Review

The role of radiotherapy in localised and locally advanced prostate cancer

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Abstract For a patient suffering from non-metastatic prostate cancer, the individualized recommendation of radiotherapy has to be the fruit of a multidisciplinary approach in the context of a Tumor Board, to be explained carefully to the patient to obtain his informed consent. External beam radiotherapy is now delivered by intensity modulated radiotherapy, considered as the gold standard. From a radiotherapy perspective, low-risk localized prostate cancer is treated by image guided intensity modulated radiotherapy, or brachytherapy if patients meet the required eligibility criteria. Intermediate-risk patients may benefit from intensity modulated radiotherapy combined with 4—6 months of androgen deprivation therapy; intensity modulated radiotherapy alone or combined with brachytherapy can be offered to patients unsuitable for androgen deprivation therapy due to co-morbidities or unwilling to accept it to preserve their sexual health. High-risk prostate cancer, *i.e.* high-risk localized and locally advanced prostate cancer, requires intensity modulated radiotherapy with long-term (≥2 years) androgen deprivation therapy with luteinizing hormone releasing hormone agonists. Post-operative irradiation, either immediate or early deferred, is proposed to patients classified as pT3pN0, based on surgical margins, prostate-specific antigen values and quality of life. Whatever the techniques and their degree of sophistication, quality assurance plays a major role in the management of radiotherapy, requiring the involvement of physicians, physicists, dosimetrists, radiation technologists and computer scientists. The patients must be informed about the potential morbidity of radiotherapy and androgen deprivation therapy and followed regularly during and after treatment for tertiary prevention and evaluation. A close cooperation is needed with general practitioners and specialists to prevent and mitigate side effects and maintain quality of life.

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1. Intensity modulated radiotherapy, hypofractionated radiotherapy and stereotactic radiotherapy

1.1. Intensity modulated radiotherapy

Intensity-modulated radiotherapy (IMRT) is the standard of care for external beam radiotherapy (EBRT) as regards localized, locally and regionally advanced prostate cancer (PCa). Individual collimator leaves move during the period of radiotherapy exposure, sculpting the computed tomography (CT) based planning target volume, resulting in a concave surface to increase the anatomical conformity and enable dose escalation (Fig. 1). Planning must be accompanied by quality assurance; details of volume, and dose constraints should be defined per protocol, and compliance assured with dose-volume histograms. Treatment verification is essential, and IMRT is often combined with some form of image-guided radiotherapy (IGRT), in which the prostate/target volume's position is verified by imaging during a treatment exposure. IMRT may also be applied to irradiation of pelvic lymph nodes in case of high risk PCa or regionally advanced PCa. Based on the results of five published randomized clinical trials, dose escalation improves biochemical and local control [1], and overall survival according to a non-randomised well conducted propensity matched retrospective analysis of the United States National Cancer Database covering a total of 42 481 patients: There is a benefit for intermediate-risk ($p < 0.001$) and high-risk PCa ($p < 0.001$) but not for low-risk ($p = 0.54$) [2]. For clinically localized PCa the ProtecT trial comparing active monitoring, radical prostatectomy and EBRT, has shown at a median follow-up of 10-year, that the PCa specific mortality was identical for radical prostatectomy
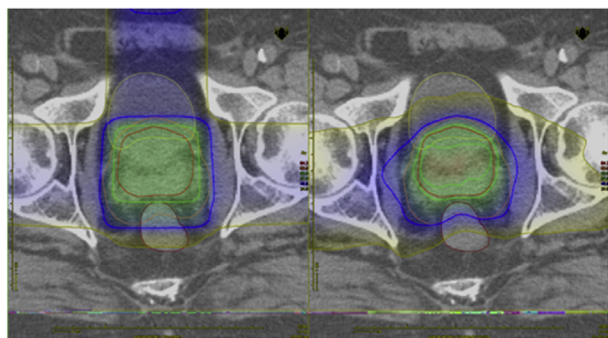

Figure 1 Dose distributions for intensity-modulated radiotherapy (IMRT) (right) and standard, conformal radiotherapy (left) to the prostate. Note the improved dose distribution and concave high dose volume with IMRT. Courtesy of Dr Gareth Jones, Velindre Hospital, Cardiff.

and three-dimensional (3D) conformal radiotherapy delivered at a dose of 74 Gy in 37 fractions with neo adjuvant androgen deprivation therapy (ADT) for 3—6 months [3]; of note, IMRT with further dose escalation, or brachytherapy were not performed.

