

OPTIMAL TREATMENT OF PATIENTS WITH HIGH-RISK PROSTATE CANCER

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Summary

Treatment options in subset of patients with high-risk prostate cancer are various: radical prostatectomy, hormonal therapy, radiation therapy, combined modality approach, addition of chemotherapy. Based on randomised trials data, optimal approach would consist of radical radiotherapy and long term hormonal therapy. If technically possible high dose radiotherapy, hypofractionation, image guided radiotherapy, simultaneous integrated boost on dominant intraprostatic lesion and HDR brachytherapy boost should be used as well.

KEY WORDS: *high risk prostate cancer, radiotherapy, hormonal therapy, dose escalation, hypofractionation, simultaneous integrated boost*

OPTIMALNA TERAPIJA BOLESNIKA S RAKOM PROSTATE VISOKOG RIZIKA

Sažetak

Kod bolesnika s rakom prostate visokog rizika postoje različite terapijske opcije: radikalna prostatektomija, hormonska terapija, zračenje, združeni pristup, dodatak kemoterapije. Prema rezultatima randomiziranih studija optimalni pristup bi bio združena primjena dugotrajne hormonske terapije i zračenja. Ukoliko tehničke mogućnosti dozvoljavaju, trebalo bi koristiti zračenje visokim dozama, hipofrakcioniranje, slikom vođenu radioterapiju, simultano integrirano povećanje doze na dominantnu intraprostaticnu leziju te primjenom brahiterapije velike brzine doze u kombinaciji s vanjskim zračenjem.

KLJUČNE RIJEČI: *rak prostate visokog rizika, radioterapija, hormonska terapija, zračenje visokim dozama, hipofrakcioniranje, simultano integrirano povećanje doze*

INTRODUCTION

According to European Association of Urology (EAU), high-risk prostate cancer patients are defined as those with PSA level above 20 ng/mL or Gleason score (GS) > 7 (ISUP grade 4/5), or cT2 tumour stage (tumour involves both lobes). cT3 and cT4 and N+ stage of the disease is considered locally advanced (1). According to NCCN guidelines high-risk prostate cancer patients are those

with PSA levels > 20 ng/mL, or GS 4+4 (GG 4) or 4+5 (GG 5) or cT3a tumour stage (extracapsular extension). Patients with cT3b stage (tumour invades seminal vesicle(s)) and cT4 stage, primary Gleason pattern 5 and those who have tumour GS 8-10 (GG 4-5) in more than 4 cylinders are considered as very high risk prostate cancer patients (2).

Treatment options in this group of patients include radical prostatectomy with pelvic lymph node dissection, radiation with androgen depriva-

tion therapy (external beam radiotherapy or combination of brachytherapy and external beam radiotherapy), combination of radiation, androgen deprivation therapy and chemotherapy or just androgen deprivation therapy.

Doubts in radiotherapy in this group of patients are:

- Whether to use radiotherapy or some other treatment modality
- Should some systemic treatment be used with radiotherapy, which one and for how long
- How to perform radiotherapy with regard to clinical target volume, radiation dose and fractionation.

TREATMENT OPTIONS

Radical prostatectomy vs. radical radiotherapy

Although many trials have proved superiority of radical prostatectomy compared with radical radiotherapy, even in patients with high risk prostate cancer, those trials are mainly retrospective population trials with imbalanced patients' populations comparing suboptimal treatment methods (Table 1) (3).

In general, patients that underwent radical prostatectomy were younger with less co-morbidities, had less aggressive disease, lower PSA levels and rarely had locally advanced disease. Shortly, studies were biased. Just based on these data and without randomised trials, it should not be concluded that radical prostatectomy is undoubtedly better treatment option than radical radiotherapy in this subset of patients (3). According to EAU guidelines, radical prostatectomy should be of-

fered to patients with high-risk prostate cancer and life expectancy of >10 years only as part of multi-modal therapy (1).

