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Professional Paper

RECENT ADVANCES IN RADIOTHERAPY MODALITIES FOR PROSTATE CANCER

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ABSTRACT: Radiotherapy is the attractive treatment option for prostate cancer and has a clear role in all stages of the disease. Over the last decade, advances in technology, imaging capabilities, and improved radiobiological understanding have deeply transformed radiotherapy for prostate cancer, allowing dose escalation and wide adoption of hypofractionation. Furthermore, the integration of magnetic resonance imaging (MRI) and improved physical precision of dose delivery have given an impetus to additionally target intraprostatic tumor lesions, previously agnostic to conventional radiotherapy target definition concept. The emerging data from randomized clinical trials and observation research show that ultra-hypofractionation is a safe approach while further follow-up is needed to assess its efficacy compared to standard fractionation. There is an ongoing uncertainty surrounding true alpha/beta ratio for prostate cancer since hypofractionation has so far failed to yield theoretically envisioned superior biochemical control outcomes. Finally, recently published randomized trial settled ongoing controversy regarding the role of elective pelvic lymph node radiotherapy in patients with high-risk prostate cancer, showing clear benefit when pelvic nodes were treated to 50 Gy. The role of partial gland dose escalation/tumor boosting is evolving, and more data is needed to adopt this approach in routine clinical care. Going forward, molecular imaging will be crucial to assess biology of the disease, predict a response potentially, and optimally personalize radiotherapy treatment decisions. In this narrative review, we critically analyzed the published literature and provided practical summary of recent prostate radiotherapy advances for busy clinicians.

Key words: *prostate cancer, radiotherapy, hypofractionation, stereotactic body radiotherapy, dose escalation, boost, clinical trials*

Introduction

Radiotherapy has been used for decades as a primary treatment modality for localized prostate cancer and was considered as comparable treatment option as opposed to surgery. However, no randomized data was available to directly compare radiotherapy and radical prostatectomy as primary treatment for localized prostate cancer both in terms of efficacy and side-effects profile. Thankfully, this was changed after the publication of UK PROTECT study in 2016, a landmark randomized trial that established equipoise between radical prostatectomy and radiotherapy as equally effective treatment options for PSA screen-detected localized prostate cancer (1,2).

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After median follow-up of 10 years, the observed rates of disease progression among patients participating in the trial were generally very low, with no significant difference between radiotherapy, surgery, and active monitoring. The updated analysis showed that the patients who were monitored at the initial stage had marginal but significantly increased risk of distant metastasis, while there was no difference in distant metastasis rates between the patients treated surgically and with radiotherapy (3).

Overview of radiotherapy options in localized disease

The indications for radiotherapy are clearly specified in the most recent NCCN guidelines, emphasizing a significant role of radiotherapy across all risk groups (4). In the low-risk group, the preferable option is the active surveillance, and radiotherapy is a treatment of choice for patients who are not candidates for surveillance or opted for active treatment (5). In intermediate-risk category, both radical prostatectomy and image-guided radiotherapy are equally appropriate options for favorable patients, while the data obtained in an unfavorable subcategory indicate that the outcomes are better if radiotherapy is combined with short-course androgen deprivation therapy (ADT) (6,7). In case of high-risk disease, the crucial approach is the combination therapy with either radiotherapy with long-term ADT or radical prostatectomy followed by adjuvant or early salvage radiotherapy ± longer course of ADT (based on the risk factors present) (8–14).

When considering radiotherapy fractionation, a practicing oncologist is faced with a series of different options supported by variable level of evidence. Prostate cancer was the premier site to open the wave of hypofractionation in clinical radiotherapy. Hypofractionation employs higher (conventional) dose per fraction than standard (1.8-2 Gy). Radiobiology of prostate cancer favors larger doses per fraction as its uniquely low alpha/beta ratio, specifically lower than alpha/beta ratio of surrounding organs-at-risk, leading to increased therapeutic ratio when high(er) dose per fraction (i.e. hypofractionation) is used (15)or could be improved. Methods and Materials: We analyzed two mature data sets on radiotherapeutic tumor control for prostate cancer, one using EBRT and the other permanent seed implants, to extract the sensitivity to changes in fractionation of prostatic tumors. The standard linear-quadratic model was used for the analysis. Results: Prostatic cancers appear significantly more sensitive to changes in fractionation than most other cancers. The estimated α/β value is 1.5 Gy [0.8, 2.2]. This result is not too surprising as there is a documented relationship between cellular proliferative status and sensitivity to changes in fractionation, and prostatic tumors contain exceptionally low proportions of proliferating cells. Conclusions: High dose rate (HDR.