The European Association of Urology (EAU) guidelines recommend a total dose of 74—78 Gy in low-risk patients (LE 1a, GR A), 76—78 Gy in combination with short-term ADT (4—6 months) in intermediate-risk patients (LE 1b GR A) when radiotherapy is given in standard fraction sizes of 1.8—2 Gy per fraction [1].

1.2. Hypofractionation (HFX)

HFX is the use of larger than standard fraction sizes of EBRT, with two modalities: Either moderate with dose per fraction ≤ 5 Gy or extreme with dose per fraction ≥ 5 Gy. The rationale is that tissues which are prone to late radiation damage (therefore permanent) such as the spinal cord, are more sensitive to large doses per fraction, and PCa is believed to behave like such late-reacting tissues [4]. The emerging evidence for improved disease control with dose escalation gave new impetus to HFX, taking the total dose beyond what was the standard.

1.2.1. Moderate dose-escalated HFX

According to a recent review [5] merging studies [6—8] using various techniques and in part including ADT, moderate HFX delivered with conventional 3D conformal radiotherapy $\pm$ IMRT has sufficient follow-up to give credence to its safety, while awaiting long-term results. Table 1 summarizes mature data of trials not powered to report on superiority in terms of efficacy, many being non-inferiority trials and powered as such. The trials are reported in two distinct phases. In the first phase, safety is the main concern, and non-inferiority is absolutely the appropriate endpoint; the studies vary according to whether toxicity is based on physician-administered scales, such as the Radiation Therapy Oncology Group (RTOG) grade, or whether it is from a patient-administered scale such as expanded prostate cancer index composite. The second phase would be the reporting of efficacy, reported as disease-free survival, or biochemical control. The largest trial reporting on disease free survival is the RTOG 0415 trial, a noninferiority trial, with 1115 men randomised, all of whom had low risk disease; at a median follow-up of 5.8 years the disease-free survival was consistent with the predefined criteria for noninferiority, however there were more late genitourinary (GU) adverse events in patients treated with hypofractionated radiotherapy [9]. The non inferiority CHHIP trial, randomized 3216 men to EBRT with conventional (74 Gy in 37 fractions over 7.5 weeks) versus hypofractionated (60 Gy in 20 fractions over 4 weeks or 57 Gy in 19 fractions over 3.8 weeks). The 5-year outcomes

Table 1 Major phase III randomised trials of moderate hypofractionation for primary treatment.

Study/Author	n	Risk, GS, or NCCN	ADT	RT regimen	BED, Gy	Median FU, month	Outcome
Lee et al. [9]	550	low risk	None	70 Gy/28 fx	80	70	5 year DFS 86.3% (n.s.)
	542			73.8 Gy/41 fx	69.6		5 year DFS 85.3%
Dearnaley et al. [10]	1077/19 fx	15% low	3—6 months,	57 Gy/19 fx	73.3	62	5 year BCDF
	1074/20 fx	73% intermediate	before and	60 Gy/20 fx	77.1		85.9% (19 fx)
	1065/37 fx	12% high	during EBRT	74 Gy/37 fx	74		90.6% (20 fx)
							88.3% (37 fx)
Aluwini et al. [6]	403	30% GS <6,	None	64.6 Gy/19 fx	90.4	60	5 year RFS 80.5% (n.s.)
	392	45% GS >7,		78 Gy/39 fx	78		5 year RFS 77.1%
		25% GS 8—10					
Catton et al. [11]	608	intermediate risk	None	60 Gy/20 fx	77.1	72	5 year BCDF
		53% T1c					both arms 85%
		46% T2a-c					HR: 0.96 (n.s)
	598	9% GS 6		78 Gy/39 fx	78		
		63% GS 7a					
		28% GS 7b					

ADT, androgen deprivation therapy; BCDF, biochemical or clinical disease failure; BED, biologically equivalent dose, calculated to be equivalent in 2 Gy fractions using an α/β of 1.5 Gy; DFS, disease-free survival; EBRT, external beam radiotherapy; FU, follow-up; fx, fractions; GS, Gleason score; HR, hazard ratio; NCCN, National Comprehensive Cancer Network; n.s., not significant; RFS, relapse free survival; RT, radiotherapy.

indicated that the 60 Gy schedule was not inferior to the 74 Gy schedule [10]. Another multicenter randomized non inferiority trial in intermediate-risk PCa [11] comparing 78 Gy in 39 fractions over 8 weeks to hypofractionated RT of 60 Gy in 20 fractions over 4 weeks has concluded that the hypofractionated RT regimen was not inferior to conventional RT but was associated with increased late toxicity.