Radical radiotherapy

Hormonal therapy vs. combined modality approach: hormonal therapy + radical radiotherapy

Lin and associates reported 5- year overall survival of patients diagnosed with clinically lymph node positive prostate cancer between 2014 and 2016. One group of patients was irradiated and treated with hormonal therapy, while patients in the control arm were given hormonal therapy only. Each group consisted of 314 patients. Combined modality approach resulted in 50% reduction of 5-year all cause mortality compared to hormonal therapy only. 5- year overall survival was 86% with radiotherapy and 71% without radiotherapy. Patients that were irradiated were younger, had less co-morbidities, higher PSA values and higher GS (GG) (4).

SPCG-7/SFUP-3 trial included 853 patients with locally advanced prostate cancer (cT3 in 78% of patients) that were receiving life-long hormonal therapy: 3 months of complete androgen blockage followed by flutamide. One group of patient received radiotherapy. 10 -year cumulative incidence of prostate cancer mortality was 23.9% in group that received only hormonal therapy and 11.9% in group of patients that were also irradiated. Overall mortality cumulative incidences were 39.4% and 29.6%, respectively (5).

Trial by Ward and associates included 1205 patients with high-risk prostate cancer defined as T3, T4 or T2 with PSA>40 ng/mL or PSA > 20 ng/

Table 1

TRIALS COMPARING RADICAL PROSTATECTOMY WITH RADICAL RADIOOTHERAPY IN HIGH-RISK PROSTATE CANCER (3)

Trial	Number of patients	Population	Follow up	Outcome: RP better than RT
Cooperberg et al. Cancer 2010	7 539	CaPSURE register, USA	4,2 years	Yes
Hoffman et al. JNCI 2013.	1 500	Prostate Cancer Outcome Study, USA	15 years	Yes
Abdollah et al. Eur Urol 2011.	404 604	SEER database, USA	5 years	Yes
Sun et al. BJU Int 2014.	67 087	SEER Medicare linked database, USA	10 years	Yes
Zelevsky et al. J Clin Oncol 2010	2 300	Institutional register, USA	8 years	Yes
Nepple et al. Eur Urol 2014.	6 000	2 tertiary centres	7,2 years	Yes
Abdollah et al. Int J Urol 2012.	68 665	SEER Medicare linked database, USA	unknown	Yes
Sooriakumaran et al. BMJ 2014	34 500	PcBaSe, Sweden	5,3 years	Yes
Boorijan et al. Cancer 2011	1 800	2 tertiary centres	10,2 years	yes

mL with GS 8 (GG 4) or higher in period 1995-2005. 602 patients were given only hormonal therapy (surgical castration or LHRH agonist) and 603 patients were also irradiated. Dose on prostate and seminal vesicles was 65 – 69 Gy and dose on pelvic lymph nodes 45Gy. Irradiated patients had better 7- year overall survival: 74% vs. 66% (6).

All these results indicate undoubted advantage of combined modality approach. Hormonal therapy as a sole treatment modality should be an option just for patients in whom irradiation would be contraindicated.

Radiotherapy vs. combined modality approach: hormonal therapy + radical radiotherapy

Meta- analysis by Bria published in 2009 included 7 trials and showed benefit of addition of hormonal therapy to radiotherapy with regard to lower rate of biochemical relapse (10% absolute difference). Patients receiving hormonal therapy had better clinical progression free survival (absolute difference 7.7%), overall survival (4.9%), tumour specific survival (5.5%) and less local and distant relapse (difference 36% and 27%, respectively) without significant difference in toxicity between two treatments (7).

However, it is not clear for how long should patients with high-risk prostate cancer receive hormonal therapy when combined with high dose radiotherapy.

Phase 3 randomised trial included 362 patients with intermediate and high risk prostate cancer. Median dose on prostate was 78 Gy. All patients received neoadjuvant and concomitant hormonal therapy; patients in experimental arm continued with goserelin for up to two years. After 5 years of follow up patients on long term hormonal therapy had statistically significant better biochemical free survival, overall survival and metastases free survival (86 vs. 95%, 89 vs. 94% and 85 vs. 93%, respectively). No significant difference in acute and late toxicity was observed between groups (8). In conclusion, benefit of long-term hormonal treatment still exists, regardless of higher radiation dose applied on prostate.

Combined modality approach, meaning radiotherapy with hormonal therapy in patients with high- risk prostate cancer is significantly better option than either of these two modalities alone.