This notion triggered a whole array of clinical research; number of important trials have been completed (16–20)phase 3, non-inferiority trial that recruited men with localised prostate cancer (pT1b–T3aN0M0, some of them are still ongoing (21,22). Hypofractionation, as opposed to conventional fractionation (typically 2 Gy per fraction to the total dose of 74-78 Gy) can be either moderate (a dose per fraction 2.5–3.5 Gy to the total dose of 57-60 Gy) or extreme (a dose per fraction 4-10 Gy typically to the total dose 37.5-40 Gy). Extreme fractionation can only be achieved by stereotactic body radiotherapy (SBRT) (23). One of the ways to escalate the dose to the prostate is by using brachytherapy, either high-dose-rate (HDR) or low-dose-rate (LDR) isotopes. Specifically, both brachytherapy modalities, characterized by advantageous rapid dose fall-off, could be used either as monotherapy or combined with external beam radiotherapy (24–26).

Finally, one of the ways to improve radiotherapy cure rates in patients with more advanced localized disease was the use of elective pelvic radiotherapy that was controversial for a long time until the randomized trial was published that probably solved the issue of pelvic radiotherapy in prostate cancer (27,28).

The overlying question is, given the number of possible options, how to choose the right dose and fractionation in everyday practice.

The examples of improved therapeutic ratio (higher dose for the tumor and smaller dose for the normal tissue) in the main hypofractionation instances in the clinic are given in Table 1.

Table 1. *Comparison of equivalent dose in 2 Gy fractions for the tumor and for the normal tissue for each radiotherapy schedule, using biologically effective dose formula (assumptions alpha/beta = 1.5 Gy for tumor, 3 Gy for normal tissue)*

Radiotherapy schedule	EQD2 tumor	EQD2 normal tissue
Conventional fractionation 74-78 Gy/37-39#	74-78 Gy	74-78 Gy
Moderate hypofractionation 60 Gy/20#	77 Gy	72 Gy
Pelvic radiotherapy (54 Gy) + HDR brachytherapy boost (21 Gy/3x)	101.9 Gy	93.8 Gy
Stereotactic body radiotherapy (SBRT) 37.5 Gy/5#	96.4 Gy	78.75 Gy

Overview of landmark moderate hypofractionation studies

So far, the total of 6339 patients have been accrued in the four main contemporary randomized trials that tested moderate hypofractionation as opposed to conventional fractionation. These are CHHIP (UK) (16), RTOG 0415 (US) (19)115 men with low-risk prostate cancer were randomly assigned 1:1 to C-RT (73.8 Gy in 41 fractions over 8.2 weeks, PROFIT (Canada, Europe) (17), and HYPRO (Dutch) trial (20)suggesting that hypofractionation could enhance the biological tumour dose without increasing genitourinary and gastrointestinal toxicity. In the multicentre phase 3, HYpofractionated irradiation for PROstate cancer (HYPRO.

The CHHIP trial was UK-based randomized, phase 3, non-inferiority trial that enrolled the patients with prostate cancer of all risk groups and randomized them to three arms: conventional fractionation (74 Gy delivered in 37 fractions over 7.4 weeks), the first hypofractionated schedule (60 Gy in 20 fractions over 4 weeks) and the second hypofractionated schedule (57 Gy in 19 fractions over 3.8 weeks). Intermediate and high-risk patients received 6 months of ADT. PROFIT trial was a Canadian-based trial that enrolled 1206 patients with low- and intermediate-risk prostate cancer and randomized them between standard treatment of 78 Gy in 39 fractions and hypofractionated treatment of 60 Gy in 20 fractions. RTOG 0415 was US-based trail that randomized 1115 patients with low-risk prostate cancer to standard arm receiving 73.8 Gy in 41 fractions and experimental arm receiving 70 Gy in 28 fractions. Finally, HYPRO trial was a Dutch study which included 820 patients with intermediate- (26%) and high-risk prostate cancer (74%) and randomized them to hypofractionated radiotherapy of 64.6 Gy in 19 fractions (EQD2 90.4 Gy) or conventionally fractionated radiotherapy of 78 Gy in 39 fractions. The majority of patients (67%) received long-course concomitant ADT (median duration of 32 months). The majority of patients were treated by means of 3D-conformal radiotherapy technique. This trial was designed as superiority trial for hypofractionated treatment arm. In a subgroup analysis, the patients with high-grade disease (Gleason score 7 and 8-10 patients) did not have the same extent of benefit of hypofractionation compared to the patients with low-grade disease (Gleason score ≤6). However, overall p-value on Forrest plot was non-significant (0.16).

