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The Very High Risk Prostate Cancer – a Contemporary Update

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Abstract

Background—Treatment of high-risk prostate cancer has evolved considerably over the past two decades, yet patients with very high-risk features may still experience poor outcome despite aggressive therapy. We review the contemporary literature focusing on current definitions, role of modern imaging and treatment alternatives in very high-risk prostate cancer.

Methods—We searched the MEDLINE database for all clinical trials or practice guidelines published in English between 2000 – 2016 with the following search terms: ‘prostatic neoplasms’ (MeSH Terms) AND (‘high risk’ (keyword) OR ‘locally advanced’ (keyword) OR ‘node positive’ (keyword)). Abstracts pertaining to very high-risk prostate cancer were evaluated and 40 pertinent studies served as the basis for this review.

Results—The term ‘very’ high-risk prostate cancer remains ill defined. The EAU and NCCN guidelines provide the only available definitions, categorizing those with clinical stage T3-4 or minimal nodal involvement as very-high risk irrespective of PSA level or biopsy Gleason score. Modern imaging with mpMRI and PET-PSMA scans plays a role in pretreatment assessment.

Local definitive therapy by external beam radiation combined with androgen deprivation is supported by several randomized clinical trials whereas the role of surgery in the very high-risk setting combined with adjuvant radiation/ androgen deprivation therapy is emerging. Growing evidence suggest neoadjuvant taxane based chemotherapy in the context of a multimodal approach may be beneficial.

Conclusions—Men with very high-risk tumors may benefit from local definitive treatment in the setting of a multimodal regimen, offering local control and possibly cure in well selected patients. Further studies are necessary to better characterize the ‘very’ high-risk category and determine the optimal therapy for the individual patient.

Introduction

Prostate cancer is a diverse disease with multiple treatment options and inconsistent outcomes. Risk stratification in patients with newly diagnosed prostate cancer allows

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physicians to choose the optimal treatment strategy for each patient. Even within the group of patients with high risk prostate cancer, based on its classic definition, there remains significant heterogeneity in outcomes. While most high-risk patients respond favorably to local definitive therapy with curative intent, a subgroup of patients may progress and succumb to their cancer. Identifying these patients with very high-risk features is important, as they may benefit from multimodal therapy, targeting both the local and systemic components of disease. In the current review we discuss the appropriate definition of very high-risk prostate cancer and recent advancements in the treatment of these patients, focusing primarily on those with locally advance disease (clinical stage T3b-T4) and lymph node metastases identified on pre-treatment imaging.

Literature Review Methods

We searched the National Institute of Health MEDLINE database for all articles published in English between January 2000 and April 2016 with the following search terms: ‘prostatic neoplasms’ (MeSH Terms) AND (‘high risk’ (keyword) OR ‘locally advanced’ (keyword) OR ‘node positive’ (keyword)). Overall, 676 clinical trials or practice guidelines were found, the titles and abstracts of which were evaluated. Forty publications pertaining to the diagnosis and treatment of very high-risk prostate cancer served as the basis for this review. Additional studies were extracted through reference lists of the latter.

Results and Discussion

Defining very high-risk prostate cancer

The current definitions of high-risk prostate cancer include various patients with wide range of prognoses, each requiring a different treatment approach.[1] High-risk prostate cancer was initially coined by D'Amico et al. as clinical T stage ≥ T2c, or Gleason score (GS) ≥ 8, or Prostate Specific Antigen (PSA) > 20mg/ml.[2] Albeit broad, this definition was adopted by the American Urological Association (AUA).[3] In order to increase its specificity, the European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) upgraded the risk level to include patients with clinical T stage ≥ T3a; the PSA level and Gleason score retained the same high-risk threshold.[4,5] However, when using these and other similar classifications, the 5 year progression free survival (PFS) after radical prostatectomy (RP) alone is inconsistent and ranges from 50% - 80% questioning their utility in identifying patients at genuine risk of treatment failure.[6]

Tumor GS may be used to refine the individual risk of relapse among high risk patients. While GS ≥ 8 is commonly used to define high risk prostate cancer, previous reports have shown that patients with GS 8 have a lower risk of biochemical recurrence than those with GS 9-10, and that the outcome of men with GS 7 and a tertiary grade 5 did not differ significantly than that of patients with GS 9-10.[7-11] In these studies, the presence of any Gleason pattern 5 was an independent predictor of adverse outcome.[10] Furthermore, patients with high-grade prostate cancer (GS 8-10) and additional adverse pathological findings including positive surgical margin, extracapsular extension, and mostly seminal vesical invasion, were at a particularly high risk of biochemical recurrence after RP.[11,12] In light of these findings the International Society of Uropathologists has recently adopted a revised

