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Review Article

Combining androgen deprivation and radiation therapy in the treatment of localised prostate cancer: Summary of level 1 evidence and current gaps in knowledge

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Introduction

Combination of external radiation therapy (RT) and androgen deprivation therapy (ADT) represents a standard of care for patients with intermediate and high-risk localised prostate cancer (LPCa) [1], and many have investigated this field of interest [2–4]. However, some points still remain to be elucidated.

We hereby propose to carry out a new review of the literature summarizing the latest updated results of the pivotal trials, while also focusing on current key questions, such as who benefits from the addition of ADT, are there optimal duration and timing for ADT and what is the relationship between RT dose and ADT.

Methods

Search strategy

Our literature search drew on the data base PubMed/MEDLINE and trial registries including ClinicalTrial.gov and Cochrane Central Register of Controlled Trials, to retrieve articles in English and in French, evaluating hormone therapy with radiation therapy in patients with LPCa.

Studies published from January 1995 to February 2022 were identified.

Selection criteria

We included phase III randomised trials and *meta*-analyses assessing the role of ADT in adult men with LPCa. Were excluded surgery trials, trials in the post-operative setting, studies in metastatic patients and retrospective studies.

Controlled vocabulary was used, with the following terms: "(randomised OR phase III OR *meta*-analysis) AND (androgen deprivation therapy OR hormone therapy) AND (radiation therapy OR radiotherapy) AND prostate AND (localised OR localized) NOT surgery NOT prostatectomy NOT metastatic".

The search was conducted between January 2021 and February 2022.

Evidence synthesis

Pivotal trials of RT and ADT combination

RT-ADT versus RT alone

Many phase III trials have compared short-term (STADT) or long-term (LTADT) androgen deprivation therapy to RT alone in localised and locally advanced prostate cancer. Data from these trials are summarised in Table 1.

Studies using long-term ADT. The EORTC 22,863 trial [5–7] showed that the addition of 3 years LH-RH agonists to RT in 415 men with localised and locally advanced PCa improved 10-year disease-free survival (DFS) (22.7 % vs 47.7 %, $p < 0.0001$) and 10-year overall survival (OS) (39.8 % vs 58.1 %, $p = 0.0004$).

The RTOG 8531 trial [8] evaluated the benefit of lifelong ADT combined with RT. Median ADT duration was 3 years. At 10 years, OS was also better in the RT plus ADT arm (49 % vs 39 %, $p = 0.002$).

Consistently with the 2 previous trials, See, Tyrell *& al.* showed that the addition of Bicalutamide led to a significant improvement of 5-year progression-free survival (PFS), and a reduction of the risk of death by 35 % [9].

Studies using short-term ADT. Similarly to the previous trial, many

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Table 1
Trial characteristics (RT plus ADT vs RT alone).

Trials	First authors	Number of patients	ADT duration in the experimental arm	ADT type	RT dose to the prostate	Pelvic irradiation and dose	Inclusion criteria	Primary endpoint	Mean follow-up (years)	Results on primary endpoint	Results on overall survival
EORTC 22,863 [7]	Bolla	415	3 years	LH-RH agonist	70 Gy	Mandatory 50 Gy	cT1-4 N0-1 M0	DFS	9.1	At 10 years: RT-ADT: 47.7 % RT alone: 22.7 % HR 0.42, 95 % CI 0.33–0.55, p < 0.0001	At 10 years: RT-ADT: 39.8 % RT alone: 58.1 % HR 0.60, 95 % CI 0.45–0.80, p = 0.0004
RTOG 8531 [8]	Pilepich	977	Lifelong	LH-RH agonist	65–70 Gy	Mandatory if evidence of nodal involvement; Optional otherwise 44–50 Gy	cT1-2 N + or T3 Tumor size < 25 cm	LR, DM	7.6	At 10 years: LR: 23 % vs 38 %, p < 0.0001 DM: 16 % vs 22 %, p = 0.0052	At 10 years: RT-ADT: 49 % RT alone: 39 % p = 0.002
[9]	See, Tyrell	1370	Lifelong	Bicalutamide	64 Gy	Not specified	cT1b-4 N0-1 M0	PFS	7.2	HR 0.56, 95 % CI 0.40–0.78, p < 0.001	HR 0.65, 95 % CI 0.44–0.95, p = 0.03
Boston trial [10]	D'Amico	206	6 months	LH-RH agonist	70 Gy	Not specified	cT1-2b N0 M0 + 1 poor prognosis factor among: -PSA > 10 ng/ml -T3b on MRI -GS 7–10	ACM *a posteriori*	7.6	At 8 years: 44 vs 30 deaths, HR 1.8, 95 % CI, 1.1–2.9, p = 0.01	
TROG 9601 [12]	Denham	802	3 months 6 months	LH-RH agonist	66 Gy	None	cT2b-4 N0 M0	LP, EFS	10.6	At 10 years, compared to RT alone: RT-ADT 3 months: LP: HR 0.49, 95 % CI 0.33–0.73, p = 0.0005, EFS: HR 0.63, 95 % CI 0.52–0.77, p < 0.0001 RT-ADT 6 months: LP: HR 0.45, 95 % CI 0.30–0.66, p = 0.0001 EFS: HR 0.51, 95 % CI 0.42–0.61, p < 0.0001	At 10 years, compared to RT alone: RT-ADT 3 months: HR 0.84, 95 % CI 0.65–1.08, p = 0.180 RT-ADT 6 months: HR 0.63, 95 % CI 0.48–0.83; p = 0.0008
RTOG 8610 [13]	Roach	456	4 months	LH-RH agonist	65–70 Gy	Mandatory if evidence of nodal involvement; Optional otherwise 44–50 Gy	Bulky tumors T2-4 N0-1 M0	OS, DSM, DM	12.6	At 10 years: DSM: 23 % vs 36 %, p = 0.01 DM: 35 % vs 47 %, p = 0.006	At 10 years: RT-ADT: 43 % RT alone:34 % p = 0.12 NS
RTOG 9408 [14]	Jones	2028	4 months	LH-RH agonist	66 Gy	Pelvic irradiation was omitted in patients with negative lymph-node dissections or with a PSA < 10 ng/ml and GS < 6 46.8 Gy	T1b-2b N0 M0 PSA < 20 ng/ml	OS	9.1	At 10 years: RT-ADT: 62 % RT alone: 57 % HR 1.17; p = 0.03	

RT: radiation therapy, ADT: androgen deprivation therapy, DFS: disease-free survival, LR: local relapse, DM: distant metastasis, PFS: progression-free survival, ACM: all-cause mortality, LP: local progression, EFS: event-free survival, OS: overall survival, DSM: disease-specific mortality, GS: Gleason score, Gy: Gray, HR: hazard ratio, CI: confidence interval NS: not significant.

authors tried to show that adding short-term ADT (3 to 6 months) was sufficient to improve the outcomes of RT alone.

