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Current and emerging therapies for localized high-risk prostate cancer

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Abstract

Introduction: Despite progress in the field of high-risk localized prostate cancer (HRPCa) treatments, high-risk patients treated with curative intent are at increased risk of experiencing PSA failure, metastatic progression and cancer-related death. The optimal treatment strategy for these patients remains a topic of debate. This review provides an overview of the current and investigational therapeutic options for HRPCa treatment.
Areas covered: A PubMed search was performed for papers on the current evidence and perspectives on the multimodality treatment of HRPCa. We focus on both primary local treatment as well as systemic treatment options. Finally, relevant ongoing trials focusing on systemic treatments (including [neo]adjuvant treatments and chemotherapy) enrolling at least 50 patients were retrieved and listed, to highlight ongoing research and treatment optimization.
Expert opinion: Disease progression in HRPCa patients is driven by local tumor extension and subclinical metastases. Therefore, the main treatment concept is a multimodal approach targeting the primary tumor with extended surgery or RT with long-term ADT and simultaneously targeting the micro-metastatic deposits. However, there is still room for further optimization. Upcoming clinical trials comparing surgery versus RT as local treatment option, numerous trials with (neo)adjuvant chemotherapy or androgen receptor signaling inhibitors will likely change the current treatment landscape. However, a multimodal treatment strategy will stay as the cornerstone in the treatment of HRPCa.

Keywords: high-risk prostate cancer; Radiation therapy; Radical prostatectomy; multimodal treatment; Androgen receptor signaling inhibitors; review;

Article highlights:

- At present, no consensus exists on the definition of high-risk localized prostate cancer resulting in different risk-stratification systems used.
- High-risk localized prostate cancer patients are at increased risk of developing biochemical recurrence following primary treatment. These patients often need multimodal therapy (radiation therapy, surgery and systemic therapy) to attain cure.
- Novel systemic therapies, including hormonal, cytotoxic, targeted, and immunologic agents, tested in the context of rationally designed clinical trials will help better refine therapies for high-risk prostate cancer. Especially biomarker-driven trials will be of increasing importance in the era of precision medicine.
- Numerous biomarkers are currently under evaluation for predictive and prognostic purposes. The development of panels or (non-)genomic biomarkers contains the potential of improving patient stratification and therapy guidance.
- New imaging modalities, such as PSMA PET/CT and multiparametric MRI demonstrate improved staging and early detection of local and metastatic disease at the time of biochemical recurrence compared with conventional imaging. Results of ongoing randomized controlled trials will provide us with key information about its role in the high-risk setting at time of diagnosis.

1. Introduction:

Prostate cancer (PCa) is estimated to be the second most frequent cancer and the fifth leading cause of cancer death in men worldwide[1]. Approximately 15% of all PCa patients present with high-risk localized disease at time of diagnosis [2]. However, PSA-based population screening is not recommended and since less PSA-screening has been performed, the number of primarily diagnosed disease in advanced (or metastatic) stage have increased in the US and in UK [3]. High-risk and locally advanced PCa (apart from non-curable metastatic disease) are responsible for most of the PCa-related deaths. Hence, if we aim to decrease PCa-related mortality, we need to focus on offering the best possible treatment strategy to those patients and prevent development of distant metastases and subsequent death from PCa. While most high-risk patients respond favorably to local therapy with curative intent, a subgroup does not. Identifying those patients is crucial, as they may benefit from multimodal therapy, targeting both the local and systemic components of the disease. According to the European Association of Urology (EAU) guidelines and a recent systematic review on primary local treatment of high-risk PCa (HRPCa) , radical prostatectomy (RP) with extended pelvic lymph node dissection (ePLND) as part of multimodal therapy, external beam radiation therapy (EBRT) + long-term androgen deprivation therapy (ADT) or EBRT with brachytherapy (BT) boost + long-term ADT should be offered to HRPCa patients [4,5].

In this review, an overview on the available therapeutic options is provided. Next, future perspectives including novel treatment strategies, the use of genomic markers and novel imaging techniques are discussed.

2. Current treatment strategies

Risk stratification of PCa into low, intermediate and high risk disease allows us to tailor treatment according to the aggressiveness of the disease. At present, no consensus exists on the definition of HRPCa, resulting in several risk stratifications used in daily clinical practice [6]. The best-established risk stratification is the one of D'Amico et al., which is adopted by the EAU, American Urological Association (AUA) and the National Institute for Health and Care Excellence (NICE) guidelines [5,7,8]. This classification used PSA recurrence to subdivide localized PCa into three risk categories (low, intermediate and high) with HRPCa defined as a PSA >20ng/ml OR biopsy ISUP 4-5 (GS 8-10) OR clinical stage ≥T2c. Ideally, outcomes in this high-risk group should be homogeneous after optimal treatment. However, a subgroup of these high-risk patients remains at an increased risk of disease progression after aggressive treatment, whilst others are cured by initial treatment with curative intent [9]. Indeed, the National Comprehensive Cancer Network (NCCN) guidelines substratify HRPCa patients into high-risk and very high-risk, as these latter have poor oncological outcomes compared

to 'regular' HRPCa patients. This substratification may help to counsel and select optimal candidates for multimodal treatment or clinical trials. Treatment options for HRPCa comprise RT or surgery targeting the disease locally, but they should be seen as part of a multimodality approach [10]. Due to the hormone responsive nature of PCa, several agents targeting the androgen pathway can be added in the (neo)adjuvant setting. They reduce androgen levels by directly inhibiting the androgen receptor (antiandrogens) or by decreasing levels of follicle-stimulating hormone (FSH) and luteinizing hormone(LH) (luteinizing hormone-releasing hormone [LHRH][ant]agonists). The landscape of possible treatments of HRPCa has evolved considerably over the past two decades, yet no consensus regarding the optimal treatment strategy has been reached.

2.1 Radiation therapy

According to the EAU guidelines, EBRT with 76-78 Gy in combination with long-term ADT (2-3 years) for high-risk and locally-advanced PCa or EBRT with BT boost in combination with 2-3 years ADT for HRPCa should be offered [5]. ADT alone should not be offered to these patients, based on data of two important randomized controlled trials (RCT) showing a prolonged clinical disease-free and overall survival (OS) with EBRT + ADT compared ADT alone[11,12]. The added value of combining ADT with EBRT vs EBRT alone in HRPCa has also been confirmed in multiple RCTs [13–17]. The TROG 96.01 trial showed lower PCa and all-cause mortality in patients treated with 6 months of neoadjuvant ADT (Goserelin + flutamide) added to EBRT of 66 Gy [13]. Bolla et al evaluated the addition of 3 years (neo)adjuvant ADT and showed statistical significant improvements in disease-free survival and OS without increased cardiovascular toxicity for the combination of EBRT with ADT [14,16]. Concerns exist regarding (cardiovascular) toxicity, and the impact of ADT on quality of life (QoL). Although data from RCTs on cardiovascular toxicity of ADT are contradictory, a meta-analysis of observational studies by Bosco et al. found a positive association between ADT and cardiovascular death [18]. Since observational studies are a better reflection of the general population, one should be careful to administer ADT to older patients or patients with multiple (cardiovascular) comorbidities. Newer RCTs including elderly and patients with a history of cardiovascular events should be performed.

