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

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

K. Plass, L. Moris, M.G. Cumberbatch, T. Van den Broeck, G. Gandaglia, N. Fossati, B. Kelly, R. Pal, E. Briers, P. Cornford, M. De Santis, S. Fanti, S. Gillessen, J.P. Grummet, A.M. Henry, T.B.L. Lam, M. Lardas, M. Liew, M.D. Mason, M.I. Omar, O. Rouvière, I.G. Schoots, D. Tilki, R.C.N. van den Bergh, T.H. van Der Kwast, H.G. van Der Poel, P.-P.M. Willemse, C.Y. Yuan, B. Konety, T. Dorff, S. Jain, N. Mottet, T. Wiegel~~**Take home message**~~

High-risk and locally advanced prostate cancer (PCa) patients are likely to undergo ~~a~~ multimodality treatment. Patients should ~~be~~ at all~~-~~ times be 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 radical prostatectomy~~RP~~ as part as multimodal therapy and external beam radiotherapy (EBRT) + long-term androgen deprivation therapy (ADT) can be recommended as primary treatment.

For high-risk localized PCa, ~~also~~ EBRT + BT can also be offered~~,~~ despite a less favo~~u~~rable 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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Benefits and Risks of Primary Treatments for High-Risk Localized and Locally Advanced Prostate Cancer: An International Multidisciplinary Systematic Review

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This systematic review was performed under the auspices of:
- 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

***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 PCa 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 with 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 androgen deprivation therapy (ADT), respectively. High levels of evidence exist for EBRT treatment, with several randomized clinical trials 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 genitourinary toxicity and sexual dysfunction, and EBRT in bowel problems.

Conclusions: 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, EBRT + BT can also be offered despite more grade 3 toxicity. Interestingly, for selected patients, for example, those 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 most likely be 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 at all times be 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 prostate cancer 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 quality of life, provided they are combined with other treatments. In the case of surgery this means including radiotherapy (RT), and in the case of RT this means either hormonal therapy or combined RT and with BT brachytherapy.

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1. 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 ten10- and 15fifteen-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 the best result in this patient cohort. Extensive evidence on the benefit of local curative treatment to improve survival already exists, and therefore, androgen deprivation therapy (ADT) alone should not be considered a valid treatment option in the setting of high-risk and locally advanced PCa [4–6]. Currently, the European Association of Urology (EAU) PCa gGuidelines recommend either radical prostatectomy (RP) with extended pelvic lymph node dissection in a multimodal approach (with possible post-operative radiotherapy [RT] ±+/- ADT), or external beam radiation therapy (EBRT) ato 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 basedbest is still lacking and has led to experience- rather than evidence-based management of patients. The aim of this systematic review (SR) is to compare the available primary local curative treatment options for high-risk localized and locally advanced PCa at diagnosis.

2. 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 the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [8] and methodology as detailed in the Cochrane hHandbook [9] (Supplementary material ~~1 and 2~~). The study population was comprised of male patients with histologically proven high-risk localized PCa (International Society of Urologic Pathologists [ISUP] grade 4–5 [Gleason score {GS} 8–10] or prostate-specific antigen [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

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oncological outcomes included PCa-specific mortality (PCSM), overall mortality (OM), biochemical failure (BF), and need for salvage treatment. Secondary non-oncological outcomes were quality of life (QoL), functional outcomes, and adverse events. Abstracts and full-text screening, and data extraction were independently performed in duplicate (L.M., M.C., G.G., N.F., B.K., and R.P.) and disagreement was resolved by discussion or reference to an independent third party (T.V.D.B.). OwingDue to the anticipated heterogeneity across studies, only a narrative synthesis was planned.

3. Evidence synthesis

3.1. 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 randomized clinical trials (RCTs) [11–34] and 66 non-randomized studies (NRSs; –4four prospective and 62 retrospective studies).

