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RESEARCH ARTICLE

HYPOFRACTIONATED RADIATION IN THE TREATMENT OF LOCALIZED PROSTATE CANCER: LITERATURE REVIEW

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Abstract

Prostate cancer is responsible of a high mortality; its prognosis has been improved in recent years thanks to radiotherapy (RT) which is considered the reference treatment for localized or locally advanced stages. However, spreading the RT sessions over almost two months poses problems of fatigue linked to repetitive movements, particularly for the oldest patients, but also of the overall cost of the treatment, including the time of occupation of the machine and transportation. To meet these constraints, other RT regimens have been developed seeking to maintain identical efficacy and toxicity while reducing the total duration of treatment. These so-called hypofractionated protocols use recent techniques of image-guided RT (IGRT) and conformal RT with intensity modulation (IMRT).

Introduction:-

Prostate cancer has become a real public health problem over the past fifteen years. It is also the 2nd leading cause of death from cancer in the elderly worldwide, according to data from the World Health Organization (WHO).

RT (radiotherapy) is one of the most common treatments for cancer and is most often used in a normofractionated regimen, i.e. comprising low doses per fraction (1.8 to 2 Gy), at a rate of 5 fractions per week and spread over several weeks of treatment (7 to 8 weeks in the case of prostate cancer) [1]. However, spreading out the RT sessions over almost two months poses problems of fatigue linked to repetitive movements, particularly for the oldest patients, but also of the overall cost of the treatment, including the time of occupation of the machine and transportation.

Besides this normofractionated RT, there are many alternative modalities reported in the literature to meet these constraints, those delivering a dose per fraction greater than 2 Gy, called hypofractionated RT [2]. Hypofractionated radiation is not a new idea in RT, it has been proposed several times throughout the history of RT [3] and has the advantage of reducing the number of irradiation fractions.

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We distinguish :

- Moderate hypofractionation: when the dose per fraction is between 2.5 and 4 Gy.
- Extreme hypofractionation: when the dose per fraction is ≥ 5 Gy, and which can only be done under stereotactic conditions, also called stereotactic radiotherapy, which involves very precise irradiation (order of magnitude of a millimeter with a very high dose gradient) [1]

Rationale:

A. Radiobiological rationale:

a. Reminder of the alpha/beta ratio of prostate cancer:

The definition of the alpha/beta ratio is now well known: it is a dose, expressed in grays (Gy), at which the immediately lethal lesions and the accumulation of sublethal lesions contribute equally to radio-induced cell death, in other words the amount of cell death corresponding to the linear component of the linear quadratic (LQ) model is equal to the amount of cell death corresponding to the quadratic component. This dose in Gray is not a reflection of tissue radiosensitivity, whether tumoral or that of healthy tissue, but rather a reflection of sensitivity to fractionation variations.

If the alpha/beta ratio is high (of the order of 10 to 20 Gy), the sensitivity to fractionation is almost nil, as evidenced by the absence of change in the iso-effect curve despite the increase in the dose by fraction, this is the case for healthy tissues responsible for early reactions and typically for the majority of malignant tumours, ie rapidly proliferating tissues with low repair capacity (figure 1).

On the other hand, a low alpha/beta ratio is correlated with greater fractionation sensitivity, and therefore with greater efficacy of high doses per fraction for tumor control, but at the same time with more marked late toxicity towards against slow-renewing tissues.

In the case of prostate cancer, we have a tumor with a low alpha/beta ratio surrounded by healthy tissue with a higher alpha/beta ratio. This differential sensitivity to fractionation in favor of healthy tissues and to the detriment of the tumor, paved the way for the deployment of extreme hypofractionation in the case of prostate cancer. [4]

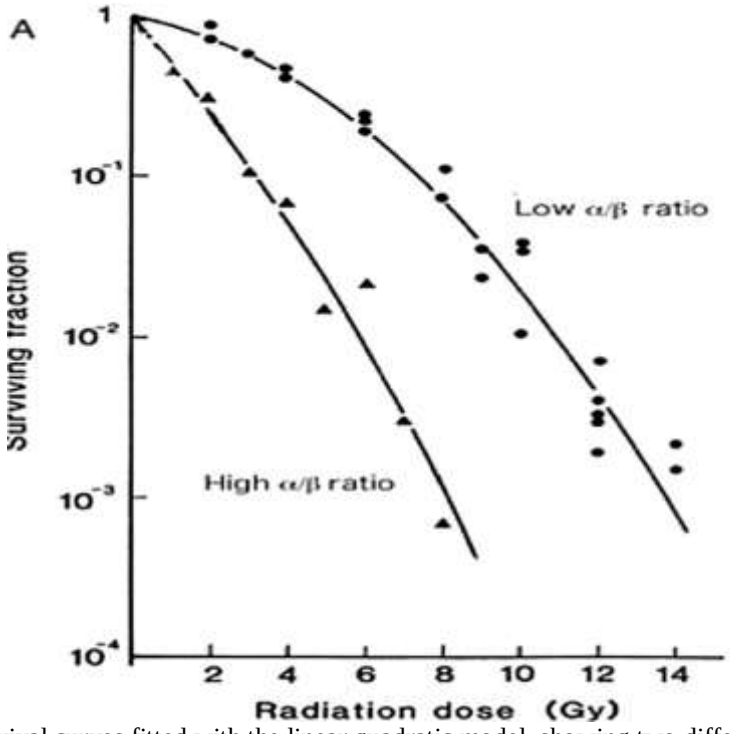


Figure 1:- Survival curves fitted with the linear quadratic model, showing two different cell types with different alpha/beta ratio. At 2Gy, there is a clear differential effect between the two cell lines. (C.Hennequin et al / Cancer/Radiotherapy 23 (2019)500-502).

b. The Dogma:
In 1999, Duchesne and Peters were the first to point out that prostate cancer, because of its slow proliferation, seemed to assimilate more to the tissues responsible for late complications than to those responsible for early complications; they hypothesized that this cancer might therefore have a low alpha/beta ratio. [5]

In the process, Brenner and Hall, based on the equality of the results obtained by 60–85 Gy in external radiation and 100-160 Gy in brachytherapy at very low dose rate (LDR), calculated an alpha/beta ratio of 1.5 Gy (with a 95% confidence interval of 0.8 to 2.2 Gy) for prostate cancer, which made it a lower value than that commonly accepted for healthy tissue responsible for late complications [5, 6].