Several RCTs show superior results for long-term ADT (2 years) compared to short-term ADT (4-8 months). Of particular interest is the superiority trial by Nabid et al, evaluating the results of EBRT + intermediate-term ADT (18 months) compared to EBRT + ADT of 36 months [19] with the purpose of reducing total time of ADT and impact on QoL, without compromising the impact on survival. Interestingly, 36 months of ADT resulted in an increased control of biochemical recurrence, but without a significant benefit in other survival domains like local failure, metastases-free survival and

OS. Together with a better toxicity profile and lower cost, intermediate-term ADT might represent a valid therapeutic option but properly designed non-inferiority trials definitely need to confirm these findings.

BT is characterized by the highly conformal dose distribution to the prostate while sparing surrounding organs at risk (except the prostatic urethra). Moreover, BT overcomes the problem of organ movement. Two different types of brachytherapy (BT) are used in PCa: permanent low-dose-rate (LDR) seed implants or high-dose-rate (HDR) afterloading. In HRPCa, BT is used as a boost in addition to EBRT) (and not as a treatment on its own), as BT alone may not adequately cover the peri-prostatic tissues [20]. Compared to LDR, HDR BT has the biological advantage of delivering high-doses per fraction, and it is easier in implanting the treatment volume. Emerging data suggest that the combination of EBRT + BT improves local control and maybe OS in HRPCa. Three prospective randomized trials have demonstrated an improvement of biochemical control when EBRT+BT was used compared to EBRT alone [20–22]. However, no difference in clinical outcomes, was observed. Also, the heterogeneity in techniques, doses, dose per fraction and length of ADT makes definitive conclusions difficult [23]. In a large retrospective cohort study with patients with GS 9-10 PCa [24], the 5-year PCa-specific mortality rate was lower in patients receiving EBRT + BT (3%) compared to RP (12%) and EBRT (13%). Moreover, EBRT+BT was also associated with a significantly lower rate of distant metastasis. Similar results were described in two other large retrospective trials [25,26]. Importantly, BT boost does not alter the fact that ADT remains a critical component in HRPCa patients. A meta-analysis compared the oncological outcomes of intermediate and high-risk patients treated by EBRT+ADT versus EBRT+BT without concomitant ADT [27]. EBRT+ADT had improved OS compared to EBRT+BT. Potential side effects caused by the additional BT should be taken into consideration, as it has been shown that BT could increase ≥ grade 3 late GU toxicity [23], however this was not confirmed in a meta-analysis of the three prospective (above mentioned) trials. This toxicity is most likely related to the BT technique used (permanent vs. temporary implants) and improvement of technological advances for definition and sparing critical structures might help decrease the urinary toxicity [23].

2.2 *Radical prostatectomy*

Historically, RP was not recommended for the treatment of HRPCa because of inadequate disease control and morbidity [28]. However, several studies demonstrated that RP is an excellent treatment modality for local disease control in HRPCa patients [29–31]. In a study by Boorjian et al., 1513 HRPCa patients underwent RP as primary treatment. Although 10-year biochemical progression-free survival (BPFS) was significantly lower in the high-risk group compared to intermediate risk (55% vs 65%

respectively), both freedom from systematic progression and cancer-specific survival (CSS) at 10 year were excellent in the high-risk population (89% and 95% respectively)[30]. Also, Spahn et al. treated 372 clinical HRPCa patients with RP resulting in good local tumor control and a comparable 10-year CSS of 87.2% [29]. Even after extensive follow-up of 20 years, excellent oncological outcomes are shown in a large series of cT3 patients treated with RP as primary treatment with distant metastases-free survival and CSS of 72% and 81% respectively [32]. Two remarks should be made about these studies. First, all high-risk patients had an increased risk of biochemical recurrence with 10-year BPFS ranging from 41% to 55%, while experiencing excellent 10-year CSS outcomes suggesting that the true impact of BCR on survival is not the same for every patient experiencing PSA relapse but that it is limited to a subgroup of patients [33]. This might be an explanation for the discrepancy between the low BPFS-rates and the excellent CSS. Second, many of the patients received adjuvant therapy (ADT or RT or both) during follow-up and the results reflect the use of a multimodality treatment rather than RP as monotherapy. Besides resulting in a good local tumor control and cancer survival, surgical intervention as primary treatment renders other benefits. One of the main advantages is the possibility of a full pathological staging after RP. Clinical staging, based on DRE, imaging and biopsy-based pathology is often imprecise and unreliable, resulting in both down- and upstaging at final pathology. Reese et al showed that clinical T-staging by means of DRE and/or TRUS can result in staging errors up to 35.4%, with more errors resulting in downstaging (55.1%) than upstaging (44.9%) at final pathology after RP [34]. Also, for the final Gleason score (GS) discrepancy exist between GS obtained at biopsy and after RP [35]. Epstein et al. showed that up to 53.1% of the biopsy GS 8 and 31.1% of the biopsy GS 9 and 10 appear to have a lower GS at final pathology [36]. Even though, the robot-assisted laparoscopic approach is associated with less blood loss and shorter hospital stay compared to the open approach, no superiority in terms of positive resection margins, complication rate, functional and oncological outcome has been observed for HRPCa. In contrast, the surgeon's capability is an important factor in final outcomes.

2.2.1 Extended pelvic lymph node dissection

Extended pelvic lymph node dissection (ePLND) which is standard in all HRPCa patients, is an important way of accurate disease staging with up to 40% of the initial clinical lymph node (LN) negative patients appearing to have metastatic LN [37]. Currently, the EAU guidelines recommend to perform an ePLND when the estimated pelvic LN involvement >5% according to the Briganti nomogram [38]. Despite the introduction of novel imaging techniques such as PSMA PET/CT, ePLND remains the gold standard for accurate LN staging despite toxicity such as lymphocele. However, the role of ePLND on survival is unclear [39].

