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Hypofractionated radiotherapy for localised prostate cancer. Review of clinical trials

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Abstract
Over the last 10 years the radiobiology of prostate cancer has been studied both in experimental research and in clinical trials of hypofractionated radiotherapy. Unlike most cancers, the α/β ratio of the prostatic carcinoma is probably lower than that of the healthy organs around the gland, although there is no agreement as to how low this α/β really is. This peculiarity implies that, theoretically, a hypofractionated schedule would increase the therapeutic gain of radiotherapy. Until now, following four published randomised trials, hypofractionated radiotherapy has shown results in terms of acute and chronic toxicity and tumour control similar to those obtained with conventionally fractionated radiotherapy. However, these studies are not conclusive. The two studies that involved significant follow-up used 2D technique and delivered low total equivalent dose. On the other hand, the two most recent trials, which administered total equivalent doses ≥78 Gy with modern techniques (IMRT, IGRT), involved the disadvantage of small samples and a short follow-up period. The results of ongoing randomised trials are necessary to confirm the advantages of hypofractionation over normofractionated radiotherapy. The impact of hypofractionated radiotherapy on the patient's health-related quality of life, and on transports and health care costs, should also be investigated.

Keywords Hypofractionated radiotherapy · Alpha beta · Radiobiology · Prostate cancer

Introduction

In the 1970s, a handful of centres in England treated prostate cancer using hypofractionated radiotherapy. In 1995, a multicentric, randomised study [1] was carried out in Canada comparing hypofractionated radiotherapy with conventionally fractionated radiotherapy, but it was not until the publication in 1999 of Brenner and Hall's study [2] of optimum fractionation for prostate cancer that major controversy arose, following a growing interest in hypofractionated radiotherapy. In the last 5 years, in addition to the publication of randomised hypofractionated radiotherapy trials [1, 3, 4], we have seen the results of many non-randomised external-beam radiotherapy studies [5–24], and, moreover, numerous clinical trials have been started. The aim of this article is to review the clinical trials of hypofractionated radiotherapy for localised prostate cancer, focused on photon-beam therapy.

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The α/β ratio of prostate cancer and late-responding tissues of rectum and bladder

A summary of the debate around the α/β value of prostate cancer has been included to show the uncertainties that remain about its radiobiology.

In 1999, Brenner and Hall [2] calculated the α/β ratio of prostate cancer based on 3-year disease-free survival after low-dose-rate brachytherapy or external-beam radiation therapy using the linear-quadratic model. The obtained α/β value was 1.5 Gy (95% confidence interval, CI: 0.8–2.2 Gy). Similar comparisons were made by Fowler et al. in 1471 patients, estimating a α/β ratio of 1.49 Gy (95% CI: 1.25–1.76) [25]. These reports were disputed, leading to many discussions over whether heterogeneity should be taken into consideration, concluding that, whether homogeneous or heterogeneous models were used, the difference was too small to be detected in clinical trials [26–30]. Wang et al. [31] recalculated the α/β, correcting some of the data used by Brenner and Hall, obtaining a value of 3.1 Gy with a 95% confidence interval between 1.7 and 4.5 Gy. The lower value was rather similar to the α/β calculated by Brenner and Hall and by Fowler. Brenner and Hall did not take into account cell repopulation, which they considered irrelevant. In fact delaying the start of radiotherapy showed little effect on the rate of biochemical recurrence [32, 33], suggesting that repopulation was irrelevant for a treatment that lasted less than 8 weeks. However Wang et al. included accelerated proliferation of surviving cancer cells that they estimated to begin between 0 and 28 days. Datasets used by Brenner and Hall have been criticised as immature (biochemical control at 3 years as a measurement of tumour control in prostate cancer) and the number of patients included quite low (367 patients) [34]. Brenner et al. [35] subsequently performed another analysis in patients treated with a combination of external-beam radiotherapy and different schedules of high-dose radiotherapy, and compared 3-year biochemical control rates between them. The estimated value of α/β was 1.2 Gy (95% CI: 0.03–4.1). Lee has pointed out the fact that in this analysis the patient-matching process by T-stage, PSA, Gleason score, age and length of follow-up would not necessarily correct all possible confounding factors [36]. A review of the intense debate concerning the radiobiology of prostate cancer and the different proposed α/β values was published by Dasu [37]. The situation could be more complex. Nahum et al. [38] reported it is possible that cellular hypoxia in the high Gleason prostate tumours could increase the α/β of the cancer cells, although on the other hand this elevation could be corrected by slowing down cell proliferation associated with the reduced nutritional intake and by other factors. The results arising from 2 published trials using hypofractionation do not contradict an estimate of α/β <3 Gy: 1.12 Gy (95% CI=–3.3 to 5.6) [1] and 2.2 Gy (95% CI=–6.0 to 10.6) [3], but the confidence interval is wide.