The EAU guidelines state that moderate HFX including IGRT to the prostate only, can be offered to carefully selected patients with localised disease (LE 1a, GR A). Moderate HFX should adhere to RT-protocols from trials with equivalent outcome and toxicity, i.e. 60 Gy/20 fractions in 4 weeks or 70 Gy/28 fractions in 6 weeks. (LE 1a, GR A) [1].

1.3. Stereotactic radiotherapy

Stereotactic radiotherapy is characterized by i) extremely accurate patient positioning, as it is achieved in neuro-oncology by using a frame that was physically attached to the patient's skull; ii) meticulously accurate radiotherapy planning to define a very small high dose volume; iii) delivery of radiation using a very small "pencil" beam, and multiple fields to provide adequate coverage of the target. These principles were modified in the Cyberknife by creating a free-standing, robotic linear accelerator head, which could deliver a pencil beam of radiation, and was capable of being orientated in any plane of rotation, able to do so isocentrically. As there is no treatment frame attached to the patient, the machine head must be capable of adjusting rapidly to any changes in patient position. The system is therefore combined with on-board image-guided localisation, with fiducial markers inserted into the prostate. It is possible to deliver stereotactic radiotherapy with a state-of-the-art Linac with full IMRT/IGRT capabilities, which has become a preferred option in some centres,

because the equipment can be used in a variety of indications.

1.3.1. Extreme hypofractionation
Stereotactic radiotherapy allows extreme HFX as part of a formal clinical trial in the treatment of localised PCa, since there have been no randomised trials comparing extreme HFX to other schedules. It is used in a number of centres, on the basis of its practical advantages, and based on the results of nonrandomised case series [5,11,12]. The largest and most mature series of nonrandomised patients had been reported by Zaorsky et al. [13] concerning 324 low-risk and 153 intermediate-risk patients treated with Cyberknife; following treatment with either 35 or 36.25 Gy delivered in five fractions: 7-year biochemical disease-free survival were 95.6% and 89.6% for low and intermediate-risk patients, respectively. Caution is needed in interpretation—the selection criteria for patients vary, in some instances which are difficult to ascertain, patients with predominantly, less than high grade disease—and the same outcomes might not be attainable in a less selected population.

EAU guidelines regard extreme HFX as being experimental, to be delivered in specialised centres in the context of a formal clinical trial; as a minimum, outcome data in terms of patient-reported toxicity and quality of life, plus oncological outcomes, should be recorded and published.

2. Permanent and high dose brachytherapy

Brachytherapy is a form of radiotherapy where a sealed radiation source is placed directly into the body. The placement of radiation sources in the prostate can be permanent or temporary. Permanent interstitial brachytherapy or seed brachytherapy, involves placing low dose

rate (LDR) radioactive sources into the prostate and leaving them permanently to gradually release radiation over time. Temporary brachytherapy involves first placing needles or catheters within the prostate and, on confirmation of accurate positioning, temporarily introducing the radioactive source into the prostate. Radiation is delivered using a high dose rate (HDR) machine where actual treatment times are minutes. A comparison of LDR and HDR prostate brachytherapy treatments is listed in Table 2.

Prostate brachytherapy is often done as a day-case under general or regional anaesthesia. The patient is placed in the lithotomy position and trans-rectal ultrasound (TRUS) is used to provide image guidance. For permanent brachytherapy, treatment may be done either as a two-step procedure, where the TRUS pre-plan takes place a few weeks before actual implantation, or as a single-step procedure, where the plan is created in the operating room and seeds inserted in real-time. HDR treatment planning can be undertaken in real-time in theatre using ultrasound or alternatively, and the patient can be woken up and CT or magnetic resonance imaging (MRI) acquired to identify the target volume and plan source delivery. Where multiple HDR treatments are used, the catheters can stay *in situ* and are used to deliver fractionated treatments; following radiation delivery the HDR needles/catheters are removed.