Gleason grading system wherein GS 8 and GS 9-10 have been separated into two different prognostic groups. Patients with GS 9-10 should be considered to have more aggressive tumors which likely warrant a multimodal treatment approach.[9]

The role of pretreatment PSA level as a determinant of 'very' high-risk disease has been evaluated by several studies. Izumi et al. reported that PSA levels exceeding 100 ng/ml were not a significant predictor of overall or cancer specific mortality, whereas the presence of clinical metastasis and high GS in this setting did predict survival. Patients who were considered at lower risk (M0 and GS < 9) had a 5-year CSS rate of 100% compared to 58% in the very high risk group (M1 and GS ≥ 9).[13] Ang et al. reported the outcome of 241 patients with PSA > 100 ng/ml at diagnosis. The overall survival (OS) in their cohort was 29% at 5-years and 18% at 10-years, significantly inferior to patients with lower PSA levels at presentation. Furthermore, there was a linear association between PSA level and risk of mortality up to a threshold of 200 ng/ml, beyond which mortality plateaued.[14] Thus, while higher PSA levels, in particular > 100 ng/ml, predict a worse outcome, the decision whether to use a multimodal approach in order to achieve local control should rely primarily on GS and metastatic status rather than the PSA level itself.

In an attempt to improve the classification of high-risk prostate cancer using multiple disease characteristics, Sphan et al. studied 712 patients with prostate cancer and PSA > 20, and found that combining additional risk factors (e.g. GS 8-10, clinical stage T3-T4) at presentation was associated with unfavorable histopathology and worse cancer specific outcome.[15] Similarly, Walz et al. and others demonstrated that patients with two or more high-risk features (PSA > 20, GS 8-10, and cT3-4) had worse biochemical recurrence free survival and prostate cancer specific survival compared to patients with a single high-risk feature.[16,17] Researchers from Johns Hopkins University utilized commonly used clinical variables to distinguish a group of men with very high-risk prostate cancer who suffered the worst outcome despite aggressive treatment. These patients, representing 15% of the total NCCN high risk cohort, had primary Gleason pattern 5, or ≥ 5 cores with Gleason sum 8–10, or multiple NCCN high risk features. In this group, biochemical recurrence free survival, metastasis free survival, and cancer specific survival were 21%, 37%, and 62% at 10 years, respectively.[18] Similarly, the pre-operative criteria that best identified NCCN-high risk patients likely to experience relapse within 1 year of surgery were Gleason pattern 5 on biopsy or ≥ 4 cores containing pattern 4 (odds ratio 3.17, P < 0.001). These men were also at higher risk of metastatic progression (adjusted HR 3.04, p < 0.001) and cancer-specific death (adjusted HR 3.27, p < 0.001).[19] In their 2014 guidelines, the NCCN defined very high-risk prostate cancer as tumors invading the seminal vesicles (T3b) or adjacent structures (T4).[5]

Nomograms derived in order to improve risk stratification of patients with prostate cancer were initially developed based on diverse patient populations; however, these algorithms may improve risk stratification within the group of high risk patients. The Cancer of the Prostate Risk Assessment post-Surgical (CAPRA-S) score[20] was evaluated in the context of high risk patients undergoing RP with or without RT.[21,22] Patients with high CAPRA-S scores (≥6) had a significantly higher risk of cancer specific mortality and a higher risk of biochemical recurrence following RT either in the adjuvant or salvage setting, thus defining a group of patients with very high risk disease.[21,22]

Recent advancements in the molecular understanding of prostate cancer has led to the development of multiple molecular tests which may improve disease risk stratification.[23] In the context of high risk prostate cancer, the Decipher test, an assay based on 22 markers related to cell proliferation, differentiation, androgen signaling, motility and immune modulation, may independently predict the development of metastatic disease and cancer specific mortality in patients treated with RP either before or after adjuvant or salvage RT.[21,23-25] Furthermore, combining the Decipher genomic classifier with validated clinicopathologic risk models improved their accuracy in predicting adverse outcome.[21,24,25] Future studies will refine the indications for the use of molecular testing and reveal additional markers which may identify very high risk patients who will benefit from aggressive multimodal therapy.[23]