Neoadjuvant chemotherapy with radiotherapy

GETUG 12 trial included 413 patients with high- risk prostate cancer that were receiving goserelin for 3 years and had local treatment, which in 87% of patients was radiotherapy (doses 74 - 78Gy). Patients randomised in experimental arm of the trial were given 4 cycles of docetaxel with estramustine prior to beginning of radiotherapy. PSA response, defined as PSA level < 0.2 ng/mL after 3 months of treatment, was achieved in 34% patients in experimental arm and in 15% of patients in control arm. After 4.6 years of follow up 4- year progression free survival rates were 85% in patients who received docetaxel/estramustine and 81% in control group (p= 0.26). 27% of patients receiving chemotherapy experienced neutropenia grade 3-4; rate of febrile neutropenia was 2% (9).

Whole pelvis irradiation

It is still unclear whether to include pelvic lymph nodes in target volume in this subset of patients.

When setting up an indication either Roach formula ($N+ = 2/3 \text{ PSA} + (\text{GS}-6) \times 10$) or nomograms are being used (10). In case the risk of lymph node involvement is >15%, whole pelvis radiotherapy is indicated. Clinically positive lymph nodes on MRI or CT scan are those larger than 10 mm in shorter diameter or larger than 8 mm, if lymph node is round. Choline PET scan has no role in lymph nodes involvement evaluation due to its low specificity (1).

Retrospective analysis of RECAP basis data involved 670 high-risk prostate cancer patients irradiated between 1993 -1999. 234 patients had just prostate irradiation- PORT (doses 55- 82.4 Gy, median 72 Gy) and 436 patients had also pelvic lymph node irradiation- WPRT (36- 56Gy, median 46 Gy). After median follow up of 77 (WPRT) and 86 months (PORT), there was no statistically significant difference between those two groups regarding 5 and 10- year biochemical failure, disease free survival, overall survival or cancer specific survival. In WPRT group early gastrointestinal and late genitourinary toxicity was more frequently observed (11).

High dose radiotherapy

A number of trials evaluated high dose radiotherapy in patients with localised prostate can-

Table 2

DOSE ESCALATION RANDOMISED TRIALS IN LOCALISED PROSTATE CANCER (1)

Trial	No of patients	Stage	Radiation dose	Follow-up	Outcome	Results
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% 78Gy (p=0,03)
PROG 95-09 Zietman et al. J Clin Oncol 2010	393	T1b-2b PSA 15ng/mL 75% GS<6	70,2 vs 79,2 Gy, proton boost 19,8 vs 28,8 Gy	median 8,9 years	10- year ASTRO biochemical failure (BCF)	all patients: BF 32% 70,2Gy, 17% 79,2 Gy (p< 0,0001) low risk: BF 28% 70,2Gy, 7% 79,2 Gy (p< 0,0001)
MRC RT01 Dearnaley et al. Lancet Oncol 2014	843	T1b-T3a N0M0, PSA<50ng/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)
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)
GETUG 06 Beckendorf et al. Int J Radiat Oncol Biol Phys 2011	306	T1b-3a, N0, M0, PSA<50ng/mL	70 vs 80Gy	median 61 month	ASTRO biochemical failure (BCF)	BF 39% 70Gy, 28% 80Gy
retrospective NCDB trial Kabasi et al, JAMA Oncol 2015	16714 13538	intermediate risk, 49% HT high risk, 77% HT	<75,6 vs > 75,6 Gy	median 85-86 months	overall survival (OS)	HR 0,84 for dose escalation (p<0,001) HR 0,82 for dose escalation (p< 0,001)

cer, regardless of the disease stage. Better 5- year biochemical free survival was observed. Trials are summarised on Table 2 (1).

Retrospective NCDB trial has analysed 42 481 patients' data: 12 229 low risk, 16 714 intermediate risk and 13 538 high risk prostate cancer patients irradiated between 2004 - 2006. They were divided into two groups regarding radiation dose: standard dose - 68.4- 75.6 Gy and escalated dose - 75.6- 90 Gy. In groups of patients with intermediate and high risk prostate cancer, better overall survival was observed with dose escalation (HR 0.84 and 0.82, p< 0.001). No benefit of dose escalation has been shown in group of patients with low risk prostate cancer (HR 0.98, p = 0.54). For every 2 Gy dose increment there was 7.8% reduction of death risk in intermediate risk patients and 6.3% reduction of death risk in high risk patients (12).