Incongruent results to those above were derived from a study of 370 patients that compared normofractionated and hyperfractionated (two daily fractions of 1.2 Gy, 6 h between both) radiotherapy delivering an isoeffective dose, assuming a prostate cancer α/β of 10 Gy [39]. Acute grade ≥2 genitourinary (GU) toxicity was higher in the normofractionated group (48.6% vs. 37.3%, p=0.03), while no significant difference was found for acute gastrointestinal (GI) toxicity. Actuarial 5-year grade ≥2 GU and GI toxicities were also higher in the normofractionated group (20.3% vs. 10.1%, p=0.05 and 10.6% vs. 6.0%, p=0.18, respectively). The 5-year biochemical control rates were 70% and 82.6% in the normofractionated and hypofractionated branches. The estimated α/β ratio was 8.3 Gy (95% CI: 0.7 to 16), although the confidence interval could not exclude even very low values of α/β. Bentzen and Ritter have pointed out that a value as high as 8.3 Gy might be an over-estimation if incomplete repair plays a role in the hyperfractionated group due to incomplete sub-lethal damage repair [40]. Williams et al [41] used individual fraction size data from 3571 patients treated with external beam radiotherapy and 185 high-dose-rate brachytherapy to directly determine the α/β of prostate cancer. Using biochemical recurrence after external radiotherapy (fraction size 1.8–2.86 Gy) the estimated α/β ratio was 3.7 Gy (95% CI: 1.1–infinity), and, also including the patients treated with brachytherapy (fraction size 5.5–12 Gy), the value was 2.6 Gy (95% CI: 0.9–4.8). As this estimate was highly dependent on the high-dose-rate data, the authors' opinion is that uncertainty will remain until high dose per fraction is used in external-beam radiotherapy studies.

Another matter is the α/β of the rectum and bladder. On the basis of experimental data with rodents, but also of studies of normofractionated and hypofractionated radiotherapy, α/β values of the rectal late-responding tissues have been found to be between 3 and 6 Gy, most probably around 5 Gy [42–47]. It has been suggested that much rectal injury is actually a result of acute toxicity, which would fit in with a high α/β value for late rectal injury [48–50]. If the prostate cancer α/β is lower than that for late rectal tissues, hypofractionated therapies could be designed with larger dose/fraction, fewer fractions, but not shortening the overall treatment too drastically, in order to keep the current acute toxicity rates. For the bladder, α/β values of 2–4 Gy have been proposed, based on clinical data from cervix brachytherapy [51] and 3–7 Gy from experimental data with rodents [52].

In conclusion, the retrospective analyses of the clinical trials mentioned above comparing external-beam radiotherapy and brachytherapy do not lead to a definitive conclusion on the α/βvalue for prostate cancer. Although the majority of analyses point to a low value, the crux of the issue is finding out how low it is compared to the nearby late-responding normal tissues. The 5-year and 10-year results from randomised external-beam radiotherapy trials, which are being carried out, will help to clear up this issue.

Table 1 Characteristics of randomised trials comparing hypofractionated radiotherapy and normofractionated radiotherapy

		Lukka [1]	Yeoh [4]	Pollack [3]	Dearnaley [53][a]
n		936	217	100	150
Technique		2D	$2D/3D_{(22\%)}$	IMRT+IGRT	IMRT
Toxicity scale		NCIC	mLENT-SOMA	mRTOG	RTOG
Dose/fraction.	HYPORT	2.625	2.75	2.7	3
Overall time (w)	NRT	6.5	6.5	7.6	7.4
	HYPORT	4	4	5.2	4
Total dose (Gy)	NRT	66	64	76*	74
	$NTD_{1.5\text{-}2}$ HYPORT	61.9–60.7	66.8–65.3	84.2–82.5*	78–75
Acute GItox	NRT	≥3: 2.6%		≥2: 8%	≥2: 48%
	HYPORT	≥3: 4.1%‡		≥2: 18%	≥2: 39%
Acute GUtox	NRT	≥3: 4.9%		≥2: 56%	≥2: 38%
	HYPORT	≥3: 8.6%‡		≥2: 48%	≥2: 43%
Median follow-up (years)		5.7	4	–	2.1
Late GItox	NRT	≥3: 1.3%		–	≥2: 11%
	HYPORT	≥3: 1.3%§		–	≥2: 4%
Late GUtox	NRT	≥3: 1.9%		–	≥2: 2%
	HYPORT	≥3: 1.9%§		–	≥2: 12%
Failure**	NRT	52.95%	35.77%	–	–
	HYPORT	59.95%	34.25%	–	–