2.2.2 Radical prostatectomy combined with systemic therapy

No compelling evidence exists regarding the benefit of (neo-)adjuvant ADT with surgery. Neoadjuvant ADT together with RP was first tested in the end of last century and consisted of LHRH agonists often in combination with first-line anti-androgens (bicalutamide). However, besides an improvement in negative surgical margins, no improvement in OS was observed and this therapeutic approach was abandoned for years. Besides inclusion of inappropriate (mainly low- and intermediate-risk) PCa patients, one possible explanation is an incomplete androgen suppression with remaining androgen-driven signaling within the tumor tissue despite a drop in serum androgens to castration-level[40,41]. The PUNCH trial, investigated the impact of neoadjuvant chemohormonal therapy (ADT + docetaxel (75 mg/m2 every 3 weeks for 6 cycles) compared to no neoadjuvant therapy in 788 HRPCa patients. Patients who received chemohormonal therapy had improved pathological outcome (surgical margins and positive LNs) but no difference in the primary endpoint, 3-year BPFS was observed[42]. Renewed interest in offering neoadjuvant hormonal therapy before RP to HRPCa grew with the development of new-generation, more potent anti-androgens (like abiraterone acetate, enzalutamide, apalutamide and darolutamide). These molecules have showed improved survival in metastatic castration-resistant and metastatic hormone-sensitive PCa and similar benefits might be expected when introduced in the localized setting[43–46]. Few prospective phase-2 studies with neoadjuvant abiraterone acetate and enzalutamide have been reported with promising outcomes regarding pathological response[41,47–49]. However, no long-term outcomes have been reported yet. Multiple clinical trials with these molecules are ongoing (table 1). Of particular interest is the phase-3 study, PROTEUS, that investigates the impact of 6 months neoadjuvant and 6 months adjuvant apalutamide + LHRH analog vs LHRH analog only in 1500 HRPCa patients with metastasis-free survival as primary endpoint. Remarkably, most ongoing studies did not include a control arm without neoadjuvant therapy as gold standard. In absence of long-term outcomes of these studies, the use of neoadjuvant therapy is not recommended by any guideline.

The role of adjuvant hormonal therapy following RP is unclear as ADT is often combined with (salvage/adjuvant) RT in most prospective studies. In postoperative LN negative patients, adjuvant ADT should not be offered since no impact on survival was observed [15,50]. However, in patients with pN1 disease, risk of relapse is higher and adjuvant treatment should be considered, depending on tumor characteristics and extend of LN involvement [39,51–54]. Messing et al compared immediate adjuvant ADT versus salvage ADT in LN positive patients after RP and concluded that early ADT in this high-risk population improves both OS and CSS [55]. However, results should be interpreted with caution since, besides being largely underpowered, deferred treatment was initiated at time of clinical progression and not PSA recurrence like you would expect nowadays and

patients had bulky nodal disease with multiple adverse tumor characteristics making the results less applicable in patients with less extensive disease. The phase-3 study, AFU-GETUG-20, is currently investigating the role of 2 years adjuvant LHRH-agonist (leuprolide) compared to active surveillance in 700 patients following RP with 10-year metastasis-free survival as primary endpoint (NCT01442246). Moreover, the phase-2 ADAM trial will investigate the role of 2 years adjuvant LHRH analog + apalutamide in HRPCa patients (NCT04295447). At present, the use of adjuvant hormonal therapy alone is not recommended for the treatment of HRPCa patients.

To summarize, RP + ePLND for HRPCa can offer desirable disease control without the need for immediate and long-term adjuvant treatment when performed by experienced urologists, but patients must be informed about the possible need for a multimodal approach to accomplish the best possible result [38]. The impact of potent anti-androgens as (neo)adjuvant therapy in HRPCa is currently under investigation.

2.3 Radiotherapy vs radical prostatectomy

It is currently not clear which of both treatment modalities (surgery or EBRT) is superior over the other. There are no RCTs with a head-to-head comparison of RP and EBRT and we can only rely on multiple retrospective series. Only the ProtecT trial randomized localized PCa patients into RP, RT or active monitoring showing no difference in cancer-specific mortality. However, only a minority of the included patients had HRPCa, so these results should not be extrapolated to this population [56]. When RP was compared to EBRT with ADT, results remain contradictory with several studies showing a survival advantage for RP over EBRT + ADT [57–60], whereas others remain inconclusive [61–65]. These retrospective comparative studies do show the need for multimodality treatment in this high-risk setting. Tilki et al suggested advantage of RP in a multimodality setting showing that RP alone resulted in a higher cancer-related death and overall mortality when compared to MaxRT (= EBRT + BT + ADT). However, when compared to RP in combination with adjuvant RT or MaxRP (RP + RT + ADT) no differences in survival was observed in patients with very HRPCa (GS 9-10)[63]. Drawing conclusions from these heterogeneous data from different non-randomized studies in different time setting is difficult and results should be interpreted with caution. For example, in a study by Zelefsky et al. showing favorable results for RP over EBRT despite statistical correction, patients receiving EBRT were older and had a higher biopsy GS at presentation [66]. Due to undocumented variables, it is possible that the EBRT group had more aggressive PCa compared to the RP group without the possibility for statistical correction. Moreover, in several retrospective comparative series, RP is compared with EBRT without ADT, which is in fact an under-treatment in this patient population [67–

70]. Finally, a difference in toxicity profiles is present between the two treatment modalities. Apart from the known genitourinary and gastrointestinal complications, other major complications should be discussed with the patient before deciding the optimal treatment [71,72]. Prospective studies on functional outcomes following RP for HRPCa remain scarce. Pompe et al, found that patients with very-high risk PCa according to the NCCN classification, did not have worse functional outcomes compared to high-risk NCCN PCa patients [73]. For both groups, return of the erectile function was observed in almost 30% and return of continence in 80% at 1 year of follow-up. Not surprisingly, functional outcome of patients who receive additional therapy (RT +/- ADT) are worse compared to patients who receive surgery only [74].

There is a clear need for prospective randomized trials that will provide reliable information on both treatment modalities in a high-risk setting, with the unique opportunity of comparing both methods while assessing health-related quality of life outcomes, urinary symptoms, erectile function and radiation effects from the baseline through therapy and in follow-up. The **SPCG15 trial** (NCT02102477) is a phase-3 study comparing RT with RP as primary treatment in a multimodality setting in HRPCa. In this study, patients receive either RP (+/- adjuvant/salvage RT) or RT + ADT. The primary endpoint is cause-specific survival and the results are expected in December 2027.

