Benefits and Risks of Primary Treatments for High-risk Localized and Locally Advanced Prostate Cancer: An International Multidisciplinary Systematic Review

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--Manuscript Draft--

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Abstract:	Context. The optimal treatment for men with high-risk localized or locally advanced prostate cancer (PCa) remains unknown.
	Objective. To perform a systematic review of the existing literature on the effectiveness of the different primary treatment modalities for high-risk localized and locally advanced PCa. The primary oncological outcome is the development of distant metastases at ≥5 years of follow-up. Secondary oncological outcomes are prostate cancer specific mortality (PCSM), overall mortality (OM), biochemical recurrence and need for salvage treatment with ≥5 years of follow-up. Non-oncological outcomes are quality of life (QoL), functional outcomes and treatment-related side effects reported.
	Evidence acquisition. Medline, Medline In-Process, Embase, and the Cochrane Central Register of Randomized Controlled Trials were searched. All comparative (randomized and non-randomized) studies published between January 2000 and May 2019 with at least 50 participants in each arm were included. Studies reporting on high-risk localized PCa (ISUP grade 4-5 [GS 8-10] or PSA >20 ng/mL or ≥cT2c) and/or locally advanced PCa (any PSA, cT3-4 or cN+, any ISUP grade/ GS score) or where subanalyses were performed on either group were included. The following primary local treatments were mandated: radical prostatectomy (RP), external beam radiotherapy (EBRT) (≥64 Gy), brachytherapy (BT) or multimodality treatment combining any of the local treatments above (+/- any systemic treatment). Risk of Bias (RoB) and confounding factors were assessed for each study. A narrative synthesis was performed.
	Evidence synthesis. Overall, 90 studies met the inclusion criteria. RoB and confounding factors revealed high RoB for selection, performance and detection bias and low RoB for correction of initial PSA and biopsy GS. When comparing RP to EBRT, retrospective series suggested an advantage for RP, although with a low level of evidence. Both RT and RP should be seen as part of a multimodal treatment plan with possible addition of (post-operative) RT and/or ADT respectively. High levels of evidence exist for EBRT treatment with several RCTs showing superior outcome for adding long-term ADT or BT to EBRT. No clear cut-off can be proposed for RT dose but higher RT doses by means of dose escalation schemes result in an improved biochemical control. Twenty studies reported data on QoL, with RP resulting mainly in GU toxicity and sexual dysfunction, and EBRT in bowel problems.
	Conclusion. Based on the results of this systematic review, both RP as part of multimodal treatment and EBRT + long-term ADT can be recommended as primary treatment in high-risk and locally advanced PCa. For high-risk PCa, also EBRT + BT can be offered, despite more grade 3 toxicity. Interesting, for selected patients, e.g. with higher comorbidity, a shorter duration of ADT might be an option. For locally advanced PCa, EBRT + BT shows promising result but still needs further validation. In this setting, it is important that patients are aware that the offered therapy will be most likely in the context a multimodality treatment plan. In particular, if radiation is used, the combination of local with systemic treatment provides the best outcome, provided the patient is fit enough to receive both. Until the results of the SPCG15 trial are known, the optimal local treatment remains a matter of debate. Patients should be at all-time fully informed about all available options and the likelihood of a multimodal approach including the potential side effects of both local and systemic treatment.

	Patient summary. We reviewed the literature to see whether the evidence from clinical studies would tell us the best way of curing men with aggressive PCa that had not spread to other parts of the body such as lymph glands or bones. Based on the results of this systematic review, there is good evidence that both surgery and radiation therapy are good treatment options, in terms of prolonging life and preserving QoL, provided they are combined with other treatments. In the case of surgery this means including RT, and in the case of RT this means either hormonal therapy or combined RT with BT.
Suggested Reviewers:	
Opposed Reviewers:	

BENEFITS AND RISKS OF PRIMARY TREATMENTS FOR HIGH-RISK LOCALIZED AND LOCALLY ADVANCED PROSTATE CANCER: An international multidisciplinary systematic review.

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- The European Association of Urology Guidelines Office Board
- The European Association of Urology Prostate Cancer Guideline Panel
- The American Society of Clinical Oncology

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ABSTRACT

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Objective. To perform a systematic review of the existing literature on the effectiveness of the different primary treatment modalities for high-risk localized and locally advanced PCa. The primary oncological outcome is the development of distant metastases at ≥5 years of follow-up. Secondary oncological outcomes are prostate cancer specific mortality (PCSM), overall mortality (OM), biochemical recurrence and need for salvage treatment with ≥5 years of follow-up. Non-oncological outcomes are quality of life (QoL), functional outcomes and treatment-related side effects reported.

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Evidence synthesis. Overall, 90 studies met the inclusion criteria. RoB and confounding factors revealed high RoB for selection, performance and detection bias and low RoB for correction of initial PSA and biopsy GS. When comparing RP to EBRT, retrospective series suggested an advantage for RP, although with a low level of evidence. Both RT and RP should be seen as part of a multimodal treatment plan with possible addition of (post-operative) RT and/or ADT respectively. High levels of evidence exist for EBRT treatment with several RCTs showing superior outcome for adding long-term ADT or BT to EBRT. No clear cut-off can be proposed for RT dose but higher RT doses by means of dose escalation schemes result in an improved biochemical control. Twenty studies reported data on QoL, with RP resulting mainly in GU toxicity and sexual dysfunction, and EBRT in bowel problems.

Conclusion. Based on the results of this systematic review, both RP as part of multimodal treatment and EBRT + long-term ADT can be recommended as primary treatment in high-risk and locally advanced PCa. For high-risk PCa, also EBRT + BT can be offered, despite more grade 3 toxicity. Interesting, for selected patients, e.g. with higher comorbidity, a shorter duration of ADT might be an option. For locally advanced PCa, EBRT + BT shows promising result but still needs further validation. In this setting, it is important that patients are aware that the offered therapy will be most likely in the context a multimodality treatment plan. In particular, if radiation is used, the combination of local with systemic treatment provides the best outcome, provided the patient is fit enough to receive both. Until the results of the SPCG15 trial are known, the optimal local treatment remains a matter of debate. Patients should be at all-time fully informed about all available options and the likelihood of a multimodal approach including the potential side effects of both local and systemic treatment.

Patient summary. We reviewed the literature to see whether the evidence from clinical studies would tell us the best way of curing men with aggressive PCa that had not spread to other parts of the body such as lymph glands or bones. Based on the results of this systematic review, there is good evidence that both surgery and radiation therapy are good treatment options, in terms of prolonging life and preserving QoL, provided they are combined with other treatments. In the case of surgery this means including RT, and in the case of RT this means either hormonal therapy or combined RT with BT.

