Journal of Cancer Science & Therapy
ISSN: 1948-5956

Sami et al., J Cancer Sci Ther 2019, 11:13

Review Article Open Access

Hypofractionated Radiotherapy in Prostate Cancer: A State of the Art in 2019

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Abstract

The low α/β ratio in prostate cancer has prompted several teams to propose and evaluate hypofractionated protocols for moderate or stereotactic radiotherapy, in order to deliver larger doses per session over a shorter spread. This allows a better observance of the treatment, while arriving at equivalent radiobiological doses, or even higher than in the standard irradiation protocols. Moreover, the fear of generating intolerable toxicities, especially urinary and gastrointestinal compromising the quality of life of patients has always been a barrier to the generalization and approval of these schemes hypofractionated by all centers. The objective of this article is to present several studies evaluating hypofractionated radiotherapy for localized prostate cancer, whether performed alone or as an adjunct to surgery. We will also discuss the role of new radiotherapy techniques and control imaging in the realization of this treatment. Finally, we discuss the practical recommendations of the hypofractionated protocol.

Keywords: Prostate cancer; α/β ratio; Hypofractionation; Post-surgery; Stereotactic

Introduction

Hypofractionated radiotherapy has long been evaluated in prostate cancer, appearing a very attractive approach to the decreased α/β ratio in prostate cancer (about 1.5) evoked in several studies and that requires increasing the dose administered per fraction for better local control. Except that side effects at the level of adjacent organs have always been discussed as to the adoption of this therapeutic attitude.

Literature Review

Hypofractionation in prostate radiation therapy

The advantage of the hypofractionated regimen in prostate cancer lies in the increase of the lethal effect of radiotherapy since the α/β ratio is low (around 1.5), reflecting the strong cell repair capacity tumor in the prostate. On one of the largest studies, made by Miralbell comprising 6000 patients, α/β was estimated at 1.4, not differing between the 3 prognostic groups [1]. In order to achieve a significant reduction in the recovery of prostate tumor cells, higher doses per fraction were tested by different teams evaluating the efficacy and tolerance associated with these doses.

The first studies of hypofractionated radiotherapy for prostate cancer began in 1990. Lukka conducted a Phase III study in Canada comparing conventional radiotherapy of 66 Gy in 33 fractions to a hypofractionated regimen of 52.5 Gy in 20 fractions, showing an increase in acute toxicity to the hypofractionated arm, with no difference in chronic toxicity or local control at 2 years [2]. In Australia, Yeoh compared on a study ranging from 1996 to 2003 2 protocols 64 Gy/32 fraction (6.5 weeks) with 55 Gy/20 fractions (4 weeks) with a median follow-up of 90 months: Survival without Biochemical progression (PSA) was better in the hypofractionated radiotherapy arm with no difference in overall survival and toxicity (urinary and gastrointestinal) was equivalent between the 2 arms. Hence the conclusion of the benefit of hypofractionation according to this study [2,3]. But these studies are criticized in the sense of: under-dosing (current doses: 74 to 80 Gy), 2D treatment (currently 3D and better still IMRT) and the non consideration of α/β before the launch of studies. But we can say that these studies have paved the way for discussion of hypofractionation in the non-metastatic prostate cancer.

The new studies were based on an α/β at 1.5 and seek the benefit of hypofractionation either in a better local control with the equivalence in toxicities, or an equivalence in the local control with reduction of the side effects [4]. Arcangeli evaluated hypofractionated radiotherapy in high-risk prostate cancer cases with 62 Gy/3.1 Gy in 5 weeks compared to conventional 80 Gy/2 Gy radiotherapy in 8 weeks. After a follow-up of 70 months, there was a reduction in risk of biochemical relapse (10.3%), in addition to an increase in local and remote PFS (progression-free survival) in a subgroup at PSA ≤ 20 [5].

Pollack included 303 low-to-high risk patients in a prospective study, randomized between conventional IMRT radiotherapy at 76 Gy/38 fractions and hypofractionated at 70.2 Gy in 26 fractions of 2.7 Gy (equivalent to 84, 4 Gy to 2 Gy). The results showed equivalence in long-term toxicities except for patients who had already before the beginning of the treatment of urinary complications which had been aggravated with the hypofractionated schema [6]. Kupelian reported in their experience on 770 patients treated according to the hypofractionated protocol of 70 Gy/2.5 Gy in a retrospective analysis the equivalence in local control and toxicities compared to the results of the standard fractionation [7].

