

Four superiority randomized trials failed to demonstrate any difference in efficacy, including metastasis-free, cancer-specific survival and overall survival (14).

HYPRO trial included 820 patients with localized T1b-4 prostate cancer. Their PSA level had to be below 60 ng/ml and they were staged as intermediate or high-risk. Patients were randomized to receive either hypofractionated or conventionally fractionated radiotherapy. Hypofractionated regimen (HF) consisted of 64.6 Gy given in 19 fractions, 3.4 Gy each, three times a week. Conventional regimen (CF) was 78 Gy in 39 daily fractions over 8 weeks. Equivalent total dose for hypofractionation was 90.4 Gy (calculated using α/β ratio of 1.5 Gy for prostate cancer), which was considerably higher than 78 Gy given in the control group in conventional manner. Concomitant hormonal therapy was given to 67% of patients; its median duration was 32 months. Relapse-free survival (RFS) was the study's primary endpoint.

After a median follow-up of 60 months, patients allocated to hypofractionation arm had a 5-year RFS of 80.5% and patients irradiated conventionally had a 5-year RFS of 77.1%. There was no difference in frequency of G ≥ 2 gastrointestinal or genitourinary toxicity 3 months upon radiotherapy. However, 120 days upon treatment, G ≥ 2 acute gastrointestinal toxicity was more frequent after hypofractionation: 42% vs. 31.2%. Regarding late toxicity, for grade 2 gastrointestinal and genitourinary adverse events, treatment arms could not be declared non-inferior. Cumulative G ≥ 3 late genitourinary toxicity was also significantly higher after HF: 19.0% vs. 12.9% ($p=0.021$). No significant difference between treatment arms has been observed

when it comes to cumulative G ≥ 3 late gastrointestinal toxicity: it was 3.3% for HF, 2.6% for CF ($p=0.55$). There were no treatment-related deaths (20, 21, 22).

In the trial published by Arcangeli, 168 high-risk prostate cancer patients underwent conventional or hypofractionated radiotherapy (HF). Conventional fractionation was 80 Gy, with 2 Gy daily fractions, 5 days a week. Hypofractionated treatment consisted of 62 Gy with 3.1 Gy per fraction; overall treatment time was 5 weeks. All patients received hormonal therapy for 9 months. After 70 months of follow up, isoeffectiveness of the 2 fractionation schedules was confirmed. In a subset of patients whose initial PSA levels were ≤ 20 ng/ml, certain benefit in favor of HF could not be excluded (23).

Similarly, in trials published by Hoffman and Pollack comparing MH with CF, no significant difference in five-year biochemical recurrence free (BRF) survival was observed (14, 24, 25, 26).

Randomized trials comparing conventional fractionation with moderate hypofractionation in patients with prostate cancer are summarized in Table 2 (14).

Extreme hypofractionation

In extreme hypofractionation (EH) radiotherapy is delivered with fractions higher than 3.4 Gy. They could be applied daily, weekly or on alternate days. Total dose is up to 35- 50 Gy. Delivery of a large radiation dose in small number of bigger fractions takes the advantage of the prostate's α/β ratio estimated to be about 1.5 Gy, which is considerably low. It is also referred to as stereotactic body radiation therapy (SBRT). Modern image-guided techniques allow deliverance of brachytherapy-like doses with sparing of adjacent tissues. It has been evaluated in a number of phase I and II trials on small groups of low-risk patients.

Two trials with longer follow-up are those by Katz and Meier (27, 28).