Therefore, a dose per fraction of 2Gy protected the tumor better than the rectum and the bladder.To improve the tumor control rate, an increase in the dose per fraction (hypofractionated RT) would be more effective than conventional fractionation.Many studies reported seemed to have established as an intangible dogma the very low value (1.2 to 1.5 Gy) of the alpha/beta ratio of prostate cancer [7-16]

c. Moderate and extreme hypofractionated radiotherapy and radiobiology
It is important to clearly separate the so-called "moderate" hypofractionation schemes, and the so-called "extreme" hypofractionationschemes which, in the majority of cases, use modern stereotactic techniques. From a strictly radiobiological point of view, this distinction is crucial.

If the LQ (linear quadratic) model can be used reasonably up to fractions values of 7Gy, we know that it becomes unreliable beyond these values. The reasons are multiple. [17]

Limits of the linear quadratic model:
Several authors (in the first place Dutreix et al. in 1990 [19] proposed modifying the LQ model by adding a linear component after 7Gy (i.e. a model of the "LQL" type: Linear-Quadratic-Linear) [18, 19], but this model have not been fully validated and the equivalence calculations are complex.

Total duration of irradiation:
The total duration of irradiation is very shortened in "extreme" hypofractionation schemes. This point is important. On the one hand, this reduction in total duration could be an advantage. In fact, it has long been considered had little impact on the results for prostate cancer, given the slowness of its proliferation.But at least one recent article challenges this other dogma. [20-22]

Duration of the radiation fraction:
It was long considered that the total time of the fraction had no impact on the biological effect, but a reference article from 2004 challenges this received idea. [23-25]. Fowler et al calculated that any fraction lasting more than an half hour was responsible for a loss of antitumor efficacy, due to the repair of sublethal lesions.

However, in the event of extreme hypofractionation, the vast majority of authors use stereotaxic techniques that are certainly very sophisticated, but whose fractions durations can exceed 20 to 30 minutes.

Role for the stroma and the microenvironment in case of extreme hypofractionation:
These two structures are increasingly the subject of attention by radiobiologists, in particular the vascular endothelium and the dendritic cells of the bone marrow (bone marrow dendritic cells, BMDCs) [26].

The impact of fractionation, and in particular of extreme hypofractionation, is difficult to assess in the literature: vasculogenesisdepends on dendritic cells and would be more sensitive to "ablative"doses that is a high doses per fraction. [27]. Apoptosis of endothelial cells could also be an important phenomenon in this situation [28]. The analysis of certain recent data goes so far as to put forward the hypothesis that in "very" hypofractionated radiation, the major targets of RT would no longer be the tumor cells themselves, but tumor microvessels, whose endothelium is likely to die rapidly [29]

B. Scientific rationale:

The non-inferiority of hypofractionated RT has been shown in randomized phase 3 trials with recruitment of more than 900 patients in the treatment of localized prostate cancer with similar efficacy and toxicity in organs at risk compared to conventional fractionation.

C. Economic Rationale:

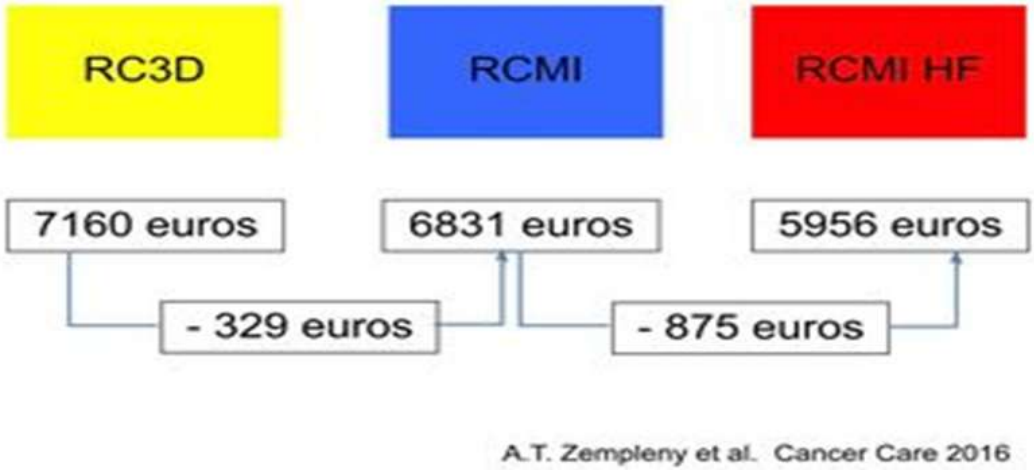
Hypofractionated RT consists of delivering a dose per fraction greater than 2Gy.
The practical advantages are obvious:

- For the patient: Saving time and money (figure 2); less iterative movement therefore less fatigue and pain related to transport.
- At the level of the RT center: Less congestion of machines given the overload of RT services and waiting times that are difficult to accept as was the casein the early 1970s in certain centers and the geographical distanceof the RT units available.

Resources are limited in terms of RT supply, even in the western world. The availability of RT devices makes it difficult to cover the needs of the populations. As a reminder, out of more than 300,000 cases of cancer diagnosed in Franceeach year, nearly 200,000 patients are treated with RT, exclusively or more often in addition (data from the National Cancer Institute [INCA]: http:/ /www.ecancer.fr/soins/radiotherapie).

One of the means of combating this "penury" of heavy equipment has been to consider, thanks to the gain in precision made possible by technological progress, shorter treatments. Some countries such as Canada or Great Britain have thus been pioneers in the development of hypofractionated RT. [30, 31]

Figure 2:- The reduction in cost when administering hypofractionated radiotherapy.