3.2. Characteristics of the included studies

Four major comparisons could be categorized: (1) cComparison of RP and RT (258, 809 patients, all NRSs), (2) cComparisons of RT with or without ADT and ADT duration (21, 353 patients, 12 RCTs, six6 NRSs), (3) cComparisons of different schedules of RT (77, 152 patients, 11 RCTs, 24 NRSs), and (4) cComparison of RP with or without additional therapies (10, 033 patients, one1 RCTs, seven7 NRSs). Both baseline study characteristics (Ssupplementary Ttables 1–4) and corresponding outcome data (Ssupplementary Ttables 5–8) are presented. –Supplementary Tables 1 and 5 summarize studies comparing RT with RP [35–64]. Supplementary Tables 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]. Supplementary Tables 3 and 7 compare different RT modalities (including BT) [11,12,19–22,24,25,28,33,34,69–92], and Supplementary Ttables 4 and 8 compare different RP modalities [16,31,93–98]. Four studies reported on RT doses below 70 Gy [37,41,55,57]. Since this does not reflect nowadayscurrent treatment, a separate table was created for these studies, excluding them from any further recommendation (Ssupplementary Ttables 9- and 10).

3.3. Risk of bias and confounding assessment

Figures 2 and 3 summarize the risk of bias (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, such aslike clinical T category, biopsy Gleason score GS, and initial PSA, were adequately

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considered through statistical adjustments in a large proportion of studies, ~~whilst~~while the correction for biopsy strategy remained unclear.

~~EVIDENCE SYNTHESIS~~

3.4. ~~Radical Prostatectomy~~RP versus RT~~Radiotherapy~~

Thirty studies compared RP with EBRT (±~~+/-~~ ADT) [35–64]. All were NRSs and ~~there were~~ no full-text RCTs were 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~~/~~ of 30 studies, and doses were <70 Gy in four of ~~4/~~30 studies [38,41,43–45,49,53,54,59,61,63]. Therefore, many of the studies in this category do not reflect contemporary practice and were not taken into account for the final recommendations.

3.4.1. Oncological outcomes

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

3.4.2. 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, and ~~LUTS~~lower urinary tract symptoms), sexual dysfunction, and gastrointestinal (GI) toxicity (i~~.~~e~~.~~, diarrhea, bleeding, and 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].

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3.5. ~~Radical Prostatectomy~~RP — ~~—~~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.

3.5.1. 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~~.~~ [31] only demonstrated an improvement in biochemical failure–free survival (BFFS) after adjuvant RT, with no difference in overall survival (OS) or PCa-specific survival (PCSS)~~ [31]~~.

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 follow-up (FU) of 11.2 yr~~s~~ [16]. Two studies investigated the effect of neoadjuvant systemic treatments [93,94]. One NRS reported an additional benefit of both BFFS and OS after 10 yr~~s~~ of FU with neoadjuvant ADT [94]. The second NRS compared neoadjuvant luteinizing hormone-releasing hormone (LHRH) analog~~ue~~ 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 with~~to~~ 111 mo in the RP~~-~~ arm.

3.5.2. 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~~.~~ [98] compared the effect of open versus robotic RP on erectile function recovery in high-risk PCa patients, showing no statistically significant difference after 24 mo of FU~~ [98]~~.

3.6. EBRT with or without ADT and comparison of ADT duration

3.6.1. EBRT alone versus EBRT + ADT

Nine studies compared EBRT alone with EBRT + ADT, including four~~4~~ RCTs (and the updated results of EORTC 22863 trial) [14,16,26,30,32] and four~~4~~ NRSs [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 trials used ~~-~~LHRH agonists with an androgen receptor (AR) antagonist for flare~~-~~ prevention [14,30,32]. Two other RCTs compared EBRT ±~~+/-~~ adjuvant bicalutamide [16,26].

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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~~ two~~2~~ studies showed improvements in PCSS [14,30,32], and ~~DMFS in~~ one~~1~~ study showed improvement in DMFS [32]. The subanalysis by Horwitz et al~~.~~ [67] 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~~.~~ [16] 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 were~~as~~ similar to previously reported data. There were no differences in other non-oncological outcomes between the randomi~~z~~sed groups.

3.6.2. 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 mo~~nths~~) versus long-term (24~~–~~36 mo~~nths~~) ADT, seven~~7~~ RCTs [13,15,17,18,23,27,29] and one~~1~~ NRS [69] were identified. Intermediate-term ADT was defined as ADT for 18 mo.

An advantage of~~for~~ long-term ADT over short-term ADT was found in four~~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~~.~~ [18], showing no differences in OS, CSS, and DFS between ~~-~~long-term ~~ADT~~ (36 mo) and intermediate-term ADT~~ [18]~~.

Only two studies reported on functional outcomes [17,18]. Nabid et al~~.~~ [18] showed no statistical difference in global QoL~~,~~ however, a clear difference in favor of intermediate-term 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~~.~~ [17] reported no differences in late GU and GI toxicity comparing 4 ~~mo~~ and 24 mo of ADT~~ [17]~~.