Trial by Katz had a median follow up of 72 months. It recruited 324 low risk patients (PSA <10 ng/ml and Gleason score <7) and 153 intermediate-risk patients, with PSA levels between 10 and 20 ng/ml or Gleason score of 7. 51 patients received androgen deprivation therapy for up to 6 months. Cyber-knife system was used to deliver SBRT with fiducial based image guidance. Applied doses were 35 Gy or 36.25 Gy, given daily in 5 fractions. After bowel preparation all patients 15-20 min prior to treatment received amifos-

Table 2. Summary table of randomized studies comparing moderate hypofractionation and conventional fractionation in prostate cancer (14)

Study	Risk	Technique	ADT (%)	No. of patients	Fractionation total dose /fractions	Treatment duration	Acute toxicity ≥grade 2 GI (%)	Acute toxicity ≥grade 2 GU (%)	Late toxicity ≥grade 2 GI (%)	Late toxicity ≥grade 2 GI + toxicity 12.9% (G3 + 41.3 (G3 + toxicity 19%)	5-year biochemical relapse free survival (%)
Superiority randomized studies											
Arcangeli (23)	LR/IR 24% HR 76%	CFRT	100	85	80 Gy/40 fractions /2 Gy per fraction	8 weeks	21	40	14	11	92.0
Hoffman (25)	LR 28% IR 71% HR 1%	IG- IMRT	23	101	62 Gy/20 fractions /3.1 Gy per fraction	4 weeks	35	47	17	16	96.0
Pollack (26)	IR 36% HR 64%	IMRT	47	151	75.6 Gy/42 fractions /1.8 Gy per fraction	8.4 weeks			5.1	16.5	92.0
			25	102	72 Gy/30 fractions /2.4 Gy per fraction	6 weeks			10	15.8	96.0
			47	151	76 Gy/38 fractions /2 Gy per fraction	7.6 weeks		47.7	22.5	13.4	85.0
			45	152	70.2 Gy/26 fractions /2.7 Gy per fraction	5.2 weeks		44.9	18.1	21.5	81.0
			67	410	78 Gy/39 fractions /2 Gy per fraction	7.8 weeks	31,2	57.8	17.7 (G3 + toxicity 2.6%)	39 (G3 + toxicity 12.9%)	77.0
			67	410	64.6 Gy/19 fractions /3.4 Gy per fraction	6.5 weeks	42	60.5	21.9 (G3 + toxicity 3.3%)	41.3 (G3 + toxicity 19%)	81.0
Non- inferiority randomised studies											
RTOG 0415 (18)	LR	IMRT 79-80% CFRT 20-21%	0	542	73.8 Gy/41 fractions /1.8 Gy per fraction	8.2 weeks	10.3	27.1	14	22.8	85.3
			0	550	70 Gy/28 fractions /2.5 Gy per fraction	5.6 weeks	10.7	27	22.4	29.7	86.3
PROFIT (19)	IR	IGRT IGRT	0	598	78 Gy/39 fractions /2 Gy per fraction	7.8 weeks			>G3 GI/GU 5.4%		79.0
			0	608	60 Gy/20 fractions /3 Gy per fraction	4 weeks			>G3 GI/GU 3.5%		79.0
CHHiP (17)	LR 15% IR 73% HR 12%	IMRT +/- IGRT	97	1065	74 Gy/37 fractions /2 Gy per fraction	7.4 weeks	25	46	13.7	9.2	88.3
			97	1074	60 Gy/20 fractions /3 Gy per fraction	4 weeks	38	49	12	11.7	90.6
			97	1077	57 Gy/19 fractions /3 Gy per fraction	3.8 weeks	38	46	11.2	6.6	85.9

LR/IR/HR: low/intermediate/high risk prostate cancer, CFRT: conformal radiotherapy, IMRT: intensity-modulated radiotherapy, IGRT: image-guided radiotherapy, ADT: androgen deprivation therapy, GI: gastrointestinal, GU: genitourinary

tine mixed in saline and instilled into the rectum. Primary outcome was biochemical disease-free survival as per Phoenix definition (bDFS). In 14 intermediate and 11 low-risk patients biochemical failures occurred. For patients in low risk group 7-year bDFS was 95.6% and for those in intermediate-risk 89.6% ($p < 0.012$). Within intermediate-risk group, patients with low intermediate-risk prostate cancer ($n = 106$), namely those with GS 6 and PSA >10 ng/ml or GS 3+4 and PSA <10 ng/ml had a significantly better bDFS compared to patients defined as high intermediate risk ($n = 47$, GS 3+4 and PSA between 10 and 20 ng/ml or GS 4+3). bDFS figures were 93.5% for low intermediate and 79.3% for high intermediate risk group. There was no difference in biochemical disease-free survival among 36.25 Gy and 35 Gy radiation doses (27).