Moderate hypofractionated radiotherapy:

A. Superiority Trials:

Long before the known work on defining the alpha/beta ratio of prostate cancers, Canadians and Australians had conducted their own randomized phase III studies, comparing two different fractionation schemes of prostate RT. [2]

There is the Canadian trial which is one of the first trials which was published by Lukka et al in 2005 randomizing 936 patients with localized prostate cancer, between 66 Gy in 33 fractions of 2 Gy (normofractionated arm), and 52.5 Gy in 20 fractions of 2.625 Gy (experimental arm, hypofractionated), i.e. 7 versus 4 weeks of RT. At 5 years, there was a trend towards an increased rate of clinical tumor progression in the hypofractionated arm (HR = 1.18 IC95 [0.99-1.41]), suggesting a possible insufficiency of the total dose delivered in this study because the equivalent dose, whether calculated by the simple LQ model or by the BED, was lower in the hypofractionated arm. During the acute period, 7% of patients in the normofractionated arm and 11.4% of patients in the hypofractionated arm experienced grade 3 or 4 gastrointestinal (GI) and genitourinary (GU) toxicities. That toxicity was found to be slightly elevated in the hypofractionated arm compared to the normofractionated arm. However, during late toxicity

monitoring, only 3.2% of patients in both arms experienced severe toxicities. Therefore, late toxicity was low in both arms. [32]

The Australian trial was published in 2003 with final evaluation in 2011 by Yeoh et al. This trial had a smaller population (217 patients). The main objective was the comparative evaluation of GU and GI toxicities. Patients were randomized between 64 Gy in 32 fractions of 2Gy (normofractionated arm), and 55 Gy in 20 fractions of 2.75 Gy (experimental arm, hypofractionated), i.e. 6 versus 4 weeks of RT. The last communication of the results found no statistically significant difference in BRFS according to the criteria of the Astro (American Society for Radiation Oncology), and better results in favor of the hypofractionated arm if the Phoenix criteria were chosen (biochemical relapse = nadir PSA + 2ng/mL). The median follow-up was 90 months, 85 patients developed a biochemical relapse including 36 patients in the hypofractionated arm and 49 patients in the normofractionated arm. BRFS, but not OS, at 90 months was significantly better with the hypofractionated regimen (53%) compared to the conventional regimen (34%).

These two trials had the merit of showing the feasibility of moderate hypofractionated RT. It is important to specify that the radiation schemes of these two studies do not take into account the fact that the alpha/beta ratio of prostate cancers is low, in addition to having used obsolete 2D external RT techniques with cumulative doses much lower than current recommendations. [28.33]

The Italian randomized trial gave rise to five successive articles between 2010 and 2014. In this trial, Arcangeli et al [34] compared a classic regimen (80 Gy in 40 fractions of 2 Gy over 8 weeks) with a hypofractionated regimen of 62 Gy in 20 fractions of 3.1 Gy over 4 weeks. This trial called for some reservations because all the patients received 9 months of hormone therapy, and the total number of patients included was not very high: 168 cases. The latest update in 2017 found no significant difference in BRFS between the two arms (at 3 years it was 87% in the hypofractionated arm and 70% in the normofractionated arm and at 8 years it was 74% in the hypofractionated arm and 66% in the normofractionated arm, p: 0.035) (Figure 17). Late rectal toxicities were 17% after 3 years follow-up in both arms (P: 0.571). The hypothesis was that the hypofractionated arm (3.1 Gy/session) would give less rectal toxicity and equivalent efficacy. The results were strictly opposite to those expected, with equivalent rectal toxicity, and improved biochemical control in favor of the hypofractionated arm.

The Fox Chase Center of Philadelphia (FCCP) trial [35] which was published by Pollack et al was a really trial of "superiority", since the chosen hypofractionated regimen (70.2 Gy in 26 fractions of 2.7 Gy) had been calculated as equivalent to 84.4 Gy per 2 Gy fractions, and was therefore expected to be superior to the conventional regimen of the reference arm (76 Gy in conventional fractionation-spreading of five 2 Gy fraction per week). In fact, the BRFS rate at 68 months was the same in both arms: 23.3% in the hypofractionated arm and 21.4% in the normofractionated arm. There was also no difference in terms of late toxicity between the two arms of the trial, but the analysis by subgroups suggested that patients with initial voiding disorders, prior to radiation, suffered more from grade 2 urinary toxicity with the hypofractionated regimen (18% in the hypofractionated arm and 8% in the conventional arm, p: 0.028)

Investigators at MD Anderson in Texas, Kuban et al reported in Astro 2010 the results of a randomized trial using IMRT and IGRT techniques comparing 75.6 Gy in 42 fractions of 1.8 Gy to 72 Gy in 30 fractions of 2.4 Gy, ie 8 against 6 weeks of prostatic irradiation. Of the 200 randomized patients, 20% received hormone therapy for four months or less. The initial hypothesis was a 20% risk reduction in favor of the hypofractionated arm. With 4.7 years of follow-up, the results show no significant difference in terms of efficacy or tolerance between the two arms [36]. The preliminary analysis did not find a clear superiority of hypofractionated irradiation in terms of controlling the disease, but it confirmed the absence of an increase in medium-term toxicity. [7]

The Dutch HYPRO trial (Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer) [37], published in 2016, is one of the superiority trials that included the most patients: 804 cases. It compares 64.6 Gy in 19 fractions over 6.5 weeks to 78 Gy in 39 fractions over 7.8 weeks (conventional arm) using IMRT and IGRT techniques. The majority of patients were in the high-risk group and received concurrent androgen blockade. After a median follow-up of 60 months, the probability of BRFS at 5 years was not different in the two arms of the trial: 77.1% in the hypofractionated arm and 80.5% in the conventional arm (p=0.36). OS was similar between the two arms: 86.2% for the hypofractionated arm and 85.9% for the conventional arm. No differences were found in terms of grade 2 or higher acute urinary toxicity between the two arms. On the other hand, the cumulative incidence of late grade 3 urinary toxicity was higher in the hypofractionated arm (19 versus 12%; p =

0.021). Finally, acute GI toxicity was significantly higher in the hypofractionated arm (p = 0.0015). If we calculate the dose equivalence of the hypofractionated arm of HYPRO with an alpha/beta ratio of 1.5 Gy, we find 90.4 Gy. We were therefore entitled, just as in the trial by Pollack et al. to expect a clear "superiority" of the hypofractionated arm, which is not the case. It should also be noted that in this trial, the reduction in total duration of radiation was minimal (6.5 weeks), unlike the trials noted above: this factor may have had a negative effect on the HYPRO trial.

MD Anderson's trial has been recently updated by Hoffman et al [38] he currently only reports a toxicity study, showing no increase in GU toxicity with a (very) moderately hypofractionated regimen at 72 Gy delivered with fractions of 2.4 Gy. On the other hand, there is an increase, but not significant, in grade 2 and 3 GI toxicity.

In summary, today, no so-called "superiority" trial has shown superiority of the hypofractionated arm, whereas the equivalent doses calculated with an alpha/beta ratio of 1.5 Gy rose to 84.4 Gy, and even at 90.4 Gy [35]. Among the hypotheses that could explain this lack of effect of such a dose escalation, one can certainly wonder if there is an upper "limit" to this escalation in external RT [39], but a higher dose escalation with a boost in brachytherapy has however demonstrated a benefit [40]. Consequently, we can also ask the question of the real value of the alpha/beta ratio chosen to calculate the equivalences.