NTD1.5-2, 2 Gy total dose equivalent if given 2 Gy/fraction (α/β prostate cancer 1.5 and 2 Gy respectively); *NRT*, normofractionated radiotherapy arm; *HYPORT*, hypofractionated radiotherapy arm; *NCIC*, National Cancer Institute of Canada; m, modified; GI_{tox}, gastrointestinal toxicity; GU_{tox}, genitourinary toxicity

[a]Clinical results of the 60 Gy at 3 Gy/fraction hypofractionated arm

*Minimum dose to PTV

‡Higher significant toxicity in this arm

§No significant differences between arms

**Biochemical or clinical failure

The theoretical rationale for hypofractionation of prostate cancer

The linear-quadratic model formula shows that the tolerance of a tissue to irradiation falls as the dose per fraction rises and its α/β value decreases. The α/β ratio in the majority of tumours and early-responding normal tissues, such as urethral and rectal mucosa, is higher (≥7 Gy) than the α/β of the nearby late-responding healthy structures (<6 Gy). With these α/β values the greatest therapeutic gain would be achieved from administering a high total dose of radiation at low doses per fraction within the tolerance of the late response tissues over a short period of time, provided the acute toxicity is acceptable (normofractionated radiotherapy, 1.8–2 Gy/fraction). In light of publications reporting the hypothesis that the α/β of prostate cancer is lower than for the surrounding healthy tissues, a therapeutic advantage can be obtained by leaning towards larger –and therefore fewer– fractions (hypofractionated radiotherapy), as, under these circumstances, prostate cancer would be more sensitive to fractioning than nearby late-responding normal tissues. Reducing the total treatment time has a small effect on the occurrence of late reactions, but in turn increases acute toxicity. Although, as Yeoh et al. have observed in the treatment of prostate cancer, it can happen that an accelerated hypofractionated schedule can cause considerable acute toxicity and this, secondarily, can cause an increase in late toxicity (consequential late effects) [4]. Fowler et al. [42] suggested that an accelerated hypofractionated regime should not have an overall treatment time much shorter than 5 weeks and never shorter than 5 fractions.

In clinical practice, the objectives when it comes to developing a new protocol for hypofractionated radiotherapy can be summarised as: (1) to reduce biochemical failure using higher total equivalent dose, while keeping the same rate of late toxicity, or (2) to maintain the same percentage of biochemical control, that is, using the same equivalent dose, but reducing late toxicity rates. Due to the fact that they are radiobiological uncertainties, caution is necessary when it comes to designing clinical trials to take the possible scenarios into account.

Clinical data from randomised trials

Tumour control

There are four randomised trials [1, 3, 4, 53] comparing hypofractionated radiotherapy and conventionally fractionated radiotherapy, summarised in Table 1. Two of them had enough follow-up to provide preliminary data on tumour control [1, 4]. Hormonal therapy was an exclu-

sion criterion in both studies. In the Canadian multicentric study [1], a total of 936 patients were treated with a 2D technique and with a minimum follow-up of 4.5 years. Both arms were well balanced, although the equivalent dose prescribed to PTV in the hypofractionated arm was lower (61.9 vs. 66 Gy for an α/β of 1.5 Gy). The estimated 5-year biochemical or clinical failure rate was higher in the hypofractionated radiotherapy arm (59.95% vs. 52.95%), although there was no difference in terms of overall survival (87.6% in the hypofractionated arm vs. 85.2% in the conventionally fractionated arm) or in 2-year positive biopsies (50.9% vs. 53.2%). The definition of failure included biochemical failure, clinical failure, beginning of hormonal therapy and prostate cancer-related death. Three biochemical failure definitions (ASTRO, Vancouver and Houston) were compared with similar results in all groups. The authors recognise that post-radiotherapy prostate biopsy is not a gold standard for measuring the effectiveness of the treatment and note that the biopsy was carried out too early and with small sampling. The Australian trial [4] included 217 patients, of whom 169 were treated with a 2D technique and 48 with 3D. The primary end point was late toxicity. Compliance with the planned follow-up was not satisfactory after 2 years, with 5-year PSA data obtained for 96 of the 182 surviving patients. The estimated 5-year biochemical±clinical relapse-free survival (57.4% vs. 55.5%, NS) and overall survival (86.4% vs. 84.1%, NS) did not differ between the hypofractionated and conventional schedules. More high-risk patients were assigned to the hypofractionated arm. The subsequent analysis excluding these patients also found no significant differences between the two groups. In this study, unlike the other one, the dose prescribed in the hypofractionated group was slightly greater than in the conventional one (66.8 vs. 64 Gy to PTV for an α/β of 1.5 Gy). The PSA nadir and shape of the PSA curves were very similar between the two groups.