INTRODUCTION

Following the introduction of prostate cancer (PCa) screening there has been a rise in the number of men diagnosed with clinically non-metastatic PCa. Nevertheless, 17-31% of these men present with high-risk localized or locally advanced disease and need curative treatment [1] since ten- and fifteen-year PCa specific mortality rates, if untreated, remain 28.8% and 35.5% respectively[2]. Although curative treatment provides a survival benefit [3], there is still no consensus regarding the optimal treatment option. In general, different strategies combining local with systemic treatment seem to have to best result in this patient cohort. Extensive evidence on the benefit of local curative treatment to improve survival already exists and therefore, ADT alone should not be considered a valid treatment option in the setting of high-risk and locally advanced PCa [4–6]. Currently the EAU PCa Guidelines recommend either radical prostatectomy (RP) with extended pelvic lymph node dissection in a multimodal approach (with possible post-operative RT +/- ADT), or external beam radiation therapy (EBRT) to a dose of 76-78 Gy or EBRT with brachytherapy (BT) boost both with long-term ADT in men with a life expectancy of ≥10 yrs [3]. Evidence on which treatment modality is best is still lacking and has led to experience- rather than evidence-based management of patients. The aim of this systematic review is to compare the available primary local curative treatment options for high-risk localized and locally advanced PCa at diagnosis.

EVIDENCE ACQUISITION

The review was conjointly commissioned and undertaken by the European Association of Urology (EAU) Prostate Cancer Guideline Panel and the American Society of Clinical Oncology (ASCO). The protocol for this review has been published online (http://www.crd.york.ac.uk/PROSPERO; CRD42017078862) [7]

Briefly, the review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [8] and methodology as detailed in the Cochrane Handbook [9] (Supplementary material 1 and 2). The study population was comprised of male patients with histologically proven high-risk localized PCa (ISUP grade 4-5 [GS 8-10] or PSA >20 ng/mL or ≥cT2c) or locally advanced PCa (any PSA, cT3-4 or cN+, any ISUP grade/ GS) [3]. The treatment options of interest included any primary local treatment with curative intent: RP, EBRT (≥64 Gy), BT or multimodality treatment (defined as a combination of primary local treatments +/- systemic treatment). The primary outcome was distant metastasis-free survival (DMFS) [10], secondary oncological outcomes included PCa-specific mortality (PCSM), overall mortality (OM), biochemical failure (BF) and need for salvage treatment. Secondary non-oncological outcomes were QoL, functional outcomes, and adverse events. Abstracts and full-text screening and data extraction were

independently performed in duplicate (LM, MC, GG, NF, BK and RP) and disagreement was resolved by discussion or reference to an independent third party (TVDB). Due to the anticipated heterogeneity across studies, only a narrative synthesis was planned.

EVIDENCE SYNTHESIS

Quantity of evidence identified

The study selection process is outlined in the PRISMA flow diagram (Fig. 1). Ninety studies met the inclusion criteria, recruiting 367,347 patients with a total of 24 RCTs [11–34] and 66 non-randomized studies (NRS, - 4 prospective and 62 retrospective).

Characteristics of the included studies

Four major comparisons could be categorized: 1. Comparison of RP and RT (258,809 patients, all NRS), 2. Comparisons of RT with or without ADT and ADT duration (21,353 patients, 12 RCTs, 6 NRS), 3. Comparisons of different schedules of RT (77,152 patients, 11 RCT, 24 NRS), and 4. Comparison of RP with or without additional therapies (10,033 patients, 1 RCTs, 7 NRS). Both baseline study characteristics (supplementary tables 1-4) and corresponding outcome data (supplementary table 5-8) are presented. Table 1 and 5 summarize studies comparing RT with RP [35–64]. Table 2 and 6 report on studies comparing RT with or without ADT and ADT duration [13–18,23,26,27,29,30,32,65–69]. Table 3 and 7 compare different RT modalities (including BT) [11,12,19–22,24,25,28,33,34,69–92] and table 4 and 8 compare different RP modalities [16,31,93–98]. A separate table was created for studies reporting on RT with doses below 70Gy (supplementary table 9-10).

Risk of bias and confounding assessment

Figure 2 and 3 summarize the RoB assessment of all studies individually. In total, 24 RCTs were included, but in most RCTs, adequate blinding was not feasible. Therefore, as with all studies of this sort, selection, performance and detection bias overall are judged to be high on purely technical grounds. Attrition and reporting bias were judged to be low. Most confounding factors, like clinical T category, biopsy Gleason score and initial PSA were adequately considered through statistical adjustments in a large proportion of studies, whilst the correction for biopsy strategy remained unclear.

EVIDENCE SYNTHESIS

Radical Prostatectomy versus Radiotherapy

Thirty studies compared RP with EBRT (+/- ADT) [35–64]. All were NRS and there were no full-text RCTs available. There was only one prospective observational study [53]. Therefore, data quality in all of these reports is low. RT was delivered as monotherapy (or the use of ADT was not documented) in 11/30 studies, and doses were <70Gy in 4/30 studies [38,41,43–45,49,53,54,59,61,63]. Less than 50% of the studies included adjuvant/salvage treatment after RP. Therefore, many of the studies in this category do not reflect contemporary practice.

Oncological outcomes

Four NRS reported on DMFS [35,36,46,55] with no statistical difference between RP and EBRT + ADT. Twenty-seven out of 30 NRS described data on OM or PSCM, in favor of RP in the majority of the studies [35,36,43,44,47,49,51,55,59,60,64]. When comparing RP to the combination of EBRT + ADT, the reported benefit in OS and cancer-specific survival (CSS) ranged from 10% to 28% [35,55,60] and 4% to 8% [35,47,51,55] respectively at 10 yrs favoring RP, even when compared to recommended EBRT doses of 76-78 Gy [47,48,51]. Of interest is the NRS by Tilki *et al.* evaluating RP in a multimodal setting. This study showed that RP without additional treatment compared to MaxRT (EBRT + BT + ADT), resulted in higher PCSM and OM rates (PCSM: HR: 2.80 [95% CI, 1.26-6.22] and all-cause mortality: HR 1.65 [95% CI, 0.94-2.91]) [40]. However, when compared to RP + adjuvant RT and/or maxRP (RP + RT + ADT), no differences in outcomes were observed.

Non-oncological outcomes

Regarding toxicity after RP or RT, two studies for locally advanced [49,62] and three for high-risk PCa [47,53,56] reported on genitourinary (GU) toxicity (i.e. need for catheterization, GU infection, hematuria, strictures, LUTS), sexual dysfunction and gastrointestinal (GI) toxicity (i.e. diarrhea, bleeding, proctitis). Despite very heterogeneous methods of reporting, studies showed generally more sexual dysfunction and urinary incontinence in patients after RP [53,56] and more GI toxicity after RT [47], which resembles the conclusions of the PROTECT-trial [99]

Radical Prostatectomy – with or without additional therapy

Eight studies compared different RP modalities [16,31,93–98], of which only one was a RCT [31], comparing salvage with adjuvant RT after RP in a high-risk PCa population.