The following table (Table 1) summarizes the Phase 3 superiority trials comparing moderate hypofractionated RT and conventional RT:

Study/Author	Number of patients	Risk	Technical	Hormone therapy	Followed (years)	Normo-fractionated Arm	Hypo-fractionated Arm
Canadian trial Lukka et al, 2005 [32]	936	LR IR HR	RT 3D	No	5	66Gy (33 x 2Gy) 7 weeks	52.5Gy (20x2.62Gy) 4 weeks
Australian trial Yeoh et al, 2011 [33]	217	LR IR HR	RT 3D	No	7.5	64Gy (32 x 2Gy) 6.5 weeks	55 Gy (20 x 2.75Gy) 4 weeks
Italian trial Arcangeli et al, 2011 [34]	168	IR HR	RT 3D	Yes 9 months	5	80Gy (40 x 2Gy) 8 weeks	62 Gy (20 x 3.1Gy) 4 weeks
FCCP trial Pollack et al, 2011 [35]	300	IR HR	IMRT	Possible 4-24 months	5	76Gy (38 x 2Gy) 8 weeks	70.2Gy (26 x 2.7Gy) 5 weeks
Investigator Trial From MD A Texas Kuban et al, 2011 [36]	200	LR IR HR	IMRT IGRT	Possible <4months	4.7	75.6Gy (42 x 1.8Gy) 8 weeks	72 Gy (30 x 2.4Gy) 6 weeks
Dutch trial HYPRO, 2017 [37]	804	IR HR	IMRT IGRT	Possible	5	78Gy (39 x 2 Gy) 7,8 semaines	64,6Gy (19 x 3,4Gy) 6,5 semaines
MD A cancer c Hoffman et al, 2018 [38]	206	LR IR HR	IMRT	Possible	8	75,6Gy (42 x 1.8Gy)	72 Gy (30 x 2.4Gy)

Table 1:- Phase 3 superiority trials comparing conventional radiotherapy with hypofractionated radiotherapy. IR:Intermediaterisk, HR: High Risk, LR: LowRisk, Nb: Number.

B. Non-inferiority trials:

Three large, well-designed randomized controlled trials with a non-inferiority assumption all reported non-inferior efficacy of hypofractionated regimens compared to normofractionated treatment [41]. These 3 studies including more than 5000 patients who presented with adenocarcinoma of the prostate at low, intermediate and high risk, published their results (table 2)

There is the English CHHIP trial (conventional or hypofractionated high dose intensity modulated radiotherapy for prostate cancer), it is undoubtedly one of the most important, it included 3216 patients (recruited in 71 centers)

between 2002 and 2011 and compares a conventional arm of 74 Gy in 37 fractions of 2Gy in two hypofractionated regimens: 60Gy in 20 fractions of 3 Gy, or 57Gy in 19 fractions of 3 Gy. The percentage of BRFS at 5 years was 88.3% in the "conventional" arm at 74 Gy, 90.6% in the hypofractionated arm at 60 Gy, and 85.9% for the hypofractionated arm at 57 Gy. The 60 Gy arm was "non-inferior" to the 74 Gy arm, but "non-inferiority" could not be demonstrated for the 57 Gy arm. Late toxicities were similar between the three arms. The authors conclusion was to consider the hypofractionated regimen of 60 Gy in 20 fractions over 4 weeks as "the new standard of care". On the radiobiological level, the authors estimated from the data of their trial that the value of the alpha/beta ratio would be 1.8 Gy. [42]

The RTOG 0415 trial (Radiation Therapy Oncology Group) randomized 1092 patients; it compares 73.8 Gy in 41 fractions of 1.8 Gy over 8.2 weeks ('conventional' arm) to 70Gy in 28 fractions of 2.5 Gy over 5.6 weeks. With a median follow-up of 5.9 years, the hypofractionated arm was found "non-inferior" on 5-year disease-free survival (DFS), BRFS and OS. While acute toxicity was similar between the two arms, more late toxicity (GU and GI) of grade 2–3 was noted in the hypofractionated arm [43]

The PROFIT trial (Prostate Fractionated Irradiation Trial) recruited 1206 patients and compared 60 Gy in 20 fractions over 4 weeks to 78Gy in 39 fractions over 7.8 weeks. After a median follow-up of 6 years, there was no difference between the two arms, whether in terms of BRFS at 5 years, OS and acute toxicity grade 3 or higher, while late GI toxicity was lower in the hypofractionated arm. The authors concluded that the hypofractionated scheme was non-inferior. From this test, the alpha/beta ratio was estimated at 1.3 Gy [44]. Among the three trials, PROFIT had some features that increase the relevance of hypofractionation in clinical practice, it is the only study of the three to prescribe IGRT to all patients. Additionally, the majority of patients included received IMRT rather than 3D RT. The large number of centers that participated in the various clinical trials meant that the infrastructure, knowledge and confidence to administer hypofractionated regimens was widespread, making adoption relatively straightforward.

Some clinicians are more cautious about hypofractionation, primarily due to concerns about long-term toxicity. The phase II trial prior to PROFIT has recently been updated with a median follow-up greater than 10 years and confirms very low rates of grade 2 GI (4%) or GU (12%) toxicity [45]. Hypofractionated irradiation on the prostate coupled with pelvic irradiation also seems feasible and safe [46].

Study	Risk	Technical	Hormono-therapy	Number of patients	NF arm	HY arm	Followed (years)	Acute Toxicity	Latetoxicity
CHHIP (NCT00392535), 2011 [42]	LR IR HR	IMRT	Possible 3-6 mois	3216 (between 2002 and 2011)	74Gy (37x2Gy)	-60Gy (20x3Gy) -57Gy (19x3Gy)	5	-	Similar
RTOG 0415 (NCT00331773), 2016 [43]	LR	RT 3 D	No	1092	73,8Gy (41x1,8Gy) 8 weeks	70Gy (28x2.5Gy) 5 weeks	5.9	Similar	More G2/G3
PROFIT (NCT00304759), 2017 [44]	IR	IMRT IGRT	Possible <3 months	1206	78Gy in 39 fractions in 7 weeks	60Gy in 20 fractions in 4 weeks	6	Similar	Lower

Table 2:- The main non-inferiority trials with a follow-up of 5years.
LR: Low Risk, IR: Intermediate risk, HR: High Risk, Week: Weeks, hormTH : Hormonal therapy,
NF arm: Normofractionated arm, HY arm: Hypofractionated arm

Extreme hypofractionated radiotherapy:

Treatment regimens have so far explored relatively mild hypofractionation but much larger doses per fraction have become a very active area of research [47].