Both studies used similar study populations, total doses and doses per fraction (2.625 Gy in the Canadian and 2.75 Gy in the Australian). The reason that treatment failure was greater, but not significant, in the Canadian study may be due to the difference in the total equivalent dose. The total dose delivered in both studies is lower than the current gold standard, ≥72 Gy in low-risk prostate cancer and ≥78 Gy in intermediate-high risk prostate cancer. The use of higher total equivalent doses and higher doses per fraction, and greater accuracy in treatment delivery and quality control is expected to obtain better biochemical recurrence-free survival.

The analysis of these data showed that their clinical results could be explained with very low α/β values for prostate cancer, although with large 95% CI: 2.2 Gy (–6.0 to 10.6) [4] and 1.12 Gy (–3.3 to 5.6). Here, comparisons have been made between two external-beam radiotherapy arms without hormonal therapy, thus avoiding any problem deriving from the comparisson between brachytherapy and external-beam radiotherapy [2, 25, 31, 35].

Late toxicity

Three randomised trials [1, 4, 53] were followed-up over 2 years and can be considered studies of late toxicity. In conventional fractionation, the majority of patients who develop late toxicity will do so within 2 years [54, 55] although it is reported that late complications have continued to occur >2 years after therapy [14]. Doses per fraction ranged from 2.625 to 3 Gy, and total equivalent doses to PTV ranged from 61.9 to 78 Gy (prostate cancer α/β of 1.5). Late toxicity scales were also different: NCIC [1], Modified LENT-SOMA [4] and RTOG [53]. The CHHIP trial was the only one that allowed hormonal treatment (3–6 months). This trial compares conventional fractionation (74 Gy in 2 Gy/fraction) with two hypofractionated schedules of 57 Gy and 60 Gy at 3 Gy/fraction, 5 fractions/week, over 4 weeks. Two trials, the Canadian and the Australian, observed no significant differences in severe late GI toxicity between the two arms [1, 4]. However, the Australian study [4] observed a no significative increase in urgency of defecation and rectal bleeding in the hypo–fractionated group (20% vs. 14%). By contrast, the CHHIP study [53] found a significant decrease in late bowel grade ≥2 toxicity in the two hypofractionated arms compared with the normofractionated arm (4% vs. 4% vs. 11%). As the mean follow-up for this study is only 2.1 years, further observation is needed to confirm these results.

The disparate results of the studies could be due to the following considerations. The RTOG/EORTC scoring scale for late toxicity [56], used in the CHHIP trial, was developed in the 2D era. Its sensitivity for detecting changes in symptoms compared to the base situation is limited to not including various frequent symptoms, such as urgency of defecation or faecal incontinence. By contrast, the Australian trial used questionnaires so patients could self-assess clinical changes, which were scored with a LENT-SOMA scale [57], which, as well as being more complete than the RTOG/EORTC, was modified by adding more symptoms. In addition, the Australian trial used a 2D technique for 78% of patients, while in the British CHHIP trial, as it was most recent, they used IMRT in all 150 patients. Finally, the equivalent total doses prescribed were different between the two arms: 2.8 and 4 Gy higher in the hypofractionated arm in the British and Australian trials respectively, and by contrast, 4.1 Gy lower in the hypofractionated arm in the Canadian trial.

Using linear regression analysis, the only prognosis factor found was a relationship between urgency of micturition at 4 years and radiation treatment volumes [4].