Lymph node involvement was traditionally considered to represent systemic disease, associated frequently with poor prognosis. In fact, the American Joint Committee on Cancer (AJCC) staging system still categorizes patients with lymph node involvement and bone metastases equally as stage IV disease.[26] However, the finding of microscopic nodal involvement at surgery may portend a better outcome than visceral or bone metastasis, particularly if the number of involved nodes is accounted for. Cheng et al. reported that patients with a single positive lymph node who were treated with RP and immediate adjuvant hormonal therapy had a prognosis comparable to that of patients without nodal involvement.[27] Briganti et al. found that patients with 2 or less positive nodes treated with RP, extended pelvic lymph node dissection and adjuvant therapy (hormonal blockade alone or in combination with RT) had a significantly better cancer specific survival at 15 years of follow-up than those with > 2 nodes (84% vs. 62% respectively, $p<0.001$).[28] Recently, Touijer et al. reported that among patients with lymph node metastases treated surgically without further adjuvant therapy, a subset of men with Gleason score < 8 and 2 or less positive lymph nodes had a particularly favorable outcome at 10 years.[29] These findings suggest that not all cases of nodal involvement should be considered uniformly as having ominous systemic disease, questioning the validity of the current staging system and treatment paradigms in this setting. While it is unclear whether microscopic lymph node involvement on final pathology can be deemed comparable to clinical nodal disease identified by modern imaging techniques, the recent EAU guidelines include cN+ patients within the category of high-risk locally advanced disease amenable for local definitive management within a multimodal approach.[30]

Table 1 summarizes the definition of very high risk prostate cancer in the current literature.

Role of modern imaging in assessment of high-risk prostate cancer

Numerous studies have demonstrated the incremental value of multiparametric magnetic resonance imaging (mpMRI) in evaluating prostate cancer.[31,32] Pretreatment assessment with diffusion-weighted MRI (DW-MRI) and use of MRI-guided biopsy have been shown to differentiate between patients with low risk and those with intermediate/high risk tumors with reference to the specimen Gleason score.[33-35] In another study evaluating the performance characteristics of 3 Tesla mpMRI , the positive predictive value for identifying extraprostatic extension was highest in the high risk cohort, approaching 89%. In fact,

mpMRI was found to be the best preoperative predictor of extraprostatic extension with an odds ratio of 10.3.[36] In light of these findings the EAU guidelines recommend a prostate mpMRI for local staging of high-risk localized or locally advanced PCa.[30]

Prostate Specific Membrane Antigen (PSMA), is a type II transmembrane protein overexpressed in nearly all prostate cancer cells and its use as a tracer during positron emission tomography (PET) scan has recently emerged as a novel promising imaging modality in prostate cancer.[37,38] Because PET PSMA can improve identification of systemic or recurrent disease[37], it would seem reasonable to explore its use in local staging of men with very high-risk prostate cancer. In a group of patients with intermediate to high-risk disease, Maurer et al. reported a sensitivity of 66% and specificity of 99% for lymph node staging with ^{68}Ga-PSMA-PET.[39] The corresponding performance characteristics of CT, MRI and PET-choline were substantially inferior.[40-43] Within a very high-risk setting, the use of PET PSMA may facilitate the identification of minimal pelvic nodal involvement potentially suitable for definitive local treatment while avoiding possible morbidity in those with widespread systemic disease.

Table 2 describes the characteristics of imaging modalities used in high risk prostate cancer.

Treatment of patients with locally advanced prostate cancer (cT3b-cT4)

1. Radical prostatectomy—While in most high-risk patients surgery is performed with curative intent, in the setting of clinical T3b-T4 prostate cancer, RP can also be considered for “debulking” the primary tumor thereby enhancing local control. Experienced surgeons often use the information provided by MRI combined with their own subjective assessment by digital rectal examination to discern tumor resectability and discuss preemptively the feasibility of unilateral/ bilateral nerve sparing versus sacrifice of the neurovascular bundles. In a Surveillance Epidemiology and End Results (SEER) based study, Johnstone et al. evaluated the outcome of patients with clinical stage T4 prostate cancer, with or without lymph node involvement, and otherwise no evidence of bone or visceral metastasis. Only a minority of these patients (7%), more commonly the younger, underwent RP alone or in combination with radiation therapy (RT) and androgen deprivation therapy (ADT). In this unique ‘very’ high risk group, treatment of the primary tumor (either by surgery or radiation) was associated with improved oncologic outcome compared to ADT alone or no treatment. This difference was evident mostly in those with regional lymph node involvement.[44] Moltzahn et al. evaluated a multi-institutional cohort of 266 patients with very-high-risk locally advanced prostate cancer (cT3b-4) treated surgically. Despite the adverse pathological features, the 10-year cancer specific mortality (CSM) was relatively low (5.6% to 12.9%), and affected by comorbidity status and age. In healthy patients (Charlson comorbidity index (CCI) < 1) CSM did not differ among age groups, suggesting RP may be appropriate even in older age. However, in sicker patients (CCI ≥ 1) the risk of dying from causes other than prostate cancer was high and CSM low questioning the incremental benefit of surgical therapy in this setting.[45] As for the surgical approach, with adequate experience, use of robotic surgery in patients with locally advanced disease appears to be comparable to traditional open RP.[46]