Given the radiobiological uncertainties for very high doses per fraction, several general reviews advised to use this type of regimen only in the context of randomized controlled trials. As a result, perhaps due to the current increased availability of new stereotaxic RT techniques, many teams have embarked on prospective phase 3 studies [48]

There is now extensive published data from non-randomised trials demonstrating that rates of efficacy and toxicity are comparable to standard therapy for low- and intermediate-risk cancers. In the United States, ASTRO and the National Comprehensive Cancer Network (NCCN) include stereotactic RT as a treatment option in localized prostate cancer [49]. Multiple prospective monocentric series have been published [50-54]. Nevertheless, published data should be interpreted with caution due to the diversity of methodologies and poor follow-up in some cases.

A meta-analysis of 14 prospective trials [55] involving a total of 2038 patients treated with stereotactic RT for localized prostate adenocarcinoma, mainly at low risk (51%) and intermediate risk (31%). Most patients had cT1-T2a prostate cancer, Gleason≤7 and median PSAs of 5 to 10 before treatment. The doses vary from 33.5 Gy to 50 Gy most often in 5 fractions. After a follow-up of 37 months, the pooled rate of BRFS was 95.4% and the pooled rate of late grade ≥ 3 GI and GU toxicities was 1% and 2% respectively.

Reference, Year	Sample Size	Medianfollow-up(mo)	FFBF*(% ormedian)	PSA Nadir	ToxicityMeasurementMethod	Late Grade ≥3 GI Toxicity(%)	Late Grade ≥3 GU Toxicity (%)	QOLConclusions
Quon,2018	152	47	NR	NR	RTOG	4.07	9.4	Prostate SBRT delivered QWimproved acute bowel and urinaryQOL compared to treatment EOD.Patients should be counselledregarding the significant short-termbenefits of a longer overall treatmenttime.
Boyer,2017	60	27.6	NR	NR	CTCAE	1.7	0	AUASS11duringSBRT, and5at5 mo EPIC 91.7 and 88.9 at 3 and 12 mo
			100% at 3y					
Hannan,2016	91	54	98.6% at 5y	0.13	RTOG	6.8	5.5	Nodifferencesamongdoselevelsfor EPIC orAUASS
Rucinska,2016	68	24	100%	0.03	RTOG	0	0	GHS/QoLwas"good"9mopost-SBRT, significantly improvedthereafter
Shikama,2016	20	30	100%	0.73	CTCAE	2.5	0	NR
D'Agostino,2016	90	28	97.8% at 27 mo	NR	CTCAE	0	0	NR
Bauman, 2015	15	6	NR	0.3	CTCAE	25	6.7%	NR
Bernetich,2014	142	38	92.7% at 5 years fortheentireco hort	0.16	RTOG	0	2	NR
Kim,2014	91	42	99%	NR	CTCAE	5.5	NR	EPIC bowel scores lower thanbaseline18monthspost-SBRT
King,2013	1100	36	93%	0.51	NR	NR	NR	UrinaryandbowelQOLdeclinemost notable within the first 3 mo, mostlyrecovered by 6 mo, stable thereafter,improvementoverbaseli nestartingat 3y
Loblaw,2013	84	55	99.9%	NR	RTOG	1	1	icant decline in long-termQOL
Alongi,2013	40	11	NR	0.2	CTCAE	0	0	NR
McBride,2011	45	45	NR	<1	CTCAE	0	2.5	Significant late decline in SHIMand EPIC sexual scores, small, latedecline in EPIC bowel domain
Madsen,2007	40	41	90%	NR	CTCAE	0	0	NR

Table 3:- Summary of outcomes of 14 prospective trials [55].

Abbreviations:

NR, not reported; FFBF, actuarial freedom from biochemical failure; PSA, prostate-specific antigen; GI, gastrointestinal; GU,genitourinary; QOL, quality of life; CTCAE, Common Toxicity Criteria for Adverse Events; AUASS; American Urologic Association Symptom Score;SBRT,stereotacticbodyradiationtherapy;EPIC,ExpandedProstateCancerIndex;RTOG,RadiationTherapyOncology Group;GHS,globalhealthscore;LR,low-risk; IR, intermediate-risk; HR,high-risk;SHIM,SexualHealthInventory in Men.

*AllstudiesbutoneutilizedthePhoenixdefinitionofbiochemicalfailure.

The mature results of the Scandinavian phase III non-inferiority trial (HYPO-RT-PC) [56] have just been published and significantly strengthen the level of evidence of efficacy and the absence of significant toxicities of the extreme hypofractionated RT. In this trial, Widmark et al randomized 1200 patients with localized prostate adenocarcinoma, mainly at intermediate risk (89%) between an external RT of 78 Gy in 39 fractions and an extreme hypofractionated RT of 42.7 Gy in 7 fractions (EQD2 - dose biologically equivalent to that delivered by fractions of 2 Gy) = 77.7 Gy with an alpha/beta ratio of 3 Gy. Combined hormone therapy was an exclusion criterion. After a median follow-up of 5 years, DFS rates were 84% in the 2 arms, respectively and no difference in reported GI, GU or sexual toxicities except for increased urinary toxicity at one year for extreme hypofractionation (6% versus 2%).

PACE-B is a multicentre phase 3 trial (37 centres: UK, Ireland, Canada) [57] which randomized 847 patients, 432 of whom were treated with conventional or moderately hypofractionated external RT and 415 with extreme hypofractionated RT. Median follow-up was 12 months, grade 1 and 2 GI and GU toxicities were low in the extreme hypofractionation regimen compared to the conventional or moderately hypofractionated regimen (53% versus 61% for grade 1 GI toxicity, 42% versus 49% for GI grade 2 toxicity, 57% versus 59% for GU grade 1 toxicity and 21% versus 26% for GU grade 2 toxicity). While GU grade 3 toxicity was slightly greater in the extreme hypofractionated regimen compared to the conventional or moderately hypofractionated regimen (urosepsis)

In conclusion, these data support the safety and efficacy of SBRT as an alternative to conventional fractionation RT for carefully selected men. However, no study has directly compared SBRT with moderate hypofractionation RT, and a true understanding of the relative benefits and risks of SBRT compared with conventional fractionation or moderate hypofractionation regimens requires published results from randomized trials. Two ongoing randomized clinical trials are comparing SBRT versus conventional or moderately hypofractionated RT (NCT01794403 and NCT03367702).