Meier's trial involved 309 patients in twenty-one center; 172 had a low-risk (cT1b-T2a, GS ≤ 6 and PSA ≤ 10 ng/ml, LR) and the remaining 137 intermediate-risk disease (cT1b-T2b with GS = 7 and PSA equal or below 10 ng/ml, or with GS ≤ 6 and PSA levels less or equal 20 ng/ml, IR). Intermediate risk group patients were further subcategorized, according to Memorial Sloan Kettering (MSK) risk classification system, as favorable or unfavorable. Prescribed dose was 40 Gy in 5 fractions. Patients were treated with Cyber-knife system. During or after SBRT antiandrogen therapy was not permitted. Biochemical failure was defined as "nadir + 2". Failure was defined as biochemical recurrence or administration of any prostate cancer therapy: salvage, antiandrogen, or systemic.

For the entire patients' group 5-year overall survival rate was 95.6% and 5-year disease free survival (DFS) rate 97.1%. The 5-year DFS rate was 97.3% for LR patients and 97.1% for IR patients. After a median follow-up of 61 months, 2 LR patients (1.2%) and 2 IR patients (1.5%) experienced G 3 genitourinary adverse events, occurring 11 to 51 months after treatment. No grade 4 or 5 toxicities occurred (28).

King et al. performed a pooled analysis of prospective phase II trials of SBRT from 8 institutions involving 1100 patients with clinically localized prostate cancer. 58% of patients had a low-risk disease, 30% intermediate-risk and 11% of patients were classified as high risk. 14% of patients were given short course of androgen deprivation therapy (ADT). Definition of PSA relapse was nadir PSA +2 ng/ml. Median radiation dose was 36.25 Gy in 4-5 fractions delivered using

Cyber knife. 5-year biochemical relapse free survival (bRFS) rate after a median follow up of 36 months was 93% for all patients. For low-risk patients 5-year bRFS rate was 95%, 84% for intermediate-risk patients and 81% for high-risk patients ($p < 0.001$). 135 patients had a follow-up of minimally 5 years. Their 5-year bRFS rates were 99% if classified as low-risk group and 93% if classified as intermediate-risk group. Addition of ADT did not result in any difference ($p = 0.71$). In conclusion, these evidences support consideration of SBRT as a therapeutic option in patients with low and intermediate-risk prostate cancer (29).

There are two phase III clinical trials comparing extreme hypofractionation with conventional fractionation: HYPO RT PC and PACE B.

HYPO-RT-PC randomizes intermediate risk prostate cancer patients to receive conventional radiotherapy consisting of 78 Gy in 2 Gy daily fractions, 5 days/week or 42.7 Gy in 7 fractions of 6.1 Gy given every other weekday, always including two weekends (HYPO- RT arm). Hypothesis of the trial is to demonstrate 10 percentage points increase (70% to 80%) in freedom from failure for patients in tested arm of the trial (HYPO-RT) 5 years upon the treatment. Failure could be PSA rise or any clinical test showing activity of the disease (30).

