LOW-RISK PROSTATE CANCER: IDENTIFICATION, MANAGEMENT AND OUTCOMES

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Abstract

Context: The incidence of low-risk prostate cancer (PCa) has increased as a consequence of prostate-specific antigen testing.

Objective: In this collaborative review article, we examine recent literature regarding low-risk PCa and the available prognostic and therapeutic options.

Evidence acquisition: We performed a literature review of the Medline, Embase, and Web of Science databases. The search strategy included the terms: prostate cancer, low risk, active surveillance, focal therapy, radical prostatectomy, watchful waiting, biomarker, MRI, alone or in combination.

Evidence synthesis: Prospective randomized trials have failed to show an impact of radical treatments on cancer-specific survival in low-risk PCa patients. Several series have reported the risk of adverse pathologic outcomes at radical prostatectomy (RP). However, it is not clear if these patients are at higher risk of death from PCa. Long term follow-up indicates the feasibility of active surveillance in low-risk PCa patients, although approximately 30% of men starting active surveillance undergo treatment within 5 years. Considering focal therapies, robust data investigating its impact on long-term survival outcomes are still required and therefore should be considered experimental. Magnetic resonance imaging and tissue biomarkers may help to predict clinically significant PCa in men initially diagnosed with low-risk disease.

Conclusions: The incidence of low-risk PCa has increased in recent years. Only a small proportion of men with low-risk PCa progress to clinical symptoms, metastases or death and prospective trials have not shown a benefit for immediate radical treatments. Tissue biomarkers, magnetic resonance imaging, and ongoing surveillance may help to identify those men with low-risk PCa who harbor more clinically significant disease.

Patient summary: Low-risk PCa is very common. Active surveillance has excellent long-term results, while randomized trials have failed to show a beneficial impact of immediate radical treatments on survival. Biomarkers and magnetic resonance imaging may help to identify which men may benefit from early treatment.

Introduction

The incidence of prostate cancer (PCa) has increased over the past two decades due to the widespread use of prostate specific antigen (PSA) screening [1]. This trend is most marked in low-risk localized PCa[2], while a considerable reduction of metastatic PCa at diagnosis has been reported[3],[4],[5].

A significant challenge is to differentiate PCa destined to cause clinical symptoms or metastases from more clinically indolent PCa that is highly unlikely to impact survival, even without immediate treatment. To this aim, several risk classifications have been proposed on the basis of clinical and pathological characteristics such as clinical stage, PSA and biopsy Gleason score. Several local active treatments have been proposed in this setting, such as radical prostatectomy (RP), external beam radiotherapy (EBRT) or active surveillance (AS). Although several different AS protocols have been proposed, it generally consists of monitoring with PSA, prostate exam, +/- MRI, and repeat prostate biopsies. It differs from watchful waiting, which is a passive approach where symptomatic progression prompts the subsequent use of palliative treatment.

The aim of this review is to evaluate currently available literature about low-risk PCa and to provide a contemporary overview of diagnostic approaches and available management options.

Evidence acquisition

A literature review was performed in June 2016 using the Medline, Embase, and Web of Science databases. The search strategy included the terms “prostate cancer”, “low risk”, “active surveillance”, “focal therapy”, “radical prostatectomy”, “watchful waiting”, “biomarker”, “magnetic resonance imaging”, alone or in combination. The search was limited to the English literature. References cited in selected articles and in review articles retrieved in our search were also used to identify manuscripts that were not included in the initial search. The articles that provided the highest level of evidence were then evaluated. When existing, prospective studies were preferred to retrospective designs. A list of articles judged to be highly relevant by the first and senior authors was circulated among the coauthors and a final consensus was reached on the structure of the review and the articles included. The systematic review was performed in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[6]. Figure 1

Evidence synthesis

Figure 1 shows a flow diagram of the selection process for this systematic review of the literature. Out a total of 723 articles screened, 189 were initially assessed for eligibility. Of these 121 were subsequently excluded and 26 were selected and included by authors. In total, 94 articles were selected and critically analyzed.

Definition of low risk PCa

Low-risk localized disease has generally been defined as clinical stage T1-T2, biopsy Gleason score ≤6 and PSA<10 ng/ml. Almost all risk classifications utilize these risk factors based on outcome data after whole-gland treatments (**Table 1**). D'Amico et al.[7] first proposed a risk group system based on data from 1,872 patients treated with radical prostatectomy (RP) or radiotherapy (RT) with or without androgen deprivation therapy. Groups were defined based on the incremental risk of developing biochemical recurrence. Consequently, the European Association of Urology (EAU)[8] and American Urological Association (AUA) adopted this risk scoring classification. The Radiation Therapy Oncology Group (RTOG) also proposed a system to predict overall and cancer-specific mortality in PCa patients treated with radiation only[9]. These grouping systems were improved by continuous multivariate models of risk such as nomograms and integrating standard pathological variables such as number of biopsy cores involved and % of cores involved[10],[11]. Although these refinements better discriminate disease risk than the simpler operational definitions, their greatest utility is in those with intermediate and high-risk disease.