Hypofractionated radiotherapy and lymph node irradiation:

Given the low alpha/beta ratio of prostate cancer, prostate hypofractionationhas been tested in many clinical studies. There is a growing body of literature suggesting that with high conformal RT and even with more sophisticated RT techniques, such as high dose rate brachytherapy or RT with IMRT/IGRT, morbidity associated with shortened Overall treatment with higher doses per fraction remains low compared to prolonged conventional RT.

Nevertheless, some patients at high risk of lymph node involvement may benefit from pelvic RT (WPRT). Although combining WPRT with hypofractionated irradiation of the prostate is possible, it remains experimental.

By combining modern advances in radiation oncology (high-throughput prostatic brachytherapy, and RT with IMRT/IGRT), it is speculated that WPRT could take advantage of recent results from hypofractionation trials, in addition to the potential improvement in clinical outcomes. [58]

A. Moderate hypofractionated radiotherapy and lymph node irradiation:

In the early 2000s, moderate hypofractionated RT was launched as a curative treatment for intermediate-risk prostate cancer using the 66 Gyregimen in 22 fractions of 3Gy, delivered with 3D RT to prostate volume only [59]. This pattern was later changed to 60 Gy in 20 fractions of 3Gy when IGRT was adopted [60]. In patients with intermediate-risk prostate cancer, the 60 Gy 20-fraction regimen has been shown to be effective in large prospective randomized trials, compared to conventional RT [44,61]

The majority of published trials of hypofractionated RT have primarily involved irradiation of the prostate alone without irradiation of lymph node areas. Admittedly, the use of new techniques of modern RT and simultaneous integrated boost (SIB) has enabled the two targets (prostate and lymph node areas) to receive different doses during the same treatment (Table 4) [62].

Encouraging results reported with hypofractionated RT using the 60 Gy 20-fraction regimen administered only to the prostate in patients with intermediate-risk disease [60] have led to the extension of this approach to patients with high-risk disease where both above-described targets were irradiated simultaneously with different doses.

There are several publications that report the results of using hypofractionated RT in patients with high-risk prostate cancer treated with two target volumes (prostate and lymph node areas) receiving different doses during the same

treatment. [63]. It is important to note that in all these trials, only the prostatic volume was the subject of a hypofractionated approach, while the dose intended for the lymph node areas was delivered according to a conventional fractionation. In general, these results are acceptable but are limited by a relatively small sample and short follow-up time, and all used 25-28 fractions instead of 20 fractions used in the recent study (McGrill).

Author	Nb. of patients	Followed (months)	Prostate dose	Lymphnode Dose	Fraction Nb
Mc Grill (actuelle)	105	74	60	44	20
Pollack(2009 ;2013)	52	68	70.2	50	26
Quon (2009 ;2012)	97	39	67.5	45	25
Adkison(2012)	53	25	70	56	28
McDonald(2012)	57	41	70	50.4	28
Fonteyne(2009)	31	3	69.3	50	25
McCammon(2009)	30	24	78	50.4	28
Pervez (2009)	60	3	68	45	28
Di Muzio (2009)	29	12	74.2	51.8	28
Magli (2018)	41	65	67.5	50	25
Sashidlharam 2016	100	45	70	50.4	28
Jorgo (2019)	156	30	70	50.4	28

Table 4:- Comparison of different radiotherapy regimens using moderate hypofractionation in the treatment of high-risk prostate cancer with pelvic node irradiation.

The McGrill study randomized 105 patients with high-risk prostate cancer treated with the IMRT technique between October 2010 and February 2014 (data collected in July 2019) [64, 65]. Eligible patients had adenocarcinoma classified as high risk (defined as clinical stage T3N0M0, PSA 20 ng/mL, or GS 8-10), and never previously exposed to hormone therapy or pelvic RT. Patients were treated with a combination therapy combining androgen deprivation (ADT) and hypofractionated RT. All patients received IMRT-IGRT hypofractionated RT to the prostate at a dose of 60 Gy in 20 fractions of 3Gy while simultaneously receiving WPRT with SIB at a dose of 44 Gy in the same 20 fractions but at 2.2 Gy per fraction. Follow-up was performed every 4 to 6 months for the first 5 years and once a year thereafter, always including PSA and testosterone measurements. GI and GU toxicity were prospectively assessed and categorized according to CTCAE (Common Terminology Criteria for Adverse Events) version 3 [66]. In summary, acute grade 2 or 3 GI toxicity was reported in 18 patients (17.2%) and acute grade 2 or 3 GU toxicity in 16 patients (15.3%). There were no acute or late Grade 4 or 5 toxicities. The cumulative rates of late Grade 2 or 3 GI or GU toxicity were 6.7% and 9.5%, respectively. Late GI toxicity was reported at a median of 10 months after hypofractionated RT, compared to 24 months for GU toxicity. Of note, 2 patients presented residual late grade 2 GI toxicity after a follow-up of more than 24 months after hypofractionated RT. Similarly, 3 patients experienced late grade 2 or 3 GU toxicity after 24 months of treatment. After a 74-month follow-up, 13 patients (12%) died, 6 from prostate cancer and 7 from other causes. 19 patients (18%) developed biochemical failure after a median of 33 months (range: 12 to 96 months), and 11 of them had evidence of metastatic disease. Of these 19 patients with biochemical failure, 4 were initially at stage T1, 12 at stage T2 and 3 at stage T3. Regarding GS, 4 patients had a GS of 7, 10 had a GS of 8, and in 5 patients the GS was 9 (no patient had a GS of 10). 12 of them (63%) were pretreated with a PSA>20ng/mL. The OS rates at 5 and 7 years were 91% and 85% respectively. Rates of BRFS and DFS at 5 and 7 years were 87% and 81%, 84% and 73%, respectively

This study, presenting the longest follow-up and largest number of patients with high-risk prostate cancer treated with hypofractionated RT of the prostate and pelvic nodes, shows that after a median follow-up of 74 months, the hypofractionated regimen of 60 Gy to the prostate and 44 Gy to the pelvic lymph nodes, both given in 20 fractions, is safe and effective, with rates of acute and late toxicity and tumor control similar to those of other alternatives curative treatment for high-risk prostate cancer. This approach shortens treatment time and is convenient for patients and the healthcare system. Randomized trials using hypofractionation for high-risk patients are warranted [63]