In the Boston trial [10], the addition of 6 months of complete androgen blockade with Flutamide to RT resulted in significant increased OS. The survival rate at 8 years was 74 % in the ADT + RT arm and 61 % in the RT alone arm ($p = 0.01$).

The TROG 9601 trial [11,12] compared RT alone to RT plus 3 months of ADT and to RT plus 6 months of ADT. At 10 years, the addition of 3 months of ADT decreased the cumulative incidence of Prostate Specific Antigen (PSA) progression, local progression (LP), and improved event-free survival (EFS) (HR 0.63, $p < 0.0001$). 6 months of ADT further reduced PSA progression and LP, led to a greater improvement in EFS (HR 0.51, $p < 0.0001$), but also decreased distant progression (DP), prostate cancer-specific mortality (PCSM), and overall mortality (0.63, $p = 0.0008$) whereas 3 months ADT did not.

In parallel, the RTOG 8610 trial [13] concluded that the addition of 4 months of ADT compared to RT alone significantly improved DM and DFS, but failed to show a statistically significant OS difference.

Finally, Jones *& al.*'s trial, RTOG 9408 [14], compared RT alone to RT and 4 months of ADT. The authors also found a significant difference in OS in favour of the addition of ADT (62 % vs 57 %, $p = 0.03$) at 10 years.

Clinical relevance of these results. These phase III, multicentre trials concluded that the addition of ADT to RT is beneficial. However, except for the RTOG 9408 trial, all these studies were designed prior to the D'Amico classification [15] and before the systematic PSA-testing era.

In addition, patients included in these trials presented mostly with locally advanced PCa, some of them with a proven lymph node involvement, or with a probable metastatic dissemination. For instance, T3 or T4 PCa was diagnosed for 91 % of the patients in Bolla *& al.*'s trial, 69.8 % in Pilepich *& al.*, 40 % in Denham *& al.* and 70 % in Roach *& al*, with bulky tumours as an inclusion criterion. 34 % of patients in EORTC 22863, 71 % in RTOG 9531, 72 % in the Boston trial, 55 % in the TROG 9601 and 70 % in the RTOG 9610 had a Gleason score (GS) 7 or more.

More importantly, the PSA level, when known, was much higher than that usually detected in patients nowadays: 56 % of patients had a PSA > 20 ng/ml in EORTC 22863. PSA was not reported by Pilepich *& al.*, 25 % had a PSA > 40 in the Boston trial, 39 % had a PSA > 20 ng/ml in TROG 9601. In RTOG 9610, the median PSA level was 22.6 ng/ml (2.2–128) in the RT-ADT group, and 33.8 ng/ml (1.9–264.6) in the RT alone group. PSA level at diagnosis is known to correlate with the dissemination of the cancer. As a consequence, a significant proportion of patients included in those trials may have been metastatic from the outset, even if a proven metastatic disease was an exclusion criterion in all the study designs.

Current international guidelines recommend the staging of the disease before treatment by performing prostatic and pelvic MRIs, bone scans and if necessary, CT-scans [1]. At the time of inclusion of these trials, such medical examinations were not mandatory. As a consequence, the lymph node or metastatic invasion was probably suboptimally determined in a large proportion of patients. Therefore, the results are arduously applicable to the majority of patients treated today, who benefit from a more precise staging.

Despite these considerations, all the studies cited above tend to prove the interest of the addition of ADT to RT. Recently, an individual patient data *meta*-analysis (n = 10.853) from the MARCAP consortium group [16] showed that the addition of ADT to RT significantly improved 12-year metastasis-free survival (MFS) (absolute 8.2 %, HR 0.85, 95 %CI 0.79–0.92) and OS (absolute 7.3 %, HR 0.87, 95 %CI 0.8–0.95).

These results provide the strongest level of evidence to support the use of ADT in LPCa.

RT-ADT versus ADT alone

Although the superiority of the combination of RT and ADT has been established, its comparison to ADT alone was needed. Three randomised, multicentre phase III trials compared RT-ADT to ADT alone, assessing the role of a local treatment with RT in localised or locally advanced PCa: SPCG 7/SFUO 3 (n = 875), NCIC CTG PR3/MRC PR07 (n = 1205) and Mottet *& al.* (n = 264). Data from these trials are summarised in Table 2.

In the SPCG 7/SFUO 3 trial [17], Widmark *& al.* found that the addition of RT to lifelong ADT led to a decrease of PCSM (23.9 % vs 11.9 %, $p = 0.01$), and overall mortality (OM) (39.4 % vs 29.6 %, $p = 0.0001$) at 10 years in men with locally advanced PCa.

Meanwhile, Warde, Mason *& al.* [18,19] showed consistent results. ADT was also given for life. The combined treatment led to a significant improvement of OS at 10 years (HR 0.70, $p = 0.001$).

Finally, the trial conducted by Mottet *& al.* actualised by *Sargos & al.* [20] concluded to a significant improvement of 8-year PFS (48 % vs 7 %, $p < 0.001$) with the addition of RT to 3 years ADT in T1b-T3 LPCa. Eight-year OS was not significantly different between the two groups, although results tended to be in favour of RT-ADT (65 % vs 57 %, $p = 0.43$).

These three trial populations were quite similar, with a majority of cT3 cN0 and high PSA levels. Among the patients, 39.5 % in the SPCG 7/SFUO 3 trial, 63 % in the NCIC CTG PR3/MRC PR07 trial and 62 % in the trial led by Mottet had a PSA > 20 ng/ml at randomisation.

Consequently, this implies that these studies were driven by high-risk patients, and might have included metastatic ones. However, if the addition of a local treatment benefited that population, it seems logical to extrapolate these results to less advanced diseases, for which local treatment remains the cornerstone.

- the combination of RT and ADT in LPCa is based on level I evidence from multiple phase III trials and *meta*-analyses.

Who benefits from ADT?

In 1998, the D'Amico classification was published [15], dividing prostatic cancer patients into three categories according to the biochemical progression-free survival (bPFS). In 2013, two subgroups in the intermediate population were found to differ in terms of bPFS, LP, DM and PCSM, after RT alone [21].More recently, the "very high-risk" group was proposed. It is currently used within the NCCN guidelines and gathers patients with multiple high-risk criteria [22].

This finer classification has led to the question of the optimal management of LPCa depending on risk of recurrence presented by the patients.