Whether patients with locally advanced tumors should be offered additional local therapy (RT) or neoadjuvant / adjuvant hormonal therapy prior to or immediately after surgery has been widely investigated. Three randomized controlled trials have established the role of adjuvant and salvage RT for patients with high risk of local failure (Table 3).[47-52] Ongoing clinical trials will help clarify whether RT is more effective as an adjuvant or salvage treatment, and assess the value of combined therapy with ADT. Optimal RT dose, targets, and field size are yet to be decided.[53]

Taken together, surgery appears to play a critical role in men with very high-risk prostate cancer as part of a multimodal comprehensive approach. The latter has been mirrored in the findings of Nezolosky et al. who reported on increased rates of RP in men with T3N0M0 prostate cancer from 12% to 44% performed between 1998 – 2012.[54]

2. Radiation therapy combined with androgen deprivation—Multiple phase III studies have shown the efficacy of combining RT with ADT in locally advanced prostate cancer (Table 3).[55-61] In a landmark paper, Bolla et al. compared the use of RT alone to RT and long term (3 years) ADT in patients with locally advanced disease. Within the subgroup of patients with T3-4 disease, combined therapy was associated with better long-term loco-regional control, reduced rates of distant metastases and improved survival at a median follow-up of 9 years.[55,56] No difference was observed in cardiovascular morbidity between the two arms.[56] A similar study, RTOG 85-31, evaluated the effectiveness of adjuvant ADT after definitive RT in patients with unfavorable prostate cancer (clinical stage T3, and regional lymph node involvement). At a median follow-up of 11 years the addition of ADT was associated with significantly improvement in 10-year overall survival (49% vs. 39%, p=0.002).[57,58] Warde et al. randomized 1 205 men with locally advanced cancers to receive lifelong ADT with or without RT to the prostate and pelvic nodes. Median follow-up was 6 years. The addition of RT was associated with an improved OS and minimal toxicity (7-year estimated OS 74% in the ADT/RT compared to 66% for ADT alone, p=0.033).[59] Similarly, the SPCG-7/SFUO-3 study included 875 patients with locally advanced prostate cancer randomized to lifelong ADT with or without RT. At a median follow-up of 7.6 years, the estimated 10-year prostate cancer specific mortality was 24% in the ADT alone group and 12% in the ADT/ RT group (p<0.001). Urinary, rectal and sexual morbidities were slightly more frequent in patients receiving RT.[60] Lastly, the intergroup randomized study evaluated the role of adding RT to lifelong ADT in the treatment of locally advanced prostate cancer (clinical stage T3-4N0-xM0 disease, PSA > 40 ng/ml or PSA 20-40 ng/ml and GS 8-10). At a median follow-up of 8 years, OS was significantly improved in patients receiving RT (HR=0.7, 95% CI 0.57-0.85, P<0.001). A similar significant reduction was seen in prostate cancer related death albeit at the expense of a higher frequency of gastrointestinal toxicity.[61] These studies serve to establish the role of combining RT and ADT as standard of care in treatment of locally advanced prostate cancer. With regard to the duration of therapy, several phase III trials demonstrated that long or intermediate term ADT (24-36 months), especially in the presence of GS 8-10, is unequivocally superior to short term ADT (≤6 months) in terms of local control and patients' survival.[62-67]

The question of whether to include the pelvic lymph nodes within the radiation portals (whole pelvic radiation - WPRT) remains unsettled. Two phase III trials evaluated the use of

WPRT versus prostate only radiation (PORT) in high-risk node negative disease.[68-70] The RTOG 9413 trial compared WPRT and PORT, both administrated with combined androgen suppression in a neoadjuvant or adjuvant form. At a median follow-up of approximately 5 years, PFS was 54% for WPRT compared with 47% for PORT (p=0.022); no OS advantage was observed.[68] In an update of this study, the use of WPRT showed a trend towards improved PFS when compared to PORT (p=0.066).[69] The GETUG-01 trial compared WPRT to PORT in high-risk patients and demonstrated no differences in 5-year PFS rates (66% for WBRT and 65% for PORT, p=0.34). No difference was observed in acute and late gastrointestinal toxicity or quality of life outcomes between the arms.[70] Using a higher radiation dose, Aizer et al. were able to demonstrate significantly improved biochemical recurrence free survival rates favoring WBRT in a high risk setting at the expense of an increase in early gastrointestinal toxicity.[71] In the largest study thus far, Amini et al. used the National Cancer Data Base to analyze the outcomes of 14 817 high-risk node-negative patients treated with WBRT vs PORT in a dose-escalated fashion. At a median follow-up of 81 months, no survival advantage was observed favoring WPRT.[72] Taken together, the data pertaining to WPRT in high-risk prostate cancer remain inconsistent, and thus additional studies and longer follow-up are required prior to establishing its role.