Detailed European Society of Therapeutic Radiation Oncology (ESTRO) guidelines on the clinical and technical aspects of both permanent and HDR brachytherapy are recommended and centres should follow strict quality assurance guidelines [14,15]. Men with pre-existing urinary symptoms are at high risk of retention after brachytherapy and/or experiencing prolonged urinary symptoms. The International Prostate Symptom Score (IPSS) can be used to screen patients with a score <9 being ideal and scores <15 acceptable [16]. Urinary flow tests are more objective. Men with peak urinary flow rates of <10 mL/s have a 30% risk of

post-implant retention and brachytherapy is generally not advised. Those with peak flow rates >20 mL/s have <10% risk of catheterization and are good candidates for brachytherapy [17]. Neo-adjuvant androgen deprivation for 3–6 months can be used to downsize the prostate in patients with enlarged glands.

Post-implantation side effects are predominantly urinary and are very common in the first weeks after treatment. Urinary symptoms are relieved by α-blockers and anti-inflammatories will help with pain and discomfort. Acute retention can occur in 10%–20% and is managed by catheterisation. Rectal side effects are usually mild. The use of brachytherapy boost with EBRT is associated with more GU side effects when compared to EBRT alone [18].

2.1. LDR brachytherapy

Patients with low risk localised PCa (clinical T1c-T2a, Gleason score 6, <50% core positive, prostate-specific antigen [PSA] <10 ng/mL) and selected patients with low volume intermediate risk localised prostate cancer (clinical T1c-T2a, Gleason score 3 + 4, PSA <10 ng/mL, <33% core positive) are suitable for permanent prostate brachytherapy alone. The biochemical control for low risk patients after 5 and 10 years has been reported to range from 71% to 93% and 65% to 85%, respectively [1].

In patients with higher risk disease there is a significant risk of extra-capsular spread that may not be included in the high dose region of a seed implant. In this situation brachytherapy may be combined with EBRT to ensure an appropriate target is treated. In the ASCENDE-RT trial, LDR boost resulted in improved PSA control when compared to EBRT alone but at the cost of higher GU late toxicity [19]. Approximately 50% of the GU toxicity was due to urethral strictures and a boost dose of 110 Gy rather than 115 Gy should be used.

Table 2	Comparison of prostate brachytherapy techniques.
	Comparison of prostate brachytherapy techniques
LDR	■ Permanent seeds implanted at single visit ■ Uses Iodine-125 (most common), Palladium-103 or Caesium-131 isotopes ■ Radiation dose delivered over weeks and months ■ Acute side effects resolve over months ■ Radiation protection issues for patient and carers ■ shielded theatre room ■ Established as monotherapy for low and selected intermediate risk localized prostate cancer ■ Established as a boost treatment with external beam radiation in higher risk or locally advanced prostate cancer
HDR	■ Temporary implantation and may need to be fractionated ■ Ir-192 (most common) Co-60 source introduced through implanted applicators (needles or catheters) ■ Radiation dose delivered in minutes ■ Acute side effects resolve over weeks ■ No radiation protection issues for patient or carers ■ Can use same HDR source for other cancer treatments ■ Need for a shielded HDR treatment room ■ Established as boost treatment with external beam radiation in higher risk or locally advanced prostate cancer ■ Single centre cohort studies demonstrate good outcomes when used as monotherapy for localised disease

LDR, low dose rate; HDR, high dose rate.

2.2. HDR brachytherapy

HDR brachytherapy is established as a boost treatment with EBRT but there is no consensus regarding the timing of HDR brachytherapy in relation to EBRT, EBRT volumes and either EBRT or HDR dose schedules. HDR brachytherapy as a boost has been prescribed with schedules including 15 Gy in three fractions, 11—22 Gy in two fractions and 12—15 Gy in one fraction [16]. HDR monotherapy has been investigated in cohort studies using schedules varying from a single to up to nine fractions. In localized disease excellent PSA control is achieved with low rates of gastro-intestinal side effects [20].

The recommendation of the EAU guidelines is that in patients with low-risk PCa and selected intermediate-risk PCa, without a previous transuretral resection and with a good IPSS and a prostate volume <50 mL, LDR brachytherapy can be offered (LE 2a, GR A).