Oncological outcomes

Two of the included studies evaluated the effect of adjuvant RT (vs salvage RT) on survival outcomes. [31,97]. The RCT by Bolla *et al.* only demonstrated an improvement in BFFS after adjuvant RT, with no difference in OS or PCSS [31].

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Four studies reported on the combination of RP with systemic therapy [16,93,94,96]. One RCT reported on adjuvant bicalutamide after RP, but did not show an OS or CSS benefit after a median FU of 11.2 yrs [16]. Two studies investigated the effect of neoadjuvant systemic treatments [93,94]. One NRS reported additional benefit of both BFFS and OS after 10 yrs of FU with neoadjuvant ADT [94]. The second NRS compared neoadjuvant LHRH analogue plus chemotherapy (estramustine, oral etoposide and paclitaxel [EEP]) before RP, showing an improved OM and BFFS [93]. However, FU of the combination arm was only 48.8 mo compared to 111 mo in the RP-arm.

Non-oncological outcomes

Only two studies reported functional outcome data. The RCT reported an increase in the 10-yr cumulative incidence of severe (grade 3) toxicity (p=0.052) and late grade ≥2 GU toxicity (p=0.003) with adjuvant RT, compared with salvage RT, while late GI toxicity did not differ between the two groups [31]. Sooriakumaran *et al.* compared the effect of open vs robotic RP on erectile function recovery in high-risk PCa patients showing no statistically significant difference after 24 mo of FU [98].

EBRT with or without ADT and comparison of ADT duration

EBRT alone vs EBRT + ADT

Nine studies compared EBRT alone with EBRT + ADT, including 4 RCTs (and the updated results of EORTC 22863 trial) [14,16,26,30,32] and 4 NRS [65,66,68], plus one subanalysis of two RCTs, the RTOG 85-31 and RTOG 86-10 [67]. The EORTC 22863 and TROG 96.01 trial used LHRH agonists with an AR antagonist for flare-prevention [14,30,32]. Two other RCTs compared EBRT +/- adjuvant bicalutamide [16,26].

There was fairly consistent evidence from the RCTs of benefits with combined EBRT+ADT, compared with EBRT alone. Although different RCTs reported on different outcomes, oncological outcomes were uniformly in favor of the combination EBRT+ADT. Three RCTs showed improvements in OS [16,26,30,32], PCSS in 2 studies [14,30,32] and DMFS in 1 study [32]. The subanalysis by Horwitz *et al.* of both RTOG 85-31 and RTOG 86-10 trials, excluding post-RP and cN1 patients, confirmed these beneficial findings for PCSS and DFMS [67].

Iversen *et al.* evaluated side effects associated with bicalutamide treatment in patients treated with RP or RT [16]. Most frequently reported side effects were gynecomastia (68.8% vs 8.3%) and mastalgia (73.7% vs 7.6%) in the bicalutamide group which was similar to previously reported data. There were no differences in other non-oncological outcomes between the randomised groups.

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Studies **of duration of ADT in the context of EBRT**

Eight studies evaluated the impact of ADT duration on oncological outcomes. For the comparison of short-term (4-6 months) vs long-term (24-36 months) ADT, 7 RCTs [13,15,17,18,23,27,29] and 1 NRS [69] were identified. Intermediate-term ADT was defined as ADT for 18 mo.

An advantage for long-term ADT over short-term ADT was found in 4 RCTs with improvements in OM, PCSM and BF [15,17,27,29]. Two RCTs reported on the development of DM both showing a significant advantage for long-term ADT [13,17]. Of interest is the RCT by Nabid *et al.* showing no differences in OS, CSS and DFS between long-term ADT (36 mo) and intermediate ADT [18].

Only two studies reported on functional outcomes [17,18]. Nabid *et al.* showed no statistical difference in global QoL, however a clear difference in favor of intermediate ADT was observed for physical QoL (p<0.001), fatigue (p=0.003), nausea and vomiting (p=0.04), constipation (p=0.03), sexual activity and function (p<0.001 and p=0.03) and specific treatment-related QoL (p<0.001) [18]. Lawton *et al.* reported no differences in late GU and GI toxicity comparing 4 mo and 24 mo of ADT [17].

Radiotherapy– Different intertreatment modalities

Thirty-five studies performed comparisons of different schedules, or combinations of modalities in the context of RT as the principal curative therapy [11,12,19–22,24,25,28,33,34,69–92]. The categories were EBRT vs EBRT + BT, EBRT/BT dose/fractionation/field size comparisons, and the addition of chemotherapy to RT as multimodality therapy.

EBRT vs BT (monotherapy or BT boost + EBRT) (+/- ADT)

There were 17 studies comparing EBRT to BT (monotherapy or as boost to EBRT) (+/- ADT) [20–22,69–72,74,76,77,82–87,92]. Of these, there was one RCT [19,20,22], two prospective comparative studies [70,84], and 14 NRS. For monotherapy, EBRT doses ranged from 70 Gy to 81 Gy and LDR-BT from 140 Gy to 145 Gy [71,74,77,84,100]. When combined with BT, EBRT doses varied between 40 to 50.4 Gy with BT doses for LDR-BT ranging from 90 to 115 Gy [20–22,76,82,83,87,92] and from 6.5 Gy in 3 fractions to 10 Gy in 2 Gy fractions for HDR-BT [70,72,85,86].

Studies comparing EBRT with EBRT + BT boost showed an improvement in oncological outcomes in favor of combination therapy. The RCT (ASCENDE-RT) reported improved BFFS for EBRT + ADT with BT boost (83%) compared to EBRT + ADT (73%, p= 0.048) at 6.5 yrs FU [22]. In the NRS, EBRT + BT boost (+/-ADT) resulted in improved DMFS in only 1 study [83], OS in 5 studies, [72,76,82,87,92], improved CSS in 4 [72,76,83,86] and improved BFFS in 3 studies [76,82,83]

Five NRS compared BT alone (+/-ADT) to EBRT (+/- ADT) [71,74,77,84,100]. Three studies suggest improved BFFS and PCSM with BT compared to EBRT [71,74,77]. However, information on the administration of ADT or EBRT doses was often missing and patients receiving BT/EBRT tended to be younger and had a lower T-category. Of interest is the study by D'Amico et al. comparing BT (+/-ADT) with EBRT + BT (+/- ADT), showing that trimodality treatment (EBRT + BT + ADT) but not treatment with EBRT alone or ADT alone compared to BT, resulted in an improved PCSM [100].