In the updated report of HYPRO trial published in 2020, the pattern of relapse was analyzed, which showed low rate of local relapse in patients with Gleason score ≥8 treated with hypofractionated regimen, compared with conventionally treated patients (29).

The main finding consistent across all four trials is a similar (not different) disease-control rate, i.e. biochemical control, in patients randomized into the hypofractionated arm versus patients who were randomized to conventionally fractionated treatment, with the exception of 57 Gy in 19 fractions arm in CHHIP trial that had inferior biochemical control and was not considered an appropriate treatment (16).

When applying the results of these trials in everyday clinical practice, one must be aware of the important caveat that the majority of patients participating in CHHIP, PROFIT and RTOG 0415 trials were low- and intermediate-risk patients. It remains to be seen whether the non-inferiority of hypofractionation holds true for truly high-risk patients.

Smaller size hypofractionation prospective trials - focus on long-term data

Fox-Chase hypofractionation trial recently published the updated results after 10 years of follow-up

(30)with sensitivity analyses for National Comprehensive Cancer Network (NCCN. In this trial, 303 men with intermediate- and high-risk prostate cancer were randomly assigned to receive conventionally fractionated IMRT (76 Gy in 38 fractions) or moderate hypofractionated IMRT (70.2 Gy in 26 fractions). All patients received ADT with the duration of 4 and 24 months being the patients with intermediate- and high-risk disease, respectively. Additionally, high-risk patients had pelvic lymph nodes radiotherapy.

Although this trial was designed to show theoretically envisaged superiority of hypofractionation in terms of biochemical control, it failed to show this in the first analysis at 5-year point. Furthermore, unlike HYPRO trial, the trend towards higher 10-year rate of distant metastasis was found in this study related to the patients treated with hypofractionated radiotherapy compared to the patients treated with conventionally fractionated radiotherapy (14.3% vs 6.4%, unadjusted HR 1.93, 95%CI 0.93-4.00, p=0.08). However, there was no statistically significant difference in other metrics found between the treatment arms (biochemical failure, local recurrence, prostate cancer-specific mortality, and overall mortality) (18,30)men with favorable- to high-risk prostate cancer were randomly allocated to receive 76 Gy in 38 fractions at 2.0 Gy per fraction (conventional fractionation intensity-modulated radiation therapy [CIMRT].

It can be concluded that moderate hypofractionation is efficacious and safe in low- and intermediate-risk prostate cancer. In terms of clinical implementation, there is no clear preference of the one hypofractionation protocol over the other. Departmental experience, capabilities and logistics should be taken into account when considering the adoption of a particular protocol. However, there may be insufficient data regarding long-term outcomes of hypofractionation in high-risk patients, although HYPRO trial clearly suggested better local control in this particular risk group.

The efficacy and safety of hypofractionation in the group of fragile patients older than 75 years was confirmed in a subgroup analysis made in CHHIP trial. Here, both hypofractionated schedules (60 Gy in 20 fractions and 57 Gy in 19 fractions) performed equally well, while urinary and bowel toxicity was overall low and similar to the toxicity rates observed in patients younger than 75 years (31).

Clinical trials in ultra-hypofractionation space

Further step towards more profound hypofractionation was made by HYPO-RT-PC trial. This Swedish-based, phase 3 non-inferiority trial enrolled 1200 intermediate- and high-risk, ADT naïve, prostate cancer patients and randomized them to conventionally fractionated regimen of 78 Gy in 39 fractions and ultra-hypofractionated schedule of 42.7 Gy in 7 fractions (EQD2 92.7 Gy). The authors published their 5-year experience in Lancet in 2019 (22). The five-year biochemical control was the same in 84% in both treatment arms. This trial established for the first time that one ultra-hypofractionated radiotherapy regimen is non-inferior to conventionally fractionated radiotherapy in intermediate-to-high risk prostate cancer patients. There were slightly more side-effects with ultra-hypofractionation, however, late toxicity was rare and similar in both treatment groups.