3.7. ~~Radiotherapy~~RT ~~–~~ ~~d~~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 versus EBRT + BT, EBRT/BT dose/fractionation/field size comparisons, and the addition of chemotherapy to RT as multimodality therapy.

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3.7.1. EBRT versus BT (monotherapy or BT boost + EBRT; (+/- ±ADT)

There were 17 studies comparing EBRT withto 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 NRSs. For monotherapy, EBRT doses ranged from 70 Gy to 81 Gy and low-dose rate BT (LDR-BT) ranged from 140 Gy to 145 Gy [71,74,77,84,100]. When combined with BT, EBRT doses varied between 40 andto 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 three3 fractions to 10 Gy in 2 Gy fractions for high-dose rate BT (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 withto 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 one1 study [83], improved OS in five5 studies, [72,76,82,87,92], improved CSS in four4 studies [72,76,83,86], and improved BFFS in three3 studies [76,82,83].

Five NRSs compared BT alone (±+/- ADT) withto EBRT (±+/- ADT) [71,74,77,84,100]. Three studies suggested improved BFFS and PCSM with BT compared withto 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 [100] comparing BT (±+/- ADT) with EBRT + BT (±+/- ADT), showing that trimodality treatment (EBRT + BT + ADT), but not treatment with EBRT alone or ADT alone compared withto 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, [20,21], 5-yr grade 3 GU toxicity was worse when treated with EBRT + LDR-BT boost + ADT compared withto dose-escalated EBRT + ADT (5 yr: 18.3% vs 5.2% respectively) [19,20]. The NRS by Khor et al [85], showed more grade 3 strictures (as GU toxicity surrogate) in the combination group (5 yr: 11.8% vs 0.3%) [85].

3.7.2. EBRT — trials of dose, fractionation, and field size

Seven RCTs [11,12,19,24,25,34,88] and 11 NRSs [28,73,75,78–81,89–91] compared different EBRT modalities.

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Four studies (two different RCTs [and one update of the trial by Arcangeli et al [11,12]–, and one NRS) compared hypofractionation and conventional fractionation [11,12,79,88], comparing conventional EBRT (78––80 Gy) withto 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 withto 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 3Dthree-dimensional-conformal RT (70––74 Gy) withto 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 progression-free survival (PFS) and BF for neoadjuvant ADT + whole-pelvis RT when compared withto 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].

3.7.3. 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 withto 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.

3.8. Locally advanced PCa

Twelve studies reported specifically on locally advanced PCa (according to the EAU PCa guidelines definition), with five RCTs [17,26,29,30,32] and seven NRSs [43,49,56,57,62,65,67]. Five NRSs compared RP withto EBRT ±+/- BT [43,49,56,57,62], showing better survival outcomes for RP compared withto EBRT ±+/- ADT in well-selected patients. Four RCTs compared EBRT + ADT versus 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

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dose and ADT duration were not reported [65]. Finally, two RCTs compared EBRT + short-term ADT withto EBRT + long-term ADT -and showed -superior DMFS for long-term ADT [17,29].

3.9. Discussion

3.9.1. Principal findings

3.9.1.1. RP versus EBRT and RP intergroup comparison

Historically, men with high-risk PCa have been managed most commonly with EBRT, ADT, or both [102,1032], whilest RP has been discouraged in this setting, due to concerns about side effects and inadequate disease control [1032–1065]. 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 versus EBRT ±+/- ADT in terms of survival outcomes and/or toxicity, but the ongoing randomized SPCG-15 trial will provide us with valuable information on this matter [1076]. 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 [1087]. 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 and no recommendations should be based on these observations. 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, it remains unclear which therapeutic approach after RP is superior-remains unclear [1098].

We can conclude thatmake the following conclusions:

- 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-RT and/or ADT) or EBRT + ADT may be offered to patients with high-risk localized and locally advanced PCa as long as it is part of a multimodal treatment scheme.
- Although too soon to make recommendations, the use of (neo)adjuvant chemotherapy with RP is currently being tested as part of the multimodality treatment of high-risk or locally

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advanced PCa [1109]. Future analysis and longer follow-upFU of these trials will provide valuable information.