3. The role of chemotherapy in the high risk setting—Three randomized controlled trials (CHAARTED[73], GETUG-15[74], and STAMPEDE[75]) have recently established a new standard for chemo-hormonal therapy administered at presentation in men with hormone-sensitive metastatic prostate cancer. The combined findings of these trials revealed an estimated 9% absolute improvement in survival at 4 years with the addition of docetaxel to standard of care.[76] Thus, it would seem reasonable to investigate the role chemotherapy with ADT and RP/RT in the very high-risk setting. Multiple phase I and II trials evaluated the role of taxane based chemotherapy in high risk locally advanced prostate cancer given either as neoadjuvant treatment prior to RP/RT[77-82], or combined with ADT and RT as part of a tri-modal approach.[83-87] Neoadjuvant chemotherapy resulted in a median tumor volume reduction of 46% and pathological downstaging in 48% of patients,[81] whereas pathological complete response was never achieved.[77-79,82] While its clinical advantage remains dubious, these studies demonstrated the feasibility of utilizing chemotherapy prior to surgery with an acceptable toxicity.

Several randomized phase III trials evaluated the role of adjuvant chemotherapy after definitive local treatment in high-risk prostate cancer (Table 3).[75,88-91] The RTOG 9902 trial assessed whether the addition of paclitaxel, estramustine, and oral etoposide would improve survival in high-risk prostate cancer patients treated with combined RT and long term ADT. The 10-year results revealed no difference in outcome, controlling for tumor stage, Gleason score, and pre-treatment PSA. Furthermore, the trial was terminated prematurely due to a high rate of thromboembolic events in the chemotherapy arm.[88] Contrary, contemporary studies demonstrated a possible benefit favoring the use of chemotherapy.[75,90,91] In a subset of patients with non-metastatic high risk locally advanced tumors comprising part of the STAMPEDE cohort, docetaxel improved failure-free survival (HR 0.60, 95% CI 0.45–0.80; p<0.001); however, OS analyses were underpowered.[75] The GETUG 12 trial evaluated the addition of docetaxel and estramustine to adjuvant ADT in high risk localized prostate

cancer treated surgically. The 8-year recurrence free survival was 62% in the combined group compared with 50% in the ADT only group (p=0.017).[90] Recently, initial results of the RTOG 0521 trial, evaluating the merits of adding docetaxel and prednisone to long term RT/ADT in high-risk patients were reported. At a median follow-up of 5.5 years, the addition of chemotherapy was associated with improved overall and disease specific survival with acceptable toxicity.[91] Thus, while it seems chemotherapy may have an important role as part of multimodal treatment in very high-risk prostate cancer, further studies and longer follow-up are required to evaluate the true role of adjuvant chemotherapy in this setting.[76]

Treatment of the primary tumor in patients with pelvic lymph node involvement

Historically, the administration of local therapy to the primary tumor in men with pelvic lymph node involvement was deemed futile. However, indirect evidence suggests clear benefit to optimal control of the primary tumor in the setting of regional lymph node metastasis.

The advantage of adding radiation therapy to androgen deprivation in patients with pathological node positive disease recognized at RP has been demonstrated in several studies.[92,93] In an attempt to identify the optimal treatment of clinically node positive disease, Rusthoven et al. evaluated 796 patients with clinical T1-4N1M0 prostate cancer, 43% of whom were treated with external beam radiation therapy. Albeit limited by the inherent bias of a retrospective analysis, the 10-year estimated OS was 45% for those treated with RT compared to 29% in those who received no local therapy; cancer specific survival rates were 67% versus 53%, respectively (p<0.001).[94] Similar findings were observed by Lin et al. who evaluated a group of 3 540 patients with clinically lymph node positive prostate cancer from the National Cancer Data Base. Approximately 32% of patients were treated with ADT alone, while 51% received ADT+RT. Using propensity score matching, treatment with ADT+RT was associated with a 50% decrease in 5-year all-cause mortality when compared to treatment with ADT alone (HR-0.5, 95% CI 0.37-0.67, p<0.001).[95] Finally, Jhonstone et al. reported on a group of 77 patients with clinical stage T4 and regional lymph node involvement in which the combination of surgery, radiation therapy and/or hormonal therapy conferred the most superior outcome compared to either therapy alone (Table 3).[44] Altogether, these studies suggest the more aggressive the local control, the better the outcome.