Contrary to the superior oncological results for EBRT + BT (+/-ADT), data on QoL and side effects are less favorable. Three studies reported on higher GU toxicity after EBRT + BT boost [20,21,85]. In the ASCENDE-RT trial by Rodda et al., 5-yr grade 3 GU toxicity was worse when treated with EBRT + LDR-BT boost + ADT compared to dose-escalated EBRT + ADT (5-yr: 18.3% vs. 5.2% respectively) [19,20]. The NRS by Khor et al., showed more grade 3 strictures (as GU toxicity surrogate) in the combination group (5-yr: 11.8% vs 0.3%) [85].

EBRT – trials of dose, fractionation, and field size
Seven RCTs [11,12,19,24,25,34,88] and 11 NRS [28,73,75,78–81,89–91] compared different EBRT modalities.

Four studies (2 different RCTs [and one update of the trial by Arcangeli et al] , 1 NRS) compared hypofractionation and conventional fractionation [11,12,79,88], comparing conventional EBRT (78-80 Gy) to moderate hypofractionation (3.1 Gy fractions to a total dose of 62 Gy and 3.4 Gy fractions to a total dose of 64.6 Gy) [11,12,88]. There were no differences in DMFS, OM, PCSM or BFFS in any of these studies. Both RCTs reported on functional outcomes with no difference in the incidence and severity of late GI or GU toxicity [11] but an increase in overall grade 3 or worse late GU toxic effects (19% vs 13%) [88] after moderate hypofractionation compared to conventional EBRT was observed.

Eight studies compared different conventional EBRT doses ranging from 68 Gy to >80 Gy [34,73,75,80,81,89,90,101], with increasing doses over the years due to the introduction of conformal and then intensity modulated RT (IMRT). One NRS compared 3D-conformal RT (70-74 Gy) to IMRT (78-82 Gy) showing better survival outcomes in the IMRT-group for BFFS, OS and CSS)[90].

Three studies evaluated the effect of pelvic irradiation in addition to EBRT, BT or both [19,78,91]. One RCT reported a significant improvement in PFS and BF for neoadjuvant ADT + whole-pelvis RT when compared to neoadjuvant ADT + prostate-only RT or whole-pelvis RT + adjuvant EBRT [19]. A second RCT reported whole-pelvis RT to be associated with a significant improvement in BFFS in the EBRT + BT group but without impact on OS or PCSS [78].

EBRT +/-chemotherapy

Three studies reported on the addition of chemotherapy [24,25,33], with EEP in the RTOG 9902 trial and docetaxel in the QRT-SOGUG phase 2b and RTOG 0521 trial [25,33]. The RTOG 0521 RCT showed improvement in OS with docetaxel compared to EBRT + ADT [24]. All trials reported a significantly higher rate of chemotherapy-related toxicities, especially in the RTOG 9902 trial which was closed early due to excess toxicity and treatment-related mortality.

Locally advanced PCa

Twelve studies reported specifically on locally advanced PCa (according to the EAU PCa guidelines definition), with 5 RCTs [17,26,29,30,32] and 7 NRS [43,49,56,57,62,65,67]. Five NRS compared RP to EBRT +/- BT [43,49,56,57,62], showing better survival outcomes for RP compared to EBRT +/- ADT in well selected patients. Four RCTs compared EBRT + ADT vs EBRT alone with outcomes in favor of the combination therapies (DMFS, OM, PCSM and/or BFFS) [19,26,30,32]. One NRS reported a reduced PCSM in patients treated with RT alone, however RT dose and ADT duration were not reported [65]. Finally, two RCTs compared EBRT + short-term ADT to EBRT + long-term ADT and showed superior DMFS for long-term ADT [17,29].

DISCUSSION

Principal findings

RP vs EBRT and RP intergroup comparison

Historically, men with high-risk PCa have been managed most commonly with EBRT, ADT or both [102,103], whilst RP has been discouraged in this setting, due to concerns about side effects and inadequate disease control [103–106]. The included retrospective studies report encouraging results for RP over EBRT with the advantage of avoiding ADT in many patients. However, no randomized data are available to evaluate RP vs EBRT +/- ADT in terms of survival outcomes and/or toxicity but the ongoing randomized SPCG-15 trial will provide us valuable information on this matter [107]. Clearly, the reported retrospective studies should be interpreted with extreme caution, as patients with good performance status and limited or no comorbidity may be more commonly considered for RP. Indeed, patients treated with RP in the included studies are younger with a less advanced tumor classification. Out of the 30 studies, 11 performed a propensity score matching for tumor and patient characteristics [38–40,43,49,51,56,59–62]. However, even this cannot completely correct for the inherent selection bias due to unmeasured confounding variables [108]. It is noteworthy that in several studies RP was compared with EBRT alone [38,41,43–45,49,53,54,59,61,64] or EBRT <70 Gy [37,41,55,57] which should be regarded as sub-optimal treatment in a contemporary high-risk setting. The same applies to RP monotherapy, which fails to be a definitive cure in many patients.

Therefore, patients must be informed about the possible need for combination therapy (RP with RT alone and/or ADT). However, which therapeutic approach after RP is superior remains unclear [109].

We can conclude that:

- No curative primary treatment modality (as part of multimodality therapy) has shown superiority over any other curative treatment option in terms of survival.
- RP (including the option for [post-operative] radiotherapy and/or ADT) or EBRT+ADT can be offered to patients with high-risk localized and locally advanced PCa as part of multi-modal therapy.

Studies in the context of primary radiotherapy

Radiotherapy represents a valid treatment option but like RP, as part of a multimodal strategy in most cases [14,16,26,30,32,67,68]. Many of the included studies were performed in the era before dose-escalated RT and should be interpreted cautiously since they used RT doses far below the recommended 76-78 Gy – indeed, with 4 studies reporting doses below 70 Gy [14,17,26,66]. Extrapolating the findings of these studies to contemporary practice therefore requires much caution.

Five RCTs have confirmed the benefit of combining EBRT with ADT, and this is very well established treatment option in current practice. However, the optimal duration of ADT (from 18 mo to indefinite) remains undefined. In a high-risk setting, long-term ADT (18-36 mo) has shown clear benefits over short-term ADT [17,29]. This is not merely an effect of ADT compensating for lower doses of RT, since the RCT by Zapatero *et al.* confirmed that even with dose-escalated RT doses (median dose of 78 Gy), long-term ADT (24 mo) results in longer BFFS and OS compared to 4 mo of ADT [27]. Due to significant side effects reducing ADT length seems desirable as long as it will not affect efficacy. Nabid *et al.* designed a superiority study comparing long-term ADT (36 mo) to intermediate ADT of 18 mo [18], showing no difference in DM, OS and CSS after 9.4 yrs FU but confirmed an improvement of certain QoL aspects (physical, emotional and social functioning and fatigue). Although the authors suggest that intermediate ADT might be non-inferior to 36 mo of ADT for OS, proper non-inferiority trials have to be performed before final recommendations can be made. Also, the use of RT doses of only 70 Gy and the low compliance of 53% to long-term ADT (vs. 88% for intermediate ADT) complicates interpretation of this study.