3. Post-operative radiotherapy: Immediate or early delayed

In high-risk PCa, the likelihood of local relapse rate rises in case of poor prognostic risk factors. Immediate (adjuvant) postoperative radiotherapy (ART) or early delayed (salvage) radiotherapy (SRT) has to be discussed as part of a multi-modal approach and the decision should be explained by the urologist to the patient before surgery.

3.1. Adjuvant radiotherapy

Three randomized clinical trials SWOG 8794 [21], EORTC 22911 [22] and ARO 96-02 [23] where an undetectable PSA was required after radical prostatectomy (RP), have shown that ART realized 4 months after RP reduces significantly the 10-year rate biochemical relapse and may improved 10-year overall survival ($p = 0.02$) [21] with respect to RT delayed until local recurrence. The greatest benefit from ART is obtained in men with pT3 and positive surgical margins or Gleason score 7—10 as additional risk factor. The dose was 60—64 Gy and in the ARO 96-02 study which exclusively utilized 3D-based treatment planning, the incidence of late grade 3 or higher adverse events was only 0.3% [24].

For patients classified as pT3pN0 with an undetectable PSA level and a high risk of local failure after RP (positive surgical margins multifocal or unifocal >2 mm, capsule rupture, and/or invasion of the seminal vesicles) two options can be offered:

- ART to the surgical bed after recovery of urinary function (LE 1a, GR A).
- Clinical and biological monitoring followed by SRT before the PSA exceeds 0.5 ng/mL (LE 1b, GR A), since the biochemical disease free survival decreases significantly beyond this threshold [25].

3.2. SRT with or without ADT for PSA only recurrence

For patients who have a detectable PSA level (>0.1 ng/mL) 3 months after RP or who develop a biochemical relapse after RP as defined by a PSA value > 0.2 ng/mL and rising, SRT of the prostate bed may offer a possibility of cure with a dose of at least 66 Gy [1]. More than 60% of patients treated before the PSA level rises to values >0.5 ng/mL, will achieve an undetectable PSA level, providing patients with 80% chance of being progression free 5 years later [26]. The correlation of the pre-SRT PSA level and SRT dose with biochemical relapse shows that there was an average 2.6% loss of relapse free survival for each incremental 0.1 ng/mL PSA at the time of SRT [26]. The randomized SAKK 09/10 trial devoted to SRT has randomly allocated 350 patients between 64 Gy and 70 Gy, with 44% conventional 3D-SRT and 56% IMRT/rotational technique in both arms. Acute GU and gastrointestinal (GI) toxicities were mostly mild, with 3 (vs. 1) GU and 4 (vs. 1) GI events for the dose escalation arm [27].

Addition of ADT to SRT improves outcomes. The GETUG-AFU 16 trial comparing RT alone (66 Gy prostate with or without 46 Gy pelvis) versus the same RT regimen + 6-month luteotrphin hormone releasing hormone (LHRHa), reported with a median follow-up of 63 months an improved 5-year progression free survival in favour of the combined approach ($p < 0.0001$) [28]. The RTOG 96-01 trial has compared RT + bicalutamide (150 mg daily) for 24 months versus RT (64.8 Gy) + placebo and has shown an improvement of the 10-year overall survival (82% vs. 78%, $p = 0.04$) [29].

3.3. Comparison of ART and SRT

Three randomized phase III trials are assessing the role of ART versus SRT together with the efficacy of ADT: RADICALS (United Kingdom), RAVES (TROG) and GETUG 17 (France). In the meantime, we can consider the 5-year results of a non-randomised well conducted propensity matched retrospective analysis comparing 390 ART to 390 SRT which showed that early SRT did not impair the biochemical disease free survival [30].

4. Combination of ADT and external irradiation for high-risk PCa

To improve the overall survival of high-risk localized PCa or locally advanced PCa (T3-4 N0-X M0, cN1-pN1 M0) the combination of a local-regional EBRT with long-term ADT is imperative to potentiate the radiation effect and to try to eradicate microscopic sub-clinical distant metastases outside the target volume. Randomized phase III trials have promoted the combination of long-term adjuvant ADT (≥2 years) as a standard of care.

