Collaborative Review – Prostate Cancer

The Contemporary Concept of Significant Versus Insignificant Prostate Cancer

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Abstract

Context: The notion of insignificant prostate cancer (Ins-PCa) has progressively emerged in the past two decades. The clinical relevance of such a definition was based on the fact that low-grade, small-volume, and organ-confined prostate cancer (PCa) may be indolent and unlikely to progress to biologic significance in the absence of treatment.

Objective: To review the definition of Ins-PCa, its incidence, and the clinical impact of Ins-PCa on the contemporary management of PCa.

Evidence acquisition: A review of the literature was performed using the Medline, Scopus, and Web of Science databases with no restriction on language up to September 2010. The literature search used the following terms: insignificant, indolent, minute, microfocal, minimal, low volume, low risk, and prostate cancer.

Evidence synthesis: The most commonly used criteria to define Ins-PCa are based on the pathologic assessment of the radical prostatectomy specimen: (1) Gleason score ≤ 6 without Gleason pattern 4 or 5, (2) organ-confined disease, and (3) tumour volume < 0.5 cm³. Several preoperative criteria and prognostication tools for predicting Ins-PCa have been suggested. Nomograms are best placed to estimate the risk of progression on an individualised basis, but a substantial proportion of men with a high probability of harbouring Ins-PCa are at risk for pathologic understaging and/or undergrading. Thus, there is an ongoing need for identifying novel and more accurate predictors of Ins-PCa to improve the distinction between insignificant versus significant disease and thus to promote the adequate management of PCa patients at low risk for progression.

Conclusions: The exciting challenge of obtaining the pretreatment diagnostic tools that can really distinguish insignificant from significant PCa should be one of the main objectives of urologists in the following years to decrease the risk of overtreatment of Ins-PCa.

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1. Introduction

As a consequence of the stage and grade migration of prostate cancer (PCa) resulting from widespread use of prostate-specific antigen (PSA) testing in combination with extended-core prostate biopsy strategies, the notion of insignificant PCAs (Ins-PCa) has progressively emerged in the last two decades. The clinical relevance of such a definition was based on previous studies that suggested that low-grade, small-volume, and organ-confined PCa may be indolent and unlikely to progress to biologic significance in the absence of treatment [1]. An accurate definition of insignificant disease may help the clinician better manage patients after radical treatment and propose alternative therapies (active surveillance) more confidently. Given the sharp increase in PCa diagnoses and the increasing concerns of overtreatment, the identification and definition of insignificant cancers is a high priority. In this article, we review the definition of insignificant prostate cancers, their incidence, and their clinical impact on the contemporary management of PCa.

2. Evidence acquisition

A review of the literature was performed using the Medline, Scopus, and Web of Science databases. We identified original articles, reviews, and editorials with no restriction on language up to September 2010. The literature search used the following terms: insignificant, indolent, minute, microfocal, minimal, low volume, low risk, and prostate cancer. The selected articles were reviewed and summarized with the consensus of all the authors of this review article.

3. Evidence synthesis

3.1. Current definition of insignificant prostate cancer

3.1.1. What is the right terminology?

The term and the definition used for insignificant cancer of the prostate varies greatly in the literature, and various terms are used somewhat interchangeably: indolent, minimal, minute, microfocal, minimal, low volume, and prostate cancer. The terms insignificant and indolent are the most common terms reported in the literature, but slight differences between the two should be emphasised. An indolent cancer is more likely defined by strict pathologic characteristics and thus has been frequently preferred in nomograms to define cancer detected by pathologic criteria alone without integrating other important variables such as patient age [3–7]. Indolent PCa refers to a cancer that would never—regardless of the lifespan of the patient—become clinically manifest according to its pathologic features. Insignificant prostate cancer is a subset of indolent cancers that also factors in patient age and comorbidity. Therefore, the term insignificant PCa may better reflect the natural history of the disease in an individual patient [8].

3.1.2. Current definitions

Despite variations in the definition of insignificant disease, the intellectual concept of Ins-PCa is well established: a low-grade, small-volume, and organ-confined PCa that is unlikely to progress to clinical and biologic significance without treatment. In clinical practice, an Ins-PCa is a PCa diagnosed in the absence of cancer-related symptoms that would not have caused disease-specific morbidity or mortality during the patient’s life if left untreated.

Stamey et al. first put forward the concept of Ins-PCa [9]. Their analysis was based on the tumour volume of incidental PCa found in 139 cystoprostatectomy specimens from patients with bladder cancer, and they proposed a volume threshold of 0.5 cm³ of the largest tumour to define subclinical disease. Patients were carefully evaluated to rule out palpable PCa, and 88% of prostate tumours had a dominant tumour nodule volume < 0.2 cm³. They used the prevalence of clinically significant PCa in the population to conclude that tumours < 0.5 cm³ are unlikely to become clinically significant within the life span of the patient and need not be treated. In subsequent works, Epstein et al. validated this threshold, and their definition of Ins-PCa based on radical prostatectomy (RP) specimens is the most widely used one definition [1,10].

In the initial definition, Epstein et al. noted that in tumours < 0.2 cm³ (“insignificant”), they never found any cancer with “capsular penetration,” although a few were positive for capsular penetration in the set between 0.2 and 0.5 cm³ (“minimal”). In 1994, the conservative threshold of 0.2 cm³ was proposed to determine an expectant policy, but to date, the current view is to use a more liberal definition, and 0.5 cm³ is already considered too stringent.