The current NCCN guideline[12] implemented divided low-risk disease into two classes: very-low and low-risk groups. Although the definition of low-risk PCa disease is consistent with the previously described, the very-low risk population includes a subgroup of low-risk patients with the following characteristics: clinical stage T1c, Gleason score ≤6, PSA<10 ng/ml, < 3 biopsy cores with cancer, ≤50% PCa involvement in any core and PSA density < 0,15 ng/ml/g, which is based on criteria proposed by Epstein[13] for determining the optimal biopsy findings associated with low-volume, low-grade cancer at

RP. In a recent update of the Epstein criteria, unilateral cancer has replaced ≤50% PCa involvement in any core[14].

The new Grade Group grading system and its impact on low risk PCa

Consensus conferences of 2005 and 2014 modified the Gleason grading system leading to the elimination of Gleason scores 2-5 and set a more restrictive definition of Gleason score 6[15],[16]. The major consequence of these changes is a more favorable prognosis of patients diagnosed with contemporary Gleason 6 compared to historical patients [17],[18]. Therefore, a new grading system composed of 5 grades where grade group 1 is equivalent to contemporary Gleason score 6 has been developed by Epstein and colleagues. Informing patients they have a potentially indolent-behaving cancer reflected in grade group 1 has the potential to permit more rational and less emotional decision-making[19],[20]. This system has been recently adopted by the WHO[21],[22], in the cancer protocol templates (CAP) and 8th revision of the TNM.

Prospective trials evaluating the management of low-risk PCa

The natural history of PCa and the impact of radical treatment on survival and functional outcomes have been investigated by several randomized trials[23],[24],[25]. Of these, only two analyzed outcomes of men with low-risk PCa (**Table 2**) [23],[24]. Wilt et al.[23] reported data from the Prostate Cancer Intervention versus Observation Trial (PIVOT) where 731 patients were randomly assigned between 1994 and 2002 to RP or observation with a median follow up of 10 years. Patients less than 75 years old were

recruited from multiple centers and had clinical stage of T1-T2NxM0 and PSA < 50 ng/ml. At 12 years, cancer-specific mortality rates were 4.4% vs. 7.4% for patients treated with RP versus patients observed, respectively (p = 0.09). Considering 296 low-risk PCa patients, 148 were treated with RP and 148 were observed. No differences were found considering survival expectations, where patients treated with RP or observation recorded both a 12-yrs CSM of 2.7% (p=0.5).

These results should be interpreted within the limitations of the study as the original power calculation was based on recruitment of 2000 cases, while it was subsequently adjusted for the recruitment of 740 men and results are therefore underpowered. Moreover, only 25% of all men had Gleason score of ≥7. Another limitation is represented by the fact that despite eligibility criteria included a 10-yr life expectancy and surgically curable disease, almost half of patients died of other causes before 10 yr and only half treated with surgery had an organ confined-disease.

Bill-Axelson et al. [24] reported Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) where 695 men with localized PCa were randomly assigned to RP or observation. Patients were treated at 14 centers in Sweden, Finland and Iceland. Eligible criteria were: PSA<50 ng/ml, clinical stage ≤T2, negative bone scan, < 75 years of age with a life expectancy of more than 10 years and no other cancer. At 18 years, overall mortality rates were 56% vs. 69% for patients treated with RP vs watchful-waiting, respectively (relative risk [RR]: 0.71, confidence interval [CI]: 0.59-0.86, p<0.001). The number needed to treat to prevent one death at 18 years was 8. At 18 years, 17.7% died from prostate cancer from the RP group with 28.7% from the watchful waiting group (RR: 0.56, CI: 0.41-0.77, p=0.001). Among the 249 low-risk PCa patients, a reduction of 15.6%

in the risk of death from any cause and 10.6% in the risk of metastases was reported (p values: 0.002 and 0.006, respectively). In contrast, the reduction of 3.8% in the risk of dying for PCa was not significant (p=0.2). The aforementioned trials enrolled patients between 1994-2002 and 1989-1999. Several notable differences can be identified when compared to contemporary low-risk patients, such as: different biopsy techniques, modifications in Gleason scoring and differences in treatments. A minority of patients included in these trials had low-risk characteristics (36% and 40%), while contemporary patients diagnosed following PSA screening more commonly have low-risk features[1].

Recently, the Prostate Testing for Cancer and Treatment (ProtecT) trial [25] presented 82,429 men between 50 to 69 years who received a PSA test between 1999 and 2009. Overall 2,664 patients were diagnosed with localized PCa; of these, 1,643 agreed to undergo randomization to active monitoring (545), surgery (553) or radiotherapy (545). With a median follow up of 10 years, there were 17 deaths from PCa, 8 in the active monitoring group, 5 in the surgery group and 4 in the radiotherapy group. Surgery and radiotherapy were associated with lower incidence of disease progression (112 in active surveillance [AS] group, 46 in RP group and 46 in RT group, $p<0.001$) and metastases (33 in AS group, 13 in RP group and 16 in RT group, $p=0.004$) but 10-year cancer specific mortality was low irrespective of the management assigned with no differences observed among treatments (98.8% in all groups, $p=0.5$). Consequently, they estimated 27 men would need to be treated with prostatectomy or 33 men with radiotherapy rather than receive active monitoring to avoid 1 patient having metastatic disease. A total of 9 men would need to be treated with RP or radiotherapy to avoid 1 patient having clinical progression. Although most patients had tumors with a Gleason

score of 6 (77%) or T1c stage disease (76%), data considering only low-risk PCa were not reported. PROTECT trial also investigated quality of life of 1,643 patients using validated questionnaires and patients treated with RP had the greatest negative effect on sexual function and urinary continence [26].