PACE B trial includes cohort of patient with low risk prostate cancer (stage T1-T2, \leq Gleason 3 + 4, PSA ≤ 20 ng/ml) within PACE trial. 874 patients in 38 centers were randomized to SBRT (36.25 Gy given in 5 fractions during 1-2 weeks) or CFMHRT (conventional fractionation, moderate hypofractionation radiotherapy; 78 Gy/39 fractions over 7.5 weeks, or 62 Gy/20 fractions in 4 weeks). Hormonal therapy was not allowed. Acute G ≥ 2 gastrointestinal (GI) and genitourinary (GU) toxicity was not significantly different between the arms. Frequency of acute G ≥ 2 GI events was 12.1% in CFMHRT group vs. 10.1% in SBRT group, $p = 0.368$. For acute G ≥ 2 GU events figures were for CFMHRT 27.2% vs. 23.2% for SBRT, $p = 0.179$. Late toxicity and efficacy data in terms of biochemical or clinical failure are pending (31).

According to NCCN (National Cancer Comprehensive Network) guidelines, extreme hypofractionation with daily doses up to 8 Gy is a treatment option for very low, low, favorable or good-prognostic intermediate NCCN risk group of patients (32).

Table 3. Reported outcomes for prostate cancer patients treated with LDR brachytherapy

Study	Number of patients	Risk group (%)			Follow up (years)	Biochemical control (%)			CSS	OS
		low	intermediate	high		Low risk	Intermediate risk	High risk		
Blasko et al (34)	230	45	46	9	9	87	79	68	100	
Zelevsky et al (35)	2693	55	40	5	8	82	70	40		
Henry et al (36)	1298	44	33	14	10	86	77	61		
Morris et al (37)	1006	58	42	0	10				99	83.5
Funk et al (38)	966	71	29	0	10	90	74		98	74
Kittel et al (39)	1989	61	30	5	10	87	79	68	97	76
Fellin et al (40)	2237	66	26	2	7	93	78	73	98	89

CSS: cause specific survival; OS: overall survival

Brachytherapy

Brachytherapy in prostate cancer can be used as a monotherapy in low and intermediate-risk patients or as a boost to external beam radiotherapy (EBRT) in intermediate and high-risk patients. Depending on the characteristics of the radioactive source, it could be delivered as low dose rate (LDR) or high dose rate (HDR) radiotherapy. The advantage of radiotherapy is that it can be completed in one day. However, it requires anesthesia, most often general, and can lead to acute urinary retention.

LDR brachytherapy uses permanent seeds. The most common sources are Iodine-125, Palladium-103 and Cesium-131 isotopes. Radiation dose is delivered over weeks and months requiring radiation protection for both patients and carers. According to ESTRO/EAU/EORTC recommendations, patients eligible for LDR would be those with stage cT1b-T2a N0, M0; ISUP grade 1 with $\leq 50\%$ of biopsy cores involved with cancer or ISUP grade 2 with $\leq 33\%$ of biopsy cores involved with cancer; an initial PSA level of ≤ 10 ng/ml; a prostate volume of < 50 cm³; an International Prostatic Symptom Score (IPSS) ≤ 12 and maximal flow rate > 15 mL/min on urinary flow test. Absolute contraindications are limited life expectancy, unacceptable operative risks, metastatic disease, ataxia telangiectasia, previous large transurethral resection that precludes seed placement and accurate dosimetry and absence of rectum. (13, 33).

Results of LDR brachytherapy trials are shown in Table 3. (34, 35, 36, 37, 38, 39, 40).

HDR brachytherapy uses radioactive sources that are being placed into the prostate temporarily. Iridi-

um-192 (IR-192) isotope is being introduced through implanted needles or catheters. Radiation dose is delivered in minutes, implantation is temporary and there are no radiation protection issues for patient or carers. Radiation can be delivered in single or multiple fractions. Fractionated HDR brachytherapy as monotherapy can be offered to patients with low- and intermediate-risk prostate cancer. In patients with intermediate and high-risk prostate cancer it can be used as a boost to external beam radiotherapy. Patients with significant urinary outflow symptoms are not candidates for HDR boost (13,41).