Although conventionally fractionated RT remains the most common RT regimen in the United States for localized prostate cancer, the clear benefits of reduced overall treatment duration and cost-effectiveness are leading to increased utilization of hypofractionated RT, especially with regard to the intensified use of extreme hypofractionation [67]

B. Extreme hypofractionated radiotherapy and lymph node irradiation:

Extreme hypofractionation, also known as stereotactic ablative body radiotherapy (SABR=stereotactic ablative body radiotherapy), delivers high doses of radiation (greater than 5Gy per fraction) to the prostate while minimizing bladder and rectum exposure to radiation. SABR has been tested extensively for low-risk and intermediate-risk prostate cancer [68]. Studies examining the role of SABR in high-risk prostate cancer have treated the prostate alone or in combination with normofractionated pelvic lymph node irradiation [69-71]

Between 2013–2020, 4 prospective clinical trials of intermediate and high-risk prostate cancer receiving dose-escalated RT to the prostate and elective lymph node radiation using extreme hypofractionation RT (25 Gy in 5 weekly fractions) were conducted. One-hundred sixty-five patients were enrolled, of whom 98 (59%) had high-risk disease. ADT was used in 141 (85%). Median follow-up was 38 months. The worst acute GU and GI toxicities respectively were 48% and 7.5% for grade 2, and 2.7% and 0% for grade 3.Cumulative incidence of late grade 2+ GU and GI toxicities at 36 months were58% and 11.3% and for late grade 3+ toxicities were 1% and 0%, respectively. No grade 4+ acute or late toxicitieswere observed. Bowel and sexual toxicity significantly worsened up to 1-year compared to baseline.Over time, urinary ($p < 0.0001$), bowel ($p = 0.0018$) and sexual ($p < 0.0001$) scores significantly improved. The 3-year biochemical recurrence-free survival was 98% [70]

In summary, lymph node radiation using extreme hypofractionation RT was associated with low rates of grade 3+ acute and late GU and GI toxicities, with favorable oncologic outcomes. Randomized phase-3 trials of ENI using conventionally-fractionated and extreme hypofractionation RT techniques to guide clinical practice are ongoing and much anticipated.

Postoperative hypofractionated radiotherapy:

Despite advances in the detection and treatment of prostate cancer, biochemical recurrence occurs in 20-40% of cases. A significant proportion of patients with unfavorable features on operative specimen study or biochemical recurrence after prostatectomy undergo postoperative RT, referred to as adjuvant or salvage RT, respectively [72-77].

The optimal dose and fractionation in the postoperative setting are not established. The ARO, SWOG and EORTC trials used a conventional fractionation scheme with RT given over 6-7 weeks at the total dose of 60-64 Gy. Retrospective reports and smaller prospective studies have used higher doses, but without significant improvement [78], and are currently being studied in the SAKK 09/10 trial (N CT01272050).

Technological improvements in treatment delivery, better understanding of prostate cancer radiobiology, and wider acceptance of regimens using higher doses over fewer fractions justify hypofractionated postoperative RT [79].

When RT is administered in a hypofractionated manner, it is essential to minimize the dose received by neighboring organs. Dose constraints for organs at risk are based on the fact that irradiation of a specific volume above a given dose increases the risk of adverse effects [80, 81]. There are important anatomical and dosimetric differences between definitive RT and postoperative RT, which may make it reluctant to implement a hypofractionated approach. Following radical prostatectomy, a considerable amount of the bladder is embedded in the prostatic compartment. Therefore, conventional postoperative RT plans encompass larger bladder volumes than prostate cancer, which fails to meet tolerance dose constraints with hypofractionation. A better understanding of bladder tolerance to RT can help determine appropriate dose limits.

As randomized trials are ongoing, there is currently no prospective phase III evidence comparing postoperative radiotherapy of hypofractionated versus normofractionated prostate. Thus, current efficacy is mostly based on retrospective analyzes (Table 5) [82-92]. The results of ongoing prospective randomized trials comparing conventional fractionated postoperative RT with moderate hypofractionated RT will provide a definitive comparison of efficacy and toxicity [93]. The ongoing phase III NRG GU003 study is a randomized study that prospectively compares conventional RT after radical prostatectomy using 66.6 Gy in 37 fractions with hypofractionation using 62.5 Gy in 25 fractions.

Adjuvant or salvage hypofractionated RT is not a standard option for prostate cancer RT outside of a clinical trial. Prospective trials are currently underway to address efficacy and safety concerns. Although small studies show conflicting data on toxicity, early data from large clinical trials appear to demonstrate that postoperative hypofractionated RT is as effective and safe as normofractionated treatments.

Study	patients	TD (Gy)	NF	Technical	MF (months)	BRFS (%)	DM (%)	OS (%)
Lee et al 2018 [82]	61	50-52.5	20	3D	36	74	0	100
Wong et al 2008 [84]	50	65-70	26-28	IMRT	24	72.9	2	96
Kruser et al 2011 [85]	108	65	26	IMRT	32.4	67	2.7	99
Lewis et al 2016 [86]	56	57.5-65	23-26	IMRT	48	75	NO	96
Fersino et al 2017 [87]	125	65.5-71.4	28-30	IMRT	18	85.5	NO	NO
Macchia et al 2017 [88]	124	62.5	25	IMRT	60	86.5	1	100
Tandberg et al 2018 [89]	167	65	26	IMRT	38.6	78.4	4	94.3
Picardi et al 2018 [90]	918	50-72.8	20-29	2D, 3D, IMRT	36	74-85	NR	NR
Siepe et al 2018 [91]	1208	37.8-74.2	21-28	3D, IMRT	60	86.5	NR	NR
Chin et al 2020 [92]	112	52.5	20	3D	120	51.5	16	75

Table 5:- Studies reporting the efficacy of postoperative prostate cancer hypofractionation.