Acute toxicity

All four randomised trials provide acute toxicity data. In the Fox Chase Cancer Center [3] more precise techniques were used, such as MRI-assisted contouring and target ultrasound-guided IMRT. This was also the only study

Table 2 Characteristics of the protocols of external photon beam hypofractionated radiotherapy in patients with non-disseminated prostate cancer

Author	N_{HYPORT}	Technique	NTD	d	$ED_{1.5}$[a]
Higgins [9]	300	2DRT	52.5	2.625	56.5
Livsey [17]	705	3DCRT	50	3.125	66.1
Koukourakis [13]	7	3DCRT	51	3.4	71.4
Bahary [7]	42	3DCRT	57	3	73.3
Yassa [24]	42	IG-IMRT	57	3	73.3
Norkus [21]	22	3DCRT	57 (36+18)	3–4.5	77.13
Kitamura [12]	31	IMRT	65–70	2.5	74.3–80
Collins [8]	232	2DRT	36	6	77.1
Martin [20]	92	IMRT	60	3	77.1
Junius [11]	38	IMRT	66	2.64	78.1
Madsen [19]	40	StRT	33.5	6.7	78.5
Kupelian [14]	770	IG-IMRT	70	2.5	80
Soete [23]	36	IMRT	56	3.5	80
Jereczek-Fossa [10]	10	3DCRT	72	2.4	80
Macias [18]	156	3DCRT	67.6–70.2	2.6	79.2–80.2
Leborgne [15]	56	IG-3DCRT	60–63	3–3.15	77.1–83.7
Arcangeli [6]	102	IG-IMRTa	56	3.5	80
Lim [16]	66	(3DCRT)+(IMRT)	67.5	2.7	81
Akimoto [5]	53	3DCRT	69	3	88.7
Pawlicki [22]	–	IMRT	36.25	7.25	90.6
Demanes [58]	209	(3DCRT)+(HDR)	(36)+(22–24)	(1.8)+(5.5–6)	(33.9)+(44–51.4)
Galalae [59]	144	(3DCRT)+(HDR)	(40–50)+(18)	(2)+(9)	(40–50)+(54)
Yoshioka [60,61]	111	HDR	48–54	6	102.8–115.7
Akimoto [62,63]	100	(3DCRT)+(HDR)	(51)+(18–25)	(3)+(5–9)	(65.6)+(46.4–54)
Martinez [64]	934	(3DCRT)+(HDR)	(36–50)+(16.5–30)	(2)+(5.5–15)	(36–50)+(33–141.4)

NHYPORT, number of patients treated with HYPORT; *NTD*, nominal total dose; d, dose per fraction; ED1.5, equivalent dose in 2 Gy/fractions (prostate cancer α/β 1.5 Gy); *IMRT*, intensity-modulated radiation therapy; *StRT*, stereotactic radiotherapy; *IG*, image-guided radiotherapy

[a]In this multicentric trial IG-IMRT was used in 2 institutions

**Biochemical or clinical failure

in which the pelvic lymph node areas were prophylactically irradiated in 35% of patients to an equivalent dose of 56 Gy. The protocol randomised patients to a hypofractionation (70.2 Gy at 2.7 Gy/fraction over 5.2 weeks) or conventional fractionation (76 Gy at 2 Gy/fraction over 7.6 weeks). The total equivalent dose was much higher in the hypofractionated arm (84.2 Gy for an α/β de 1.5 Gy). A small but significantly higher GI grade ≥2 toxicity was observed in the hypofractionated arm (18% vs. 8%), but lower GU grade ≥2 (48% vs. 56%). Also, the Canadian and Australian trials [1, 4] found a significant increase in GI and GU toxicity in the hypofractionated group when comparing symptoms at the end of radiotherapy with the baseline. On the other hand, the CHHIP trial [53] reported similar acute bladder and bowel toxicity (RTOG GU toxicity grade ≥2 was 43% in hypofractionation vs. 38% in normofractionation) although the rate of bowel toxicity grade ≥2 was higher in the conventional arm (39% vs. 48%). When interpreting the results, it must be considered that more violations of the rectum and bladder constraints are recorded in the hypofractionated arm, partly due to the fact that they were more difficult to adhere to as they were calculated with an α/β of 1.5 for the rectum, and that PTV margins were slightly smaller in this arm. It was observed that the peak in acute toxicity occurred earlier in hypofractionation, mainly in intestinal symptoms, and quickly fell after the completion of radiotherapy [3, 53].