A randomized phase-III trial compared external beam radiotherapy (EBRT) alone with EBRT combined with high-dose-rate brachytherapy boost (HDR-BTb) in 218 patients with localized prostate adenocarcinoma. Patients in EBRT arm received a total dose of 55 Gy in 20 daily fractions while patients in HDR-BTb arm received EBRT 35.75 Gy in 13 fractions followed by HDR-BT boost of 2x 8.5 Gy in 24 h. Biochemical/clinical relapse-free survival (RFS) was the primary endpoint. Secondary endpoints were overall survival (OS), urinary and bowel toxicity. After 4 years median time to relapse was 116 months in EBRT + HDR-BTb group, compared to 74 months in EBRT only group. ($p = 0.04$). In multivariate analysis treatment arm, risk category and ADT were significant covariates for risk of relapse. Differences in OS were not significant. Incidence of severe late urinary and bowel morbidity was similar: the 5 and 7-year incidence for patients with any severe urinary symptom was 26% and 31% for those treated with EBRT + HDR-BTb compared with 26% and 30% for patients in EBRT

Table 4. Studies of post-prostatectomy salvage radiotherapy (13)

Study	No of patients	Median follow-up (months)	pre-SRT PSA (ng/ml) median	RT dose	ADT	bNED/PFS (year)	5-year results
Bartkowiak, et al. 2017 (44)	464	71	0.31	66.6 Gy	no	54% (5.9)	73% vs. 56%; PSA < 0.2 vs. ≥ 0.2 ng/ml p < 0.0001
Soto, et al, 2012 (45)	441	36	< 1 (58%)	68 Gy	24%	63/55% (3) ADT/no ADT	44/40% ADT/no ADT p < 0.16
Stish, et al. 2016 (46)	1,106	107	0.6	68 Gy	16%	50% (5) 36% (10)	44% vs. 58%; PSA ≤ 0.5 vs. > 0.5 ng/ml p < 0.001
Tendulkar, et al. 2016 (47)	2,460	60	0.5	66 Gy	16%	56% (5)	SRT; PSA < 0.2 ng/ml 71% 0.21-0.5 ng/ml 63% 0.51-1.0 ng/ml 54% 1.01-2.0 ng/ml 43% > 2 ng/ml 37% p < 0.001

ADT = androgen deprivation therapy; OS = overall survival; SRT = salvage radiotherapy, bNED = biochemically no evidence of disease, PFS = progression free survival

only arm ($p = 0.5$). The incidence of severe bowel events was 7% and 6%, respectively, at 5 and 7 years ($p = 0.8$) (42).

Radiotherapy in disease relapse - salvage radiotherapy

In case of locoregional relapse of the disease, with radiotherapy is possible to achieve cure or at least long-term control, even in previously irradiated patients.

In patients who experience biochemical relapse after radical prostatectomy, who were not irradiated and in whom diagnostic procedures exclude metastatic disease, salvage radiotherapy is indicated. It refers to irradiation of prostate and seminal vesicles bed with doses up to 72 Gy with the addition of hormonal therapy. The role of whole pelvic irradiation is still undetermined. While it is still unclear whether radiotherapy should be given in adjuvant setting in patients with higher risk of locoregional relapse, or as a salvage treatment upon biochemical recurrence, it is undoubtedly proved that early salvage therapy is better than late. Therefore, irradiation should begin when PSA levels reach values between 0.2 and 0.5 ng/ml, or even earlier, with PSA level below 0.2 (43, 44).

Studies of salvage radiotherapy are summarized in Table 4 (13, 44, 45, 46, 47).

Regarding recommended dose, King et al have compared 60 Gy and 70 Gy in 38 and 84 patients with pathologically negative lymph nodes, respectively. Radiotherapy was given beyond 6 months after radical prostatectomy and when PSA was detectable. Whole pelvic RT up to 50 Gy was delivered to 59% of patients. 56% of patients also received 4-months total androgen suppression with LHRH agonist and oral antiandrogen. Biochemical relapse was defined as detectable PSA level confirmed on repeat testing and rising on subsequent testing. After a median follow-up of >5 years 60 patients experienced biochemical relapse. Median time to relapse was 1.2 years. For patients receiving RT alone the 5-year biochemical relapse free survival (bRFS) rate was 17% vs. 55% ($p = 0.016$), and for those receiving prostate-bed-only RT it was 23% vs. 66% ($p = 0.037$) for doses of 60 Gy vs. 70 Gy, respectively. Approximately 2.5% improvement in 5-year bRFS was achieved for each additional Gy. Therefore, a clinically significant dose response from 60 Gy to 70 Gy was observed in the setting of salvage RT after prostatectomy (48).