Pathological findings at radical prostatectomy in patients with low risk PCa

Many studies have evaluated pathological findings at RP in patients with low-risk PCa (Table 3). Evaluating predictors of upstaging or upgrading are potentially helpful in identifying low-risk PCa patients who may benefit from early whole-gland treatment. Dinh et al.[27] analyzed data of 10,273 low-risk PCa patients who had RP in the SEER database. Upgrading and upstaging were identified in 44% and 9.7%, respectively. Similar findings have been observed in other retrospective studies [28],[29],[30],[31], suggesting risk of harboring pathological Gleason score >6 ranged from 30% to 55% and risk of pathological Gleason 8-10 disease was minimal (0.7% to 1.7%). Extraprostatic extension was reported in 9- 26% and positive surgical margin rate ranged from 11%-16%. Lymph node metastases at final pathological report were exceedingly rare (range: 0.6%-0.7%). Among men with very low-risk PCa, the risk of extraprostatic extension at RP is approximately 25%[32], while upgrading has been reported in approximately 33% [32],[33]. Although upstaging and upgrading rates were lower in very low-risk PCa when compared to low-risk PCa, the risk of harboring adverse pathologic features is still considerable.

Weiner et al.[29] evaluated the impact of delayed RP (untreated for a minimum of 6 months) in 17,943 low-risk PCa patients and found half of patients experienced at

least one adverse pathologic outcome at RP specimen, although delaying RP up to 12 months did not change the risk of adverse pathology. Auffenberg et al.[34] recently evaluated 2,858 low-risk PCa patients from practices in Michigan Urological Surgery Improvement Collaborative (MUSIC). Among the group, 778 (27%) underwent immediate RP while AS was the primary strategy for 1,359 (48%). Compared to those treated with immediate RP, men undergoing delayed surgery were more likely to have Gleason score 7 or greater (69.2% vs. 48.8%, respectively: p=0.004). However, no difference was found considering positive margin rates, extraprostatic extension, seminal vesicle invasion or lymph node metastases[35].

Predicting adverse pathologic features at RP in low-risk PCa patients might be of paramount importance for selecting appropriate AS candidates. However, it has to be highlighted that typically patients underwent RP after a single diagnostic biopsy. In contrast, patients included in AS protocols often undergo multiple staging biopsies and frequently MRI.

Active surveillance

AS is an attractive option for patients with low-risk PCa. Tosoian et al.[36] reported data of 1,298 very-low and low-risk PCa patients enrolled in an active surveillance protocol between 1995 and 2014. The surveillance protocol included semiannual PSA and digital rectal examinations with an annual 12-14 core biopsy for most men. Curative intervention was recommended for disease reclassification, defined as biopsy findings no longer meeting the inclusion criteria. The median treatment-free survival (TFS) rate was

8.5 years and cumulative incidence of TFS was 50% and 43% at 10 and 15 years. Cancer-specific survival at 10 and 15 years were both 99.9%. The excellent long-term results reflect the strict inclusion criteria, rigorous follow-up, and low threshold for recommending treatment.

Godtman et al.[37] updated the experience of the Göteborg screening trial (ISRCTN54449243) which enrolled very low, low and intermediate risk PCa patients between 1995 and 2014 to AS. Patients had PSA every 3-12 months and biopsy in cases of progression (defined as PSA and/or T-stage progression) or every 2-3 years in men with stable disease. For men with very low-risk cancer, 15-year cancer-specific survival was 100% but decreased to 94% for men with low-risk PCa.

The Prostate Cancer Research International Active Surveillance (PRIAS) [38] group recently reported the largest known AS experience. The original inclusion criteria were: Gleason ≤6, clinical stage ≤cT2c, PSA ≤10 ng/ml, two or fewer cores positive for PCa, PSA density ≤0.2 ng/ml per cubic centimeter, and fitness for curative treatment. Inclusion criteria and follow-up schemes were modified over the study period. Changes regarded the inclusion of patients with minimal Gleason 3+4 (≤10% tumor involvement per biopsy core, maximum 2 cores positive) if age ≥70 yr. Follow up strategy required a PSA test every 3 months and a digital rectal examination every 6 months for the first 2 years. Thereafter, PSA was done every 6 months and digital rectal examination yearly. Repeat biopsies were scheduled at 1, 4, 7 and 10 years after diagnosis. Follow up and criteria to switch to active treatment also changed during the study period. Through 2014 they were: Gleason ≥7, more than two positive cores, stage > cT2 or PSA-DT < 3 yr (if at least four PSA values are available). Subsequently, these criteria were changed because

of the high number of patients dropped from AS and concerns for high rates of unnecessary treatment[39]. Specifically, a PSA DT <3 years is no longer used to switch to active treatment. Also, the presence of two positive cores triggers an MRI with targeted biopsy but not by itself a switch to active treatment. The original criteria explain the low TFS rates, with 48% and 27% at 5 and 10 yr, respectively. Rates of treatment and long-term outcomes are entirely dependent on eligibility criteria, follow up strategies and thresholds for intervention (Table 4). Almost all series included in our manuscript evaluate TFS rate which consist in the number of patients still on AS after a certain period. The decision to submit patients to whole-gland treatment rather than continue with AS is mainly related to the reclassification of the tumor with an increased risk of progression. Almost 2 out 3 patients are still in AS after 5 year of follow up, although in some series these percentages drop to 50%. Long term follow up is provided by some series which indicate a 15 yr TFS ranging from 34% to 55%. Low-risk patients on AS record excellent long-term survival outcomes with 10-year cancer-specific survival ranging from 98.1% to 100%. These data suggest that even in stringent schemes, there are limited number of patients who died from PCa. Based on these data, AS should be discussed as a management option for any man with very low-risk or low-risk PCa. Welty et al.[40] defined factors associated with progression in patients enrolled to AS. They found PSA density, number of biopsies and time between biopsies were significantly associated with biopsy reclassification or local treatment.