Conclusion

Various criteria may be used to define very high-risk prostate cancer. The paradigm of deeming patients with truly high-risk disease unfit for surgical treatment needs to be revisited. Men with locally advanced tumors may gain benefit from modern imaging techniques and local control by either RP or RT, while those with node positive disease may benefit from local definitive treatment in the setting of a multimodal regimen, offering cure in well-selected patients. Further studies are necessary to better characterize the ‘very’ high-risk tumors and determine the optimal therapy for the individual patient.

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Table 1

Definition of very high risk prostate cancer in the current literature

Source	Definition
Spahn et al.[15]	≥ 2 high-risk features (PSA > 20 ng/mL, GS 8-10, and cT3-4)
Walz et al.[16]	
Joniau et al.[17]	GS 8-10 in combination with ≥ 1 other high-risk factor (PSA > 20 ng/mL and cT3-4)
Sundi et al.[18]	Primary Gleason pattern 5, or ≥ 5 cores with GS 8–10, or multiple NCCN high risk features
Sundi et al.[19]	Primary Gleason pattern 5, or ≥ 4 cores containing pattern 4
NCCN guidelines [5]	T3b-T4
EAU guidelines [30]	any PSA, any GS, cT3-4 or cN+ *

PSA = prostate specific antigen; GS = Gleason score; NCCN = National Comprehensive Cancer Network; EAU = European Association of Urology

* Definition used to describe high risk locally advanced tumors.

Table 2
Imaging modalities in high risk prostate cancer

Modality	Detection of ECE~	Detection of SVI~	Detection of positive LN~	Advantages and limitations
CT	Sensitivity = 0.75 Specificity = 0.6 [40]	Sensitivity = 0.33 Specificity = 0.6 [40]	Sensitivity = 0.42 (0.26-0.56) Specificity = 0.82 (0.8-0.83)[41]	Not useful for determining the local extent of disease and for local staging[40] Performs poorly in the detection of lymph node metastases[41]
MRI (overall)#	Sensitivity = 0.57 (0.49–0.65) Specificity = 0.91 (0.88–0.93)[32]	Sensitivity = 0.58 (0.47–0.68) Specificity = 0.97 (0.95–0.98)[32]	Sensitivity = 0.39 (0.22-0.56) Specificity = 0.82 (0.79-0.83)[41]	Overall, MRI has high specificity but poor and heterogeneous sensitivity for local PCa staging[32] mpMRI can accurately detect small-volume significant tumors, localize and stage PCa[31] May be used for fusion biopsies with TRUS and post treatment local surveillance[31] May be used to predict PCa aggressiveness[33-35] Performs poorly in the detection of lymph node metastases[41]
mpMRI	1.5T with coil: Sensitivity = 0.84 Specificity = 0.89 3T without coil: Sensitivity = 0.71 Specificity = 0.91 [31]	Sensitivity = 0.61-0.78 Specificity = 0.96-0.98[31]		
PET choline&	Sensitivity = 0.27 PPV = 0.57[43]	Sensitivity = 0.66 PPV = 0.66[43]	Sensitivity = 0.49 (0.4-0.58) Specificity = 0.95 (0.92-0.97)[42]	May improve detection and localization of cancerous foci especially when combined with mpMRI[37] PSMA-PET-MRI can be used to perform targeted biopsies, increasing the diagnostic performance of the biopsies[37] May improve detection of metastatic spread[37] May be used to identify recurrent prostate cancer, including at serum PSA values < 0.5 ng/ml[37] Not all prostate cancers have substantial PSMA overexpression[37] PSMA is not globally available due to regulatory restrictions and not reimbursed by health care providers[37]
PET PSMA%	Sensitivity = 0.5 Accuracy = 0.71[38]	Sensitivity = 0.73 Specificity = 1[38]	Sensitivity = 0.66 (0.49-0.8) Specificity = 0.99 (0.94-1)[39]	

ECE = extra-capsular extension; SVI = seminal vesicle invasion; LN = lymph node; CT = computed tomography; MRI = magnetic resonance imaging; mpMRI = multi-parametric magnetic resonance imaging; PCa = prostate cancer; TRUS = trans-rectal ultrasound; PET = positron emission tomography; PPV = positive predictive value; PSMA = prostate-specific membrane antigen; PSA = prostate specific antigen

~Values represent percent and 95% confidence intervals.

#Endorectal coil slightly improves sensitivity for identifying SVI; sensitivity may be improved with higher field strength and the use of functional imaging techniques.

&Values for detecting ECE and SVI were obtained when using a ^{11}C-choline PET combined with computed tomography.

%Values for detecting ECE and SVI were obtained when using PET-PSMA combined with computed tomography.

