Review – Prostate Cancer

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, magnetic resonance imaging, 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. 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 yr. 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 prostate cancer 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.

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1. Introduction

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

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, and/or without magnetic resonance imaging (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.

2. 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 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 guidelines (Fig. 1) [6].

3. Evidence synthesis

Fig. 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 31 were selected and included by authors. In total, 99 articles were selected and critically analyzed.

3.1. 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 – Definition of very-low and low-risk prostate cancer

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

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

(Table 1). D’Amico et al [7] first proposed a risk group system based on data from 1872 patients treated with 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 [8] and American Urological Association adopted this risk scoring classification. The Radiation Therapy Oncology Group 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 the percentage 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 National Comprehensive Cancer Network guidelines [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 et al [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].

3.2. 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 with historical patients [17,18]. Therefore, a new grading system composed of five grades where grade group 1 is equivalent to contemporary Gleason score 6 has been developed by Epstein and colleagues [13]. Informing patients that 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 World Health Organization [21,22], in the cancer protocol templates and 8th revision of the TNM.

3.3. 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 [23–25]. 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 where 731 patients were randomly assigned between 1994 and 2002 to RP or observation with a median follow up of 10 yr. Patients aged less than 75 yr were recruited from multiple centers and had a clinical stage of T1–T2NxM0 and PSA ≤ 50 ng/ml. At 12 yr, the cancer-specific mortality rates were 4.4% versus 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-yr cancer-specific mortality 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 the 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 a Gleason score of ≥ 7. Another limitation is represented by the fact that despite eligibility criteria including 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 on the Scandinavian Prostate Cancer Group Study Number 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 yr of age with a life expectancy of more than 10 yr, and no other cancer. At 18 yr, overall mortality rates were 56% versus 69% for patients treated with RP vs watchful waiting, respectively (relative risk: 0.71, confidence interval: 0.59–0.86, p < 0.001). The number needed to treat to prevent one death at 18 yr was eight. At 18 yr, 17.7% died from PCa from the RP group vs 28.7% from the watchful waiting group (relative risk: 0.56, confidence interval: 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 = 0.002 and p = 0.006, respectively). In contrast, the reduction of 3.8% in the risk of dying from 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 with 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 [26].

Recently, the Prostate Testing for Cancer and Treatment trial [25] presented 82 429 men between 50 yr and 69 yr who received a PSA test between 1999 and 2009. Overall 2664 patients were diagnosed with localized PCa; of these, 1643 agreed to undergo randomization to active monitoring (545), surgery (553), or radiotherapy (545). With a median follow-up of 10 yr, there were 17 deaths from PCa, eight in the active monitoring group, five in the surgery group, and four in the radiotherapy group. Surgery and radiotherapy were associated with lower incidence of disease progression (112 in the AS group, 46 in the RP group, and 46 in the RT group, p < 0.0001) and metastases (33 in the AS group, 13 in the RP group, and 16 in the RT group, p = 0.004) but the 10-yr 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 one patient having metastatic disease. A total of nine men would need to be treated with RP or radiotherapy to avoid one 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. The Prostate Testing for Cancer and Treatment trial also investigated quality of life of 1643 patients using validated questionnaires and patients treated with RP had the greatest negative effect on sexual function and urinary continence [26].

3.4. Pathological findings at RP 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 Surveillance, Epidemiology, and End Results database. Upgrading and upstaging were identified in 44% and 9.7%, respectively. Similarly findings have been observed in other retrospective studies [28–31], suggesting that the risk of harboring pathological Gleason score >6 ranged from 30% to 55% and the risk of pathological Gleason 8–10 disease was minimal (0.7–1.7%). Extraprostatic extension was reported in 9–26% and positive surgical margin rate ranged from 11% to 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 with 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 mo) 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 mo did not change the risk of adverse pathology. Auffenberg et al [34] recently evaluated 2858 low-risk PCa patients from practices in Michigan Urological Surgery Improvement Collaborative. Among the group, 778 (27%) underwent immediate RP while AS was

| 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

<table>
<thead>
<tr>
<th>References</th>
<th>Design</th>
<th>Study period</th>
<th>Population</th>
<th>Pathologic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weiner et al 2015 [29]</td>
<td>Retrospective</td>
<td>2010–2011</td>
<td>17 943 Low-risk D’Amico PCa</td>
<td>pGS &gt; 6: 42.8% pT3–4: 9.3% pN1 or pGS &gt; 6 or pT3–4: 45.2% PSM: 15.8%</td>
</tr>
<tr>
<td>Mullins et al 2012 [30]</td>
<td>Retrospective</td>
<td>1983–2010</td>
<td>1560 Low-risk D’Amico</td>
<td>pGS 7: 27.8% pGS 8–10: 1.9% pT3–T4 or ≥ 7 GS: 38.3% LNI: 0.6%</td>
</tr>
<tr>
<td>Innadze et al 2016 [31]</td>
<td>Retrospective</td>
<td>1998–2008</td>
<td>1102 Low risk</td>
<td>pGS 7: 49% pGS 8–10: 0.7% pT3–T4: 16% LNI: 0.7% PSM: 11%</td>
</tr>
</tbody>
</table>