Integrated boost on macroscopic lesion in prostate

Dose escalation leads to better outcome in patients with high risk prostate cancer, but further increment is limited by surrounding tissue tolerance. Since prostate cancer relapses occur in area

where macroscopic tumour is located – dominant intraprostatic lesion (DIL), it is reasonable to apply higher dose on that exact part of prostate using simultaneous integrated boost (SIB).

FLAME trial included 541 patients with prostate cancer, 84% of which had high risk cancer. In experimental arm (284 pts) dose of 77 Gy in 35 fractions to the entire prostate gland was administered with an integrated boost up to 95 Gy to the macroscopic lesion. Control arm received 77Gy in 35 fractions to the entire prostate only. After median follow up of 22 months data regarding disease control were still lacking, but data regarding toxicity were published. No significant difference was found between both treatment arms for genitourinary toxicity. Urinary symptoms related to quality of life were not significantly different across treatment arms (13).

Phase 3 trial by Sundahl included 410 patients with T1-4N0M0 prostate cancer; 48% of them had high risk prostate cancer. Prescribed dose on prostate was 78Gy in 38 fractions; patients that had visible dominant intraprostatic lesion on MRI were given 82 Gy in 38 fractions on that par-

Table 3

PHASE 3 TRIALS – HYPOFRACTIONATION IN PRIMARY RADIOTHERAPY OF PROSTATE CANCER (1)

Trial	No of patients	Risk factors	Radiation regimen	BED	Median follow up	Outcome	Toxicity
Lukka et al. J Clin Oncol 2005	466 470	60% GS6 31% GS7 9% GS 8-10	52,5Gy/20 66Gy/33	62Gy 66Gy	68 months	5- year free from biochemical failure (FFBF) 40 vs 43% (NS)	Gr3 2vs 1% (NS)
Arcangeli et al. Int J Radiat Oncol Biol Phys 2010	83 85	26% GS 7 74%GS>7	62Gy/20 80Gy/40	81,4Gy 80Gy	70 months	5- year FFBF 85 vs 79% (NS), statistically significant for GS> 4+3	3 - years Gr2 and higher GU 16 vs 11% (NS) GI 17 vs 14% (NS)
Pollack et al J Clin Oncol 2013	151 152	34% GS 6 47% GS 7 19% GS 8-10	70,2Gy/26 78Gy/36	84Gy 78Gy	68 months	5- year biochemical or clinical disease free (BCDF) 23 vs 21% (NS)	5- year Gr2 and higher GU 13 vs 13% (NS) GI 9 vs 9% (NS)
Aluwini et al Lancet 2015	403 391	30% GS 6 and less 45% GS 7 25% GS 8-10	64,6Gy/19 78Gy/39	90,4Gy 78Gy	49 months	no data	3 - months Gr2 and higher GU 23 vs 22% (NS) GI 13 vs 13% (NS)

ticular area (SIB; dose equivalent 86Gy for α/β 1.5) or more, if tolerated by surrounding tissues. No difference between groups was observed in 6 – year risk for development of late grade 2 and 3 genitourinary or bowel toxicity. After 36, 42, 72 and 96 months of follow up, in group of patients that received SIB higher frequency of urinary incontinence was noticed (14).

Hypofractionation

Hypofractionation stands for irradiation in daily fractions higher than 2 Gy. It is assumed that α/β ratio of prostate cancer is about 1.5, which makes it sensitive on fraction size. Besides expected clinical benefit, hypofractionation lowers number of radiation sessions, which shortens overall treatment time. If doses higher than 4 Gy per fraction are to be applied, it is necessary to use image guided radiotherapy (IGRT) or stereotactic irradiation. In published trials short biochemical disease control is similar between treatment arms but long term effects on organs at risk (bladder and bowel) are not yet completely known, bearing in mind short follow up. Phase 3 trials are summarized on Table 3 (1).