The combination of EBRT + BT boost aims to increase doses to the prostate whilst minimizing radiation to the surrounding organs. Only the ASCENDE-RT trial randomized patients to 46 Gy + EBRT boost to a total of 78 Gy or to pelvic 46 Gy + LDR-BT boost and reported superior 9-yr BFFS rates of 62% to 83% respectively, despite a general increase in late GU-toxicity [20–22]. In multiple

retrospective series this combination demonstrated excellent results with better local tumor control compared to EBRT alone. However, in most studies, patient and tumor characteristics were more favorable in the combination group with younger patients and lower clinical T-categories.

Hypofractionation has been developed to deliver equivalent biologically effective doses to the tumor with a higher dose per fraction; based on the fact that PCa cells are more sensitive to large-dose fractions compared to the surrounding normal tissue. Both HDR-BT and EBRT schemes have tried to implement this but controversy remains. The RCTs by Arcangeli *et al.* and Incrocci *et al.* showed conflicting results in late complications, but equivalence [11,12,88] in PCa deaths with moderate hypofractionation (62-64.6 Gy with 3.1-3.4 Gy per fraction) in high-risk PCa. From an economical and patient-friendly point of view, both moderate and extreme hypofractionation can offer great advantage with fewer fractions but further, well-designed non-inferiority trials are needed to confirm their role.

Data on the use of irradiation of the lymph nodes are limited in this SR and studies mostly report data for mixed patient groups (cN0-X)[19,78,91]. The RTOG 9413 trial showed a benefit of whole-pelvis RT with neoadjuvant ADT in high-risk PCa patients compared to prostate-only RT, highlighting the benefit of prophylactic pelvic RT and the interaction with hormonal therapy [19]. Two RCTs, RTOG 0924 and PIVOTAL-boost are in progress, which will compare whole-pelvis versus prostate-only RT and provide more information on hard clinical endpoints (such as OS) and the toxicity profile of whole-pelvis RT.

Finally, different trials evaluated the benefit of adding chemotherapy to curative local treatments with the aim of treating micro-metastatic disease. Optimizing chemotherapy regimens and time of delivery (neoadjuvant or adjuvant) remains experimental. The GETUG-12 trial suggested an improved relapse-free survival with docetaxel + ADT vs ADT alone [110]. The phase 2b trial by Carles *et al.* reported good tolerability of low weekly doses of docetaxel, but without benefits in 5-yr BFFS, PFS and OS [33]. Its successor, the RTOG 0512 trial, revised treatment schedules with adapted RT schemes and docetaxel instead of EEP [24]. In a population with 84% GS 8-10 patients, an improvement in OS was observed with adjuvant docetaxel following RT after 5.7 yrs of FU. In contrast, the recently presented long-term results for M0 high-risk PCa patients in the STAMPEDE trial did not show an improved OS with docetaxel before RT + long-term ADT[111]. However, upfront docetaxel did improve PFS and failure-free survival in this patient population without excess in late toxicity, which might influence future treatment decision making. An improved insight in patient profiles will be needed to identify those patients who will likely benefit from adjuvant chemotherapy. Other additional systemic therapy, including novel endocrine agents (like abiraterone acetate, apalutamide and enzalutamide) are currently being tested in clinical trials, combining systemic with

local treatment for increased disease control, which is discussed to a fuller extend in a systematic review by Tosco *et al.* [112].

We can conclude that:
- In patients with localized high-risk or locally advanced disease, EBRT with long-term ADT (24-36 mo) +/- BT boost (HDR or LDR) are valid treatment options. ADT mostly consisted of a LHRH analogue combined with a one-month anti-androgen for flare prevention.
- Adjuvant ADT should be continued for at least 24 mo; however for all high-risk patients, there is insufficient evidence to support prolonging ADT for another year. Comorbidity at the time of diagnoses and treatment-related side effects must be taken into account when deciding on ADT duration.
- Although results are promising, there are not enough mature data to encourage the general use of adjuvant chemotherapy in the multimodality treatment of high-risk or locally advanced PCa. The recently presented data from the MRC STAMPEDE trial in high-risk M0 patients will add greatly to the current knowledge [111].

Finally, our SR evaluated the effects of local treatment on QoL. In general, both radical and systemic treatments result in significant side effects, which affect QoL of patients and their families who are confronted with the diagnosis. We can conclude that patients treated with RP experience mainly GU toxicity and sexual dysfunction, while EBRT can result in GI problems. Attention should be drawn to these side effects and proper support should be organized.

Implications for clinical practice and further research

Patients with high-risk localized or locally advanced PCa frequently have recurrence driven by subclinical metastases and microscopic local tumor extension. Further optimization of treatment will therefore rely on improvement of multimodality treatment and development of novel therapeutic strategies. However, not only treatment but also classification of patients into prognostic groups is key for an optimal treatment. A recent SR on the impact of BCR after treatment with curative intent proposed an additional risk-stratification (EAU high-risk BCR and EAU low-risk BCR) based on risk factors for clinical progression and worse survival (short PSA-DT and a high final GS after RP, and high biopsy GS and a short interval to BCR after RT). Such a classification system can guide clinical decisions to initiate salvage treatment. A first validation of this classification system was performed in a large series of patients with BCR after RP, showing its potential and applicability in daily practice [113]. However, further validation is still mandatory in both post-RP and post-RT settings. Another

rapidly evolving area is the use of (non-) genomic biomarkers and molecular imaging [114–117]. Such prognostic and predictive tools offer an alternative way of patient stratification supplementary to our clinical system and may guide clinicians in the decision whether to intensify follow-up and treatment schemes.

Limitations and strengths of this systematic review

This study represents the first SR comparing both oncological effectiveness and functional outcomes focusing on local treatment in high-risk and locally advanced PCa. This review was performed based on robust methodological standards and as a collaborate project involving two multidisciplinary panels of experts (EAU Prostate Cancer Guidelines Panel and ASCO) including a patient representative [8,9,118]. Limitations include the retrospective nature of the majority of studies, and the overall clinical and methodological differences between studies, contributing to the heterogeneity of data. Variation was apparent in baseline patient characteristics, type, duration and correct administration of ADT as well as the variety in RT doses. These inter-study differences limit direct comparison of data and preclude further strong or new recommendations. Ongoing big data projects, such as PIONEER and ICECaP, will define validated core outcome sets for both localized and metastatic PCa which should be used in future clinical trials [119]. Finally, clinical staging and stratification depended on standard imaging techniques with chest radiograph, abdominal CT and isotope bone scan in all included RCTs. However, the field of imaging and staging is rapidly evolving, with promising data for mpMRI, PET/CT and PSMA PET/CT for local staging and detection of lymph node and bone metastases. Results from current trials will enlighten us on the use and benefit of these new modalities for the management of high-risk and locally advanced PCa.

