What does large randomized trials tell us about the fractionation sensitivity of prostate cancer?

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Abstract: Seven randomized clinical trials have tested the use of moderate hypofractionation (2.1-3.5 Gy per fraction) compared to conventional fractionation (1.8-2.0 Gy per fraction) in radiotherapy for localized prostate cancer. The trials find that moderate hypofractionation results in acceptable PSA-control and morbidities that are comparable to conventional fractionation schedules. Extrapolation of the results from the earliest randomized trials indicated a low $\alpha/\beta$-values for prostate cancer, but the more recent – and large – studies suggest that the value is moderately or considerably higher. Moderate hypofractionation schedules (ie. 20 x 3 Gy) are now being implemented in routine practice. They are cost-effective and convenient, but they are not consistently concordant with fractionation sensitivity parameters extrapolated from clinical trials on moderate hypofractionation of prostate cancer.

1. Introduction
Standard external beam radiation therapy (EBRT) is delivered with 1.8-2.0 Gy/fractions with 5 weekly fractions over 7-9 weeks. There are several arguments for use of more hypofractionated schedules. Years ago it was lack of resources, whereas nowadays the competition with robotic assisted prostatectomy is the driving force behind hypofractionation. However, there are also biological arguments for choosing hypofractionation in frequently occurring cancers such as breast- and prostate cancer. According to these, the therapeutic ratio improves by use of hypofractionation of localized prostate cancer due to a high fractionation sensitivity (low $\alpha/\beta$-value) of the slowly proliferating prostate cancer cells.

Brenner and Hall suggested that the $\alpha/\beta$-value for prostate cancer was 1.5 Gy (0.8-2.2) in a study comparing isoeffective doses from EBRT, low- (LDR) and high dose rate (HDR) brachytherapy studies [1]. The endpoint was PSA relapse and patients were stratified by pretreatment PSA level. The study was criticized for the inclusion of brachytherapy data, but Mirabell et al found a similarly low $\alpha/\beta$-value with narrow confidence interval of 1.4 Gy (0.9-2.2) in a modeling study of EBRT alone stratified for risk groups [2].

Moderate hypofractionation most often refers to the use of doses in the range 2.1-3.5 Gy per fraction and extreme hypofractionation with dosed above 3.5 Gy per fraction. The present review focus on randomized trials where the experimental arm is moderate hypofractionation and the comparator is standard fractionation.

2. Conventional fractionated radiation therapy of prostate cancer
Randomized clinical trials have demonstrated the efficacy of radiation therapy delivered with normofractionation. In a recent update of the Scandinavian Prostate Cancer Group 7 trial, the 15-year
cancer-specific mortality reduced from 34% to 17% and the overall survival was prolonged by 2.4 years when radiation therapy was given in combination with life-long bicalutamide to high risk prostate cancer compared to the antiandrogen therapy alone [3]. The improved cancer-specific survival was found in all tumor stage-, PSA- and age-groups. The morbidity related to the treatment was manageable. There was moderate - but significantly more - urinary, bowel and sexual bother in radiation therapy group.

More detailed analysis of the morbidity based on patient reported outcome measures (PROM) following radiation therapy with conformal techniques and conventional doses for prostate cancer revealed more morbidity and bother related to urinary-, bowel- and sexual function than we measure with use of physician administrated scoring systems. In a long-term morbidity study, some patients experience incontinence for solid stool, ability to defer defecation for less than 15 minutes, unproductive call for stool, clustering of stool and mucus in stool to minor degree [4]. These five factors are furthermore related to a reduced quality of life in those who suffered. It is an important message that detailed PROMs may identify morbidity that is not revealed from the less sensitive traditional scoring systems. When new radiation technology is introduced we should be aware that it potentially may have slightly worse morbidity profile than our conventional therapy.

3. Moderate hypofractionation of prostate cancer

Seven randomized clinical studies compare moderate hypofractionation with conventional fractionated radiation therapy for prostate cancer (table 1). They vary in size, inclusion criteria and use of anti-androgen deprivation therapy (ADT) as well as in design. Importantly, most studies have different equivalent dose in 2-Gy fractions (EQD2) between the arms when assuming an $\alpha/\beta$-value of 1.5 Gy. As an example, there is a 12 Gy difference in EQD2 between the two randomization arms of the HYPRO study.