Low-risk group

To our knowledge, no phase III trial assessed the benefit of the addition of ADT to RT in this specific population. Among the previously reported trials, only one tend to answer the question. Indeed, a post-hoc subgroup analysis from the RTOG 9408 was performed and found only a significant benefit of the addition of ADT in 10-year-bPFS in low-risk patients and a lower local failure on repeat prostate biopsy at 2 years. The difference observed in OS or DSM in the overall population was only found in the intermediate population.

Another interesting point is that DSM at 10 years in the RT alone group was 1 %, suggesting that RT by itself is an effective treatment in low-risk patients.

These findings, combined with the fact that ADT is not side effect free, do not support the use of ADT in patients who present with a low-risk LPCa.

- ADT is not recommended in the treatment of low-risk LPCa [1].

Intermediate-risk group

Three of the historical trials comprised patients who bear a resemblance to the current intermediate-risk group patients [10,12,13].

Table 2
Trial characteristics (RT-ADT versus ADT alone).

Trials	First authors	Number of patients	ADT duration in the experimental arm	ADT type	RT dose to the prostate	Pelvic irradiation and dose	Inclusion criteria	Primary endpoint	Mean follow-up (years)	Results on primary endpoint	Results on overall survival
SPCG 7/ SFUO 3 [17]	Widmark	875	Lifelong	LH-RH agonist	70 Gy	Pelvic lymph nodes were not intentionally irradiated, but some of the obturatorious nodes were included in the standard target volume	T1b-T3 PSA < 70 ng/ml N0	PCSS	7.6	At 10 years: RT-ADT: 23.9 % ADT alone: 11.9 % RR 0.44, 95 % CI 0.30–0.66	At 10 years: RT-ADT: 39.4 % ADT alone: 29.6 % RR 0.68, 95 % CI 0.52–0.89
NCIC CTG PR3/ MRC PR07 [19]	Warde, Mason	1205	Lifelong	LH-RH agonist	64–69 Gy	Pelvic irradiation was omitted if the treating physician judged that pelvic RT was Inappropriate 45 Gy	T3-4 N0/x or T1-2 + PSA > 40 ng/ml or T1/2 + PSA 20–40 ng/ml + GS 8–10	OS	8.0	At 8 years: HR 0.70, 95 % CI 0.57–0.85, p = 0.001	NCIC CTG PR3/MRC PR07 [19]
[20]	Mottet	264	3 years	LH-RH agonist	70 Gy	All patients received pelvic RT 44–48 Gy	cT3-4 N0 or pT3N0 < 80 years old	PFS	5.7	At 5 years: RT-ADT: 60.9 % ADT alone: 8.5 % p = 0.0001	At 5 years: RT-ADT: 71.4 % ADT alone: 71.5 % NS

ADT: androgen deprivation therapy, RT: radiation therapy, PFS: progression-free survival, OS: overall survival, PCSS: prostate cancer-specific survival, GS: Gleason score, Gy: Gray, HR: hazard ratio, RR: relative risk, CI: confidence interval, NS: not significant.

Intermediate-risk patients accounted for 54 % of the RTOG 9408 trial population (n = 1068) and 18 % of the TROG 9601 one (n = 91). In the Boston trial, 57 % of patients had a GS 7, 23 % had a GS 6 or less but a PSA level between 10 and 20 ng/ml; all of the 206 patients had a localised cT1b to cT2b disease. As previously reported, these studies are in favour of the addition of short-term ADT (STADT) to RT and are positive on their primary endpoint and overall survival.

Two post-hoc subgroup analyses are available for this very population. Jones *& al.* found that the addition of ADT improved OS and DSM at 10 years in intermediate-risk patients, contrary to Denham *& al.*, which failed to show an advantage. The main hypothesis for these contradictory results is the small size of the intermediate subgroup in the TROG 9601 population, potentially leading to an inadequate power.

To our knowledge, there is no phase III trial that has focused on the specific intermediate-risk population.

Optimal duration of short-term ADT. As previously mentioned, RT plus STADT seems to be the adequate treatment for intermediate-risk patients. Many phase III studies assessed whether there is an optimal duration for STADT. Data from these trials are summarised in Table 3.

The ICORG 9701 trial [23] compared 4 versus 8 months of ADT plus RT in a small population described as driven by intermediate-risk patients at the time the trial was designed. However, when the latest NCCN classification is used, only 17 % of the patients are at intermediate-risk, 50 % are at high-risk and 32 % at very high-risk.

Armstrong *& al.* failed to demonstrate any statistically significant difference in OS (90 % vs 83 %, NS), or bPFS at 5 years, probably because high-risk patients may need longer ADT than 8 months.

The RTOG 9910 trial [24] tried to show 4 months ADT was superior to 9 months ADT. 84 % of the 1579 patients had an intermediate-risk LPCa.

At 10 years, there were no significant differences in DSS, DM or OS. The intermediate-risk subgroup was stratified further into single intermediate-risk factor or multiple-factor groupings in a post-hoc analysis. Again, there were no differences according to risk group.

Additionally, the Canadian multicentre trial [25] concluded that there was no benefit in the addition to RT of 8 months ADT when compared to 3 months ADT in a composite population (43 % of intermediate-risk, 31 % of high-risk and 26 % of low-risk patients), in terms of failure-free survival (FFS) and OS at 7 years. The post-hoc subgroup analysis carried out showed a significant improvement of FFS only in the high-risk subgroup. No difference was found in the intermediate population, which is consistent with the previous results.

D'Amico *& al.* published a *meta*-analysis to determine if 6 months ADT is superior to 3 or 4 months, in addition to RT [26], using individual patient data of the TROG 9610 [11] subgroup who received 4 months of ADT, those of the ICORG 9710 trial [23], and those of the Boston trial [10] who received 6 months of ADT. At 10 years, 6 versus 3 or 4 months of ADT was associated with a reduced risk of PCSM (aHR, p = 0.004). When assessed in subgroups, AHRs were 0.67 (p = 0.35), 0.47 (p = 0.01), and 0.59 (p = 0.14) for men with GS 6, 7, and 8 to 10 LPCa, respectively.

These findings support the use of no<6 months ADT in intermediate (or high-risk) patients. The strongest evidence for the benefit of 6 months ADT was in men with GS 7.

Favourable and unfavourable intermediate-risk subgroups. In 2012, Castle *& al.* published a retrospective series of patients with LPCa treated with or without ADT [27]. Patients were classified as low-risk, favourable intermediate-risk (GS 6, ≤ T2b or GS 7(3 + 4) and T1c), marginal intermediate-risk (GS 7(3 + 4) and T2a-b), unfavourable high-risk (GS 7 (4 + 3) or T2c) or high-risk, with statistically different prognosis between the groups.