Multiple non-inferiority phase III trials such as RTOG0415 and PROFIT favorably evaluated hypofractionated radiotherapy by comparing the 70 Gy/2.5 Gy regimen with that of 73.8 Gy/1.8 Gy in terms of efficacy and tolerance [7]. Dearnaley, through the CHHiP (High Intensity Modulating or Hypofractionated Intensity Modulated Radiation Therapy in Prostate Cancer) trial comparing the 74 Gy/2 Gy regimen with the hypofractionated 60 Gy/3 Gy or 57 Gy/3 Gy compared to toxicities generated over a 5-year decline. The results

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Received November 09, 2019; **Accepted** December 17, 2019; **Published** December 24, 2019

Citation: Sami H, Barkiche S, Kaiss H, Elouarzazi S, Lalya I, et al. (2019) Hypofractionated Radiotherapy in Prostate Cancer: A State of the Art in 2019. J Cancer Sci Ther 11: 315-318.

were summarized in a very satisfactory local control with the current techniques, a better observance of the treatment with tolerable side effects with the hypofractionated protocols [8].

Therapy and Oncology), and ASCO (American Society of Medical Oncology) have made recommendations regarding hypofractionated radiotherapy in localized prostate cancer, which have been approved by the American Society of Radiation Therapy and Oncology. Urology, the company ESTRO (European Society of Radiotherapy and Oncology) and the Royal College of Australia and New Zealand of radiotherapists, admitting the benefit of this radiotherapy in moderate doses concerning local control and rates of toxicity, which were similar with moderate doses (60 Gy in 20 fractions of 3 Gy or 70 Gy in 28 fractions of 2.5 Gy) which could be proposed as a therapeutic option to any patient especially at low or intermediate risk (consensus 100%) candidate for external radiotherapy on localized prostate cancer. The results were not so obvious for ultra-hypofractionated doses (above 3.5 Gy/fraction) that are only recommended in clinical trials. While indicating the need for IMRT and IGRT by adopting these schemes [9].

Hypofractionated radiotherapy as an adjunct to surgery

Two Italian studies evaluated adjuvant radiotherapy in IMRT with hypofractionated regimens (in integrated boost): 56.8 Gy/2.27 Gy; 59.7 Gy/2.39 Gy; 61.25 Gy/2.45 Gy and 62.5 Gy/2.5 Gy. The conclusion was the absence of treatment-limiting toxicity, ultimately recommending the dose of 62.5 Gy/2.5 Gy [7-10]. Kruser Published their experience in hypofractionated radiotherapy at 65 Gy/25 fractions in 108 patients after prostatectomy with PSA≥ 0.44 ng/ml. The results were encouraging with a 4-year biochemical PFS of 67% +/- 5.3%. With moderate toxicities (one grade 3 genitourinary, no gastrointestinal grade 3 toxicity or other long-term toxicity grade 3. Also with good local control [11,12].

But the largest study was that of Cozzarini including 1176 patients and in which hypofractionation of 58 Gy/20 fractions in tomotherapy was evaluated. Initially in 2008 when they had not observed a difference in terms of toxicity, especially genitourinary (G 2, 3) or gastrointestinal (G2). But after a follow-up of 68 months, the urinary toxicity proved to be more important. On this observation, the authors warned of the risk of severe urinary toxicity after the hypofractionated pattern on the prostatectomy bed [11]. On these results, we can say that adjuvant radiotherapy in hypofractionated regimen is a favorable option in terms of tolerance towards acute toxicities (especially genitourinary), but this remains to be confirmed in the long term.

It is possible, however, that the IGRT with grain trust could help reduce the rate and grade of toxicity. This hypothesis initiated several teams to test the impact of these means of control, including Gladwish which reported on 30 patients treated with IGRT and grains: 1 case with acute grade 3 toxicity, with no other toxicity ≥ 3 in the long run. Nevertheless, follow-up could only be performed on 24 patients lasting less than 2 years [13]. Thus, this long-term impact still requires time and large cohort studies to be confirmed.

The hypofractionation with pelvic irradiation

Since the tolerance of the treatment also depends on the volume irradiated, studies have evaluated the impact of associating conventional pelvic radiotherapy including ganglionic areas with hypofractionation on the prostate. Adkison Studied the combination of hypofractionated prostate radiotherapy at 70 Gy/2.5 Gy with 56 Gy pelvic-ganglion radiotherapy (standard fractionation) and demonstrated good tolerance [14].