Table 3

Summary of results from selected studies evaluating the treatment of very high risk prostate cancer patients with locally advanced or clinically node positive disease

Study	No. of Patients	Eligibility criteria	Treatment	Median follow-up	Outcome
Radical prostatectomy for patients presenting with locally advanced disease					
Johnstone et al.[44]	1,093[#]	cT4, N0 or N1, M0	RP ± RT/ADT vs. RT vs. ADT vs. RT+ ADT vs. NT	NA	5-year OS 72.6% (RP ± RT/ADT), 61.8% (RT), 41.5% (ADT), 71.1% (RT+ADT), 39.8% (NT) Patients treated locally (RT, RP) had significantly better OS than ADT alone or NT
Moltzahn et al.[45]	266	cT3b-4, N0 or N1, M0	RP + PLND ± adjuvant ADT and/or RT	9.3 years	10-year CSS 87.1%- 94.4%; 10-year other-cause mortality 10%-38%
Adjuvant radiation therapy after radical prostatectomy for patients with adverse pathology					
EORTC 22911[47,48]	1,005	pT2-3, N0 + ≥1 risk factor: PSM, SVI, EPE	RP + adjuvant RT vs. RP + observation[$]	10.6 years (IQR 8.4-12.5)	10-year biochemical PFS 60.6% vs. 41.1% (HR 0.49; 95% CI 0.41–0.59; p<0·0001); 10-year clinical PFS 70.3% vs. 64.8% (HR 0.81; 95% CI 0.65–1.01; p=0.054); 10-year OS 76.9% vs. 80.7% (HR 1.18; 95% CI 0.91–1.53; p=0.202); 10-year CSS 96.1 vs. 94.6% (HR 0.78; 95% CI 0.46–1.33; p=0.341)
SWOG 8794[49,50]	431	pT3, N0 ± PSM	RP + adjuvant RT vs. RP + observation[$]	12.7 years (IQR 11.4-15.1)	10-year metastasis free survival 71% vs. 61% (HR 0.71; 95% CI 0.54-0.94; p=0.016); 10-year OS 74% vs. 66% (HR 0.72; 95% CI 0.55-0.96; p=0.023)
ARO 96-02[51,52]	388	pT3-4, N0 ± PSM and undetectable PSA after RP	RP + adjuvant RT vs. RP + observation[$]	9.3 years	10-year biochemical PFS 56% vs. 35% (HR 0.51; 95% CI 0.37–0.70; p<0.0001); Metastasis free survival and OS were not significantly improved by RT[%]
External beam radiation therapy + long term androgen deprivation therapy					
EORTC 22863[55,56]	415	cT1-2 + WHO grade 3 or cT3-T4 + any histological grade[^]	RT vs. RT + ADT (3 years)	9.1 years (IQR 5.1-12.6)	10-year RFS 23% vs. 48% (p<0.001); 10-year OS 40% vs. 59% (p<0.001); 10-year PCM 30% vs. 10% (p<0.001)
RTOG 85-31[57,58]	977	cT3 or N1 or RP + PSM and/or SVI	RT vs. RT + ADT (lifelong)	11 years	10-year OS 39% vs. 49%, p=0.002; 10-year CSS 78% vs. 84%, p=0.005; 10-year metastasis free survival 61% vs. 76%, p<0.0001
Warde et al.[59]	1,205	T3-4, N0/Nx, M0 or T2 + PSA>40 or T2 + PSA>20 + GS>8	ADT (lifelong) vs. ADT + RT	6 years (IQR 4.4–8.0)	7-year OS 66% vs. 74% (HR 0.77; 95% CI 0.61–0.98; p=0.033); 7-year CSS 81% vs. 91% (HR 0.54, 0.27–0.78, p=0.0001)