The unfavourable intermediate-risk and high-risk patients who had ADT in addition to RT had a significant improvement of their 5-year FFS, contrary to those with low-risk, favourable or marginal intermediate-risk LPCa.

The following year, Zumsteg *& al.* proposed to sunder the intermediate-risk group of D'Amico's classification into favourable (FIR) and unfavourable intermediate (UIR) risk groups [21]. Indeed, the

Table 3
Trial characteristics (trials assessing different ADT durations).

Trials	First authors	Number of patients	Arm A ADT duration (months)	Arm B ADT duration (months)	Type of ADT	RT dose to the prostate	Pelvic irradiation and dose	Inclusion criteria	Primary endpoint	Mean follow-up (years)	Results on primary endpoint	Results on overall survival
ICORG 9701 [23]	Armstrong	276	4	8	LHRH agonist	70 Gy	No	cT3-4 or GS > 6 or PSA > 20 and N0 M0	bPFS	8.5	At 5 years: 4 months ADT: 66 % 8 months ADT: 63 % 95 % CI −0.007–0.28 NS	At 5 years: 4 months ADT: 90 % 8 months ADT: 83 % NS
RTOG 9910 [24]	Pisansky	1579	4	9	LHRH agonist	70.2 Gy	Pelvis was targeted if one of the following existed: T3-4, GS 7 and PSA 4–20 ng/ml T3-4, GS 6, and PSA 10–20 ng/mL T2a, GS 7, and PSA 10–20 ng/mL T1b-1c, GC 8–10, and PSA 10–20 ng/mL; T2a-T4, GS 6, and PSA > 20 ng/mL. 46.8 Gy	T1b-4 and GS 2–6 and PSA 10–100 ng/ml Or T1b-4 and GS 7 and PSA < 20 ng/ml Or T1b-1c and G 8–10 and PSA < 20 ng/ml	DSS	9.4	At 10 years: 4 months ADT: 95 % 9 months ADT: 96 % HR 0.81, 95 % CI 0.94–0.98, p = 0.45 NS	At 10 years: 4 months ADT: 66 % 9 months ADT: 67 % HR 0.95, 95 % CI 0.63–0.70, p = 0.62 NS
Canadian multicentre trial [25]	Crook	378	3	8	LHRH agonist	66 Gy	If the risk of lymph node involvement was > 10–15 %, the pelvis was treated 45–46 Gy	cT1c-4 N0 M0	FFR	6.6	At 5 years: 3 months ADT: 72 % 8 months ADT: 75 % p = 0.18 NS	At 7 years: 3 months ADT: 81 % 8 months ADT: 79 % p = 0.7 NS
RT0G 9202 [30]	Hanks, Horwitz, Lawton	1554	4	28	LHRH agonist	65–70 Gy	Mandatory 44–46 Gy	cT2c-4 N0 and PSA < 150 ng/ml	DFS	19.2	At 15 years: LTADT: 16 % STADT: 10 % p < 0.0001	At 15 years: LTADT: 30 % STADT: 27 % p < 0.03
EORTC 22,961 [31]	Bolla	970	6	36	LHRH agonist	70 Gy	Small pelvic irradiation fields, covering only the prostate and seminal vesicles, were allowed only when lymph nodes were not invaded 50 Gy	cT1-2b N1 or cT3-4 N0-1 and PSA < 40xNSV	OS	6.4	At 5 years: LTADT: 84.8 % STADT: 81.0 % HR 1.42, 95 % CI upper limit 1,79 p = 0.65 for non-inferiority	
DART 01/05 [32]	Zapatero	355	4	28	LHRH agonist	78 Gy	Elective pelvic radiotherapy and dose were left to the criteria of each participating centre	cT1c-3b N0 and PSA < 100 ng/ml	bPFS	5.3	At 5 years: LTADT: 90 % STADT: 81 % HR 1.88, 95 % CI 1.12–3.15, p = 0.01	At 5 years: LTADT: 95 % STADT: 86 % HR 2.48, 95 % CI 1.31–4.69, p = 0.009
TROG 0304 RADAR [33]	Denham	1071	6	18	LHRH agonist	66 Gy-74 Gy or 46 Gy + brachytherapy boost	Not allowed	cT2b-4 N0 Or cT2a and GS > 6 and PSA < 10 ng/ml	PCSM	10.4	At 10 years: ITADT: 13.3 % STADT: 9.7 % Sub-HR 0.70, 95 % CI 0.50–0.98, adjusted p = 0.035	At 10 years ACM: ITADT: 28.0 % STADT: 32.3 % Sub-HR 0.83, 95 % CI 0.68–1.02, adjusted p = 0.081 NS
PCS IV [34]	Nabid	630	18	36	LHRH agonist	70 Gy	Mandatory 44 Gy	cT1c-4 N0M0	OS	9.4	At 5 years: LTADT: 91 % ITADT: 86 % P = 0.07 NS	

ADT: androgen deprivation therapy, RT: radiation therapy, LTADT: long term ADT, STADT: short term ADT, ITADT: intermediate term ADT, DFS: disease-free survival, OS: overall survival, PCSM: prostate cancer-specific mortality, ACM: all-cause mortality, bPFS: biochemical progression-free survival, DSS: disease-specific survival, FFR: freedom from local failure, GS: Gleason score, Gy: Gray, HR: hazard ratio, CI: confidence interval, NS: not significant.

authors found in a retrospective study that these two groups of patients differ from each other in terms of bPFS, LF, DM and PCSM when treated by RT alone.

Since, the question of the addition of ADT in the FIR group has been raised, but evidence remained partial and of low grade.

More recently, Zumsteg *& al.* published a secondary study of RTOG 9408 [28], in which intermediate-risk patients were divided in the two previously cited subgroups. It resulted in the first ever published significant difference in OS (69 % vs 61 % HR 1.19; p = 0.03) at 15 years between FIR and UIR groups. In each group, the benefit of ADT was analysed. Unlike patients with FIR, those with UIR significantly benefited from ADT in terms of DM, PCSM (HR 0.40, P < 0.001), but not OS.

In spite of the fact that this is a non-planned secondary analysis, results are based on a phase-III study population, leading to the highest quality evidence to date supporting the idea of limiting ADT use to patients with UIR disease. Phase III trials on this subject are expected to provide elucidating evidence for this long-standing unanswered question.