Disease relapse in pelvic lymph nodes

Patients with lymph node metastasis only have a better prognosis than those with metastasis on other sites with median overall survival and cancer-specific survival of 43 and 61 month, respectively (49).

Subgroup of patients with pelvic lymph nodes metastasis only after radical prostatectomy, regardless of previous prostate bed adjuvant radiotherapy, should be referred to as potentially curable. They should be offered local treatment, with or without hormonal therapy.

In multicenter trial published by Ost et al., 72 prostate cancer patients with ≤ 3 lymph nodes at the time of recurrence were treated with SBRT, which was defined as a radiotherapy dose of at least 5 Gy per fraction to a biological effective dose of at least 80 Gy to all metastatic sites. The median distant progression-free survival was 21 months and most relapses (68%) occurred in nodal regions. Relapses after pelvic nodal SBRT were located in the pelvis. 5-year distant progression free survival was 13% (50).

Tran et al. reviewed data of 53 oligorecurrent prostate cancer patients treated with elective nodal radiotherapy (ENRT). 38 patients had a single nodal metastasis located in the pelvis. All patients underwent ENRT between 45 and 50.4 Gy with a boost on positive nodes up to 69 Gy. Concomitant androgen deprivation therapy was administered to all patients for a median time of 6 months. After a median follow-up of 44 months, the 5-year biochemical disease-free and distant progression-free survival (DPFS) rates were 43% and 58%, respectively (51).

In the trial published by Lepinoy, comparison between salvage extended field radiotherapy (s-EFRT) and salvage involved field radiotherapy (s-IFRT) in patients with ^{18}F -fluorocholine (FCH) PET/CT+ nodal oligorecurrences from prostate cancer in terms of times to failure (TTF) and toxicity was made. Of 62 patients with positive lymph nodes only who underwent FCH PET/CT for a rising PSA level after radical prostatectomy or radiotherapy, 35 had s-IFRT and 27 had s-EFRT. 3-year failure rates were 55.3% in the s-IFRT group and 88.3% in the s-EFRT group ($p=0.0094$). There was a strong trend toward better outcomes with s-EFRT even after adjusting for concomitant androgen-deprivation therapy. After a median follow-up of 41.8 months (range 5.9-108.1 months), no differences were observed in acute or late gastrointestinal and genitourinary toxicities of grade 2 or more between the two groups (52).

These data suggest that in subgroup of patients with pelvic nodal relapse only, extended field radiotherapy should be treatment of choice rather than stereotactic irradiation of affected lymph nodes.

Discussion

There is a robust data available proving efficacy of radiotherapy in prostate cancer in different stages of the disease. Introduction of ISUP grade system, further stratification of risk groups and different study endpoints, as well as their definition, makes the interpretation and comparison of those trials truly challenging.

Dose escalation led to better biochemical control of the disease, which has in some trials translated into better survival, especially in patients in higher risk groups. The impact of dose escalation on acute and late treatment toxicities is quite inconsistent across the published trials but, in general, late gastrointestinal toxicity is more frequently observed in patients receiving higher radiation doses. According to NCCN guidelines, doses between 72 and 81 Gy, standard fractionation, are acceptable across the risk groups (32).