Upon taking a closer look, it can be found interesting that the majority of patients were treated using 3D-conformal technique, so the investigators had to rely on image-guidance approach based on fiducial markers.

Another important trial that assesses ultra-hypofractionation is UK-based PACE-B study that enrolled 874 patients with low- and favorable intermediate-risk prostate cancer and randomized them to conventionally fractionated or moderately hypofractionated radiotherapy (78 Gy in 39 fractions or 62 Gy in 20 fractions, respectively) or stereotactic body radiotherapy (SBRT) with 36.25 Gy in 5 fractions. So far, the authors have published the results focusing on the acute toxicity being a co-primary endpoint together with biochemical control. Opposite to HYPO-RT-PC trial, in PACE-B trial the incidence of total grade ≥2 toxicity was similar in both treatment arms (12% vs 10% (p=0.38) in the patients randomized to conventionally fractionated or moderately hypofractionated radiotherapy and stereotactic body radiotherapy group, respectively). In the latest two-year update presented at the ASTRO annual meeting in 2021, there was no difference in grade 2+ GI toxicity, however, GU toxicity was somewhat higher in the SBRT arm when measured using the CTCAE grading schema: 11.8% compared to 5.8% in the conventional fractionation arm. The biochemical outcomes are to be reported in 2023 (21).

Clinical implications of prostate cancer alpha/beta ratio uncertainties

Early hypofractionation trials (Fox Chase, HYPO-RT-PC) were initially designed as superiority trials based on the assumptions of low alpha/beta ratio for prostate cancer, which was considered to be in the range of 1.5 Gy (18,22)men with favorable- to high-risk prostate cancer were randomly allocated to receive 76 Gy in 38 fractions at 2.0 Gy per fraction (conventional fractionation intensity-modulated radiation therapy [CIMRT]. However, mature trial results widely refuted theoretically anticipated hypofractionation advantage (i.e. superiority) (30)with sensitivity analyses for National Comprehensive Cancer Network (NCCN.

Actually, what was largely observed at best, was the non-inferiority of hypofractionation compared to standard fractionation. This led to the possibility that prostate cancer alpha/beta ratio is not that low, as several studies reported higher alpha/beta ratio values, even exceeding 4 Gy (32,33).

If alpha/beta ratio was indeed 4 Gy, this would completely abate theoretically anticipated dose escalation advantage associated with hypofractionation. The recent radiobiology analysis made by Vogelius and Bentzen and published in 2020 showed that it is probably correct that prostate cancer alpha/beta ratio is inherently low, around 1.5 Gy when trials with moderate hypofractionation are considered, however, according to Widmark trial of ultimate hypofractionation (42.7 Gy in 7 fractions=6.1 Gy per fraction), the associated alpha/beta ratio on logistic regression is around 3 Gy. Therefore, we need more data in SBRT era on larger doses per fraction to draw more firm conclusions about true alpha/beta ratio (34).

Furthermore, this analysis showed that there might be a dose-threshold effect on dose-response curve. With EQD2 going beyond 80 Gy, it seems that the gain associated with further dose escalation would be marginal at best, suggesting plateau of the dose-response curve for doses ≥80 Gy (34).

Improving outcomes with partial-gland dose-escalation

Since there is limit to safe whole prostate dose escalation with external beam radiotherapy, a therapeutic gain may possibly be achieved if we specifically target and boost portion of the prostate containing the bulk of the tumor called dominant intraprostatic lesion (DIL). The widespread use of MRI allowed to dissect prostate anatomy and to clearly visualize intraprostatic tumors, which enabled their targeting with radiotherapy (35).