- The European Society of Radiation Oncology (ESTRO) and the European Association of Urology (EAU) currently recommend to add short-term ADT (4–6 months) to RT in patients with intermediate-risk LPCa, irrespective of the subgroup.

High-risk group

As previously reported, the improvement of patients' outcomes from the addition of ADT to RT was demonstrated in populations driven by high-risk patients in large phase III randomised trials, testing long-term or short-term ADT [5,8,11,9], leading to a strong external validity.

In the post-hoc risk analysis of the RTOG 9408 trial, Jones *& al.* failed to find the OS and DSM improvement of the overall analysis in the high-risk patients (n = 226).

On one hand, this could be explained by the size of the sample, possibly not large enough to observe a significant difference between the RT alone and the RT plus ADT groups. On the other hand, the duration of ADT used in this trial, 4 months, might be too short to be beneficial to the patients with quite an aggressive disease.

Denham *& al.* also performed a post-hoc subgroup analysis. The addition of 6 months ADT to RT led to a decrease of PCSM in high-risk patients. The gain was not found in patients with a PSA level > 20 ng/ml at baseline, suggesting that 6 months ADT is probably not long enough for patients with a more advanced disease.

Therefore, it appears legitimate to combine ADT and RT for men with high-risk LPCa. However, assessing the adequate duration of hormone deprivation was paramount.

Long-term versus short-term ADT. Three randomised phase III trials compared LTADT versus STADT, in addition to RT. Data from these trials are summarised in Table 3.

The RTOG 9202 trial [29,30] was the first to confront different durations of ADT. Hanks *& al.* compared RT + 4 months of ADT versus RT + 28 months of ADT in locally advanced PCa. LTAD was found to be superior to STAD in DFS, LP, DM, DSS and OS (12 % relative reduction; p = 0.03), after a median follow-up of 19.6 years.

Interestingly, a post-hoc analysis focusing on patients with a GS 8–10 began to show a significant OS advantage of LTAD even in the first report at 5 years. At 15 years, it resulted in 25 % mortality risk reduction and 4 % absolute mortality reduction, generating the hypothesis that LTADT would benefit this population.

Bolla *& al.* got analogous results in the EORTC 22,961 trial [31]. In this non-inferiority study, 6 months ADT was found inferior to 36 months ADT in addition to RT. The 5-year overall mortality for short-term and long-term suppression was 19.0 % and 15.2 %, respectively (HR 1.42, p = 0.65).

More recently, the DART 01/05 trial [32] demonstrated that 28 months ADT plus RT extended 5-year bDFS and 5-year OS (HR 2.48, p = 0.009) when compared to RT and 4 months ADT in patients with intermediate and high-risk LPCa.

A planned sub-group analysis found that the benefit in OS with long-term deprivation was significant for patients with high-risk disease, but not for those with intermediate-risk disease.

An additional trial, TROG RADAR [33] assessed the role of an intermediary term of ADT (ITADT). In a 2x2 factorial design, RT (66, 70, 74 or 46 Gy plus a brachytherapy boost were possible treatment plans) plus 6 versus 18 months were compared. Another randomisation tested the contribution of zoledronic acid. 18 months ADT was found superior in terms of bPFS and CSS (13.3 % vs 9.7 %, HR 0.70, p = 0.035), especially in patients with GS 8–10, but this did not traduce in OS at 10 years.

More recently, Nabid *& al.* [34] compared 36 months with 18 months ADT, hypothesizing that LTADT was superior to ITADT in selected high-risk patients (mostly PS 0–1, T ≤ 2). The 5-year OS rates were 91 % for long arm and 86 % for short arm (p = 0.07). The authors performed a post-hoc analysis of the data beyond 5 years and concluded that it is conceivable that 18 months of ADT is not inferior to 36 months for OS. This result must be carefully analysed. The fact that this trial failed to prove superiority of the LDADT over IDADT should not be considered as irrefutable proof of the equivalence between the two arms, or of non-inferiority of the ITADT. Moreover, the compliance was questionable, since 24.5 % of patients in the 36 months arm received 18 months ADT or less, probably reducing the difference between the 2 groups. It is also probable that 5 years is too short to assess a benefit in OS in localised, albeit high-risk, PCa.

When gathered, all these results indicate that, in high-risk patients, RT plus LTADT is superior to RT plus STADT.

More data could bring answers to better understand if ITADT is non-inferior to LTADT, when added to RT. In the meantime, 18 months of ADT may be carefully proposed to selected patients, like those with substantial comorbidities in a competitive risk setting.

- Long-term ADT is recommended in combination to RT in the treatment of high-risk LPCa according to the EAU-EANM-ESTRO-ESUR-SIOG guidelines [1]

RT dose and ADT

Dose escalation and ADT

All studies mentioned above, except the DART 01/05 trial, used what was referred to as "conventional doses" of RT, between 64 and 74 Gy (tables 1, 2, 3).

The improvement of irradiation techniques and the advent of intensity-modulated RT (IMRT) allowed physicians to increase the dose up to 80 Gy. Many phase III trials compared conventional to high dose RT (HDRT) for PCa treatment. HDRT led to an improvement of PFS, with no difference in PCSM and OS at 10 years [35–39].

Even though trials on the addition of ADT showed an impact in OS with a long-term follow-up, the usefulness of the addition of ADT to HDRT remained to be assessed.

As previously mentioned, Zapatero *& al.* [32] found that lengthening the ADT duration from 4 to 28 months benefited intermediate and high-risk patients in bPFS, MFS and OS at 5 years, in addition to RT at the dose of 78 Gy to the prostate.

Two phase III trial intended to prove the benefit of the addition of ADT to RT even with HDRT: the GETUG 14 and the EORTC 22,991 trials.

In the GETUG 14 trial [40], 80 Gy RT plus 4 months of ADT was better than RT alone at 5 years (21 % vs 10 %, p = 0.001), in a population driven by intermediate-risk patients. There was no difference in OS between the two groups (94 % vs 93 %) at 5 years. Results should be considered carefully though as the trial was prematurely closed because of a low accrual rate, hence a plausible lack of power.

Furthermore, 5 years may not be long enough to expect a benefit in OS; a longer follow-up could result in a significant difference between the groups.

In parallel, the EORTC 22,991 [41,42] compared RT to RT plus 6 months ADT in patients with intermediate and high-risk LPCa. The radiation dose was at the discretion of the investigator, who had the choice between 70 Gy, 74 Gy or 78 Gy to the prostate. The addition of ADT significantly improves 5-year-bPFS (HR 0.52, p = 0.001) and 5-year-cPFS in the whole population and in all dose subgroups. However, in the latest update, 10-year OS was not significantly different between the two groups (80 % vs 74.3 %, p = 0.082).