Moderate hypofractionation (MF) with daily doses up to 3.4 Gy is convenient due to shorter overall treatment time but could also lead to better disease control regarding low α/β ratio of prostate cancer. It has proven its non-inferiority in a number of trials in terms of biochemical control of the disease. Again, no consistent conclusions regarding toxicity could be made: no difference between the two arms was reported in CHHiP and PROFIT trial, while in RTOG trial late toxicity was more common with MF (17, 18, 19). As far as superiority trials are concerned, four of those failed to demonstrate any difference in efficacy, including metastasis-free, cancer-specific survival and overall survival between moderate hypofractionation and conventional fractionation. According to ASTRO (American Society for Radiation Oncology), ASCO (American Society of Clinical Oncology) and AUA (American Urological Association) guidelines, in men with low, intermediate and high risk prostate cancer, moderate hypofractionation should be offered with regimens of 60 Gy in 20 fractions and 70 Gy in 28 fractions, since they are supported with the largest evidentiary base. One optimal regimen cannot be determined since most of the multiple fractionation schemes evaluated in clinical trials have not been compared head to head. Though MH has a similar risk of acute and late genitourinary and late gastrointestinal toxicity compared to conventionally fractionated radiotherapy, one should bear in mind limited follow-up beyond five years for most trials (53).

Extreme hypofractionation (EH), also referred as stereotactic body radiation therapy (SBRT), has been evaluated in a number of small phase I and II trials and the results of two-phase III trials comparing it with conventional fractionations are awaiting. According to ASTRO, ASCO and AUA guidelines, it can be offered in men with low-risk prostate cancer who decline active surveillance as an alternative to conventional fractionation. In men with intermediate-risk prostate cancer it may also be offered as an alternative to conventional fractionation, but the task force strongly encourages that these patients be treated as part of a clinical trial or multi-institutional registry. In men with high-risk prostate cancer EH should not be used outside of a clinical trial. Acceptable doses are 35 to 36.25 Gy in 5 fractions of 7 to 7.25 Gy (53).

Brachytherapy presents a valuable treatment option proven in a number of clinical trials, either as a sole modality in low and intermediate risk prostate cancer patients or combined with external beam radiotherapy in both intermediate and high-risk patients. Nevertheless, after summarizing evidence from recent randomized trials, American Brachytherapy Society Task Group finds out that combination of brachytherapy and external beam therapy may become the standard of care for patients with high-risk prostate cancer (54). Unfortunately, its availability can be limited. When opting for brachytherapy in order to keep its toxicity to a minimum, patient selection seems to be crucial (33).

In case of disease relapse, if it is locoregional, radiotherapy can still be a curative method. When it comes to biochemical relapse in previously unirradiated patients, radiotherapy of the prostate and seminal vesicles bed should be delivered early, before PSA reaches the level of 0.5 ng/ml. Patients with metastases in pelvic lymph nodes only should be treated with curative intent with a whole pelvis irradiation instead of an involved field.

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Sažetak

RADIOTERAPIJA RAKA PROSTATE: PRIMARNA RADIOTERAPIJA I RADIOTERAPIJA U POVRATU BOLESTI

K. Antunac

Radioterapija predstavlja jedan od osnovnih modaliteta liječenja bolesnika s rakom prostate u gotovo svim stadijima bolesti. Može se koristiti kao vanjsko zračenje, kao brahiterapija (unutarnje zračenje) ili kombinacija ove dvije metode. Više doze zračenja su dokazano učinkovitije od nižih a umjereno hipofrakcionirano zračenje dozama do 3,4 Gy po frakciji je jednako učinkovito kao i zračenje standardnim frakcioniranjem od 1,8- 2 Gy po frakciji. Stereotaksijsko zračenje dozama od 3,4 do 7,25 Gy po frakciji predstavlja vrijednu opciju kod određenih podskupina bolesnika. U slučaju lokoregionalnog povrata bolesti, zračenje se može provoditi s ciljem izlječenja bolesnika.

Ključne riječi: *rak prostate, radioterapija, brahiterapija, hipofrakcioniranje, stereotaksijsko zračenje, spasonosna radioterapija*