2.4 Indications for adjuvant or salvage treatment after RP

High-risk patients treated with initial RP but with adverse risk factors such as high PSA levels, pT3, positive surgical margins, and GS of ≥8, are at an increased risk for relapse and decisions have to be made whether to offer additional therapy [75,76].Both ADT and RT can be offered as adjuvant or salvage treatment. As discussed above, the role of ADT alone after surgery remains controversial. Besides androgen ablation, RP renders the possibility to treat patients with adjuvant or salvage RT (+/- ADT). In certain high-risk series, more than 40% of patients after initial RP will not recur at 10-year follow up and adjuvant RT might be seen as possible overtreatment with subsequent unnecessary adverse event [76,77]. The EORTC 22911 and ARO 96-02 trials compared adjuvant RT after RP with a wait-and-see policy, showing only improvement in biochemical progression-free survival, without improvement in overall survival with adjuvant RT after 10 years of follow-up [76,78]. On the other hand, the SWOG trial comparing adjuvant RT with standard of care in pathological advanced PCa did show an improved distant metastasis-free survival and OS in patients treated with adjuvant RT[79]. Very interesting are the presented data of the RADICALS phase-3 trial, investigating the timing of RT (RADICALS-RT; adjuvant RT or early salvage RT in case of PSA failure) in patients receiving RT following RP [75], showing no improvement in biochemical-free survival but an increase in urinary toxicity with adjuvant RT. They promote a conservative approach where early

salvage RT should be offered at time of PSA failure. Several ongoing clinical trials are trying to further elucidate the role of adjuvant or salvage therapy after RP or radiation therapy. The RAVES phase-3 trial (NCT00860652), which is equivalent to the RADICALS-RT trial, presented similar biochemical failure-free survival rates with lower levels of GU toxicity for early salvage RT but failed to show non-inferiority to adjuvant RT [80]. Finally, the GETUG-17 (NCT00667069) study compares adjuvant RT + 6 months of LHRH agonist versus salvage RT + 6 months of LHRH agonist in patients with pT3R1 pN0 or pNx disease following RP, with similar results as RAVES and RADICALS-RT trials. Prospective preliminary meta-analysis called, ARTISTIC, suggested that (early) salvage RT provides similar outcomes in terms of PSA relapse compared to adjuvant RT and prevents many patients from potential RT-induced side effects [81]. However, in absence of these survival data, the EAU-guidelines still recommend to offer adjuvant RT to highly selected patients with severe adverse pathological features such as positive lymph nodes (pN1) following RP. The optimal duration of concomitant ADT with salvage RT is not yet determined. The GETUG-AFU-16 trial compared early SRT alone with early SRT plus 6 months of androgen-deprivation therapy in patients experiencing BCR (PSA should be <0.5ng/ml) after RP [82]. Patients receiving the combination treatment were significantly more likely to be free of PSA relapse and clinical progression at 5 years. These results were confirmed by the RTOG 9601 trial, in which patients were randomized between salvage RT alone or salvage RT plus 2 years of bicalutamide 150 mg daily [83]. At 12 years of follow-up, an overall survival of 5% in favor of the combination group was noted with the greatest benefit in patients with aggressive pathological features. Despite the results of those 2 trials, the optimal duration of ADT is not yet clear, as retrospective evidence suggests that a longer administration of might be beneficial [84,85]. In the RADICALS trial [86], there is a subsequent randomization for hormone therapy duration (no hormonal therapy versus RT with short-term hormonal treatment versus RT with long-term hormonal therapy). The LOBSTER trial compares 6 versus 24 months of ADT together with high-dose salvage RT in the case of BCR after RP in pN0 PCa patients [87]. In contrast to the salvage setting, no clear evidence exists to add concomitant ADT to adjuvant RT.

The addition of concomitant chemotherapy to EBRT+ADT has been studied in several randomized trials (GETUG-12, RTOG 0521, STAMPEDE). The NRG Oncology RTOG 0521 trial randomized HRPCa patients between EBRT + 2 years LHRH agonist or EBRT + 2 years LHRH agonist + 6 cycles of docetaxel [88]. The four-year OS rate was 89% in the LHRH only arm compared to 93% in the chemo-hormonal arm (HR 0.69; 90% CI 0.49-0.97; p=0.034). The GETUG-12 study, randomly assigned HRPCa patients into treatment with EBRT, a LHRH agonist (3 years) + 6 cycles of docetaxel + estramustine phosphate or EBRT and a LHRH agonist only (n=206) [89]. The 8-years relapse-free survival was 62% in the chemo-ADT group compared to 50% in the ADT only group (HR 0.71; 95% CI 0.54-0.94;

p=0.017). With a median follow-up of 8.8 years (IQR 8.1-9.7), there was no difference in metastasis-free or OS. In the multi-arm study STAMPEDE, patients with high-risk, locally advanced, metastatic or recurrent PCa starting first-line hormone therapy were included with standard of care EBRT given in 62% of the cases (mandatory for N0M0 since 2011 and optional in case of N+M0 disease) [90]. Survival reports were reported for three research comparisons testing the addition of zoledronic acid, docetaxel, or their combination to standard of care versus standard of care alone. For the non-metastatic group, only an improvement of failure-free survival could be established, with survival data being immature. However, when considering the use of concomitant chemotherapy, one should balance the potential benefit against possible side effects. In the STAMPEDE trial, for example, there was increased grade 3-5 toxicity described in 52% of the patients receiving concomitant docetaxel.

3 Future perspectives in the treatment of high-risk prostate cancer

The therapeutic landscape of localized HRPCa is still a highly evolving field. This is apparent by the numerous clinical trials ongoing for both RP and RT. Additional advances in monotherapies (RP and EBRT) are limited by the tolerability of extended surgery and dose limitations, but also due to subclinical metastases. Treatment optimization will therefore rely on improvement of multimodality treatment and development of novel therapeutic strategies. Table 1 provides an overview of ongoing trials involving RT as primary treatment. They focus on treatment intensification with a multimodality approach with the purpose of eradicating both the primary tumor and possible micrometastases, not (yet) visible on conventional imaging (bone scan and computer tomography). Of interest are the ATLAS (NCT 02531516), the ENZARAD (NCT 02446444) and the DASL-HiCaP study (NCT04136353). These phase-3 RCTs investigate the benefit of the addition of a second-generation anti-androgen (apalutamide, enzalutamide and darolutamide respectively) to an LHRH agonist in HRPCa patients treated with EBRT to evaluate if newer, more specific anti-androgens have prolonged effects in this difficult-to-treat patient population. The importance of simultaneously treating pelvic LN by means of prophylactic whole pelvic RT (WPRT) is still an ongoing debate. For many other solid tumors, prophylactic lymph nodal RT is the standard of care, but no definitive evidence of either benefit or harm is available for PCa. The recently published NRG/RTOG 9413 trial shows an improved biochemical failure and progression-free survival with WPRT compared to RT to the prostate alone (PORT), despite an increase in grade 3 gastro-intestinal toxicity. Finally, two ongoing trials explore the role of concomitant chemotherapy with EBRT as primary treatment. The addition of chemotherapy cannot be seen as a standard of care, but it can be tempting approach when combined with local curative treatment, since residual disease resistant to RT or ADT or the existence of micrometastases can be potentially eradicated by chemotherapy. PEACE2 (NCT01952223) is a four-arm phase-3 study investigating the effect of WPRT with concomitant cabazitaxel. Patients are randomized to either