Current European guidelines[8] recommend AS with a level of evidence of 2a for patients with low risk PCa and >10 years of life expectancy. Current NCCN guidelines [12] distinguished very low risk and low risk PCa. Very low-risk PCa should be considered

to AS when their life expectancy is between 10 and 20 years. In contrast, when life expectancy is less than 10 years, observation is recommended. For low risk PCa patients, AS is an option along with EBRT, brachytherapy and RP for patients with more than 10 year of estimated life expectancy. Patients with less than 10 year of expected survival should be observed only.

Focal therapy for low risk PCa

Focal therapy may represent a viable option for men with low or intermediate-risk PCa[41]. The main purpose of focal therapy is to selectively ablate tumors while attempting to limit toxicity by sparing the neurovascular bundles, sphincter and urethra. In this regard, low volume unifocal or unilateral tumors represent the ideal target for this approach although at the time no high quality long-term data exist supporting this theory and therefore should be offered very cautiously[42],[43]. Several types of ablative technologies are available: high-intensity focused ultrasound (HIFU), cryotherapy, photodynamic therapy (PDT), laser interstitial thermotherapy (LITT), electroporation, radiation frequency ablation and focal brachytherapy[44],[45]. At this time, focal therapy should be considered an experimental approach that might potentially reduce toxicity compared to whole-gland treatment. High quality prospective trials are required to demonstrate oncologic or quality-of-life benefits over other available options[8]. A selection of studies reporting oncological outcomes in low-risk PCa patients treated with focal therapy is presented in **Table 5**.

Several studies reported excellent outcomes for low risk PCa patients treated with HIFU. Feijoo et al. [46] recently reported data of 67 patients with low-risk PCa treated with HIFU where 75% had a negative biopsy at 6 months after treatment. Complications were reported in a small portion of men (8% Clavien-Dindo grade 2 and 2.8% grade 3) and full continence was achieved in all patients. Potency (defined as IIEF score ≥22) was maintained in 11 of 21 patients. These findings confirm previous data of Ahmed et al. which[47] reported similar results in 41 PCa patients (11 low risk PCa). Excellent functional outcomes were reported while 77% of patients were free of tumor at 6-month biopsy. In general, the quality of evidence is poor and further data are required.

Current guidelines recommend cryotherapy as an option in organ confined PCa and with minimal tumor extension [48],[49],[50]. The usage of focal cryoablation is increasing over whole gland-cryoablation as oncological outcomes appear similar (in select patients) with lower rates of urinary, sexual or bowel dysfunction[51]. Negative follow-up prostate biopsy was reported in 55%-86% of patients. Considering functional outcomes, complete continence was in 98.4% - 100%. However, the use of different definitions of potency and the lack of preoperative functional data makes it difficult to fully evaluate this outcome. In the largest study [47] evaluating erectile function after cryoablation, maintenance of spontaneous erection was reported in 58% of patients.

Donnelly et al. [52],[53] reported the only randomized control trial comparing focal versus whole-gland therapy: cryosurgery vs EBRT. Overall, 244 patients with localized PCa were randomized, but of these only 20 had low-risk characteristics (10 treated with cryosurgery and 10 with EBRT). With a median follow up of 100 months, 3-year disease

progression was observed in 23.9% and 23.7% of patients treated with cryoablation and EBRT, respectively. However, no analyses were done considering low risk PCa only.

These results were confirmed in a recent meta-analysis where data from 3,995 patients across 19 studies compared cryotherapy vs. RP vs. EBRT[54]. There was no evidence that mortality (4-year survival was 93% for cryotherapy and 91% for EBRT) or other specific outcomes were different between cryotherapy and EBRT. However, all the studies included were considered at high risk of selection bias. Considering functional outcomes, urinary incontinence at 1 year was lower for cryosurgery than for RP. Considering overall complications, no significant difference was reported, however patients treated with cryosurgery or EBRT had lower rates of urethral stricture than patients treated with RP.

Standard diagnosis and implications for research in low risk PCa

The classification of localized PCa into low, intermediate and high risk groups has provided a useful system for reporting outcomes and to guide physicians in selecting patients who might benefit from whole-gland treatments. However, even the low-risk PCa category is a heterogeneous group with an outcome not invariably favorable. For instance, a high proportion of patients clinically defined as low risk may harbor adverse pathologic features at RP. Strategies exist to minimize over detection of low risk PCa. According to current guidelines, prostate biopsy should be offered to patients with a concerning digital rectal examination or elevated PSA [41]. PSA is organ-specific but not cancer-specific and therefore higher levels may be dependent on benign conditions and

the risk of having a Gleason ≥7 is not zero even in patients with low PSA ranging between 0.8% to 6.7%[55]. PSA should be always repeated before having a prostate biopsy. Moreover, its value should be considered in context of the age and health of an individual man. Life expectancy must be considered as a fundamental part of the decision making in low risk PCa where local treatment is not associated with improvement in survival. However, these parameters are not entirely sufficient and there is a potential need for biomarkers to individualize the risk of harboring a clinical significant PCa. Ideally, these markers should be able to differentiate the majority of patients with truly indolent disease, suitable for observation only, from the minority with significant PCa that may benefit from early treatment.