Study	No. of Patients	Eligibility criteria	Treatment	Median follow-up	Outcome
SPCG-7/SFUO-3[60]	875	cT1b-T2, N0, M0 + WHO grade 2-3, or cT3, N0, M0 + any WHO grade, and PSA≤70 ng/ml[&]	ADT (lifelong) vs. ADT + RT	7.6 years (range 0.2–11.9 years)	10-year CSS 76% vs. 88% (RR 0.44, 95% CI 0.30–0.66, p<0.001); 10-year OS 61% vs. 70% (RR 0.68, 95% CI 0.52–0.89, p=0.004); 10-year biochemical RFS 25% vs. 74% (RR 0.16, 95% CI 0.12–0.20, p<0.0001)
Intergroup randomized study[61]	1,205	cT3-4, N0/Nx, M0 or cT1-2 with either PSA > 40 ng/ml or PSA 20-40 ng/ml and GS 8-10	ADT (lifelong) vs. ADT + RT	8 years (range, 0-15.2 years)	10-year OS 49% vs. 55% (HR=0.7, 95% CI 0.57-0.85, P<0.001); CSS higher in combined treatment (HR 0.46, 95% CI 0.34-0.61, p<.001); 10-year PFS 46% vs. 74% (HR 0.31, 95% CI 0.25-0.39)
Early chemotherapy for high risk locally advanced disease					
RTOG 9902[88]	397	High risk PCa (PSA 20-100ng/mL and GS ≥ 7 with any T stage, or clinical stage ≥T2 and GS 8-10 and PSA ≤ 100ng/mL), N0, M0	ADT (2 years) + RT + CT (estramustin, etoposide, and paclitaxel) vs. ADT + RT	9.2 years (range 0.4-13.3) [~]	10-year OS 63.1% vs. 65.4% (HR 1.04; 95% CI 0.76-1.43; p=0.81); 10-year RFS 25.8% vs. 22.2% (HR 0.94; 95% CI 0.75-1.19, p=0.61)
STAMPEDE[75]	638/ 2,962 [*]	High risk locally advanced PCa with ≥2 of the following: T3-4, GS 8–10, and PSA ≥40 ng/mL	SOC vs. SOC + zoledronic acid vs. SOC + docetaxel vs. SOC + zolderonic acid and docetaxel	3.6 years (IQR 2.5-5)	5-year OS 55% vs. 57% vs. 63% vs. 60%; Survival advantage for SOC + docetaxel (HR 0.78, 95% CI 0.66–0.93; p=0·006) and for SOC + docetaxel + zoledronic acid (HR 0.82, 95% CI 0.69–0.97; p=0·022) compared to SOC only Failure free survival was improved in patients with non-metastatic disease (HR 0.60, 95% CI 0.45–0.80; p<0.001)
GETUG 12[90]	413	Treatment-naïve PCa + ≥1 risk factor: pT3–T4, GS ≥8, PSA >20 ng/mL, or pN1 [+]	ADT (3 years) + local treatment + CT (docetaxel and estramustine) vs. ADT + local treatment	8.8 years (IQR 8.1–9.7)	8-year RFS 62% vs. 50% (adjusted HR=0.71, 95% CI 0.54–0.94, p=0.017)
RTOG 0521[91]	562	GS 7-8, any T stage, and PSA > 20 or GS 8, stage ≥T2, any PSA or GS 9-10, any T stage, any PSA; All had PSA ≤150	ADT (2 years) + RT + CT (docetaxel + prednisone) vs. ADT + RT	5.5 years	4-year OS 93% vs. 89% (HR 0.68, 95% CI 0.44-1.03, 1 sided p=0.03); 5-year RFS 73% vs. 66% (HR 0.76, 95% CI 0.57-1.00, 2 sided p=0.05)
External beam radiation therapy for clinically node positivedisease					
Rusthoven et al.[94]	796	cT1-4, N1, M0	RT vs. no local treatment	5.2 years	10-year OS 45% vs. 29% (HR 0.58; 95% CI 0.48-0.71; p<.001); 10-year CSS 67% vs. 53% (HR 0.61; 95% CI 0.47-0.80; p<.001)
Lin et al.[95]	3,540	cN1, M0 or Mx	ADT + RT vs. ADT alone	5.2 years	5-year OS 71.5% vs 53.2% (HR 0.50; 95% CI 0.37-0.67; p < .001)

No. = number; RP = radical prostatectomy; RT = radiation therapy; ADT = androgen deprivation therapy; NT = no treatment; NA = not applicable; OS = overall survival; PLND = pelvic lymph node dissection; CSS = cancer specific survival; EORTC = European Organization for Research and Treatment of Cancer; PSM = positive surgical margins; SVI = seminal vesicle invasion; EPE = extraprostatic extension; IQR = inter-quartile range; PFS = progression free survival; HR = hazard ratio; CI = confidence interval; SWOG = Southwest Oncology Group; WHO = World Health Organization; RFS = recurrence free survival; PCM = prostate cancer mortality; RTOG = Radiation Therapy Oncology Group; SPCG = Scandinavian Prostate Cancer Group; SFUO = Swedish Association for Urological

Oncology; RR = relative risk; PCa = prostate cancer; CT = chemotherapy; STAMPEDE = Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy; SOC = standard of care; GETUG = Genito-Urinary Tumor Group

[#]72 patients underwent radical prostatectomy.

[$]Treatment was delayed until biochemical or clinical relapse.

[%]The study was underpowered to evaluate the endpoints of metastasis free survival and overall survival.

[^]Patients with cT3-4 disease represent approximately 90% of the study cohort.

[&]78% of patients had a T3 disease.

[~]The trial was terminated prematurely due to a high rate of thromboembolic events in the chemotherapy arm.

[*]Represents the number of patients with newly diagnosed high risk N0M0 disease and the total number of patients included in the study.

[+]All patients underwent a staging pelvic lymph node dissection.