3.9.1.2. Studies in the context of primary radiotherapyRT

Radiotherapy RT 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 four studies reporteding doses below 70 Gy [14,17,26,66]. Extrapolating of 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 a 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. [27] confirmed that even with dose-escalated RT doses (median dose of 78 Gy), long-term ADT (24 mo) results in longer BFFS and OS thancompared to 4 mo of ADT [27]. OwingDue to significant side effects, reducing ADT length seems desirable as long as it will not affect efficacy. Nabid et al. [18] designed a superiority study comparing long-term ADT (36 mo) withto intermediate-term ADT of 18 mo [18], showing no difference in DM, OS, and CSS after 9.4 yrs of FU, but confirmed an improvements of certain QoL aspects (physical, emotional, and social functioning and fatigue). Although the authors suggest that intermediate-term 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. AlsoIn addition, the use of RT doses of only 70 Gy and the low compliance of 53% to long-term ADT (vs. 88% for intermediate-term ADT) complicates interpretation of this study.

The combination of EBRT + BT boost aims to increase doses to the prostate whilest 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% and% 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 withto 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 thancompared to the surrounding normal tissue. Both HDR-BT and EBRT schemes

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have tried to implement this, but controversy remains. The RCTs by Arcangeli et al. [11,12] and Incrocci et al. [88] 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 with~~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. Optimization of~~ing~~ chemotherapy regimens and time of delivery (neoadjuvant or adjuvant) remains investigational. The GETUG-12 trial suggested ~~an~~ improved relapse-free survival with docetaxel + ADT versus ADT alone [1~~1~~10]. The phase 2b trial by Carles et al. [33] 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 yr~~s~~ 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 [11~~2~~1]. However, upfront docetaxel ~~did~~ improved PFS and failure-free survival in this patient population without excess in late toxicity, which might influence future treatment decision making. –An improved insight into patient profiles will be needed to identify those patients who will likely benefit from adjuvant chemotherapy. Other additional systemic therapies~~y,~~ including novel endocrine agents (such as~~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~~ greater ~~extend~~ extent in an SR~~systematic review~~ by Tosco et al. [11~~3~~2].

We can conclude ~~that~~that the following:

- 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 an LHRH analog~~ue~~ combined with a 1~~one~~-mo~~nth~~ anti-androgen for flare prevention.

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- Adjuvant ADT should be continued for at least 24 mo; however, for all high-risk patients, there is insufficient evidence to support prolonging of 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 [112~~1~~1].

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.

3.9.2. 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. Numerous trials with (neo)adjuvant chemotherapy and new ~~androgen receptor~~AR~~-~~-targeted therapies as part of the multimodal approach are currently tested and will likely change the treatment landscape. However, not only treatment, but also classification of patients into prognostic groups is the key to~~for an~~ optimal treatment. A recent SR on the impact of biochemical recurrence (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~~ doubling time and a high final GS after RP, and a 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 [1143]. 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 [1154–1187]. 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 FU~~follow-up~~ and treatment schemes. Our SR did not report on the use of focal therapy in this setting. Until now, d~~D~~ata on ablative therapies are ~~until now~~

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relatively new and fail to provide long-term outcome data. Especially in the high-risk and locally advanced setting, there is a paucity ~~on~~ of comparative studies with sufficient FU~~follow-up~~ time. Therefore, it cannot be recommended in today's practice [11~~9~~8,11~~9~~2~~0~~]. However, we want to stress that the treatment landscape of PCa is a dynamic field with constant progression and change. The recommendation of today might be outdated the next year. It is our responsibility to keep up to date within a highly changing field.

3.9.3. Limitations and strengths of this ~~systematic review~~SR

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 collaborative~~e~~ project involving two multidisciplinary panels of experts (EAU Prostate Cancer Guidelines Panel and ASCO) including a patient representative [8,9,12~~1~~0]. 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. To overcome the problem of RT studies reporting on doses <70 Gy, we created a separate table and excluded the~~m~~ studies from interpretation of the results. 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 [12~~1~~2]. Finally, clinical staging and stratification depended on standard imaging techniques with chest radiograph, abdominal computed tomography (CT), and isotope bone scan in all included RCTs. However, the field of imaging and staging is rapidly evolving, with promising data for multiparametric magnetic resonance imaging (mpMRI), positron emission tomography (PET)/CT, and ~~PSMA~~ prostate-specific membrane antigen 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. It should be acknowledged that ~~with~~ the recommended use of MRI for local staging and subsequent MRI fusion targeted biopsies resulted in upgrading of the PCa identified [12~~3~~2]. However, mpMRI fusion biopsies are a recent development, and therefore, studies using this technique were not included as these~~y~~ do n'ot have sufficient FU~~follow-up~~.