Biomarkers

PSA isoforms may help to identify patients at increased risk of harboring adverse pathologic features at biopsy. Tosoian et al.[56] used PSA isoforms in a cohort of 167 patients enrolled in AS program to predict unfavorable findings on annual biopsy. [-2]proPSA and prostate health index (PHI) provided the greatest predictive accuracy for high grade cancer. Similar findings have been observed by other authors[57],[58],[59]. Several studies indicate that fPSA and PSA isoforms may be helpful in predicting adverse pathologic features, however the overlap between favorable and unfavorable groups makes it difficult to currently include these parameters in preoperative predictive models[60]. A four kallikrein (4k) panel has been used[61] to investigate the presence of high grade cancer in men on AS. Plasma was collected before the first and subsequent AS biopsies in 718 men enrolled in the prospective Canary PASS trial. The use of 4K

improved AUC from 0.74 to 0.78 in predicting reclassification at first AS biopsy (defined as Gleason ≥7). The test however, showed no benefit for the prediction of reclassification at subsequent biopsies.

Urinary markers have also shown promising results in predicting adverse pathologic features. Prostate cancer antigen 3 (PCA3) and TMPRSS2:ERG are commercially available. PCA3 is a prostate-specific gene expressed in 95% of PCa and overexpressed in cancer tissue[62]. PCA3 levels are independent of prostate volume and PSA, but may be higher with more aggressive tumors[63]. A recent meta-analysis included 11 studies and found PCA3 can help to select patients at increased risk of an aggressive cancer even after a prior negative prostate biopsy[64]. PCA3 has been also combined with clinical data to improve selection of patients at higher risk of harboring aggressive cancers[65]. TMPRSS2:ERG has been used in combination with PCA3; TMPRSS2:ERG has high specificity while PCA3 has high sensitivity for PCa. A combination of PCA3 and TMPRSS2:ERG (MiPS: Michigan Prostate Score) has been validated by Tomlins et al.[66] who found this novel tool outperforms standard clinical criteria for predicting PCa and high-grade PCa on biopsy. Specifically, they evaluated 1244 men presenting for biopsy, and found that models incorporating T2:ERG had greater AUC than PSA for predicting PCa or high grade PCa on biopsy. Interestingly, the utility of both urine TMPRSS2:ERG and PCA3 was described for men on active surveillance[67]. The findings by Lin et al.[67] therefore suggest these biomarkers could be used to find aggressive PCa in low risk PCa patients, however the biomarkers were not independently significant upon multivariable analyses.

Several histopathologic biomarkers have showed promising results in the prediction of aggressiveness of PCa after being diagnosed at biopsy. Ki-67 is a nuclear protein associated with ribosomal RNA synthesis that is typically measured by immunohistochemistry to assay cell proliferation. Its prognostic values has been shown many times[68],[69],[70] and should be considered by physicians for men with low risk PCa. PTEN loss has a well-established role in PCa. and has been related to a less favorable prognosis[71]. Murphy et al.[72] described PTEN loss is infrequent in clinically insignificant PCa and therefore when present a higher-grade tumor should be suspected[73,74]. However, at this time, none of the above histological tests are in routine clinical use.

Commercially available tissue-based prognostic panels do exist [75], however only OncotypeDX® and Prolaris® have been validated on men with low risk PCa. OncotypeDX® is a test developed by Genomic Health (Redwood City, California) following PCa diagnosis. This tool is a quantitative RT-PCR assay performed on FFPE tissue from needle biopsies incorporating 12 cancer related genes representing four biological pathways (stromal response; androgen signaling; proliferation; cellular organization) and 5 reference genes which are algorithmically combined to calculate the Genomic Prostate Score (GPS) [76]. The derived GPS ranges from 0 to 100 with the higher the number correlating with a higher probability of harboring adverse pathology (primary Gleason 4 or ECE) at RP in men diagnosed with low or low-intermediate risks prostate cancer at prostate biopsy. Cullet et al.[77] described 431 patients with very low, low, and intermediate risk-stratified PCa at biopsy, and demonstrated the ability of

OncotypeDX® to provide independently significant value in predicting adverse pathology at RP and BCR.