PORT + ADT +/- cabazitaxel or WPRT + ADT +/- cabazitaxel. Progression-free survival is the primary endpoint and results are expected in November 2020. Another trial is investigating the concomitant use of docetaxel with ADT and EBRT to the prostate in the same high-risk population (NCT00116142). Table 2 provides an overview of the ongoing trials with RP as primary treatment. Most trials are currently testing the benefit of neoadjuvant systemic therapies in patients with HRPCa. Unlike for EBRT, to role of upfront ADT still remains to be decided. Historical series could not show a survival benefit with the combination of ADT with RP. However, with the development of newer, more potent antiandrogens there is a renewed interest in neoadjuvant hormonal therapy with multiple phase-2 studies evaluating second-generation anti-androgens in localized HRPCa settings: neoadjuvant apalutamide (NCT03080116, NCT03767244), neoadjuvant apalutamide and abiraterone (NCT03279250, NCT03436654, NCT02903368 and NCT02789878), neoadjuvant enzalutamide and abiraterone (NCT02268175). In most of these studies, complete pathological response and minimal residual disease at final pathology are the primary endpoints. Similar to the EBRT trials, the use of chemotherapy is also being evaluated (adjuvant or concurrent) with RP. One ongoing trial is investigating neoadjuvant cabazitaxel + abiraterone acetate (NCT02543255) in HRPCa patients. Genomic biomarkers might improve risk stratification of non-metastatic PCa patients and might influence therapeutic decision making. Recently, the NCCN guidelines recommend to the use of Decipher and Prolaris tumor-based molecular assays in men with HRPCa and a life expectancy of > 10 years. When combined with the NCCN risk stratification for localized PCa, Decipher, a 22-gene genomic classifier, improved the estimation of risk to develop distant metastases compared to the NCCN risk groups only [91]. Moreover, Decipher was a significant and independent predictor of metastasis in HRPCa patients following local therapy [92,93]. Currently, the Decipher assay is used in the phase-3, PREDICT-RT (NRG GU009), trial to optimize treatment decisions in HRPCa patients. Patients with high decipher scores will be randomized to either standard of care (definitive RT + 2 years ADT) or standard of care + treatment intensification with apalutamide and abiraterone. Patients with low decipher scores will be randomized to either standard of care (definitive EBRT + 2 years ADT) or definitive EBRT + 1 year ADT (treatment de-intensification). Decipher might also help to identify patients who would benefit from adjuvant therapy following RP. It was suggested that post-RP patients with positive surgical margins or pT3 with high Decipher scores might benefit from adjuvant RT, while an 'early salvage RT' strategy might be preferred for patient with low scores [94]. Ongoing trials such as the NRG-GU002 and the ERADICATE trial, have incorporated the decipher genomic classifier to optimize treatment outcome following RP. Identification of germline mutations in a clinical trial setting could also be useful for mutation-dependent treatment intensification). For example, patients with non-metastatic PCa who developed mCRPC, frequently (23%) had mutations in DNA damage repair genes (BRCA1, BRCA2, ATM) [95]. These mutations are often found in localized

PCa with high GS (ISUP grade group ≥3) and high pathological T-stage (≥pT3)[96,97]. Therefore germline genetic testing might be considered in localized PCa patients with high-risk features such as T3-disease or higher, intraductal/ductal pathology or ISUP 4-5 [98]. These men might benefit of PARP inhibitors such as Olaparib in clinical trial setting (NCT03047135). Olaparib has already demonstrated to delay the time to progression in mCRPC patients who are progressive under abiraterone or enzalutamide [99].

4 Expert Opinion:

HRPCa is a disease with poor outcomes if not curatively treated. There are several very important aspects to ensure the best care for these patients: adequate staging, first-line treatment, prediction and recognition of early progression after initial treatment and appropriate treatment of disease progression.

Recent evidence shows that a multimodal approach is the cornerstone of the treatment of HRPCa and this message should be translated to the patient. RP + ePLND or RT + long-term ADT should both be recommended as equal first-line treatment modalities [81]. In this setting, it is very important that all pro and cons should be discussed with the patient. Robot-assisted, laparoscopic or open RP with ePLND are recommended when the patient chooses surgical treatment. There is no clear evidence of difference in long-term functional and oncological outcomes between these surgical treatment options. The recommended EBRT dose is 76-78 Gy. However, the combination of EBRT with BT boost provides promising results. ADT should be continued for at least two years. There is insufficient evidence to support prolongation of ADT up to 3 years. So far, there is no long-term follow-up data which demonstrates the effectiveness of neoadjuvant treatment in HRPCa patients. Therefore, neoadjuvant treatment should not be recommended in daily practice. Recent evidence also shows that ADT monotherapy does not ensure adequate disease control and should not be considered as a valid treatment option in HRPCa patients [4].

Histopathological cancer features such as stage pT3b-4, positive surgical margins, ISUP 4-5, pN1, are well known predictors for disease progression following RP and have been used in various prediction models [4,100,101]. Recent studies have shown that PSA persistence (≥0.1 ng/ml) at two months after RP demonstrated a high probability for clinical progression and cancer-specific mortality in HRPCa cohorts[102,103]. PSA persistence is an early objective marker post-surgery which could reflect cancer behavior. It is also very likely that this parameter will be incorporated in future predictive models. PSA dynamics at biochemical recurrence can also be considered an important

predictor of disease progression. The EAU PCa guideline panel proposed a high-risk BCR subgroup (PSA-doubling time ≤1 year and pathological GS 8–10 for RP; interval of biochemical failure (IBF) ≤18 months and biopsy GS 8-10 for RT) and low-risk BCR subgroup (PSA-doubling time>1 year and pathological GS<8 for RP; IBF >18 months and biopsy GS <8 for RT) [81]. This model has recently been validated and show high predictive accuracy [73]. Numerous biomarkers are currently under development and evaluation for predictive and prognostic purposes. It is highly unlikely that a single biomarker will be able to guide treatment. Therefore, the development of panels or (non-)genomic classifiers contain this potential. Such classifiers are being designed or have been already tested and validated [104–107]. One of the key questions in recent genomic studies is understanding if primary tumor biopsies can be used for molecular stratification to identify patients with increased risk of disease progression [95]. In such cases initiation of DNA repair-targeting therapies could be rationale.

Finally, new imaging modalities, such as PSMA PET/CT and multiparametric MRI demonstrate improved staging and early detection of local and metastatic disease at the time of BCR compared with conventional imaging (bone scan, abdominal and chest CT). Moreover, a very recent RCT in HRPCa patients demonstrated the superiority of PSMA PET/CT in comparison with conventional imaging for the detection of pelvic node metastases and distant metastases prior to local therapy [108]. If these results are confirmed by other studies, it is very likely that PSMA PET/CT will replace conventional imaging in HRPCa patients and can change the initial treatment of these patients.