4. Conclusions

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In this collaborative SR~~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 SR~~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 also be offered~~,~~ despite more grade 3 toxicity. Interestingly, for selected patients, ~~e.g.~~for example, those 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 for~~that~~ patients to be~~are~~ aware that the offered therapy will ~~be~~ most likely be in the context of a multimodality treatment plan. In particular, if radiation is used, the combination of local and~~with~~ systemic treatment provides the best outcome, provided that 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~~-~~ times be fully informed about all available options and the likelihood of a multimodal approach, including the potential side effects of both local and systemic treatment.

This SR was performed under the auspices of the EAU Guidelines Office Board, the EAU Prostate Cancer Guideline Panel, and the American Society of Clinical Oncology.

***Author contributions*:** Lisa Moris had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Moris, Cumberbatch, Gandaglia, Fossati, Kelly, Pal, Van den Broeck, van den Bergh, Willemse, Yuan.
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Janssen. Dr. E. Briers has received grant and research support from IPSEN, the European Association of Urology, and Bayer; is an ex officio board member for Europa UOMO; is an ethics committee and advisory group member for REQUITE; is a patient advisory board member for PAGMI; and is a member of SCA and EMA PCWP. Professor Gillessen has served on advisory boards for Orion, Innocrin, Clovis, Bayer, AAA International, Roche, Menarini, Sanofi, and ProteoMedix; receives company speaker honorarium from Janssen; and has served on the IDMC for Janssen. Professor Dr. J.P. Grummet received speaker honorarium from Mundipharma, a travel grant from Astellas, and a research grant from Cancer Australia; and is the owner of MRI PRO Pty Ltd., an online training platform. Professor Dr. A.M. Henry participates in trials by Cancer Research UK and the National Institute of Health Research; her department receives research grants from Cancer research UK, The Medical Research Council, and the National Institute of Health. Professor Dr. M. De Santis is a company consultant for Amgen, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Dendreon, Eisai Inc., ESSA, Ferring, GSK, Incyte, IPSEN, Janssen Cilag, Merck, MSD, Novartis, Pfizer, Pierre Fabre Oncologie, Roche, Sanofi Aventis, SeaGen, Shionogi, Synthon, Takeda, Teva, OncoGenex, and Sandoz; receives speaker honoraria from Amgen, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Ferring, GSK, IPSEN, Janssen Cilag, Merck, MSD, Novartis, Pfizer, Pierre Fabre Oncologie, Roche, Sanofi Aventis, Synthon, and Takeda; participates in trials run by the Technical University Munich, Amgen, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Dendreon, Eisai Inc., Ferring, GSK, IPSEN, Incyte, Janssen Cilag, Merck, MSD, Novartis, Pfizer, Pierre Fabre Oncologie, Roche, Sanofi Aventis, SOTIO, and Cancer Research UK; participates in various trials as a member of the EORTC GU group; and has received research grants from Pierre Fabre Oncologie, and travel grants from Amgen, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Dendreaon, Ferring, GSK, IPSEN, Incyte, Janssen Cilag, Merck, MSD, Novartis, Pfizer, Pierre Fabre Oncologie, Roche, Sanofi Aventis, SeaGen, Shionogi, Synthon, Takeda, and Teva/OncoGenex. Professor Dr. M.D. Mason is a company consultant for Ellipses Pharma and Oncotherics. Professor Dr. H.G. van der Poel is a company consultant for Intuitive Surgical; has participated in trials for Astellas and Steba Biotech; and has received grant and research support from Astellas. Professor Dr. S. Fanti is a company consultant for Bayer and ANMI; has received speaker honorarium from Bayer, Genzyme, ANMI, and GE Healthcare; and participates in trials by Amgen, Bayer, BMS, Genzyme, Janssen, Merck, and Novartis. Dr. T.B.L. Lam is a company consultant for and has received company speaker honoraria from Pfizer, GSK, Astellas, and IPSEN. Professor Dr. P. Cornford is a company consultant for Astellas, IPSEN, and Ferring; receives company speaker honoraria from Astellas, Janssen, IPSEN, and Pfizer; participates in trials run by Ferring; and receives fellowships and travel grants from Astellas and Janssen. Professor Dr. N. Mottet is a company consultant for Janssen, GE, BMS, Sanofi, and Astellas; has received speaker honoraria from Astellas, Pierre Fabre, Steba, Janssen, and Ferring; and has received fellowships and travel grants from Astellas, IPSEN, Sanofi, Janssen, and Roche. Professor Dr. T. Wiegel is an advisory board member for IPSEN; receives company speaker honoraria from IPSEN and Hexal; is a member of the Janssen Steering Committee; and has participated in the ATLAS/AUO trial. Dr. L. Moris, Mr. M.G. Cumberbatch, Dr. G. Gandaglia, Dr. N. Fossati, Mr. B. Kelly, Mr. R. Pal, Dr. T. Van den Broeck, Dr. R.C.N. van den Bergh, Dr. M.I. Omar, Dr. M. Lardas, Mr. M. Liew, Professor Dr. O. Rouvière, Dr. I.G. Schoots, Professor Dr. T.H. van Der Kwast, Dr. P-P. M. Willemse, Dr. C.Y. Yuan, Professor Dr. B. Konety, Professor Dr. T. Dorff, and Professor Dr. S. Jain have nothing to declare.