CONCLUSION

In this collaborative systematic review performed under the auspices of the EAU Prostate Cancer Guideline Panel and ASCO, we evaluated current evidence on the effectiveness of local primary therapy in high-risk and locally advanced PCa. Based on the results of this systematic review, both RP as part of multimodal treatment and EBRT + long-term ADT can be recommended as primary treatment in high-risk and locally advanced PCa. For high-risk PCa, also EBRT + BT can be offered, despite more grade 3 toxicity. Interesting, for selected patients, e.g. with higher comorbidity, a shorter duration of ADT might be an option. For locally advanced PCa, EBRT + BT shows promising result but still needs further validation. In this setting, it is important that patients are aware that the offered therapy will be most likely in the context a multimodality treatment plan. In particular, if radiation is used, the combination of local with systemic treatment provides the best outcome,

provided the patient is fit enough to receive both. Until the results of the SPCG15 trial are known, the optimal local treatment remains a matter of debate. Patients should be at all-time fully informed about all available options and the likelihood of a multimodal approach including the potential side effects of both local and systemic treatment.

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Illustration

Figures

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-analysis flow chart.
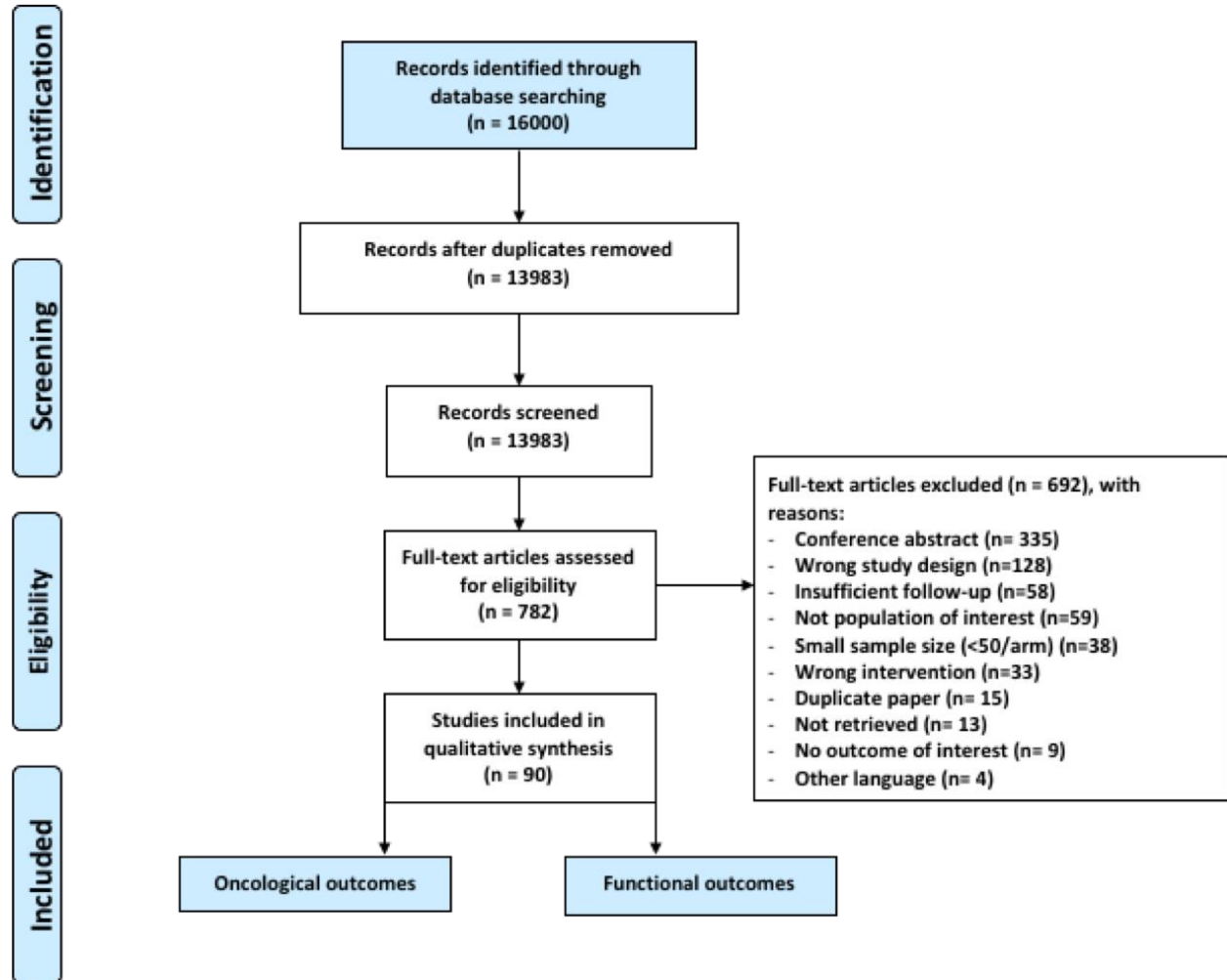
Fig. 2–Risk of bias summary graph.
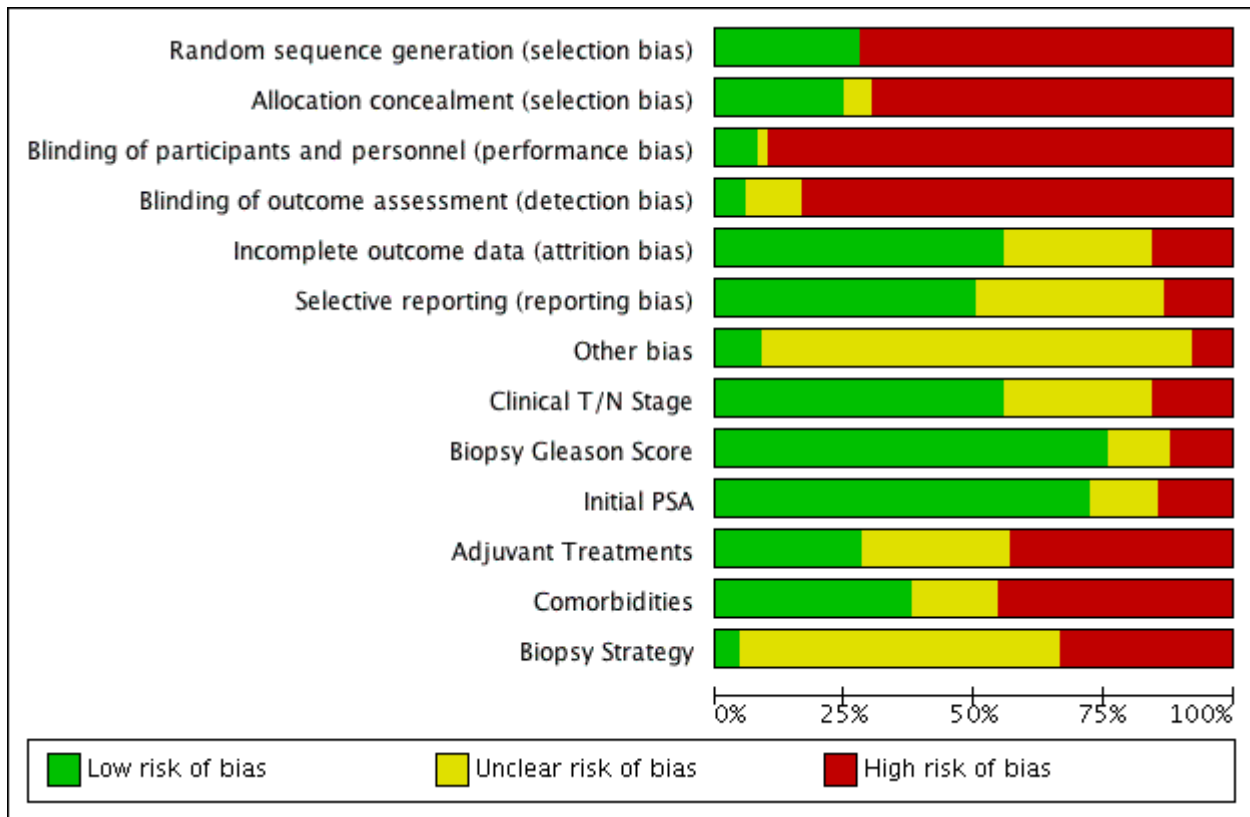
PSA = prostate-specific antigen.