Correct prediction and early detection of disease recurrence are important for the timely initiation of additional treatments. After surgery in HRPCa, unfavorable disease characteristics are often seen at histopathology. There is no strong evidence that adjuvant RT provides benefit on long-term oncological outcomes compared with salvage RT. However, early salvage RT shows superior results in comparison with delayed salvage RT. The optimal way to stratify patients for the timing of salvage treatment is based on the previously mentioned clinic-pathological predictors. Up to now, there is a lot of data but so far, no level 1 evidence of improved outcomes, regarding the effectiveness of up-front chemotherapy or androgen receptor signaling inhibitors (abiraterone, enzalutamide, apalutamide or darolutamide) after surgery. Such data are awaited and badly needed in the subgroup of patients with very aggressive PCa. Adjuvant chemotherapy after RT did show superiority on overall survival in HRPCa patients [88]. However, a significantly higher rate of chemotherapy related toxicities was registered. The long-term results of STAMPEDE study in non-metastatic patients are still awaited [109]. The data of salvage focal therapies in radio-recurrent PCa are scant and these therapies should not be considered a validated treatment option in HRPCa patients. Indeed, the landscape of HRPCa treatment is dynamic. The evidence that is expected likely might change treatment modalities that are (not) recommended today.

5. Conclusions

Men with HRPCa frequently have disease progression driven by local tumor extension and subclinical metastases. The main concept of treatment in these men is a multimodal approach targeting the primary tumor with extended surgery or RT with long-term ADT and simultaneously targeting the micro-metastatic deposits. However, further optimization is needed. Upcoming clinical trials comparing surgery versus RT as primary high-risk treatment option, numerous trials with neo- and adjuvant chemotherapy or ARSI will likely change the current treatment landscape. Clearly, a multimodal treatment strategy will stay as the cornerstone in the treatment of HRPCa. However, clinicians and patients should be aware that multimodality treatment results in worse functional outcomes.

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Table 1: Ongoing studies with radical prostatectomy as primary treatment

Reference	Phase	High risk factors for inclusion	Arms	Primary e
		Androgen deprivationt herapy		
NCT03767244	3	NS	**Arm1**:neoadjuvantLHRH agonist/antagonist + Apalutamide during 6mo followed by RP **Arm2**: neoadjuvant LHRH agonist/antagonist + Fixed dose tablets (250 mg of abiraterone acetate/60 mg apalutamidewith prednisone during 6 mo followed by RP **Arm3**: neoadjuvant LHRH agonist/antagonist + Placebo during 6 mo followed by RP	Pathologi complete Metastasi survival
NCT03436654	2	- GS 8-10 OR - GS 4+3 with one of the following features: PSA ≥ 20 mg/mL within 2 mo prior to diagnostic biopsy MRI suspicious for radiographic T3 disease; defined as >75% probability of extracapsular extension or seminal vesicle invasion in the opinion of the reading radiologist OR GS 3+4 or 4+3 and Oncotype DX Genomic Prostate Score of >40 With or without clinical N1 (size >1.5cm in the short axis)	**Arm1:** Neoadjuvant LHRH agonist/antagonist + Apalutamide followed by RP **Arm2:** Neoadjuvant LHRH agonist/antagonist + Apalutamide + Abiraterone followed by RP	Pathologi complete minimal r disease
NCT03279250	2	Clinical >/= stage T1c/T2 tumor with GS>/=8 b) Clinical stage >/=T2b tumor with GS>/=7 and PSA >10 ng/ml	**Arm1:** 6mo neoadjuvant LHRH Agonist + Apalutamide followed by RP **Arm2**: 6mo neoadjuvant LHRH Agonist + Apalutamide + Abiraterone Acetate + Prednisonefollowed by RP	Pathologi ≤ ypT2
NCT03080116	2	Intermediate (at least 2 of the following factors: cT2b, biopsy GS 7, PSA 10-20ng/ml) or high-risk PCa (clinical stage≥T2c and/or biopsy GS≥8 and/or PSA>20ng/ml), cN0-cN1, cM0	**Arm1**: 3mo neoadjuvant LHRHantagonist + Apalutamide followed by RP **Arm2**: 3 mo neoadjuvant LHRHantagonist + placebo followed by RP	Pathologi complete minimal r disease
NCT03009981	3	Biochemically recurrent PCa following RP with PSA doubling time ≤ 9 mo at the time of study entry.	**Arm1:** RP followed by 52 weeks salvage LHRHantagonist **Arm2**: RP followed by 52 weeks salvage LHRHantagonist + Apalutamide **Arm3:** RP followed by 52 weeks salvage LHRHantagonist + Apalutamide + Abiraterone	PSA progr free-survi
NCT02903368	2	- GS ≥ 4+3=7 OR - GS 3+4=7 AND at least one of the following: PSA >20 ng/dl or T3 disease (as determined by MRI).	**Arm1:** 6 mo neoadjuvant LHRH Agonist + Apalutamide + Abiraterone Acetate + Prednisone followed by RP **Arm2:** 6mo neoadjuvant LHRH Agonist + Abiraterone Acetate + Prednisone followed by RP **Following RP:** Arm1: observation Arm2: Adjuvant 12 mo LHRH Agonist + Apalutamide + Abiraterone Acetate + Prednisone	Pathologi complete minimal r disease
NCT02789878	2	- Tumor stage T3 by digital rectal examination, or - Primary tumor GS ≥ 8, or - PSA ≥ 20 ng/mL	**Arm1:** 3mo neoadjuvant LHRH agonist + Abiraterone followed by RP **Arm2**: 3mo neoadjuvant LHRH agonist + Abiraterone + Apalutamide followed by RP	Pathologi response
NCT02268175	2	- Intermediate-risk disease defined as GS 4+3=7 disease OR - High-risk disease defined as GS 8-10 OR PSA > 20 ng/dL OR T3 disease (by prostate MRI)	**Arm1**: 6mo neoadjuvant LHRH agonist + Abiraterone + Enzalutamide followed by RP **Arm2:** 6mo neoadjuvant LHRH agonist + Enzalutamide followed by RP	Pathologi complete minimal r disease

NCT01753297 (PRIORITI)	4	High risk criteria of disease progression, defined as follows: - GS ≥8 on prostatectomy specimen, and/or Pre RP PSA level ≥20 ng/mL, and/or Primary tumour stage 3a (pT3a) (with any PSA level and any GS) - Post-RP PSA levels ≤0.2 ng/mL at 6 weeks	**Arm1:**RP + AdjuvantLHRH agonist **Arm2:**RP + Active surveillance	Biochemic free survi
NCT01442246	3	- postoperative GS> 7; - postoperative GS = 7 with the presence of high-grade Gleason patterns (5); pT3b patients.	**Arm1:**RP + AdjuvantLHRH agonist for 24 mo **Arm2:** RP + Active surveillance	Metastasi survival
NCT04295447 (ADAM)	2	One of the following RP - GS ≥8, any T-stage, any iPSA - GS 6 or 7, any iPSA and ≥pT2c or -iPSA >20 ng/ml, any GS, any T-stage.	**Arm1:** RP + Active surveillance **Arm2:** RP + adjuvant apalutamide for 30 months	Progressio survival
Chemohormonal therapy				
NCT02543255 (ACDC-RP)	2	PSA > 20, GS ≥ 8 as determined by the local pathologist; or T2c-3 based on DRE, pathologic review +/- imaging	**Arm1:** 6mo neoadjuvant abiraterone + prednisone + LHRH agonist + cabazitaxel, followed by RP **Arm2:**6mo neoadjuvant abiraterone + prednisone + LHRH agonist, followed by RP	Pathologi complete
NCT00653848 (AdRad)	3	- T2 with GS 7(4+3) and PSA >10 ng/ml to < 70 ng/ml - T2 with GS 8-10, any PSA < 70 ng/ml - any T3 tumour	**Arm1**: Adjuvant six cycles of docetaxel every third week + hormonal treatment **Arm2**: Adjuvant hormonal treatment	PSA progr Rate
Other				
NCT01385059	2	High-risk prostate cancer as defined by 1 of the 3 following criteria: - Baseline PSA > 20 - Clinical stage >= T3a and - GS 8-9	**Arm1**: neoadjuvant Axitinib and RP **Arm2**: RP	Changes i metastati density