4.1. Randomized phase III trials of use and duration of ADT in combination with EBRT (Table 3)

The most powerful conclusion from these trials comes from EORTC trial 22863, which is the basis for the combination of EBRT and ADT as standard practice [31]. ADT starts either at the onset of EBRT, or 2—3 months before to induce size reduction of the prostate and improve lower urinary tract symptoms, the concomitant component remaining crucial

Table 3 Major phase III randomized trials of use and duration of ADT in combination with RT for PCa.

Trial	Year	TNM stage	n	Trial	ADT	RT	Effect on OS
EORTC 22863 [31]	2010	T1-2 poorly differentiated and M0, or T3-4 N0-1 M0	415	EBRT ± ADT	LHRHa for 3 years (adjuvant)	70 Gy RT	Benefit at 10-year for combined treatment ($p = 0.0004$)
RTOG 85-31 [32]	2005	T3 or N1 M0 (15% RP)	977	EBRT ± ADT	Orchiectomy or LHRHa	65—70 Gy RT	Benefit for combined treatment ($p = 0.002$) mostly caused by patients with Gleason score 7—10
D'Amico [7—10]	2008	T2 N0 M0 (localised unfavourable risk)	206	EBRT ± ADT	LHRHa plus flutamide for 6 mo.	70 Gy 3D-CRT	Significant benefit ($p = 0.01$) that may pertain only to men with no or minimal comorbidity
TROG 96-01 [39]	2011	T2b-4 N0 M0	802	Neoadjuvant ADT duration	LHRHa plus flutamide 3 or 6 mo. before, plus concomitant	66 Gy 3D-CRT	Benefit in PCa-specific survival ($p = 0.04$)
RTOG 94-13 [40]	2007	T1c-4 N0-1 M0	1292	ADT timing comparison	2 mo. neoadjuvant plus concomitant vs. 4 mo. adjuvant	Whole pelvic RT vs. prostate only; 70.2 Gy	No significant difference between neoadjuvant plus concomitant vs. adjuvant androgen suppression therapy groups (interaction suspected)
RTOG 86-10 [38]	2008	T2-4 N0-1	456	EBRT ± ADT	LHRHa plus flutamide 2 mo. before, plus concomitant	65—70 Gy RT	No significant difference at 10 year
RTOG 92-02 [33]	2008	T2c-4 N0-1 M0	1554	Short vs. prolonged ADT	LHRHa given for 2 years as adjuvant after 4 mo. as neoadjuvant	65—70 Gy RT	10-year OS benefit in subset with Gleason 8—10 for long-term ADT ($p = 0.006$)
EORTC 22961 [34]	2009	T1c-2ab N1 M0, T2c-4 N0-1 M0	970	Short vs. prolonged ADT	LHRHa for 6 mo. vs. 3 years	70 Gy 3D-CRT	Better 5-year OS with 3-year treatment ($p = 0.006$)
SPCG-7/SFUO-3 [35]	2014	T1b-2 Grade 2—3, T3 N0 M0	875	ADT ± EBRT	LHRH a for 3 mo plus continuous flutamide	70 Gy 3D-CRT vs. no RT	Lower 15-year cancer specific mortality (30.7%) vs. (12.4%) favouring combined treatment ($p < 0.0001$)
NCIC CTGMRC/PR3/ PRO7/SWOG [36]	2015	T3-4 (88%), PSA >20 ng/mL (64%), GS 8—10 (36%) N0 M0	1205	ADT ± EBRT	Continuous LHRHa	65—70 Gy 3D-CRT vs. no RT	10-year OS benefit for combined treatment ($p < 0.001$)
French study [37]	2012	T3-4 N0 M0	273 264	ADT ± EBRT	LHRHa for 3 year	70 Gy 3D-CRT vs. no RT	Better 5-year progression free survival for combined treatment ($p < 0.001$)

ADT, androgen deprivation therapy; 3D-CRT, three-dimensional conformal radiotherapy; EBRT, external beam radiotherapy; GS, Gleason score; HR, hazard ratio; LHRHa, luteinising-hormone-releasing hormone agonist; mo., months; OS, overall survival; PCa, prostate cancer; RT, radiotherapy.

to potentiate EBRT. For long-term ADT, the results of phase III randomized trials—EORTC 22863 [31], RTOG 85-31 [32], RTOG 92-02 [33], EORTC 22961 [34], SPCG-7/SFUO-3 [35], NCIC/MRC PR3/PR07 [36], and French study [37] are displayed in Table 3, as are those related to short term ADT: RTOG 86-10 [38], TROG 96-01 [39], and RTOG 94-13 [40].