In multivariate analysis, a high dose to the rectum composite DVH V_{65Gy}/V_{50Gy} was related to an increase in GI toxicity grade ≥2 in both arms (p=0.046) [3]. The possibility that late GI toxicity may be a consequential effect of acute GI toxicity is supported by multivariate analysis, which shows that an increased acute GI toxicity score at 1 month after radiotherapy independently predicted for increased GI late scores at 2, 3, 4 and also possibly 5 years [4]. A small bladder volume at CT planning was associated with an increase in GU acute effects (p=0.010) [3]. Linear regression analysis showed a relationship between the urgency of micturition score at 4 years and PTV volume [4].

Clinical data from non-randomised trials

Acute toxicity and late toxicity of hypofractionated radiotherapy prospective trials are summarised in Tables 2 and 3. Most of the studies use a fractioning between 2.5 and 3.5 Gy. The toxicity is similar to that produced using conventional fractionation. In general, very few patients present grade 3 toxicity, while a percentage of less than 30% suffer

Table 3 Non-randomised trials of hypofractionated radiotherapy in prostate cancer

Author	Scoring scale	Median follow-up (months)	Acute GI	Acute GU	Late GI	Late GU
Livsey [17]	RTOG/EORTC	48	–	–	Grade 2: 5%; Grade 3: 0%	Grade ≥2: 9%; Grade 3: 1%
Bahary [7]	–	–	Grade 3: 0%	Grade 3: 0.9%	–	–
Yassa [24]	CTC	48	Grade 2: 36% Grade 3: 5%	Grade 2: 36%; Grade 3: 8%		
Norkus [21]	RTOG/EORTC	–	Grade 2: 9.1%	–		
Kitamura [12]	–	37	Grade 1: 5.3%	Grade 1–2: 15.8%	Grade ≥ 2: 0%	Grade ≥2: 0%
Martin [20]	RTOG/EORTC	38	Grade 2: 11%; Grade 3: 1%	Grade 2: 25%; Grade 3: 0%	Grade 2: 5.1%; Grade 3: 0%	Grade 2: 10%; Grade 3: 1.2%
Junius [11]	RTOG/EORTC	20	Grade ≥2: 16%	Grade ≥2: 26%	16m-Grade ≥2: 18%a	–
Madsen [19]	AUA, CTC	41	Grade 1–2: 39%; Grade 3: 0%	Grade 1–2: 48.5%; Grade 3: 2.5%	Grade 1–2: 37%; Grade 2: 7.5%	Grade 1–2: 45%; Grade 2: 20%
Kupelian [14]	RTOG/EORTC	45	Grade 2: 9%; Grade 3: 0%	Grade ≥2: 19%; Grade 3: 1%	Grade ≥2: 4.5%	Grade ≥2: 5.2%
Soete [23]	RTOG/EORTC	–	Grade 2: 36%; Grade 3: 0%	Grade 2: 44%; Grade 3: 0%	–	–
Macias [18]	RTOG/EORTC	–	Grade 2: 8.3%; Grade 3: 0%	Grade 2: 30.8%; Grade 3: 0.6%	–	–
Leborgne [15]	RTOG/EORTC	60	Grade ≥2: 4.5–29%	Grade ≥2: 23–29%	–	–
Arcangeli [6]	RTOG/EORTC	–	Grade 2: 38%; Grade ≥3: 0%	Grade 2: 39%; Grade ≥3: 4%	–	–
Lim [16]	CTC	–	Grade 3: 0%	Grade 3: 7.6%	–	–
Demanes [58]	RTOG/EORTC	87	–	–	Grade 3–4: 0%	Grade 3–4: 7.7%
Galalae [59]	RTOG/EORTC	96	–	–	Grade 2: 4.1%	Grade 2: 2.3%
Yoshioka [60,61]	RTOG/CTCAE	27	Grade 2–3: 30%	Grade 1: 9.3%, Grade 2: 2.3%		
Akimoto [62,63]	RTOG/EORTC	31	Grade ≥2: 30.1%	–	Grade ≥2: 25%*	–

AUA, American Urology Association score; CTC, Common Toxicity Criteria score
[a]Grade 2 or worse rectal bleedingw
Late toxicity is actuarial late toxicity