Guckenberger evaluated on 150 patients the regimens 76.2 Gy/33 fractions or 73.9 Gy/32 fractions with pelvic irradiation in 41 high-risk cases with a dose of 45 Gy/1.8 Gy; On a 50-month follow-up, only 2 patients had G3 toxicity and more than 80% had no long-term toxicity. In addition, acute toxicity G1-2 was observed in 85% within 6 weeks after treatment. But the most encouraging is that genitourinary toxicity ≥ G2 was observed in less than 10% at 6-12 months, increasing to 22.4% at 60 months [15]. On a univariate analysis, the absence of significant influence of pelvic irradiation in combination with prostatic hypofractionated radiotherapy on acute or chronic toxicity ≥2 was demonstrated, with a biochemical PFS of 82% and for high-risk case of 78% [7]. And so, this association seems well feasible with an acceptable toxicity rate.

Interest of IMRT/IGRT in hypofractionated radiotherapy

Current radiotherapy techniques have made it possible to closely conform the target volume to the treated volume, thus enabling higher dose gradients to be created in specific areas while at the same time protecting the organs at risk. These techniques were therefore adopted by new trials of prostatic hypofractionated radiotherapy to reduce the rate of toxicities mentioned in previous studies using the old techniques. The results of the studies (Arcangeli, Dearnaley, Pollack, McDonald, Adkinson, Kupelian, Martin) [7] are summarized in the absence of ≥ G2 toxicity.

Pollack, in one of the most relevant trials, initially reported in 2006 the results of their randomized study in two arms: 76 Gy/38 fractions and 70.2 Gy/26 fractions which revealed the absence of difference concerning toxicity (gastrointestinal and genitourinary), apart from a slight increase in gastrointestinal toxicity during the 2nd, 3rd and 4th weeks of treatment. After 68.4 months, there was no significant difference between the two arms in terms of chronic toxicity, except for patients with prior urinary complications [6]. So IMRT and IGRT remain the most appropriate techniques for the hypofractionated scheme.

Intense hypofraction/Stereotactic radiotherapy

Most trials evaluated this hypofractionation stereotactic for prostate cancer at low risk [16]. One of the most important studies is that of CRKing, evaluating in Phase II prospective from 2003 to 2009, 67 cases of low-risk prostatic cancers with a dose of 36.25 Gy in 5 fractions with CyberKnife and a follow-up of 2, 7 years : The results reported grade 3, 2 and 1 urinary toxicities respectively in 2, 3 and 13 patients, and for rectal G 3, 2 and 1 toxicities in 0, 1 and 7, respectively. The biochemical PFS was 94%, similar to the other therapeutic options. But despite these good results, C.K. King and his co-authors recommend great precisions about the use of this scheme and keep it in clinical trials, until long-term results are sufficient and satisfactory. This study also investigated the impact of treatment spread on tolerance by evoking the significant decrease in rectal toxicities observed with treatment every 2 days compared to daily treatment [17].

King also evaluated stereotaxic radiotherapy in terms of effect on quality of life with a 36.25 Gy regimen in 4-5 fractions, in 864 patients in a Phase II trial with 6 follow-up. years, of which 194 patients were followed for 5 years, having shown toxicities during the first 3 months after treatment, resolving after 6 months and remaining stable for 5 years, hence the conclusion of good tolerance and the good quality of life of the patients who benefit [18].

In addition, only a few trials evaluated intermediate and high risk cases; Katz are among those who studied in 211 patients at intermediate

risk (81) and high risk (12), with 35 Gy/5 fractions (the first 50 patients), and 36.25/5 fractions (7.25 Gy) on a decline of 60 months. The result was the absence of acute toxicity ≥ grade 3, ≤ 5% acute toxicity grade 2. The chronic grade 2 urinary or rectal toxicities were 2% with 35 Gy and 5% with 36.25 Gy, with respect to long-term toxicity. term grade 3: 2% (urinary). Biochemical PFS: 90.7% for intermediate risk cases and 74.1% for high risk cases. Thus, the results were encouraging according to this study [19]. Note that only 12 high-risk patients were included.

Through these different results, intense hypofractionation radiotherapy in localized prostate cancer is encouraging as a therapeutic option. But until now, patients should be included in clinical trials, especially for high-risk cases.

GETUG recommendations

The French genitourinary group GETUG, considering results of phase III studies randomized recently on a total of 8 trials including 3 non-inferiority trials with 4537 patients, the majority of which at intermediate risk and with doses per fraction of 2.4 at 3.4 Gy in a total of 57 to 72 Gy, using IMRT as an irradiation technique and referring mainly to the CHHiP and PROFIT trials, provided recommendations for the routine practice of moderately hypofractionated radiotherapy in prostate cancer [20].