The EAU guidelines state that in patients with high risk-localized PCa, the use of a total dose of 76—78 Gy (when given in standard fraction sizes of 1.8—2 Gy per fraction) in combination with long-term ADT (2—3 years) is recommended (LE 1a, GR A) while EBRT is offered in combination with long-term ADT (2—3 years) in patients with locally advanced cN0 PCa (LE 1a, GR A).

4.2. Pelvic lymph-node irradiation combined with ADT

There is no level 1 evidence for prophylactic whole pelvic irradiation but this modality could be recommended since pelvic lymph-node irradiation was performed for EORTC and RTOG trials. The pelvic lymph-node target volume must cover the nodes overlying the external iliac artery and vein, the nodes within the obturator fossa located cranially and caudally to the obturator nerve, and the nodes medial and lateral to the internal iliac artery; with IMRT, pre-sacral nodes can be included easily. Clinical or pathological node-positive (N+) patients do not always develop a systemic disease and many data—RTOG trial 85-31 [41], an homogeneous matched patients cohorts [42], United States National Cancer Data Base [43], STAMPEDE Trial [44]—suggest that the combination of whole pelvic irradiation plus immediate long-term ADT may be beneficial.

The EAU guidelines recommend that in patients with cN+ or pN+ PCa pelvic irradiation can be offered in combination with immediate long-term ADT (LE 2b, Grade B) [1].

4.3. Side effects

ADT with LHRHa may induce hot flushes, fatigue, weight gain, loss of libido and erectile dysfunction, insulin resistance, lower bone mineral density with an increase risk of bone fracture, increased cardiovascular events, metabolic syndrome, anaemia and impact on cognitive function. These side effects, as assessed by a self-administered questionnaire, will impact on a varying degree with the prevalent comorbidities of the patients and the duration of the treatment [45]. Retrospective analyses of the EORTC and RTOG have shown that long-term ADT did not increase the cumulative incidence estimates of cardiovascular mortality as compared with short-term or no ADT [32,35,46,47]. Overweight status is associated with PCa mortality in men undergoing combined treatment, and prevalent diabetes is associated with greater all-cause and non PCa mortality [48]. Many studies demonstrated that long-term ADT was associated with an increased risk of fractures and prevention of bone mineral loss through lifestyle modification is recommended, as well as the use of bisphosphonates in case of osteoporosis [49]. These potential side-effects have to be discussed with patients to evaluate the risk-benefit ratio, taking into account—age, WHO performance status, co-morbidities, sexual health, lifestyle, tobacco usage and body mass index—to enable them to mitigate adverse effects by stopping smoking, reducing their weight, improving diet and increasing physical exercise. To reduce the risk of adverse effects, other parameters should be assessed—glycemia, hyperlipidemia, use of blood pressure medication or oral anticoagulation, control of bone mineral density—so that comorbidity treatments are adjusted appropriately by general practitioners, endocrinologists and cardiologists.

4.4. New modalities of ADT

A better understanding of androgen receptor signaling and mechanism underlying resurgent androgen receptor activity has induced major breakthroughs in the development of novel androgen-ablative and androgen receptor antagonist strategies to more effectively inhibit receptor activity [50]. The third generation gonadotrophin hormone releasing hormone antagonist degarelix is being used in advanced PCa and its definitive superiority over LHRH analogues remains to be proven by on going randomized phase III trials. Abiraterone acetate, a potent and selective inhibitor of CYP 17—enzyme required for androgen biosynthesis in the testes, adrenal glands, and prostate tissue—is investigated in randomized phase III trials with LHRH agonist and EBRT for high risk PCa. Enzalutamide, a novel androgen receptor antagonist that binds the androgen receptor and prevents both androgen receptor translocation and DNA binding, is investigated with LHRH agonists and EBRT for high risk PCa.

Conflicts of interest

The authors declare no conflict of interest.

Author contributions

Study concept and design: Michel Bolla, Ann Henry, Malcom Mason, Thomas Wiegel.
Data acquisition: Michel Bolla, Ann Henry, Malcom Mason, Thomas Wiegel.
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Drafting of manuscript: Michel Bolla, Ann Henry, Malcom Mason, Thomas Wiegel.
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