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Figures

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Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-analysisPRISMA flow chart.
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses.

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Fig. 2 – Risk of bias summary graph.
PSA = prostate-specific antigen.

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Fig. 3 – Risk of bias assessment for individual studies.
NRS = non-randomized study; RCT = randomized clinical trial.

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Illustration

Figures

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-analysis flow chart.

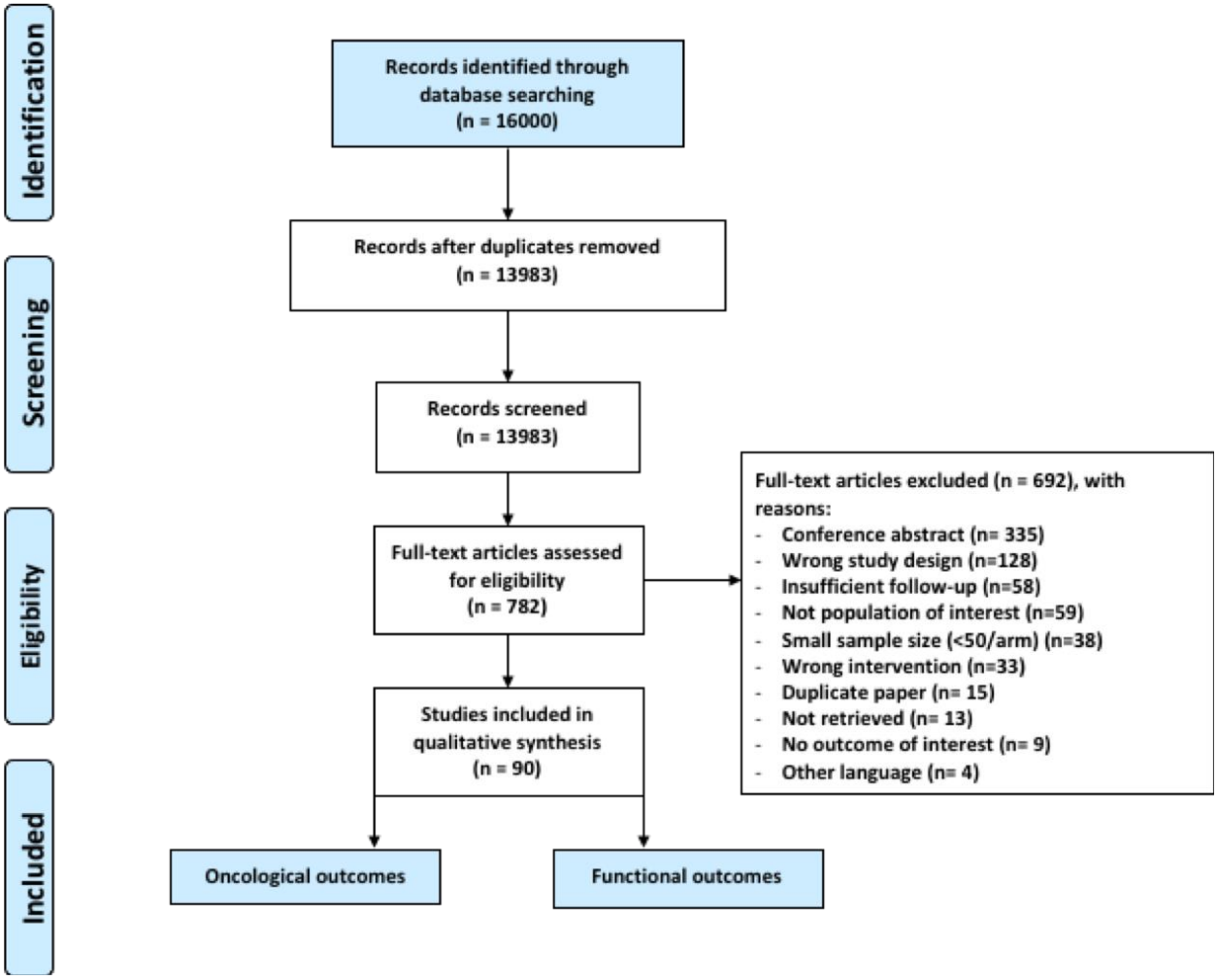
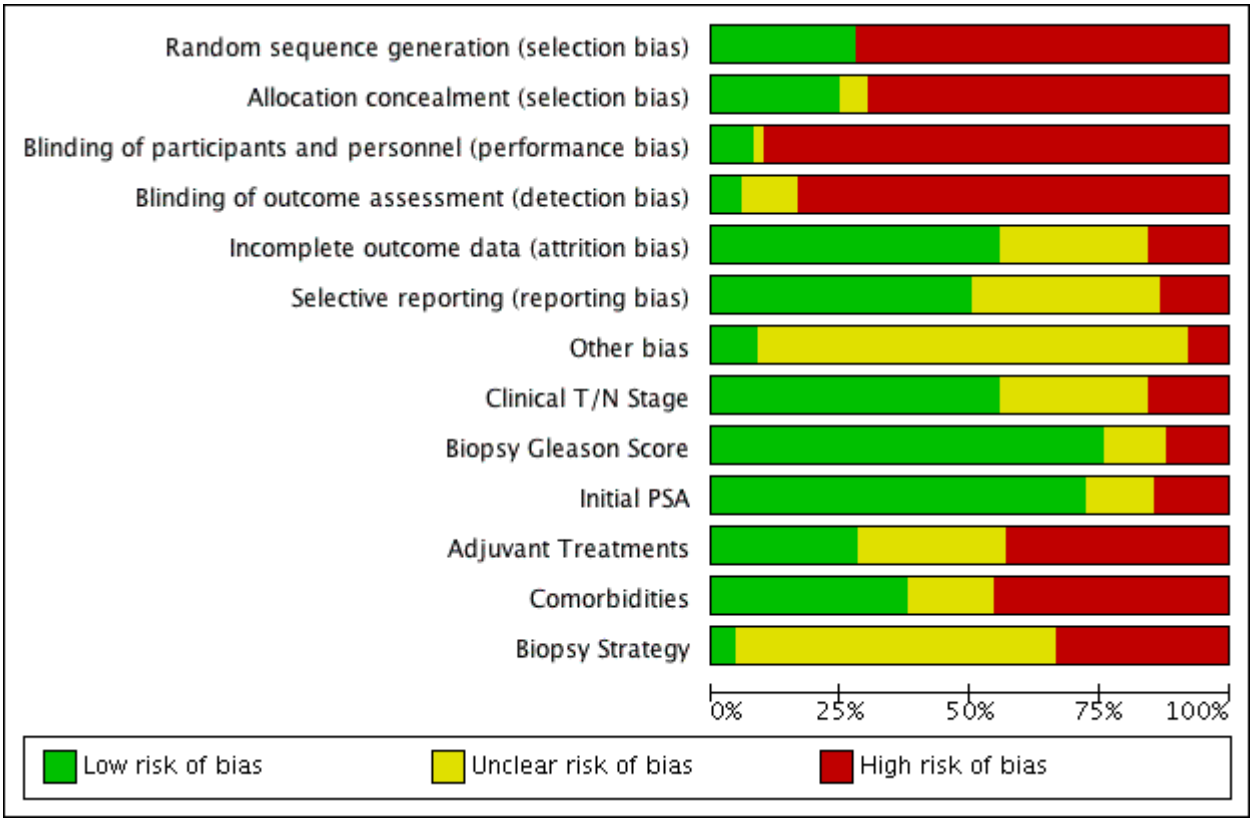
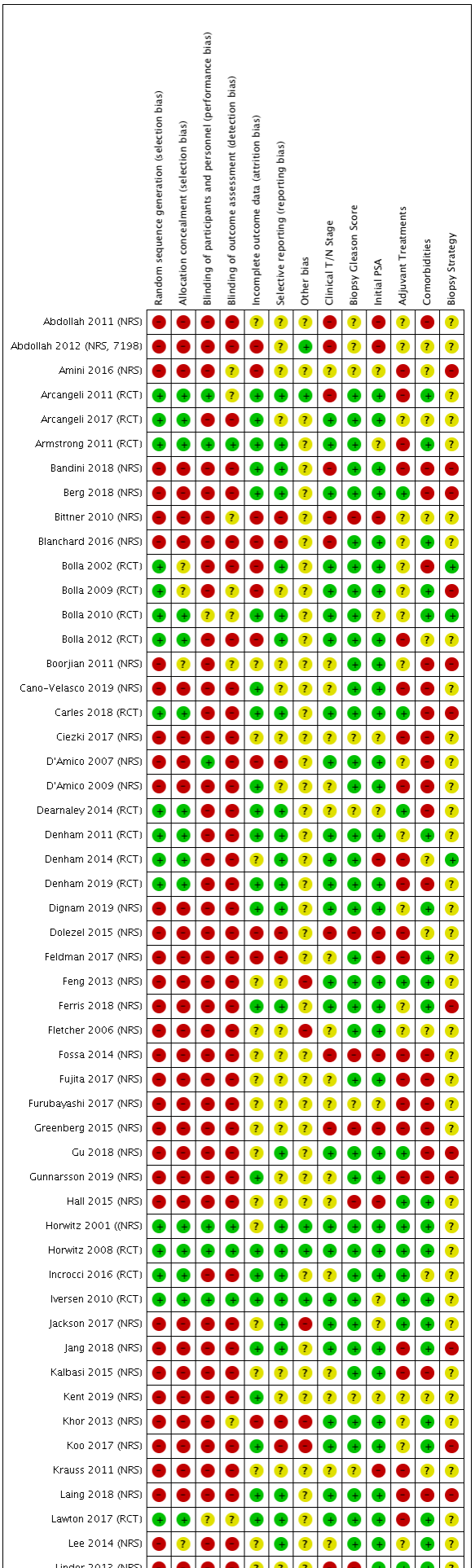