In the next few years, results from the GETUG AFU 18 trial [43], comparing 70 Gy and 80 Gy RT to the prostate with 3 years of ADT in high-risk LPCa, are expected.

- The addition of ADT to RT improves patient prognoses, irrespective of the radiation dose delivered.

Dose fractionation and ADT

The α/β ratio for PCa gives it a sensitivity to the fraction dose variation. As a consequence, many studies evaluated the efficacy of hypofractionated (2.5 to 3.4 Gy per fraction) regimen to treat LPCa [44–47] in the last few years. Hypofractionated radiation therapy (HRT) was non-inferior to normofractionated radiation therapy (NRT) in terms of PFS, with no difference in OS, and with acceptable gastro-intestinal and urinary toxicities. HRT is now a gold standard regimen for the treatment of LPCa. Among those trials, two allowed the use of ADT.

The CHHiP trial [45] compared a NRT to 60 Gy (20x3Gy) and 57 Gy (19x3Gy) in 3216 men with low, intermediate and high-risk LPCa. Among them, 97 % received a STADT of 3 to 6 months. Despite a higher proportion of acute gastrointestinal toxicities in the HRT arms (grade II or more: 38 % vs 38 % vs 25 %; p = 0.0001), the proportion of acute urinary toxicities, clinician reported and patient reported side effects at 5 years were not significantly different.

The HYPRO trial [47] compared 78 Gy to 64.6 Gy (19x3.4 Gy) in men with intermediate and high-risk LPCa. 66 % of patients received STADT or LTADT with a median duration of 32 months. Results in terms of side-effects were consistent with those obtained by Dearnaley *& al.*, with a significant higher rate of acute gastrointestinal toxicities, and equal acute urinary toxicities and late toxicities at 3 years.

We did not find any trial comparing RT plus ADT to RT alone in a hypofractionated scheme. However, the results of the CHHiP and HYPRO trials suggest that the addition of ADT to HRT is acceptable in terms of toxicity, whether STADT or LTADT is chosen.

RT plus ADT: Which sequence to adopt?

Phase III trials focusing on ADT plus RT followed different protocols: neoadjuvant, concomitant, adjuvant or a mix of these (Fig. 1). Some have tried to compare these sequences.

The NRG/RTOG 9413 [48] trial was a superiority trial comparing 2 months neoadjuvant and 2 months concomitant (NHT) versus 4 months adjuvant hormone therapy (AHT), and radiation to the prostate alone (PORT) versus the radiation of the prostate plus pelvis (WPRT) on intermediate and high-risk LPCa. Patients were randomised in 4 groups: NHT plus WPRT group, NHT plus PORT group, WPRT plus AHT group, PORT plus AHT group.

The 10-year PFS was statistically different in the four groups (p = 0.002): 28.4 % in the NHT plus WPRT group, 23.5 % in the NHT plus PORT group, 19.4 % in the WPRT plus AHT group, and 30.2 % in the PORT plus AHT group.

Pairwise comparisons showed that NHT plus WPRT was better than

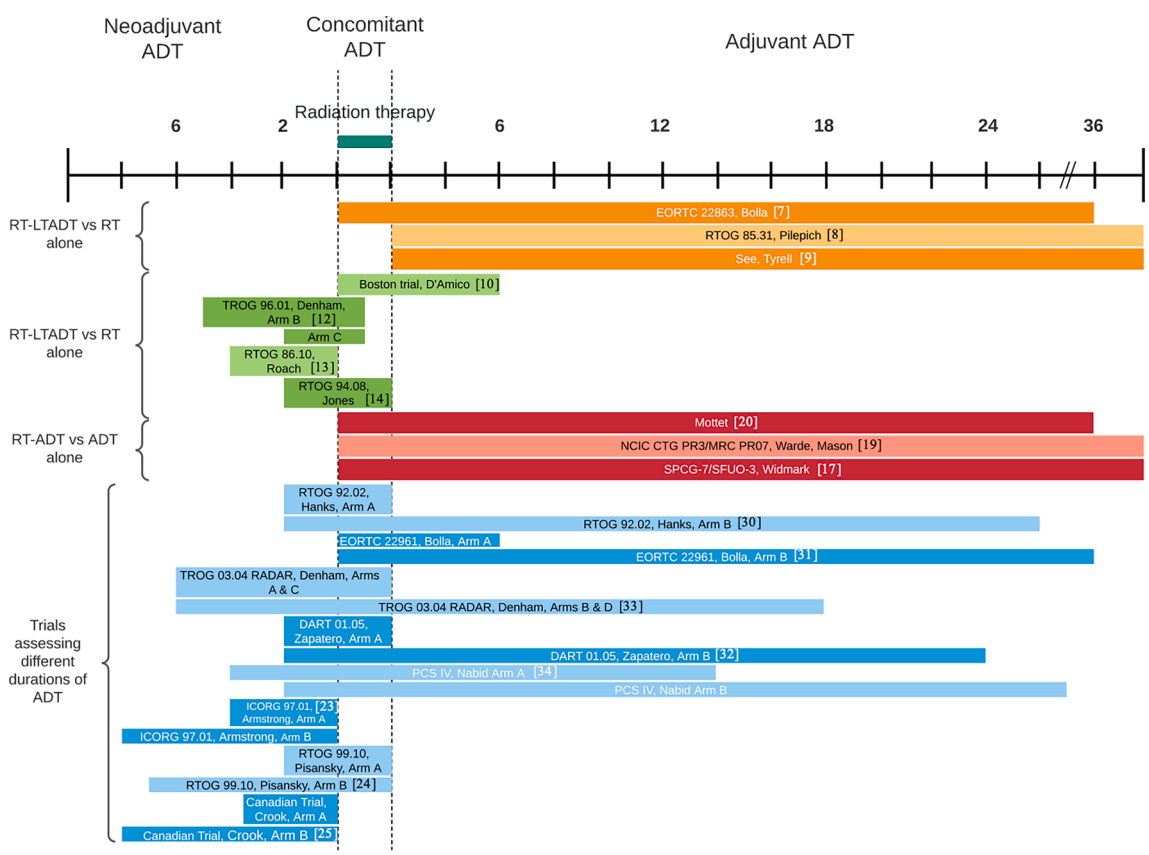

Fig. 1. Timeline with duration and sequencing of ADT in combination with RT. Trials in green had positive results on their primary endpoint, trials in red did not. Trial in orange could show positive results on its primary endpoint after no interactions between ADT and zoledronic acid were observed. *ADT: androgen deprivation therapy, RT: radiation therapy, LTADT: long-term ADT, STADT: short-term ADT.*

NHT plus PORT (p = 0.023), and better than WPRT plus ADT (p = 0.017). PORT plus AHT was found to be superior to WPRT plus AHT (p = 0.0024) and NHT plus PORT (p = 0.0032).