grade 2 toxicity. With respect to effectiveness, monitoring is generally short in order to obtain robust results. Of the 22 studies included in Table 2, we will comment in greatest depth on the 2 which, using 3DCRT or IMRT techniques, recruited a large number of patients (>100) and exceeded 2 years' follow-up [14, 17]. Livsey et al. [17] treated 705 patients with 3DCRT at 3.13 Gy/fraction to the prostate plus seminal vesicles until completing 50 Gy (66.1 Gy for α/β of 1.5 Gy) in 3.1 weeks. No hormonal treatment was added. The median follow-up was 4 years. The actuarial 5-year biochemical-free survival (ASTRO definition) rate was 82%, 56% and 39% for good, intermediate and poor prognosis groups respectively, similar to normofractionated radiotherapy for this total dose level. To make up for the fact that in a retrospective survey minor late toxicity is not usually properly picked up in clinical records, 101 patients were randomly selected and interviewed in greater depth. Among them there was no RTOG grade toxicity, GI ≥2 was 5% and GU ≥2 was 9%. Meanwhile, Kupelian et al. [14] treated 770 consecutive patients with ultrasound-guided IMRT 2.5 Gy/fraction to 70 Gy (80 Gy for an α/β of 1.5 Gy) in 5 weeks. The median follow-up in this prospective trial was 3.75 years. The actuarial 5-year (ASTRO definition) rate was 95%, 85% and 68% for low-, intermediate- and high-risk disease. The late GI RTOG grade 2, grade 3 and grade 4 toxicities were 3.1%, 1.3% and 0.1%. The corresponding data for late GU toxicity was 5.1%, 0.1% and 0%. The acute GI toxicity scores were 2 in 9%, and ≥3 in 0%. It is observed that, if the percentage of the rectum receiving the prescribed dose was restricted, the scores significantly improved ($p<0.001$). For acute GU symptoms the RTOG scores were grade 2 in 18% and grade ≥3 in 1%.

Leborgne and Fowler [15] compared the acute toxicity of 3 non-randomised cohorts of contemporaneous patients treated using a fractioning of 2 Gy, 3 Gy and 3.15 Gy to a total nominal dose of 76–80, 60 and 63 Gy, respectively. Accelerated hypofractionated radiotherapy for 4 days/week, 5 weeks, in fractions of 3 Gy was shown to be the safest alternative, particularly with respect to acute rectal toxicity, which was similar to that after standard fractionation. By contrast, the 3.15 Gy/fraction schedule clearly showed higher percentages of grade ≥2 toxicity than the 3 Gy/fraction (NS) schedule or the 2 Gy/fraction ($p<0.001$) schedule.

Lim et al. [16] treated 66 high-risk patients with 1.8 Gy/fraction to pelvic lymph nodes using a conventional four-field technique with a concomitant 0.9 Gy/fraction IMRT

boost to the prostate over 5 weeks. Acute toxicity was well tolerated, with GI grade ≥2 of 39%, GI grade ≥3 of 0%, GU grade ≥2 of 36% and GU grade ≥3 of 7.6% (Common Terminology Criteria for Adverse Events v.3.0).

Galalae et al. reported interesting results [59] for 324 hormone-naïve patients treated with accelerated hypofractionated radiotherapy using a HDR brachytherapy boost delivered in 2–3 fractions of 5.5–11.5 Gy. The high-risk patients receiving an equivalent dose >94 Gy (assumed α/β of 1.2) had significantly better biochemical control and lower local recurrences which translated into a significant decrease in distant metastases (22% vs. 9%) when compared with the ≤94 Gy group. The described regimen was well tolerated in terms of late toxicity and health-related quality of life [65].

As in previous sections, care must be taken when interpreting the data because of the small number of patients per arm in many studies, the use of hormonal therapy in some of them, the different toxicity scoring scales, the different RT techniques (2D, 3D, inverse planning, target and organ-at-risk contouring, PTV margins, prescription point, dose constraints, etc.) and the different dose per fraction, total equivalent dose delivered and overall treatment time.

Most of the studies are of moderate hypofractionated regimens treating a small number of patients with a median follow-up of 4.1 years. Although it is not possible to obtain a direct estimate of α/β for carcinoma of the prostate, their results are compatible with a low α/β ratio. In addition, its complication rates are generally quite similar to those appearing after normofractionated therapy.