Prolaris® is a prognostic test developed by Myriad Genetics (Wakara Way, Salt Lake City, UT) and used on biopsies from low and very low-risk patients. This test is based on the expression of 31 cell cycle progression and 15 housekeeping genes and is an extension of their breast cancer test. The result is represented by a proliferative index, expressed as a cell cycle progression (CCP) score[78]. Bishoff et al. [79] analyzed 582 patients from the Martini Clinic (n=283), Durham Veterans Affairs Medical Center (n=176) and Intermountain Healthcare (n=123), and showed an association of the biopsy CCP score with adverse outcomes after surgery. Cuzick et al.[78] in a larger study evaluated the CCP score and its ability of predicting BCR in a U.S. cohort of RP patients and mortality in a U.K. cohort of patients predominantly diagnosed via TURP. Additionally, the CCP was validated by Freedland et al. [80] in primary external radiation treated patients. Cooperberg et al. [81] analyzed 413 RP patients and reported a combined CCP and CAPRA-S score for the overall cohort and the low-risk subset more accurately predicted BCR compared to either alone.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) traditionally has been used following prostatic biopsy for staging. However, there is an emerging data suggesting its role in patient selection for, and monitoring during, active surveillance. Multiparametric magnetic resonance imaging (mpMRI) is a combination of anatomical imaging using T1-weighted

(T1W) and T2-weighted (T2W) sequences with one or more functional imaging methods. The combination of anatomic and functional MRI has been shown to improve the detection of PCa[82].

Considering low risk PCa, several studies analyzed patients (potentially eligible for AS protocols) treated with RP and preoperatively investigated with MRI[83],[84],[85],[86],[87],[88]. Unfortunately, different definitions of unfavorable pathology, biopsy schemes and inclusion criteria were used. Ploussard et al.[86] failed to assess any improved prediction of high risk and/or non-organ confined disease in RP for those patients selected for AS based on an extended 21-core biopsy scheme and stringent AS criteria. However, other findings support the use of mpMRI in the accrual of patients for AS. In this setting, Turkbey et al.[85] analyzed preoperative data of 133 patients staged with mpMRI. Lesions were identified in mpMRI for 126 patients with a sensitivity of 93%. In context, a misclassification occurred in 16 patients and with use of mpMRI could be avoided in 12 of these. The impact of MRI in low and intermediate risk PCa candidates for AS has been evaluated recently in a meta-analyses by Schoots et al[89], who found that a suspicious lesion at MRI for PCa was found in two-thirds of men otherwise suitable for AS. MRI therefore helps in determining clinically significant disease at repeat biopsy especially when biopsies are targeted to suspicious MRI lesions. Finally, a positive MRI is more likeably to be associated with upgrading at RP (Gleason score >6) than a negative MRI (43% vs. 27%). Consequently, the PRECISE recommendations suggested indications of MRI for men on AS [90]. Experts developed a checklist of items for reporting MRI and key recommendations include reporting the index lesion size and the change over time on a 1-5 scale. The PRECISE recommendations might be helpful

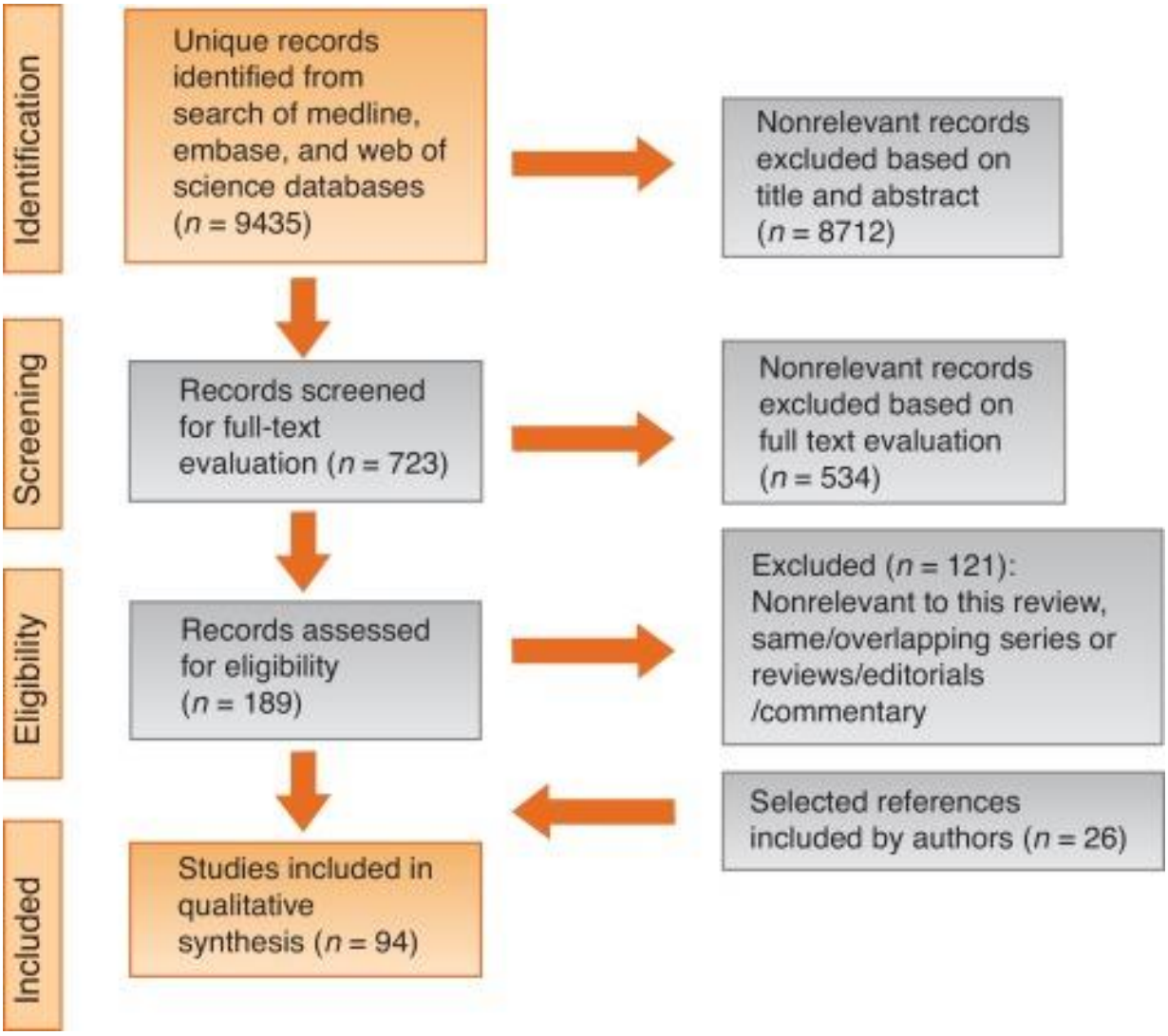
for physicians to facilitate data collection and distinguish measurement error and natural variability in MRI from true radiologic progression in PCa patients in AS schemes. Similarly, MRI fusion biopsy may play a role in low risk PCa patients. Tran et al.[91] examined the role of MRI fusion biopsy for men with low risk PCa managed with AS, finding that some lesions observed with MRI fusion were missed with the standard systematic sampling. In contrast, upgrading also occurred in areas outside targeted biopsy, suggesting the need of systematic sampling even in the context of MRI fusion biopsy. These results confirm previous findings on this topic[92],[93],[94],[95].