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

the primary strategy for 1359 (48%). Compared with 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 frequent MRIs.

3.5. AS

AS is an attractive option for patients with low-risk PCa. Tosioan et al [36] reported data of 1298 very-low and low-risk PCa patients enrolled in an AS protocol between 1995 and 2014. The surveillance protocol included semianual PSA and digital rectal examinations with an annual 12–14 core biopsies 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 yr and cumulative incidence of TFS was 50% and 43% at 10 yr and 15 yr. Cancer-specific survival at 10 yr and 15 yr were both 99.9%. The excellent long-term results reflect the strict inclusion criteria, rigorous follow-up, and low threshold for recommending treatment.

Godman 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 mo and biopsy in cases of progression (defined as PSA and/or T-stage progression) or every 2–3 yr in men with stable disease. For men with very low-risk cancer, 15-yr cancer-specific survival was 100% but decreased to 94% for men with low-risk PCa.

The Prostate Cancer Research International Active Surveillance [38] group recently reported the largest known AS experience. The original inclusion criteria were Gleason < 6, clinical stage ≤ T2c, PSA < 10 ng/ml, two or fewer cores positive for PCa, PSA density < 0.2 ng/ml/cm³, 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 aged ≥ 70 yr. Follow-up strategy required a PSA test every 3 mo and a digital rectal examination every 6 mo for the first 2 yr. Thereafter, PSA was done every 6 mo and digital rectal examination yearly. Repeat biopsies were scheduled at 1 yr, 4 yr, 7 yr, and 10 yr 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 doubling time < 3 yr (if at least 4 PSA values are available). Subsequently, these criteria were changed because of the high number of patients who dropped from AS and concerns for high rates of unnecessary treatment.
Specifically, a PSA doubling time <3 yr 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 yr 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 of 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 two out three patients are still in AS after 5 yr 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-yr cancer-specific survival ranging from 98.1% to 100%. These data suggest that even in stringent schemes, there are a 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.

Current European guidelines [8] recommend AS with a level of evidence of 2a for patients with low-risk PCa and >10 yr of life expectancy. Current National Comprehensive Cancer Network 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 yr and 20 yr. In contrast, when life expectancy is less than 10 yr, observation is recommended. For low-risk PCa patients, AS is an option along with EBRT, brachytherapy, and RP for patients with more than 10 yr of estimated life expectancy. Patients with less than 10 yr of expected survival should be observed only.

### 3.6. Focal therapy for low-risk PCa

Focal therapy may represent a viable option for men with low or intermediate-risk PCa [41,100]. 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, laser interstitial thermotherapy, 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 with 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 are presented in Table 5.

<table>
<thead>
<tr>
<th>References</th>
<th>Design population</th>
<th>Study period</th>
<th>Patients</th>
<th>Median follow-up</th>
<th>TFS (%)</th>
<th>Overall/disease specific survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>[37]</td>
<td>Randomized, population based trial screen-detected PCa</td>
<td>1995–2014</td>
<td>244 (51%) and 126 (27%) very low and low risk, respectively</td>
<td>96 mo</td>
<td>TFS: 10 yr: 47% 15 yr: 34%</td>
<td>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%</td>
</tr>
<tr>
<td>[38]</td>
<td>Multicentric prospective PRIAS update</td>
<td>2006–2015</td>
<td>5302</td>
<td>19 mo</td>
<td>During follow-up, 527 patients (21,18% underwent active therapy TFS: 2 yr 77.3%</td>
<td>NA</td>
</tr>
<tr>
<td>[39]</td>
<td>European Randomized Screening for Prostate Cancer</td>
<td>1993–2007</td>
<td>509 patients 381 low risk</td>
<td>89 mo</td>
<td>152 (40%) Low-risk patients treated during follow-up TFS:10 yr 50% for low-risk patients</td>
<td>Low risk OS 10 yr: 79% CSS 10 yr: 99%</td>
</tr>
<tr>
<td>[40]</td>
<td>Prospective randomized</td>
<td>1995–2014</td>
<td>1298</td>
<td>60 mo</td>
<td>Median treatment-free survival was 8.5 yr</td>
<td>OS: 10 yr 93% OS: 15 yr 69% CSS: 10 yr 99.9% CSS: 15 yr 99.9%</td>
</tr>
<tr>
<td>[41]</td>
<td>Prospective study</td>
<td>2002–2011</td>
<td>471</td>
<td>68 mo</td>
<td>TFS: 5 yr 70%</td>
<td>OS: 2 yr 99% OS: 5 yr 96</td>
</tr>
<tr>
<td>[42]</td>
<td>Prospective study</td>
<td>1995–2013</td>
<td>993</td>
<td>77 mo</td>
<td>TFS 5 yr: 75.7% TFS 10 yr: 63.5% TFS 15 yr: 55.0%</td>
<td>CSS: 10 yr 98% CSS: 15 yr 94%</td>
</tr>
</tbody>
</table>