Unfortunately, according to the authors, the post-hoc analysis of interaction conducted between RT and HT statistically invalidated to collapse the groups into NHT and AHT, and WPRT and PORT, making it impossible to conclude on the superiority of one sequence over another.

Laverdière *& al.* [49] published two successive trials to evaluate different sequences and durations of ADT administered when administered with RT in T2-T3 LPCa.

In the L-101 study, patients were randomised into RT alone group, RT + NHT 3 months group and RT + NHT CHT and AHT 10 months group. There were significant differences in 7-year-bPFS between arms 1 and 2 (42 % vs 66 %; p = 0.009), and between arms 1 and 3 (42 % vs 69 % p = 0.003), but no difference between the two groups with ADT.

In the L-200 study, at 4 years, bPFS was not found to be statistically different between RT plus 5 months neoadjuvant and concomitant ADT versus RT plus 10 months neoadjuvant, concomitant and adjuvant ADT.

The Ottawa 0101 trial [50] is to our knowledge, the only randomised trial focusing solely on the sequence of short-term ADT in addition to RT in intermediate and high-risk patients. The patients received 6 months ADT whether 4 months neoadjuvant plus 2 months concomitant ADT or 2 months concomitant and 4 months adjuvant ADT.

At 10 years, biochemical relapse-free survival (bRFS) did not significantly differ between the two groups, neither did OS (76.4 % vs 73.7 %, p = 0.70).

Because of a lower relapse rate than anticipated, this study may have lacked power to show a statistical difference between the two groups.

Recently, the patients' reported outcomes were published, and no differences were found in the bowel or urinary symptoms between adjuvant and neoadjuvant approaches.

Spratt *& al* [51] published a *meta*-analysis to evaluate the optimal sequencing of ADT with RT, using individual patient data from the RTOG 9413 and the Ottawa 0101 trials. The patients who received a WPRT in the RTOG 9413 trial were excluded from the analysis, though all other patients from the two trials were included.

After 15 years, PFS (29 % vs 36 % HR 1.25; p = 0.01), bPFS, DM, and MFS were all significantly improved in the adjuvant group. There were however no significant differences in OS. Furthermore, there were no differences in late grade 3 gastrointestinal or genitourinary toxicities between the groups.

In the MARCAP *meta*-analysis, no significant benefits to MFS were seen at 10 years with neoadjuvant extension of ADT, based on individual data of patients from TROG 9601, ICORG 9701 and RTOG 9910 trials (HR 0.95; p = 0.50). However, based on data from RTOG 9202, EORTC 22961, DART 01/05 and TROG RADAR trials, adjuvant extension of ADT was found to be beneficial to MFS (HR 0.84; p < 0.0001) [16].

To our knowledge, these data represent the highest level of evidence available supporting AHT over NHT in terms of efficacy and without any further late toxicity.

Discussion and future directions

Over the past two decades, management of patients with LPCa has significantly changed. From the first trial of *Bolla & al.* [5] which showed the positive impact of the addition of ADT to RT, evidence based on clinical trials has never ceased to improve our understanding of ADT.

Here, we gathered pieces of evidence available in the literature on the use of hormone therapy in LPCa, in order to optimise its combination with RT.

RT plus ADT is a standard of care for patients with intermediate or high-risk LPCa. However, even if the evidence is meagre, the use of ADT in the treatment of patients with low-risk LPCa does not appear to be beneficial.

Conversely, the duration of ADT remains a challenging question. Even though it is commonly accepted that intermediate-risk patients require short-term ADT, on the other hand, high-risk patients need longer ADT, whilst the optimal duration is still being debated.

Reducing the duration of ADT without any impact on the effectiveness became a new axis of research. 36 months ADT failed to prove its superiority over 18 months in this population (25). The hypothesis that intermediate-term ADT is non-inferior to long-term ADT, albeit speculative, could allow physicians to propose 18 months ADT in selected patients, presenting 1 high-risk criterion, and comorbidities such as cardiovascular risk factors. For the others, especially those with a very high-risk LPCa, long-term ADT plus RT might remain the standard of care.

Moreover, the dichotomisation between favourable and unfavourable intermediate-risk LPCa is now well established.

In the light of recent data, the standard of care should differ in those two subgroups. The secondary analysis of the RTOG 94.08 [28] constitutes a strong piece of evidence that patients with FIR-LPCa may not require the addition of ADT to RT, and that short-term ADT should be reserved for UIR-LPCa.

One needs to be cautious, though. Indeed, 4 months ADT might be too short to show its impact, as demonstrated by D'Amico *& al* [26]. A randomised trial with a proper short-term ADT in FIR-LPCa could bring answers.

Modern LPCa treatment requires high doses or hypofractionation, allowed by image-guided RT (IGRT). The profit of the addition of ADT seems to be independent from the dose used, and the safety of its combination with HDRT or HRT has been demonstrated. Choice of RT regimen should not interfere with the indication of ADT.

In recent years, ultra-hypofractionated RT (UHF-RT) has been assessed in many trials to replace HDRT and HF-RT, the underlying idea being to deliver a more ablative dose to the prostate. The HYPO-RT-PC [52] trial was the first to date to show non-inferiority of the UHF-RT compared to conventional fractionation in FFS, with higher acute urinary toxicity but similar late ones. Although the population was exclusively composed of patients with intermediate and high-risk LPCa, none of them received ADT.

Moreover, there is currently a gap in knowledge: if ADT improves RT results by providing a synergetic effect, there is to our knowledge no evidence that this benefit would remain with UHF-RT. More data are needed on this subject.

The sequence of RT-ADT to adopt also seems to be primordial. Spratt *& al.* [51] found that STADT concomitant and adjuvant ADT was superior to neoadjuvant and concomitant ADT.

Intriguingly, the sequence may have had an impact on the results of the different trials evaluating different durations of ADT (Fig. 1). The EORTC 22,961 [31], TROG RADAR [33] and DART 01/05 [32] trials all prolonged their adjuvant ADT duration, and resulted in better outcomes in the LTADT groups.

On the contrary, the Quebec L-101 [50], the ICORG 9701 [23], RTOG 9910 [24] and the Canadian multicentre [25] trials assessed the extension of the neoadjuvant component. They failed to demonstrate an improvement with longer durations. Lengthening the adjuvant component rather than the neoadjuvant one might have led to positive results.