Fig. 2–Risk of bias summary graph.



PSA = prostate-specific antigen.

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


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)
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Bolla 2012 (RCT)
Boorjian 2011 (NRS)
Cano-Velasco 2019 (NRS)
Carles 2018 (RCT)
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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)

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

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Instructions to typesetter

Figure 1

Set ‘n’ in italic font.

Insert a space as a thousand separator for numbers >9999.

Ensure a single space on both sides of ‘=’.

Change ‘(<50/arm) (n=38)’ to ‘(<50/arm; *n* = 38)’.

Figure 2

Set all labels in sentence case except for PSA and T/N.

Figure 3

Set all labels in sentence case except for PSA, T/N, NRS, and RCT.

Letter to the reviewer

We thank the reviewer for providing some interesting input, which will contribute to the completeness of this systematic review.

1. "...surgery as part of multimodal therapy... " does not imply simply adding post-op RT (as is currently stated in the lay summary). Neoadjuvant chemo (especially taxanes) +/- androgen deprivation therapy especially androgen receptor targeted therapies, should be mentioned in the "future perspective" discussion, realizing of course there are no results as yet from these trials

We agree with this statement and added a small line in the section in the discussion of RP treatment.

2. “until the results of SPCG 15 are available……”. CALGB 90203” – neoadj ADT +/ chemo – should also provide additional information on the role of surgery and multi-modal therapy in locally advanced disease.

We specifically mentioned the SPCG15 trial in the context of the comparison of RT to RP in the high-risk/locally advanced setting, since there are no other trials (yet) to this tackle this comparison. CALGB 90203 puts RP in a multimodal setting. Since it didn’t provide long-term outcomes yet and the trial is still ongoing, we did not capture it in our systematic review. However, for completeness we referred to this study in the section on future perspectives and in the discussion on RP .