RP: radical prostatectomy; R: recruiting; ANR: Active, not recruiting, NR: not recruiting; NS: not specified; PSA: prostate-specific antigen; GS: Gleason Score; mo: months; PCa: Prostate Cancer; RT: Radiotherapy; EBRT: external beam radiotherapy;

Table 2: Ongoing trials with radiotherapy as primary treatment

Reference	Phase	High risk factors for inclusion	Arms	Prima
		Androgen deprivation therapy		
NCT03417336 (SHORT)	NA	- GS 7 - 10 + T1c - T2b + PSA < 50 ng/mL or - GS 6 + T2c - T4 or ≥ 50% tumor invasion at biopsies + PSA < 50 ng/mL or - GS 6 + T1c - T2b + PSA > 20 ng/mL	**Arm1**: HDR brachytherapy with 15Gy in 1 fraction + external radiotherapy 25Gy in 5 fractions + concomitant ADT (3yrs) **Arm2**: External RT. 25Gy in 5 fractions + a 40Gy prostate boost in stereotaxic conditions + concomitant ADT (3yrs)	Acute
NCT03380806	2	stage T3 or higher and/or GS 8 or higher and/or initial PSA level above 20	**Arm1**: pelvic (lymph node and prostate) treatment of 45Gy in 25 fractions + prostate boost: conventional RT (CRT) of 33 - 35 Gy in 16 fractions +3 yrs concomitant LHRH agonist **Arm2**: pelvic (lymph node and prostate) treatment of 45Gy in 25 fractions + prostate boost: SBRT boost treatment of 19.5 - 21 Gy in three fractions + concomitant 3yrs LHRH agonist	Qualit
NCT02799706	3	PSA ≥ 10 ng/ml and two of the following 4 criteria: - PSA ≥ 20 ng/ml, - GS ≥ 8, - cN1 (regional LN with a short axis length >10mm by CT scan or MRI) or pathologically confirmed lymph nodes (pN1), - cT3-T4 (by MRI or core biopsy) (i.e. If PSA≥ 20 ng/ml then only one of the other 3 risk factors is needed)	**Arm1**: EBRT to a total dose of 78-80 Gy + 18mo concomitant of LHRH agonist **Arm2**: EBRT to a total dose of 78-80 Gy + 18 mo concomitant of LHRHantagonist	Progre surviv
NCT02772588	2	GS 8-10 PSA ≥20 ng/mL within two mo prior to registration Clinical Stage ≥T3 disease, as determined by standard digital rectal examination (DRE) Radiographic stage ≥T3 disease as determined by a ≥75% probability of extracapsular extension or seminal vesicle invasion per reading radiologist Any GS 9 or 10 disease OR >4 cores of GS 8 disease	**Arm1**: 6mo concomitant LHRH agonist + Apalutamide + Abiraterone, with Stereotactic, Ultra-Hypofractionated RT	Bioche
NCT02594072 (ASSERT)	NA	High risk is defined by any of: ≥T3a, PSA > 20, or GS ≥ 8 Intermediate risk is defined by: T1/T2 and/or GS ≤ 7 and/or PSA ≤20 and not low risk	**Arm1**: Stereotactic ablative RT 36.25 Gy in 5 fractions over 5 weeks + 6 (intermediate) or 18 (high risk) LHRH agonist **Arm2**: EBRT with a prescribed dose of 73.68 Gy in 28 fractions (5 treatment days per week over 5.5 weeks).	Acute toxicit
NCT00268476 (STAMPEDE)	NA	At least two of: T category T3/4, PSA≥40ng/ml or GS 8-10	**Arm1**: RT + ADT **Arm2**: RT + ADT + Abiraterone	Overa
NCT02531516 (ATLAS)	3	GS>=8 and >=cT2c, 2) GS>=7, PSA >=20 ng/mL, and >=cT2c	**Arm1**: 30mo concomitant LHRH agonist + apalutamide with RT to the prostate (74-80Gy) **Arm2**: 30mo concomitant LHRH agonist with RT to the prostate (74-80Gy)	Metas surviv
NCT02446444 (ENZARAD)	3	GS 8-10 OR GS of 4+3 AND clinical T2b-4 AND PSA >20ng/mL OR N1 disease (involvement of lymph nodes at or below the bifurcation of the common iliac arteries) defined radiologically as greater than 10mm on short axis using standard CT or	**Arm1**: 24mo concomitant LHRH agonist + enzalutamide with RT (78 Gy in 39 fractions or 46 Gy in 23 fractions plus BT boost) **Arm2**: 24mo concomitant LHRH agonist with RT (78 Gy in 39 fractions or 46 Gy in 23 fractions plus BT boost)	Overa