Accuracy of the treatment delivery and hypofractionation

In radiotherapy treatment, the outcome may worsen as the number of fractions decreases due to patient repositioning and organ movement. A small reduction in TCP (<1%) was observed by Craig et al. when they carried out a Monte Carlo simulation of hypofractionated and conventional treatments, assuming α/β of 1.5 Gy for prostate cancer and 3.0 Gy for the rectum [66]. Hypofractionated schedules significantly compensated for the geometric uncertainty effect as estimated TCP gains using high doses per fraction (20%). Song et al. have reported a similar gain in TCP due to hypofractionation (up to 21.8%), which was significantly higher compared with the losses due to geometric uncertainties (small if image-guided radiotherapy is used, or with a reduction of up to 8.6% in TCP if a conventional external laser-guided setup is used) [67]. Departments without high-tech equipment can develop hypofractionated therapy provided that the dose per fraction is not very high and the overall time does not fall below 5 weeks. The use of high-precision setup techniques (abdominal ultrasound scan, helical Kv on-rail CT, Kv or Mv cone-beam CT, implanted seed markers, electromagnetic transponder, stereotactic body radiotherapy) are mandatory to exploit the full potential of hypofractionation, using a larger dose/fraction (4–7 Gy) and paying attention to maintaining a total number of fractions greater than 5 and few fractions per week [42]. Specific research on image-guided hypofractionated treatments is being carried out [19, 20, 68–72]. Madsen et al. [19] reported a phase I/II trial treating 40 patients in 6.7 Gy/fraction to 33.5 Gy (78 Gy for α/β of 1.5 Gy). They used no coplanar fields and daily stereotactic target location using implanted fiducials. With almost 3.5 years follow-up, no grade 1–2 late toxicity has been observed in 37% (GI) and 45% (GU) of patients (Common Toxicity Criteria). No patient experienced grade ≥3 late toxicity. As for acute toxicity, 1 patient suffered GU grade 3, 48.5% of patients had GU grade 1–2 and 39% GI grade 1–2 toxicity. Similar results were reported by King et al. [68] after the treatment of 41 patients with Cyberknife (36.25 Gy in 7.25 Gy/fraction). After a median follow-up of 33 months there were 2 patients with RTOG grade 3 late urinary toxicity and none with RTOG grade 3 rectal complications.

Apart from implementing image guidance, a technique for avoiding prostate movement secondary to rectal filling should be tested in radiotherapy departments. Fiorino et al. [73] found rectal emptying using a daily enema to be an efficient tool. The insertion of an air-filled rectal balloon seems to achieve proper immobilisation of the prostate gland, to have dose measurement advantages and to be well tolerated [74, 75]; however, there is no complete agreement in this regard [76].

The use of the IMRT technique with hypofractionated schedules could improve local control and/or lower rectal toxicity, although the benefit of IMRT seems to be limited as long as standard PTV margins are applied [77].

The increased sophistication in treatment delivery means that two radiotherapy treatments, for example 3D six-field multi-leaf collimated radiotherapy and helical tomotherapy, with the same prescribed nominal dose result in a significantly different distribution of doses. With the hypofractionated schedules, could these differences be translated into excessive toxicity or greater tolerance? This issue must be taken into account when it comes to reporting trials in order to facilitate the comparison of results.

The therapeutic gain derived from hypofractionation, added to toxicity reduction because of the use of tighter margins and accurate dose delivery, both made possible by using image guidance and dose distribution tailored to individual anatomy thanks to intensity-modulated radiotherapy, can represent an important challenge in prostate cancer treatment. In the next few years, with the increasingly widespread use of high-precision setup and delivery systems, the use of more shortened schedules (between 5 and 15 fractions) will be more common.

Conclusions

This article is a review of published hypofractionated external-beam radiotherapy clinical trials for the treatment of lo-

calised prostate cancer. Though opinions are not unanimous, the majority of studies of this issue conclude that the α/β for a prostate tumour can be less than 3 Gy. Considering that the α/β for late responding rectal tissues may be 4–6 Gy, there is a possibility of a significant therapeutic gain. So far, this theoretical advantage has not been clearly proven. Nor have studies using current radiotherapy techniques revealed any disadvantages of hypofractionated radiotherapy in comparison with conventionally fractionated radiotherapy with regards to late toxicity or biochemical relapse-free survival. In the next few years we will know the results for toxicity and tumour control of randomised studies comparing both schedules. By analysing these data we will have better knowledge of the α/β ratio for prostate cancer. If hypofractionation proves not to be superior but to be similarly effective to conventional radiotherapy, quality of life studies may be useful to decide on its application in normal clinical practice as social and economic advantages may be derived from any reduction in the total treatment time. If, on the other hand, randomised studies designed ex profeso to obtain a real estimate of the α/β value for carcinoma of the prostate demonstrate the advantages of hypofractionation, its incorporation as standard treatment, together with IMRT and daily target localisation, will mean a far-reaching change in the management of localised prostate cancer.

Conflict of interest The authors declare that they have no conflict of interest relating to the publication of this manuscript.

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