CSS = cancer-specific survival; NA = not applicable; OS = overall survival; PCa = prostate cancer; TFS = treatment-free survival.
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 mo 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 International Index of Erectile Function score ≥ 22) was maintained in 11 of 21 patients. These findings confirm previous data of Ahmed et al. [47] which 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-mo 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 [48–50]. 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 achieved 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] and Robinson et al. [53] reported the only randomized control trial comparing focal versus whole-gland therapy: cryosurgery versus 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 mo, 3-yr 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 3995 patients across 19 studies compared cryotherapy versus RP versus EBRT [54]. There was no evidence that mortality (4-yr 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 yr 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.

### 3.7. 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 overdiagnosis of low-risk PCs. 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% and 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 the individual man. Life expectancy must be considered as a fundamental part of the decision making in low-risk PCs 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 PCs that may benefit from early treatment.

3.8. Biomarkers

PSA isoforms may help to identify patients at increased risk of harboring adverse pathologic features at biopsy. Tosioan et al. [56] used PSA isoforms in a cohort of 167 patients enrolled in an AS program to predict unfavorable findings on annual biopsy. [-2]proPSA and Prostate Health Index provided the greatest predictive accuracy for high grade cancer. Similar findings have been observed by other authors [57–59]. Several studies indicate that free PSA 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 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 four kallikrein improved area under the curve 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 PCs 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 PCs. A combination of PCA3 and TMPRSS2:ERG (Michigan Prostate Score) has been validated by Tomlins et al. [66] who found this novel tool outperforms standard clinical criteria for predicting PCs and high-grade PCs on biopsy. Specifically, they evaluated 1244 men presenting for biopsy, and found that models incorporating T2:ERG had a greater area under the curve than PSA for predicting PCs or high-grade PCs on biopsy. Interestingly, the utility of both urine TMPRSS2:ERG and PCA3 was described for men on AS [67]. The findings by Lin et al. [67] therefore suggest these biomarkers could be used to find aggressive PCs 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 PCs after being diagnosed at biopsy. Ki-67 is a nuclear protein associated with ribosomal RNA synthesis. Its prognostic values has been shown many times [68–70] and should be considered by physicians for men with low risk PCs. PTEN loss was consistently studied in PCs and has been related to a less favorable prognosis [71]. Murphy et al. [72] described PTEN loss as infrequent in clinically insignificant PCs 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 PCs. 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 evaluating 12 genes representing four different pathways (stromal response; androgen signaling; proliferation; cellular organization) and 5 reference genes which are combined to calculate the Genomic Prostate Score (GPS) [76]. The 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) in men diagnosed with low or intermediate risks PCs at prostate biopsy. Cullet et al. [77] reported data from 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 pathologic features at RP and BCR.

Prolaris® is another test developed by Myriad Genetics (Wakara Way, Salt Lake City, UT) and validated on biopsies from very-low and low-risk patients. This test is based on the evaluation of the expression of 31 cell cycle progression and 15 housekeeping genes. The result is represented by a proliferative index, expressed as a cell cycle progression (CCP) score [78]. Bishoff et al. [79] analyzed 582 patients treated in several referral centers 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.

3.9. MRI

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, AS. Multiparametric MRI (mpMRI) is a combination of anatomical imaging using T1-weighted and T2-weighted 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 [83–88]. 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 nonorgan-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-analysis 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 like 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 [92–95].

4. Conclusions

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 AS 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.

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