		MRI, or biopsy proven		
NCT04136353 (DASL-HiCaP)	3	EITHER planned for primary RT and judged to be at very high risk for recurrence based on any of the following: - Grade Group 5, OR - Grade Group 4 AND one or more of the following: clinical T2b-4 OR MRI with seminal vesicle invasion OR extracapsular extension OR PSA > 20ng/mL, OR - Pelvic nodal involvement OR Post-radical prostatectomy ≤ 365 days prior to randomisation and planned for RT with persistent PSA (≥ 0.1 ng/mL which has not fallen on two occasions at least one week apart) or rising PSA (PSA > 0.1 ng/mL and rising on two occasions at least one week apart) judged to be at very high risk for recurrence based on any of the following: - Grade Group 5, OR - Grade Group 4 AND pT3a or higher, OR - Pelvic nodal involvement	**Arm1**: 24mo concomitant LHRH agonist + darolutamide with curative intent RT **Arm2**: 24mo concomitant LHRH agonist with curative intent RT	Metas surviv
NCT02353819	1	PSA ≥20 OR GS ≥ 8 OR Appropriate staging studies identifying as AJCC stage cT3+	**Arm1**: 24 mo concomitant androgen deprivation therapy with Stereotactic Ablative Radiotherapy (SABR)	Maxin tolera
NCT02303327	3	T3 or T4, GS> 8, and/ or PSA > 20 (ng/ml or µg/L).	**Arm1**: Standard fractionation RT: 46 Gy in 23 fractions (EBRT) and a 15-Gy HDRB boost in conjunction with 28 mo of concomitant LHRH agonist. **Arm2**: Hypofractionated dose escalation RT: 68 Gy in 25 fractions in conjunction with 28 mo of concomitant LHRH agonist.	Acute toxicit
NCT02302105 (POP-RT)	NA	High risk PCa based on Staging and Risk of Pelvic Nodal Metastases ≥ 20% as per the Roach formula (2/3 PSA) + [(GS - 6) x 10] If GS 8-10 - Any PSA, T1- T3a N0 M0 If GS 7 - PSA > 15, T1-T3a N0 M0 If GS 6 - PSA > 30, T1-T3a N0 M0 T3b-T4a N0 M0, Any GS, Any PSA	**Arm1**: Prostate RT Only 66-68 Gy in 25 fractions will be prescribed for the prostate PTV + Concomitant ADT during 2-3 yrs **Arm2**: RT 66-68 G) in 25 fractions will be prescribed for the prostate PTV and 50 Gy in 25 fractions to nodal region + Concomitant ADT during 2-3 yrs	Bioche recurr surviv
NCT02296229	NA	Pre-biopsy PSA >= 20 Biopsy GS 8-10 Clinical stage T3	**Arm1**: SBRT 5 fractions +/- concomitant ADT during 9 mo	Bioche progre surviv
NCT02229734 (FASTR-2)	2	Not specified	**Arm1**: RT 7 Gy per week over 5 weeks (35Gy) + concomitant LHRH agonist during 18mo	toxicit
NCT01985828	NA		**Arm1**: Short or Long term (6 mo - 3 yrs) ADT + 45-50.4 Gy and Pelvis Intensity Modulated radiation therapy (IMRT) per current standard of care + 21 Gy (7 Gy x 3) CyberKnife boost	Bioche Diseas surviv
NCT01962324 (PARAPLY-1)	NA	high risk PCa with a risk of lymphatic spread >15% according to the MSKCC nomogram	**Arm1**: Simultaneous integrated boost to intraprostatatic tumor and lymph nodes (SIB DE radiation therapy)	PSA p free s
NCT01685190 (PIVOTAL)	2	Estimated risk of pelvic lymph node involvement ≥30% * and either: - BS 9 or 10 or - BS 8 and one other high risk feature (T3± disease or PSA >20) or - BS 7 and 2 high risk features (T3± disease and	**Arm1**: IMRT of 74Gy in 37 fractions delivered over 7.5 weeks. + concomitant ADT **Arm2**: Participants will receive prostate and pelvis IMRT with a dose of 74Gy in 37 fractions delivered over 7.5 weeks to the prostate and 60Gy in 37 fractions delivered over 7.5weeks to the pelvis.	Bioche progre surviv

		PSA ≥30)		
NCT01546987	3	- GS ≥ 9, PSA ≤ 150 ng/mL, any T stage - GS ≥ 8, PSA < 20 ng/mL, T stage ≥ T2 - GS ≥ 8, PSA ≥ 20-150 ng/mL, any T stage - GS ≥ 7, PSA ≥ 20-150 ng/mL, any T stage	**Arm1**: LHRH agonist/antagonist + dose escalated RT **Arm2**: LHRH agonist/antagonist + dose escalated RT + TAK-700	Overa
NCT01488968 (CHIRP)	NA	High-risk PCa (stage T3 or T4) and/or PSA greater than or equal to 20 ng/ml and/or GS 8-10	**Arm1**: Standard RT in 39 sessions + Long term ADT **Arm2**: Hypofractionated RT in 25 sessions + long term ADT	Bioche
NCT01444820	3	High risk defined clinically as: T3 or T4, GS> 8, and/ or PSA >20 .	**Arm1**: hypofractionation RT 25 fractions (68Gy) **Arm2**: Conventional RT 38 fractions (76Gy)	Acute toxicit
NCT01368588	3	- GS 7-10 + T1c-T2b (palpation) + PSA < 50 ng/mL (includes intermediate- and high-risk patients) - GS 6 + T2c-T4 (palpation) + PSA < 50 ng/mL OR - GS 6 + >= 50% (positive) biopsies + PSA < 50 ng/ml - GS 6 + T1c-T2b (palpation) + PSA > 20 ng/mL	**Arm1**: high-dose RT of the prostate and seminal vesicles + ADT **Arm2**: whole-pelvic RT (WPRT) + ADT	Overa
			<u>Chemohormonal therapy</u>	
NCT01952223 (PEACE2)	3	Two of the following criteria for high-risk: GS ≥ 8 T3 or T4 disease (T3 defined by MRI is acceptable) PSA equal or greater than 20 ng/mL	**Arm1**: pelvic RT(pelvic RT (prostate, seminal vesicles, ilio-obturator, presacral lymph nodes) (46 or 50 Gy according to the centre)+ prostate-only boost up to 74-78 Gy + 3 yrs concomitant LHRH agonist/antagonist **Arm2**: Prostate only RT (prostate + seminal vesicle RT (46 or 50 Gy according to the centre) + prostate-only boost up to 74-78 Gy + concomitant ADT and cabazitaxel 4 cycles **Arm3**: pelvic RT(pelvic RT (prostate, seminal vesicles, ilio-obturator, presacral lymph nodes) (46 or 50 Gy according to the centre)+ prostate-only boost up to 74-78 Gy) + 3 yrs concomitant LHRH agonist/antagonist + 4 cycles cabazitaxel **Arm4**: Prostate only RT (prostate + seminal vesicle RT (46 or 50 Gy according to the centre) + prostate-only boost up to 74-78 Gy) + Concomitant ADT for 3 yrs	Progre survi
NCT00116142	3	- T1b, T1c, T2a and PSA greater than (>) 10 or GS equal or greater than 4+3=7 or PSA velocity > 2.0 ng/ml per yr - T2c, T3a, T3b, or T4	**Arm1**: Concomitant Androgen Suppression Therapy and RT **Arm2**: Concomitant Docetaxel (60 mg/m² q 3 weeks for 3 cycle at the start of treatment followed by weekly Docetaxel at 20 mg/m² per week beginning at week one of RT and continuing for seven weeks.) plus androgen suppression therapy and radiation therapy	Overa

PCa: Prostate Cancer; RT: Radiotherapy; EBRT: external beam radiotherapy; IMRT: Intensity Modulated RT; BT: brachytherapy; GS: Gleason Score; RP: Radical Prostatectomy; mo: months; yrs: years; R: recruiting; ANR: Active, not recruiting, NR: not recruiting