Indications: Low or intermediate risk localized prostate cancer. However, it is not recommended in post-prostatectomy or lymph node irradiation [20].

Dose-fractionation-spreading: Several regimens have been used in the studies, but the GETUG recommendation for routine practice is 60 Gy in 20 fractions and 4 weeks [21,22].

Imaging: MRI is the recommended imaging that allows fusion with CT scan imaging, +/- preceded by implantation of gold grains for better accuracy to target the prostate [20].

Acquisition: Should be supine, arms on the chest with compression by blocks of knees and feet or a shell. The rectal diameter should be <4 cm and ideally ≤ 2 cm. The bladder should be semi-full (approximately 350 ml) with the dome protruding from the femoral heads, to ensure good reproducibility. The acquisition field extends from L4-L5 to small trochanters with 2-3mm slices [21].

Target volumes: are also based on SFRO recommendations (French Society of Radiation Oncology): It is not necessary to delineate the macroscopic tumor volume (GTV). The anatomic-clinical target volume (CTV) comprises the entire prostate (better visible by fusion with MRI and thanks to the fiducial grains) with the first cm of the seminal vesicles for intermediate risk cases, without inclusion of the ganglionic areas. The projected target volume (PTV) is obtained by an expansion of 7 to 10mm beyond the CTV but this margin can be different according to the centers and their control modalities (IGRT) [20].

Organs at risk: The rectum: up to 2 cm above and below the CTV with a diameter of 3-5 mm (3 mm according to PROFIT). The bladder or bladder wall: in its entirety with an expansion of 3-7mm (PROFIT: 3 mm). The femoral heads: from the upper limit to the lower edge of the small trochanter. Slender intestines: from 2 cm above the PTV [21].

Radiotherapy techniques: All IMRT techniques are allowed, whether stationary or dynamic (VMAT) [20].

Dose Constraints: Bladder: V48 ≤ 25% or V41 ≤ 50%. Rectum: V46 ≤ 30% or V37 ≤ 50%. Femoral heads: V43 ≤ 5%. In the intestines, it has not been determined dose constraint, but if they are in contact with the PTV hypofractionation of the dose should be avoided [21,22].

Ballistics: Isodoses 95% (57 Gy) and 100% (60 Gy) must cover respectively 99% of the PTV and 99% of the CTV. The maximum dose for 1 cm^3 of PTV should not exceed 63 Gy [21].

Control imaging: By IGRT (imaging-guided radiotherapy) depends on 2 means: CBCT (cone-beam volume imaging) or MVCT (high-energy cone tomography), allowing the evaluation of the repositioning with respect to target volumes and organs at risk. But also by kV or MV images that visualize the fiducials (intra-prostatic gold grains implanted at least 10 days before the simulation scan [23,24].

The implementation of the hypofractionated regimen also requires a good selection of anatomically eligible patients: a rectal wall distant from the target volume, a prostate volume ≤ 100 cm^3 and the absence of hip prostheses [25]. Thus, the GETUG recommendations are based on a review of the literature taking into account the efficacy (local control) and tolerance (toxicities), providing a practical management with the hypofractionated regimen currently considered among the therapeutic options (essentially low or intermediate risk case).

Conclusion

While older studies were disappointing with the hypofractionation of radiotherapy in localized prostate cancers because of insufficient doses and old techniques, more recent studies have reported encouraging results for local control while preserving the quality of life without intolerable toxicity. Thus, hypofractionated radiotherapy stands out among the therapeutic options for localized prostate cancer, especially in low and intermediate risks.

Key Messages

- Since the α/β ratio is low in the prostate (approximately 1.5), hypofractionated radiotherapy has been widely evaluated for a better lethal effect in localized prostate cancer.
- Hypofractionated radiotherapy has been approved in recent studies with more appropriate regimens and techniques, especially for low and intermediate risk cases.
- Hypofractionation of radiotherapy as an adjunct to prostatic surgery can lead to major toxicities, especially urinary.
- The combination of pelvic radiotherapy with hypofractionation in the prostate seems to be feasible given the lack of significant influence on toxicities.
- The techniques of IMRT and IGRT are the most adapted to the realization of hypofractionated radiotherapy.
- Stereotaxic radiotherapy also seems an interesting option in terms of local control and tolerance.

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