Conclusion

The incidence of low risk PCa has increased as a consequence of PSA-based screening. High quality prospective trials have not shown a definitive survival benefit for whole-gland treatments compared to observation. Long-term active surveillance has shown encouraging results, while more robust data are required to understand the potential role of focal therapy. Tissue biomarkers and MRI may improve risk stratification of low risk PCa to identify the proportion of men who might benefit from early treatment.

Figures

Figure 1- Flow diagram of evidence acquisition in a systematic review for patients affected by low risk prostate cancer.



Tables

Table 1.
Definition of very-low and low-risk prostate cancer

	Definition very low risk	Definition low risk
D'Amico et al 1998 [7]	—	PSA < 10 ng/ml, GS < 7, & cT1–cT2a
European Association of Urology-ESTRO-SIOG (Mottet et al 2016) [8]	—	PSA < 10 ng/ml, GS < 7, & cT1–cT2a
American Association of Urology	—	PSA < 10 ng/ml, GS < 7, & cT1–cT2a
National Comprehensive Cancer Network (Carroll et al 2016) [12]	cT1c, GS < 7, PSA < 10 ng/ml, presence of disease in fewer than 3 biopsy cores, ≤ 50% PCa involvement in any core & PSA density < 0.15 ng/ml/g	cT1–cT2a, GS < 7, PSA < 10 ng/ml
Radiation Therapy Oncology Group (Roach et al 2000) [9]	GS < 6 & T1–2N0	GS < 7 & T1–2Nx
Cancer of the Prostate Risk Assessment Score (Cooperberg et al 2005) [11]	Age, PSA, clinical stage, biopsy GS, percentage of positive biopsy cores	

GS = Gleason score; PCa = prostate cancer; PSA = prostate-specific antigen.

Table 2.
Characteristics of randomized trials prospectively evaluating low-risk prostate cancer (PCa)

References	Design	Study period	Population	Treatment	Median follow-up (yr)	Results	Conclusion
Wilt et al 2012 [23]	Prospective trial: PIVOT trial	1994–2002	296 Low-risk D'Amico patients: 148 RP vs 148 WW	WW vs RP	10.0	CSM: 12 yr: 2.7% vs 2.7% for RP vs WW (p = 0.5), respectively OM: 12 yr: 37.2% vs 31.8% for RP vs WW (p = 0.4), respectively	RP in low-risk PCa did not reduce metastases, CSM, or OM in comparison to WW
Bill-Axelson et al 2014 [24]	Prospective trial: SPCG-4	1989–1999	249 Low-risk D'Amico patients: 118 RP vs 131 WW	WW vs RP	23.2	Reductions of 15.6% OM and 10.6% metastases; the reduction of 3.8% CSM was not significant	The reduction of OM and metastases risk for RP patients but no difference in CSM

CSM = cancer-specific metastasis; OM = overall mortality; RP = radical prostatectomy; WW = watchful waiting.

Table 3.
Characteristics of studies evaluating the role of surgery in patients with low-risk prostate cancer