In phase 3 CHHip trial 3216 patients with prostate cancer T1b-T3aN0M0 were randomised in 3 groups with regard to radiation regimen: 74 Gy in 37 fractions, 60 Gy in 20 fractions and 57 Gy in 19 fractions. IMRT and SIB were used. WPRT

was not performed. 97% of patients received neoadjuvant and concomitant hormonal therapy. In each group 12% of patients had high risk prostate cancer. IGRT was not used in 53% of patients in each group. After median follow up of 64 months the proportion of patients who were biochemical or clinical failure free at 5 years was 88.3 for 74 Gy, 90.6% for 60 Gy/20 and 85.9% for 57 Gy/19. 60 Gy was non- inferior to 74 Gy, but non- inferiority could not be claimed for 57 Gy/19 compared with 74 Gy. No significant difference between treatment groups was observed for late toxicity: frequencies of grade 2 and higher bowel and bladder adverse reactions were 13.7% and 9.1 % respectively for 74 Gy, 11.9% and 11.7% for 60 Gy/20 and 11.3% and 6.6% for 57 Gy/19 (15).

HYPRO trial enrolled 820 patients with intermediate-risk to high-risk T1b-T4NX-N0MX-M0 localised prostate cancer with a PSA of 60 $\mu\text{g/L}$ or less. They were randomly assigned (1:1) to either hypofractionated radiotherapy of 64.6 Gy (19 fractions of 3.4 Gy, three fractions per week) or conventionally fractionated radiotherapy of 78 Gy (39 fractions of 2 Gy, five fractions per week). Based on an estimated α/β ratio for prostate cancer of 1.5 Gy, the equivalent total dose in fractions of 2 Gy was 90.4 Gy for hypofractionation, compared with 78 Gy for conventional fractionation. 67% of patients received concomitant androgen deprivation therapy (median duration 32 months). The primary endpoint was relapse-free survival. After me-

dian follow-up of 60 months, 5-year relapse-free survival was 80.5% for patients assigned hypofractionation and 77.1% for those allocated conventional fractionation. 3 months after radiotherapy, no difference in frequency of grade 2 or worse genitourinary or gastrointestinal toxicity was observed between treatment groups. However, the cumulative incidence of grade 2 or worse acute gastrointestinal toxicity by 120 days after radiotherapy was higher in patients given hypofractionation: 42% vs. 31.2% in the standard fractionation group. There were no treatment-related deaths (16, 17).

NCI Canada trial randomized 936 patients with cT1-T2 prostate cancer whose PSA levels were <40 µg/L to either hypofractionated radiotherapy of 52.5 Gy (2.62 Gy per fraction) or conventionally fractionated radiotherapy of 66 Gy (33 fractions of 2 Gy). 20% of patients in each treatment arm had PSA level 15 µg/L or higher, therefore could be defined as high-risk patients. The primary outcome was biochemical or clinical failure (BCF). Median follow up was 5.7 years. At 5 years, the BCF probability was 52.95% in the long arm and 59.95% in the short arm, favouring the long arm. No difference in 2-year postradiotherapy biopsy or in overall survival was detected between the arms. Acute toxicity was higher in the short arm (11.4%) compared with the long arm (7%). However, late toxicity was similarly low in both arms (3.2%). It is to be noticed that patients did not receive concomitant androgen deprivation therapy and that prescribed doses were much lower than those prescribed nowadays. (18).

HDR brachytherapy as boost

In patients with high-risk prostate cancer high dose rate (HDR) brachytherapy could be used as a dose escalating boost delivered in combination with external beam radiotherapy. Iridium-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. Patients with significant urinary outflow symptoms are not candidates for HDR boost (19, 1).

A randomised phase-III trial compared external beam radiotherapy (EBRT) alone with EBRT combined with high-dose-rate brachytherapy boost

(HDR-BTb) in 218 patients with localised prostate adenocarcinoma. About 50% of patients in each arm had high-risk prostate cancer. 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. (log rank $p = 0.04$). 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 only arm (log rank $p = 0.5$). The incidence of severe bowel events was 7% and 6%, respectively, at 5 and 7 years; (log rank $p = 0.8$) (20).

CONCLUSION

According to literature, recommended therapy for high risk prostate cancer patients would be high dose radical radiotherapy with long term hormonal therapy. Depending on each centre experience as well as technical possibilities, use of simultaneous integrated boost, brachytherapy HDR boost or hypofractionation should be taken into consideration.

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