TD: total dose, MF: median follow-up, NF: number of fractions, BRFS: biochemical relapse-free survival
DM: distant metastases, OS: overall survival, NR: not reported

Future prospects:

Prostate SBRT has been the subject of intense investigation in the context of low- and intermediate-risk disease, but less so for high-risk prostate cancer or in a salvage post-operative situation. However,prospective trials are demonstrating its potential to safely and efficiently delivery. These encouraging data establish a strong rationale toevaluate prostate and pelvic SBRT in a randomized setting.The ASCENDE-SBRT trial and PRIME trial (NCT03561961) are a phase III Randomized controlled trials assessing the efficacy of SBRT in both prostate and elective lymph nodes. Adjuvant or salvage hypofractionated RT is not a standard option for prostate cancer RT outside of a clinicaltrial.Essential information on this topic is currently being gathered through ongoing clinical trials, but these trials require long periods of follow-up and data maturation.

Recommendations:-

ASTRO, ASCO (American Society of Clinical Oncology), and AUA (American Urological Association) have proposed an evidence-based guideline for external hypofractionated RT in localized prostate cancer, which has been endorsed by the ASTRO board of directors [94-97]. The main recommendations developed are [94]:

Recommendation 1: In patients with low-risk prostate cancer who refuse active surveillance and receive external prostate RT with or without seminal vesicle irradiation, moderate hypofractionationshould be offered.

Recommendation 2: In patients with intermediate-risk prostate cancer receiving external prostate RT with or without seminal vesicle irradiation, moderate hypofractionationshould be offered.

Recommendation 3: In patients with high-risk prostate cancer receiving external RT into the prostate but not including the pelvic lymph nodes, moderate hypofractionationshould be offered.

Recommendation 4: In patients who are candidates for external RT, moderate hypofractionationshould be offered regardless of the patient's age, comorbidity, anatomy or urinary function. However, radiation oncologist should discuss the limited follow-up beyond 5 years for most of the existing randomized controlled trials evaluating moderate hypofractionation.

Recommendation 5: Patients should be informed of the slightly increased risk of acute GI toxicity with moderate hypofractionation. Moderately hypofractionated external RT has a similar risk of acute and late GU toxicities and late GI toxicity compared to conventionally fractionated external RT. However, radiation oncologist should discuss limiting follow-up beyond 5 years for most existing randomized trials evaluating mild hypofractionation.

Recommendation 6: The regimens of 60 Gy delivered in 20 fractions of 3Gy and 70 Gy delivered in 28 fractions of 2.5Gy are suggested as they are supported by the largest evidence base. It is impossible to determine an optimal regimen because most multiple fractionation regimens evaluated in clinical trials have not been compared with each other.

Recommendation 7: One moderately hypofractionated regimen is not suggested over another for specific risk groups, and the efficacy of moderately hypofractionated external RT regimens does not appear to be affected by patient age, comorbidity, urinary anatomy or function.
Recommendation 8: In patients with low-risk prostate cancer who refuse active surveillance and choose treatment with external RT, ultra hypofractionationcan be offered as an alternative to conventional fractionation.
Recommendation 9: In patients with intermediate-risk prostate cancer receiving external RT, ultra hypofractionationmay be offered as an alternative to conventional fractionation. The working group strongly encourages that these patients be treated within the framework of a clinical trial or a multi-institutional registry.
Recommendation 10: In patients with high-risk prostate cancer receiving external RT, the task force does not suggest offering ultra hypofractionation outside of a clinical trial or multi-institutional registry due to insufficient comparative evidence.
Recommendation 11: Ultra hypofractionated prostate RT of 35 to 36 Gy in 5 fractions of 7 to 7.25 Gy at the planning target volume may be offered to low-risk and intermediate-risk patients whose prostate is less than 100 cm^3.
Recommendation 12: Ultra hypofractionation of the prostate into five fractions at doses greater than 36 Gy within the planning target volume is not suggested outside of a clinical trial or multi-institutional study setting due to the risk of late toxicity.
Recommendation 13: Hypofractionation of the prostate into five fractions with consecutive daily treatments is not suggested due to the potentially increased risk of late urinary and rectal toxicity.
Recommendation 14: At least 2 dose-volume constraints for the rectum and bladder should be used for moderately or ultra hypofractionated RT (one near the full prescribed dose and one in the mid-dose range).
Recommendation 15: The use of risk organ constraints for moderately or ultra hypofractionated external RT that differ from those in a published reference study is not recommended due to the risk of acute and late toxicity.
Recommendation 16: The use of definitions of target volume and associated margin for hypofractionated external RT that deviate from those of a published reference study is not recommended, particularly for ultra hypofractionated regimens.
Recommendation 17: IGRT is universally recommended when administering moderately or ultra hypofractionated external RT.
Recommendation 18: Unmodulated 3D RT techniques are not recommended when administering RT to the moderately fractionated or ultra hypofractionated prostate.

As a summary, several large-scale randomized controlled studies demonstrate that mild hypofractionation achieves similar prostate cancer control outcomes and late toxicity rates as conventional fractionation. Moderate hypofractionation has significant potential benefits for patient comfort and resource utilization. Moderately hypofractionated RT should be offered to patients who choose RT for the treatment of prostate cancer. Although follow-up is limited beyond 5 years in completed trials, the working group nevertheless concluded that the existing evidence base is large enough to justify the routine use of moderate hypofractionation. It reached a weaker consensus for ultra hypofractionated RT. To date, the evidence base largely consists of prospective, single-arm trials in localized low-risk and, to a lesser extent, intermediate-risk diseases, and with limited follow-up. No published efficacy data from randomized controlled studies are currently available.

Conclusion:-

It is obvious that hypofractionated irradiation protocols will occupy an important place in the treatment of prostate cancers for reasons of patient comfort and lower treatment costs, provided that the toxicity and efficacy are equivalent to the regimens conventional.

Moderate hypofractionated RT has become a therapeutic option validated by the majority of learned societies. It makes it possible to divide the number of fractions by a factor of 2. The level of evidence is very robust with a median follow-up of five to six years in randomized trials.

Extreme hypofractionated RT is acquiring a very high level of evidence also with data from randomized trials showing the absence of acute toxicity and late toxicity in addition to efficacy which is not inferior to normofractionated RT with a median follow-up also of 6 years. The number of fractions is divided by a factor of 5 to 8.

More than a decade after the arrival of RT with dose escalation and IGRT in the treatment of localized prostate cancer, times are changing and short RT should quickly become unavoidable standard to our patients.

Competing interests:
We (authors) declare that we have no conflict of interest.

Authors Contribution:
AbdelhakMaghous and Khalid Hadadi performed research and share the first position in this manuscript
E.M, M.H, M.B, N.Z, A.B, I.L, K.A, M.E and H.S designed and coordinated research and drafted the manuscript. All authors read and approved the final manuscript.

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