References	Design	Study period	Population	Pathologic findings
Dinh et al 2015 [27]	Population based-SEER	2010–2011	10 273 Low-risk D'Amico patients	pGS > 6: 44% pT3–T4 N0–1: 9.7%
Song et al 2014 [28]	Retrospective	2007–2012	382 Low-risk D'Amico PCa	pGS 3 + 4: 44.7% pGS4 + 3: 8.9% pGS 8–10: 1.7% pT3–T4: 13.3% PSM: 16.2%
Weiner et al 2015 [29]	Retrospective	2010–2011	17 943 Low-risk D'Amico PCa	pGS > 6: 42.8% pT3–4: 9.3% pN1 or pGs > 6 or pT3–4: 45.2% PSM: 15.8%
Mullins et al 2012 [30]	Retrospective	1983–2010	1560 Low-risk D'Amico	pGS 7: 27.8% pGS 8–10: 1.9% pT3–T4 or ≥ 7 GS: 38.3% LNI: 0.6%
Imnadze et al 2016 [31]	Retrospective	1998–2008	1102 Low risk	pGS 7: 49% pGS 8–10: 0.7% pT3–T4: 16% LNI: 0.7% PSM: 11%
Carlsson et al 2016 [33]	Prospective multicentric	2008–2011	338 Very low-risk patients	pT3–T4 or >6 pGS: 34.5% pGS >6: 31.5% PSM: 16.4%
Beauval et al 2012 [32]	Retrospective	2003–2008	919 Very low-risk patients	pGS 3 + 4: 26.1% pGS 4 + 3: 7% pGS 8–10: 1.2% pT3–T4: 23.5% PSM: 12.5%

PCa = prostate cancer; pGS = pathological Gleason score; PSM = prostate specific membrane antigen.

Table 4.
Characteristics of prospective studies evaluating active surveillance in patients with low risk prostate cancer

References	Design population	Study period	Patients	Median follow-up	TFS (%)	Overall/disease-specific survival
[37]	Randomized, population based trial screen-detected PCa	1995–2014	244 (51%) and 126 (27%) very low and low risk, respectively	96 mo	TFS: 10 yr: 47% 15 yr: 34%	Overall population: CSS 10 yr: 99% CSS 15 yr: 96% Very low risk: CSS 10 yr: 100% CSS 15 yr: 100% Low risk: CSS 10 yr: 100% CSS 15 yr: 94%
[96]	Multicentric prospective PRIAS	2006–2012	2494	19 mo	During follow-up, 527 patients (21.1%) underwent active therapy TFS: 2 yr 77.3%	CSS 100%
[38]	Multicentric prospective PRIAS update	2006–2015	5302	—	1768 Treated during follow up/TFS: 5 yr: 48%, 10 yr 27%	NA
[97]	European Randomized Screening for Prostate Cancer	1993–2007	509 patients 381 low risk	89 mo	152 (40%) Low-risk patients treated during follow-up TFS:10 yr 50% for low-risk patients	Low risk OS 10 yr: 79% CSS 10 yr: 99%
[36]	Prospective randomized	1995–2014	1298	60 mo	Median treatment-free survival was 8.5 yr	OS: 10 yr 93% OS: 15 yr 69% CSS: 10 yr 99.9% CSS: 15 yr 99.9%
[98]	Prospective study	2002–2011	471	68 mo	TFS: 5 yr 70%	OS: 2 yr 99% OS: 5 yr 96
[99]	Prospective study	1995–2013	993	77 mo	TFS 5 yr: 75.7% TFS 10 yr: 63.5% TFS 15 yr: 55.0%	CSS: 10 yr 98% CSS: 15 yr 94%

CSS = cancer-specific survival; NA = not applicable; OS = overall survival; PCa = prostate cancer; TFS = treatment-free survival.

Table 5.
Selection of studies evaluating outcomes of low-risk prostate cancer patients treated with focal therapy

References	Energy	Study period	Patients	Median follow-up (mo)	Inclusion criteria	Functional outcomes	Survival
[47]	HIFU	2007–2010	41 patients. 11 low risk	6	PSA ≤ 15 ng/ml, Gleason score ≤ 4 + 3, stage ≤ T2	100% Pad free at 3 mo and 12 mo IIEF-15 scores were similar at baseline and 12 mo (p = 0·06)	77% of patients were free of cancer at 6-mo biopsy
[46]	HIFU	2009–2013	71	12	Unilateral, clinical stage T1c–T2a, maximum positive biopsies < 33%, Gleason score ≤ 7 (3 + 4), PSA < 15 ng/ml	100% continence. At 3 mo no significant changes for both IPSS and ICS. IIEF-5 score ≥ 22 was maintained in 11 of 21 preoperatively potent patients	Negative control biopsy was noted in 75% evaluated patients; specifically, negative biopsy in the treated lobe was seen in 83% patients
[49]	Cryotherapy	2009–2012	48	13	Unilateral, cT1c–cT2a, PSA < 10 ng/ml, low volume index lesion, and GS ≤ 6	Urinary symptoms were unchanged. No difference at 6 mo in IIEF-5 score	Follow-up prostate biopsies negative for the treated lobe in 86%
[48]	Cryotherapy	2002–2011	73	44	Unilateral low-intermediate PCa	Continence and potency was achieved in 100% and 86% of patients, respectively	75% had negative postoperative biopsies. Matched-pair comparison with RP revealed similar oncologic outcomes
[100]	Cryotherapy	2002–2009	77	24	Low D'Amico risk (57%)	Continence: 100% The mean IIEF score decreases were 4.9 and 1.9 points, at 6 mo and 12 mo, respectively	Of the 22 patients, 10 (45.5%) had confirmed prostate cancer. Overall biochemical and pathological progression-free survival rates were 72.7% and 87%

GS = Gleason score; ICS = International Continence Society; IIEF = *International Index of Erectile Function*; IPSS = International Prostate Symptom Score; PCa = prostate cancer; PSA = prostate-specific cancer; RP = radical prostatectomy.

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