The *meta*-analysis by D'Amico *& al.* [26] concluded that 6 months was superior in PCSM to 3–4 months ADT in addition to RT. In fact, D'Amico *& al.* compared 2–3 months of neoadjuvant plus 1 months concomitant ADT to 4 months of neoadjuvant and concomitant ADT plus 2 months of ADT.

Optimizing the timing to begin ADT might be as important as optimizing the duration and could even be the real driver of the ADT efficacy. Studies seem necessary to evaluate the right timing to begin ADT without any change in its duration.

Moreover, there is no clear evidence to support one sequence over the other when WPRT is performed. Again, one needs new data.

Use of ADT, raises the issue of toxicity. Side effects are well-documented and comprise, cardiovascular events, asthenia, muscle loss, hot flashes, can also lead to depression diabetes, [53–56] and might

even be responsible for dementia [57–59]. Interestingly, in an update, D'Amico *& al.* performed a post-randomization analysis of the Boston trial, defining subgroups through levels of comorbidity. After a median follow-up of 16.62 years, RT alone versus RT and ADT was associated with a significantly decreased cardiac and overall mortality (HR 0.17, $p < 0.001$), in men with moderate or severe comorbidity [60]. Hence, patients under ADT require a multidisciplinary management, including the GP and, if needed, the cardiologist and the endocrinologist.

LHRH agonists are the most commonly prescribed form of ADT and are used in the large majority of trials. LHRH antagonists appeared to be a safer option regarding cardiovascular toxicity. Data from 6 trials comparing both concluded that using antagonists resulted in significantly less cardiovascular events (CE) at 12 months [61]. Since these results were from a post-hoc analysis, the possibility of uncontrolled bias in cardiovascular risk factors could not be excluded and conclusions were difficult to draw.

Recently, the PRONOUNCE trial was the first to prospectively compare the cardiovascular safety of Degarelix, a LHRH antagonist, and Leuprolide. The study was prematurely terminated because of a default of accrual. Although, no difference in major adverse CE (MACE) was found at 12 months [62]. In parallel, a real-world retrospective cohort of 7.800 patients who met the PRONOUNCE trial eligibility criteria also showed that degarelix was not associated with a lower risk of MACE than leuprolide [63].

Thus, latest data suggest that agonists and antagonists appear to be similar in terms of cardiovascular safety.

One future direction about ADT lies on its combination with other drugs to improve patients' outcomes. In men with high-risk LPCa, intensifying treatments has been under investigation. The use of new generation hormone therapy (NGHT) has been evaluated in this purpose.

In a *meta*-analysis of results of two randomised phase 3 trials from the STAMPEDE protocol[64], the addition of oral abiraterone acetate and oral prednisolone with ($n = 1060$) or without ($n = 914$) enzalutamide to LTADT in patients with high risk non-metastatic PC, was associated with a better MFS compared with LTADT alone (6-years-MFS 82 % vs 69 %; HR 0.53, $p < 0{\cdot}0001$). OS, PCSM, bPFS and PFS were also significantly improved in the association groups. However, there was no difference in MFS between enzalutamide and abiraterone acetate compared with abiraterone acetate alone (interaction HR 1.02, 0.0–1.50, $p = 0{\cdot}91$). Local RT was performed in 85 % of men ($n = 1684$) to the prostate and seminal vesicles.

In these studies from the STAMPEDE protocol, an adaptive multiarm multistage platform for randomized controlled trials, the "high-risk" group was defined as node positive or, if node negative, having at least two criteria among tumour stage T3-T4, GS 8–10 and PSA $\geq$ 40 ng/mL or relapsing with high-risk features. This definition comprises both the locally advanced and the very-high risk groups from the NCCN.

In another arm of the STAMPEDE protocol, intensification with Docetaxel also improved OS. Even if the population was driven by men with metastatic diseases, 24 % ($n = 697$) were N0M0 and the improvement of OS was found in the N0 group in the subgroup analysis. The hazard ratio for OS in 96 patients with nonmetastatic disease was 0.93 (95 % CI 0.60–1.43) with the addition of docetaxel to EBRT and ADT [65].

The NCCN guidelines thus allow the use of Abiraterone acetate + prednisolone or 6 cycles of Docetaxel in addition to LTADT and RT as an option in treatment of patients with very high-risk LPCa [22].

Data from ATLAS (intensification with Apalutamide) [66] and ENZARAD (intensification with Enzalutamide) [67] are also expected in a near future.

The addition of new drugs to ADT and RT raises new questions: for instance, it is not known how these drugs affect the efficacy of RT, and if new RT schedules are more suitable for combination with NHT or Docetaxel. The duration of the combination of ADT with NHT or chemotherapy is also an issue that needs to be assessed in future trials.

Another line of research consists in finding novel prognosis biomarkers that could help in a personalized treatment approach.

The use of genomic in PCa could shake-up the actual consensus on the use of ADT. Predictive biomarkers could improve risk stratification. For instance, the Decipher tissue-based 22 genes genomic classifier was proved to be associated with DM, PCSM, and OS independent of standard clinicopathologic variables in patients requiring salvage RT after PT and is already validated in the post-operative setting [68]. According to the NCCN, patients with high Decipher score should be strongly considered for EBRT and addition of ADT when the opportunity for early EBRT has been missed [69].

Decipher could also be used to guide intensification or de-intensification of treatment in LPCa.

The ongoing GUIDANCE trial aims to evaluate the omission of ADT in men with unfavourable intermediate-risk LPCa and a low gene risk score, as well as the addition of Darolutamide to STADT and RT in patients with UIR PLCa and a high genre risk score [70].

Another ongoing trial, PREDICT RT, will assess 12 months of ADT compared to 24 months in men with high risk LPCa and a low gene risk score, and intensification with Apalutamide in patients with high-risk LPCa and high gene risk score [71].

Although this classifier or others such as Prolaris or Oncotype Dx are not recommended for standard clinical practice yet [72], they may help to select an optimal patient management strategy in a near future.

Other prognosis markers are currently being evaluated. For instance machine and deep learning [73] or radiomics, which consists in extracting data from imaging examination to lead to better diagnoses [74] might help to more precisely classify patients, in order to tailor the treatment strategy.

Conclusion

Androgen deprivation therapy is paramount in the management of intermediate and high-risk prostate cancer. Even though progresses have been made, many questions still remain unanswered.

Proper timing for ADT initiation, treatment intensification in high-risk LPCa and de-escalation in intermediate risk LPCa or the use of prognosis and predictive biomarkers must constitute future axis of research in order to improve the outcomes of our patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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