Two studies used low radiation dose in EBRT for low- and intermediate risk prostate cancer [5;6]. The EQD2 was higher than the conventional arm in the Lukka study whereas the hypofractionated arm was the hottest in the Yeoh study. With a non-inferiority design, the Lukka study concluded that biochemical control in the hypofractionated arm was not non-inferior and might be inferior to conventional fractionation. In contrast, the hypofractionated arm had superior relapse free survival in the Yeoh study. Differences in EQD2 between randomization arms may explain the results of the two trials, and the studies are in accordance with a low $\alpha/\beta$-value ranging 1-2 Gy for prostate cancer.

The Italian Arcangeli study compared two arms with comparable EQD2 in high-risk patients who all received 9 months ADT [7]. This study has a relatively low power (n=168) and was published with a relatively short median follow-up time of 32 months, but it found a clear improvement in biochemical progression free survival in patients treated with hypofractionation. This study therefore favours a very low $\alpha/\beta$-value. The treatment related morbidity was modest and there was no difference between the two fractionation arms.

The Pollack study compared two schedules with a difference in EQD2 of 6 Gy where the hypofractionated arm was the hottest [8]. The study included all risk groups. The CTV-PTV margin was slightly smaller in the hypofractionated arms. They found no difference in the combined endpoint of biochemical and clinical failure between the arms assessed with both the American Society for Therapeutic Radiation Oncology (ASTRO) and the nadir+2 principles. Considering the higher EQD2 in the hypofractionated arm, this study does not favour a low $\alpha/\beta$-value. Acute and late morbidities were acceptable and not different between the arms, but a subgroup of patients with considerable pretreatment lower urinary tract symptoms suffered more long-term side-effects when treated with hypofractionation.

The UK CHHiP non-inferiority study was presented at the ECC2015 in Vienna [9]. Dearnaley et al. compared three arms where the conventional 74 Gy arm had comparable EQD2 to the 57 Gy in 19 fractions arm with an $\alpha/\beta$-value of 1.5 Gy and to the 60 Gy in 20 fractions arm with an $\alpha/\beta$-value of 2.5 Gy. The study population had a <30% risk of vesicular invasion and was primarily in the intermediate-risk group. The study showed non-inferiority between the 20 fraction arm and the conventional arm and therefore in accordance with an $\alpha/\beta$-value in the range of 2.5 Gy and not an ultra-low value. In the evaluation of the toxicity, there as no difference in the severity of acute and late side-effects with the
exception of earlier appearance of acute effects in the hypofractionated compared to the conventional schedule. PROM data from the CHHiP trial with a median follow-up of more than 4 years revealed relatively mild morbidity in all three arms and no differences between the them [12].

Table 1. Randomized clinical trials comparing moderate hypofractionation to conventional fractionated radiotherapy for prostate cancer.

| Author          | N  | RT schedule               | EQD2 (Gy) | Endpoint and Efficacy                  | Morbidity                  |
|-----------------|----|---------------------------|-----------|----------------------------------------|----------------------------|
| Lukka [5]       | 936| 66 Gy/33 frx, 55.2 Gy/20 frx | 66, 62    | BCF 53% vs. 60%, HR=1.18 (0.99-1.41), hypo not non-inferior | More acute morbidity with hypo |
| Yeoh [6]        | 217| 64 Gy/32 frx, 55 Gy/20 frx | 64, 67    | BCF 34% vs. 53%, Hypo best             | More GU morbidity with conv |
| Arcangeli [7]   | 168| 80 Gy/40 frx, 62 Gy/20 frx | 80, 81    | 4-year FFBF*, 82% vs. 60%, Hypo best   | NS                         |
| Pollack [8]     | 303| 78 Gy/39 frx, 70.2 Gy/26 frx | 78, 84    | BCF 23% vs. 21%, NS                    | NS                         |
| Dearnaley [9]   | 3216| 74 Gy/32 frx, 57 Gy/19 frx, 60 Gy/20 frx | 74, 74, 77 | 5-yr PFR, HR=0.83 (0.68-1.03), HR=1.20 (0.99-1.45), Hypo (60 Gy) not inferior | NS                         |
| Lee (RTOG) [10] | 1092| 74 Gy/41 frx, 70 Gy/28 frx | 70, 80    | DFS, HR=0.85 (0.64-1.14), NS           | More late GU and GI morbidities with hypo |
| Incrocci (HYPRO) [11] | 800| 78 Gy/39 frx, 64.6 Gy/19 frx | 78, 80    | DFS, HR=0.86 (0.63-1.16), NS           | NS                         |

*a Late morbidity was primary endpoint
*b 90% CI; other HR are given with 95% CI

Abbreviations: EQD2: equivalent dose in 2 Gy fractions under the assumption of α/β=1.5 Gy; BCF: combined biochemical and clinical failure rate; FFBF: freedom from biochemical failure; PFR: progression free rate; DFS: disease free survival; HR: hazard ratio; NS: non-significant; vs: versus.