Fig.3 – Risk of bias assessment for individual studies.

Risk of bias table. Legend: + = low risk (green), − = high risk (red), ? = unclear risk (yellow).

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Clinical T/N Stage	Biopsy Gleason Score	Initial PSA	Adjuvant Treatments	Comorbidities	Biopsy Strategy
Abdollah 2011 (NRS)	−	−	−	−	?	?	?	−	?	−	?	−	?
Abdollah 2012 (NRS, 7198)	−	−	−	−	?	?	+	−	?	−	?	?	?
Amini 2016 (NRS)	−	−	−	?	−	?	?	?	?	?	−	?	−
Arcangeli 2011 (RCT)	+	+	+	?	+	+	+	−	+	+	−	+	?
Arcangeli 2017 (RCT)	+	+	+	−	+	?	?	+	+	+	?	?	?
Armstrong 2011 (RCT)	+	+	+	+	+	?	+	+	+	?	+	+	?
Bandini 2018 (NRS)	−	−	−	−	+	+	?	+	+	+	+	?	?
Berg 2018 (NRS)	−	−	−	−	+	+	?	+	+	+	+	?	?
Bittner 2010 (NRS)	−	−	−	?	−	+	+	−	+	+	?	?	?
Blanchard 2016 (NRS)	−	−	−	−	−	+	+	−	+	+	?	?	?
Bolla 2002 (RCT)	+	?	−	−	+	?	+	+	+	+	?	+	+
Bolla 2009 (RCT)	+	?	−	?	−	?	+	+	+	+	?	+	−
Bolla 2010 (RCT)	+	+	?	?	+	?	+	+	+	?	?	+	+
Bolla 2012 (RCT)	+	+	−	−	+	?	+	+	+	+	−	?	?
Boorjian 2011 (NRS)	−	?	−	?	?	?	+	?	+	+	+	−	−
Cano-Velasco 2019 (NRS)	−	−	−	−	+	?	?	+	+	+	+	−	?
Carles 2018 (RCT)	+	+	−	−	+	+	+	+	+	+	+	−	−
Ciezki 2017 (NRS)	−	−	−	?	?	?	?	+	?	?	−	−	?
D'Amico 2007 (NRS)	−	−	+	−	−	?	?	+	+	+	?	−	?
D'Amico 2009 (NRS)	−	−	−	−	+	?	?	+	+	+	+	−	?
Dearnaley 2014 (RCT)	+	+	−	−	+	?	?	+	+	+	+	−	?
Denham 2011 (RCT)	+	+	−	−	+	+	?	+	+	+	?	−	?
Denham 2014 (RCT)	+	+	−	−	?	+	?	+	+	+	?	?	+
Denham 2019 (RCT)	+	+	−	−	+	?	+	+	+	+	−	?	?
Dignam 2019 (NRS)	−	−	−	−	+	?	+	+	+	+	?	+	?
Dolezel 2015 (NRS)	−	−	−	−	−	?	+	−	−	+	?	?	?
Feldman 2017 (NRS)	−	−	−	−	−	?	+	+	−	−	+	?	?
Feng 2013 (NRS)	−	−	−	−	?	?	−	+	+	+	+	+	?
Ferris 2018 (NRS)	−	−	−	−	+	?	+	+	+	?	−	−	?
Fletcher 2006 (NRS)	−	−	−	?	?	?	−	+	+	+	?	−	?
Fossa 2014 (NRS)	−	−	−	−	?	?	?	−	−	−	−	−	?
Fujita 2017 (NRS)	−	−	−	−	?	?	?	−	+	+	−	−	?
Furubayashi 2017 (NRS)	−	−	−	−	?	?	?	?	?	?	−	−	?
Greenberg 2015 (NRS)	−	−	−	−	?	?	?	−	−	−	?	−	?
Gu 2018 (NRS)	−	−	−	−	+	+	?	+	+	+	−	−	−
Gunnarsson 2019 (NRS)	−	−	−	−	+	?	?	+	+	+	?	−	?
Hall 2015 (NRS)	−	−	−	−	?	?	?	+	+	+	?	−	?
Horwitz 2001 ((NRS)	+	+	+	+	?	+	+	+	+	+	+	?	?
Horwitz 2008 (RCT)	+	+	+	+	?	+	+	+	+	+	+	?	?
Incrocci 2016 (RCT)	+	+	+	−	+	?	?	+	+	+	?	?	?
Iversen 2010 (RCT)	+	+	+	+	+	+	?	+	?	+	+	?	?
Jackson 2017 (NRS)	−	−	−	−	?	+	−	+	?	+	+	+	?
Jang 2018 (NRS)	−	−	−	−	+	?	+	+	−	−	−	?	−
Kalbasi 2015 (NRS)	−	−	−	−	?	?	+	+	+	+	−	?	?
Kent 2019 (NRS)	−	−	−	−	+	?	+	?	?	?	?	?	?
Khor 2013 (NRS)	−	−	−	?	−	−	−	+	+	+	?	+	?
Koo 2017 (NRS)	−	−	−	−	+	?	+	+	+	?	+	?	−
Krauss 2011 (NRS)	−	−	?	?	?	?	?	+	?	−	−	?	?
Laing 2018 (NRS)	−	−	−	−	+	?	?	+	+	+	−	?	−
Lawton 2017 (RCT)	+	+	?	?	+	?	+	+	+	+	+	+	?
Lee 2014 (NRS)	−	?	−	−	?	?	?	+	+	+	?	−	?
Linder 2013 (NRS)	−				?	?	?	−					?