The authors performed stereotactic boost to DIL using volumetric modulated arc therapy and reported early efficacy and toxicity endpoints in the recent JCO publication. In the FLAME trial, the authors hypothesized that focal boosting of the macroscopic visible tumor with external beam radiotherapy would increase biochemical control in patients with localized prostate cancer. They recruited 571 patients with intermediate- and high-risk prostate cancer and randomized them to either standard treatment (77 Gy in 2.2 Gy daily fractions) or to the addition of integrated simultaneous tumor boosting to 95 Gy (2.7 Gy fractions, EQD2=115.8 Gy). The majority of patients received long-term ADT. The reported 5-year biochemical control was 92% in focal boost arm and 85% in the standard arm ($p<0.001$) without additional toxicity associated with focal dose escalation.

Interestingly, there was numerical, not statistically significant improvement in distant metastasis control in patients who received focal boost, which potentially indicates that additional dose to the primary lesion was able to eradicate subsequent micrometastatic clones (36).

New data on the role of elective pelvic lymph node radiotherapy

Elective pelvic radiotherapy has been a matter of controversy for decades. Several trials, plagued with a number of limitations, failed to establish improved outcomes when pelvic nodes were treated (27). An important trial was published recently, POP-RT that reconsidered this issue. In this randomized phase 3 trial, 224 PSMA-PET or MRI-staged patients with high-risk or very high-risk prostate cancer, with predicted pelvic lymph node involvement of >20% based on Roach formula were assigned to prostate only treatment (68 Gy in 2.72 Gy per fraction, EQD2=78-81 Gy) or to prostate plus pelvis radiotherapy (50 Gy in 25 fractions). All patients received long-term ADT. The primary endpoint was 5-year biochemical relapse-free survival. The trial was terminated early due to lower-than-expected events rate after 10 years of follow-up. Both biochemical control and metastasis-free survival were significantly improved in pa-

tients who were randomized to combination treatment (HR 0.23 and 0.35, respectively). When the pattern of relapse was analyzed, it was clear that the patients treated with prostate only radiotherapy had more both pelvic recurrences and distal metastasis. Apart from the patients older than 66 years, all other groups benefited from pelvic radiotherapy according to subgroup analysis (28).

This trial established pelvic radiotherapy as the standard of care in adequately staged patients with high-risk prostate cancer.

Conclusions

Prostate cancer radiotherapy has evolved over the last decade as the important trials paved the way to a wide adoption of moderate hypofractionation in the routine care. COVID-19 pandemics additionally gave impetus to shorten the previously protracted radiotherapy courses to minimize the risk of infection and to save clinical and human resources which were under enormous pressure. More data is anticipated regarding extreme hypofractionation which is the subject of several ongoing trials. Targeted dose escalation is a promising approach; however, the question remains whether the DIL necessarily represents the aggressive biology which drives treatment resistance and gives rise to metastasis. Moreover, despite dose escalation, nodal and distant metastases are still predominant patterns of failure. Finally, pelvic radiotherapy should be considered in high-risk patients, while for older patients, prostate only radiotherapy would suffice.

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Sažetak

ZADNJA POSTIGNUĆA U RADIOTERAPIJI RAKA PROSTATE

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SAŽETAK: Radioterapija je neizostavan oblik liječenja raka prostate i ima ulogu u svim fazama bolesti. Zadnjeg desetljeća napreci u tehnologiji i radiobiologiji su preobrazili radioterapiju raka prostate te omogućili eskalaciju doze i hipofrakcioniranje. Nadalje, integracija magnetske rezonance i povećana fizikalna preciznost isporuke radioterapije omogućila je ciljanje intraprostatičkih tumora. Mnoge studije pokazuju da je ultra hipofrakcioniranje obećavajući koncept liječenja, iako postoje mnoge nejasnoće o pravom alfa-beta omjeru raka prostate te posljedičnom stvarnom terapijskom benefitu hipofrakcioniranja. Recentno objavljena studija ukazala je na korist elektivne radioterapije zdjeličnih limfnih čvorova u bolesnika sa visokorizičnim rakom prostate. Nadalje, u tijeku su studije koje će ocijeniti valjanost daljnje intraprostatičke eskalacije doze. Moderno molekularno oslikavanje donosi veliku promjenu u načinu kako shvaćamo i liječimo rak prostate. U ovom preglednom članku kritički smo analizirali literaturu i dali smjernice za svakodnevnu radioterapijsku kliničku praksu.

Ključne riječi: *rak prostate, radioterapija, hipofrakcioniranje, stereotaksijska radioterapija, eskalacija doze, kliničke studije*