Two large randomised, non-inferiority, phase III studies were presented at the ASTRO 2015 in San Antonio [10;11]. The RTOG 0415 study presented by Lee et al. and the Dutch HYPRO study presented by Incrocco et al. including low-risk and intermediate- to high-risk localised disease, respectively. The RTOG 0415 study arms were designed to be biologically iso-effective at the α/β-value of 10 Gy. The primary endpoint, disease free survival (DFS), with a median follow-up of 5.8 years was 86% and 85%, which was not statistically different. Late genitourinary and gastrointestinal side effects were slightly more prevalent in the hypofractionated arm. With a median follow-up of 5 years, the HYPRO study primary end-point, relapse free survival, was 80% and 77% in favour of hypofractionation, but not statistically different from the conventional arm. Preliminary results from the toxicity analysis revealed no differences in early and late toxicity between the two arms. In both these studies, the EQD2 was considerably higher in the hypofractionated arm when assuming a low α/β-value of 1.5 Gy, and with non-inferiority both studies indicate a much higher α/β-value.

4. Discussion

Consistently, the seven studies showed that moderate hypofractionation lead to acceptable biochemical control, and the largest of the studies concluded that moderate hypofractionation with sufficient dose was not inferior to the conventional fractionated regimen. It was most clearly shown by the CHHiP trial where the 20 x 3 Gy regimen was non-inferior to the conventional 37 x 2 Gy regimen whereas the 19 x 3 Gy was not non-inferior to the conventional schedule. All studies showed that moderate hypofractionation with the right doses and delivered with modern IMRT and IGRT was associated with
tolerable morbidity. In some of the studies, there was slightly more late morbidity in the hypofractionated arms, but the additional morbidities were in most cases grade 2 and relatively mild. Moderate hypofractionation seems to be safe and several institutions have adopted the moderately hypofractionated schedules. However, it will be important to follow the patients in long-term follow-up with use of sensitive scoring systems such as the PROM questionnaires.

Modeling studies have indicated that prostate cancer may have a very low $\alpha/\beta$-value in the range of 1.5 Gy which favours hypofractionation. Slow proliferation may be associated to the high fractionation sensitivity and low rate of proliferation has been shown in prostate cancer [13]. The early randomized trials were in accordance with the modeling studies, all indicating a high fractionation sensitivity. In contrast, the more recent trials are inconsistent with the earlier studies. Among these are three large studies, CHHiP, RTOG0415 and HYPRO indicating moderately or considerably higher $\alpha/\beta$-values compared to the early randomized trials and to the modeling studies. These inconsistencies are puzzling and could be explained by differences in risk groups, Gleason grades and use of ADT between the studies. Intuitively, low $\alpha/\beta$-value is expected in low Gleason-grade and low-risk patients in general, but there are no such correlation found between the seven randomized studies. Neither is there a correlation between fractionation sensitivity and use of ADT.

There are a number factors to declare when comparing studies on moderate hypofractionation. The variation between the studies in terms of design, total doses, fractionation schedules as well as the differences between the study populations may be important confounders. Furthermore, the hypofractionated schedules were delivered with shorter overall treatment times and the shortening of overall treatment time differ between the studies.

These trials open a new discussion on the $\alpha/\beta$-value of prostate cancer and results on more extreme hypofractionation of prostate cancer are awaited. Among these is the Scandinavian HYPO-RT-PC trial comparing extreme hypofractionation with 7 x 6.1 Gy and conventional 39 x 2 Gy. The study has now completed inclusion of 1200 intermediate-risk prostate cancer patients. A number of cancer centers and cooperative trial groups have decided to change to a moderately fractionation schedule as standard of care in radiation therapy for localized prostate cancer. Moderate hypofractionation seems to be associated with acceptable morbidity and seems safe with use of modern highly precise radiation technologies. It is cost-effective, convenient and competitive to robotic assisted prostatectomy, but findings from clinical trials do not consistently support a high fractionation sensitivity of prostate cancer.

5. Reference List
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