NRS = non-randomized study; RCT = randomized clinical trial.

Letter to the reviewers –Eur Urol

We thank all reviewers for their time and effort in evaluating our work.

We would like to address these comments and highlight the changes to improve the quality of this work.

Reviewer 1:

We rewrote parts of the text as well as changed the structure and corrected for any misspellings to make it easier to read.

The scope of this project was to perform a formal systematic review with a solid methodological approach. Therefore, it summarizes all the available and relevant evidence on which the various treatment strategies rely and evaluate the quality of the included studies. We cannot exclude papers based on their quality. This can be, however, a clear sign that proper, high quality studies need to be performed in certain fields.

We do agree with the fact that outdated treatments should not be recommended. We highlighted this problem in the text and created a separate table with studies using treatment protocols (EBRT <70Gy) that should be recommended anymore. However, if we limit too much the inclusion period, the follow-up period is too short and will never lead to clinically significant findings (distant metastasis free survival, prostate cancer specific survival).

Finally, regarding the review of **Tosco et al**, this paper was not available and not registered in the PROSPERO database at the time our systematic review was performed. Furthermore, it highlights very distinct topics compared to our work:

- It focusses mainly on systemic treatment (⇔ we focus on primary local therapies)
- We decided to work with pre-treatment criteria (clinical classification system) only, while Tosco et al also included papers based on post-surgery results
- In fact, we see both papers as complementary: the initial management for patients is of major importance (our focus) and the treatment will later be individualized based on post-treatment (pathological) results (pT, pN, post-PSA, ISUP grading etc), which is more the focus of Tosco's paper.

We adapted the text so that this complementary aspect is more clear, highlighting the importance of the two papers.

Reviewer 2:

Reviewer 2 also mentions the Tosco SR in which we refer to our previous answer to reviewer 1.

Apart from two RCTs on EBRT and ADT duration, the quality of the evidence for treatment of locally advanced PCa remains low. It is clear and correct that treatment strategies that we offer should be individualized and based on the available evidence at that time. The focus of the systematic review was highlighting this existing evidence on the primary local treatment. We do not give recommendation on the total clinical pathway for each patient. Since the paper by Gillessen *et al.* is a consensus paper, these results are not an intended subject of a systematic review.

Due to the heterogeneity in the included studies, only a narrative review could be performed. Even though, the current evidence does not allow us to put RP forward as the first therapeutic option in this patient population. We agree with the statement on personalized medicine, but this should be based on the available evidence and discussed with each patient individually.

Suggestion concerning the introduction were taken into account and the text was adapted accordingly. We clarified active treatment (= curative treatment).

We updated the sections evidence acquisition and evidence synthesis. Since this is already an extensive review, we decided to report exclusion criteria in the supplementary text. We reported for each category, the number of RCT and NRS (non-randomized) studies, which translates into LEs. We believe that adding LE information will impair legibility.

In regard to the comment concerning EBRT alone versus EBRT + ADT, the benefit of ADT is indeed confirmed by several RCTs. Still discussion remains about the duration of ADT. Two or three years ADT have both been shown to give a benefit, but have never been compared directly. Intermediate duration (as reported in the study by Nabid *et al.*) is highly questionable and the study has critically been commented on in our SR. We agree that comorbidity at the time of diagnosis must be taken into account when deciding on ADT duration but is remains unclear if this should be the only or main factor to decide between 2 and 3 years of ADT.

Reviewer 3:

The reviewer correctly pointed out that we did not reported on ablative therapies. Neither HIFU nor Cryotherapy/ablation nor Photodynamics are reasonable alternatives to the established curative treatment options for high-risk patients, according to the latest EAU guidelines. For this systematic review, we decided upfront to focus on established treatment modalities only. Papers with ablative treatment modality in one (or more) arms were therefore excluded.

We discussed the use of chemotherapy as part of multimodality therapy more in detail, with attention to the recently published studies (RTOG 0512, STAMPEDE, GETUG 12). However, our systematic review focusses mainly on local treatment modalities for high-risk and locally advanced prostate cancer.

We agree with the fact that in some of the included studies, the EBRT dose are suboptimal and should not be recommended any more in daily practice. We clarified this throughout the text and we created a separate table with studies reporting on EBRT doses below 70Gy to separate them from studies with accurate doses. By excluding these studies (4 different studies) the observation did not change. However, due to low level of evidence, we cannot conclude that one (RP or EBRT) is superior to the other. Concerning our current conclusion: we did not state that RP is better nor that they are equal. We stated that no superiority of any local modality has been shown be superior with any other, which is fair as this is only based on published data.

Reviewer 4:

We agree with the fact that in some of the included studies, the EBRT dose are suboptimal and should not be recommended any more in daily practice. Reviewer 1 also mentions this and we refer to our previous answer to reviewer 1. In short, we clarified this throughout the text and we created a separate table with studies reporting on EBRT doses below 70Gy to separate them from studies with accurate doses. By excluding these studies (4 different studies), the observation did not change. This is also explained above, in one of the replies to the first reviewer. However, due to low level of evidence, we cannot conclude that one (RP or EBRT) is superior to the other.

The impact of newer imaging modalities, like mpMRI, is yet unclear. This is almost not (yet) reported in trials and MRI standardization for local staging is not so old, which results in studies with only a short follow-up period. The other staging imaging modalities have no place yet. Excluding non-mpMRI studies would not leave many papers to discuss, while the purpose of a systematic review is

to show the entire state of knowledge and not only focus on the most recent data. However, since this is a highly evolving and interesting domain, we added a small section on modern imaging to the text.

Take home message

High-risk and locally advanced PCa patients are likely to undergo a multimodality treatment. Patients should be at all-time fully informed about all available options and the likelihood of a multimodal approach including the potential side effects of both local and systemic treatment.

For high-risk localized and locally advanced PCa, both RP as part as multimodal therapy and EBRT + long-term ADT can be recommended as primary treatment.

For high-risk localized PCa, also EBRT + BT can be offered, despite a less favourable toxicity profile. In selected high-risk PCa patients, a shorter duration of ADT might be considered.

Until the results of the SPCG15 trial are known, the optimal local treatment remains a matter of debate.

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