To date, the most commonly used criteria to define Ins-PCa are based on the pathologic assessment of the RP specimen (Fig. 1 and 2) and include three well-established prognostic factors, as described by Ohori et al. and Epstein et al.: (1) a Gleason score ≤ 6 without Gleason pattern 4 or 5,
(2) organ-confined disease (no extraprostatic extension, seminal vesicle invasion [SVI], or lymph node involvement [LNI]); and (3) a tumour volume <0.5 cm³ [1,10,11]. The categorisation of the tumour was based on the mass with the largest tumour volume (ie, the dominant, or index tumour) [1].

3.1.3. Factors influencing the definition of insignificance

Some factors have to be taken into account when defining the significance of PCa based on RP specimens. First, the pathologic sampling of the RP specimen has to be complete. The specimens should ideally be step-sectioned at 3-mm intervals. Slices 5 mm in thickness may not be adequate for the evaluation of prognostic factors such as extraprostatic extension and microscopic bladder neck invasion. The method currently recommended by the International Society of Urological Pathology (ISUP) is called a cone technique, and it samples to the apex and the base (vs a shaved approach). Another methodologic confounder is how tumour volume is calculated [12]. The independent prognostic value of planimetry and volume estimation methods in determining tumour volume has been reported in various studies [13–16]. However, the study of tumour volume as a prognostic factor has been hampered by the lack of a convenient and accurate method for determining PCa volume (standard quantitative methods, planimetry) [12]. The total tumour volume or the volume of the largest or dominant tumour have both been calculated and used in the literature [7,10,16]. Thus, differences in tumour volume measurements between studies may limit comparisons between different study findings. The first reports of Stamey and Epstein included only the dominant tumour nodule [1,9].

An additional point worth discussing is the update on Gleason grading made during the ISUP consensus conference in 2005 [17]. This update, although barely recognised by most urologists, led to a significant upgrade of tumours towards a Gleason 4 pattern in prostatectomy specimens as well as in biopsies. This definition differs from Gleason’s original description of pattern 4, which consisted almost entirely of cribriform patterns without depicting fused glands or ill-defined glands with poorly formed glandular lumina. In addition, currently, virtually all cribriform glands are considered Gleason pattern 4, as opposed to the original Gleason system, which included cribriform Gleason pattern 3. Because most “definitions” of insignificant prostate cancers rely on Gleason grading and were made before 2005, this update may result in a decrease in diagnosed Ins-PCa. There is some controversy in the literature about the prognostic difference between Gleason score 6 cancers with or without grade 4. Some authors did not find strong differences in biochemical recurrence (BCR) between the two groups [13,18–20]. Otherwise, Epstein et al. have found in all their studies that in RP specimens, Gleason score 6 cancers with tertiary (<5%) pattern 4 had a worse prognosis than pure Gleason score 3 + 3 = 6 cancers [20]. Their findings emphasised that 3 + 3 and 3 + 4 behaved differently in terms of pathologic stage and biochemical progression.

Immunohistochemistry with markers against basal cells (high-molecular cytokeratin, p63), PSA, and alpha-methyl-coenzyme A racemase can be helpful for the diagnosis of small foci in PCa. These antibodies have to be used judiciously in light of the morphology on routine haematoxylin and eosin–stained sections, as all of these ancillary tests have significant false-positive and false-negative results.

Zonal tumour location is an important feature for the detection of PCa as well as for its prognosis. About 20% of cancers are predominantly located in the transition zone [21,22]. These tumours are often missed by conventional core biopsy techniques, because routine biopsy protocols do not sample the transition zone. However, these transition zone tumours constitute the majority of the so-called incidental prostate cancers detected in transurethral resection specimens performed for benign prostatic hyperplasia. Clinical studies demonstrate that transition zone cancers are less likely to develop PSA recurrence after RP as compared to peripheral zone tumours of equal size [21]. Cancers originating in the transition zone are more likely to behave in an indolent fashion and therefore could more easily be defined as insignificant.

3.2. Incidence of insignificant prostate cancer in clinical, screening, and autopsy series

3.2.1. Clinical and screening series

The reported incidences of Ins-PCa in RP specimens from clinical and screening settings are listed in Table 1. The rates range from 2.3% to 25% in unselected RP specimens [23–48]. Higher rates are reported in series including only clinical stage T1c and/or Gleason score 6 (3 + 3) PCa. Some of the variations in the incidence of Ins-PCa may be attributable to several factors, such as patient selection or the impact of clinical or screening practices.
3.2.2. Autopsy series

Autopsy series are interesting, because they provide insight into the true prevalence of PCa. Unfortunately, few of them have investigated the frequency of low-grade and low-volume PCa that would be pathologically described as Ins-PCa in living patients. This rate in a small autopsy series of 48 cases was estimated to be 10.4% [49]. The term Ins-PCa should be strictly used in living patients, because any cancer found at the autopsy is clinically insignificant by definition. In a subsequent series of 164 autopsy specimens, 25 incidences of PCa (15.4%) were found, including 9 low-grade and low-volume PCa instances that would be pathologically described as Ins-PCa in living patients (36% of PCa cases) [50]. Stamatiou et al. have previously found that most of the impalpable cancers found in autopsy studies were potentially insignificant tumours [51]. They reported 70.7% low-volume (<1 cm³) PCa in a series of 40 PCa cases diagnosed from 212 autopsy specimens. In another autopsy series from 57 men without clinically suspected PCa, the prostates were completely embedded and sectioned in 3-mm steps using the cone method. Interestingly, tumour volumes were also measured with computer-assisted planimetry. Eleven cancers were insignificant according to the criteria (no Gleason 4, volume <0.5 cm³, diploid), representing 59.7% of all cancers detected and 19.3% of all prostates examined [52]. Apparently, there is a wide variation in the proportion of low-volume PCa among the few available autopsy studies.

Konety et al. have examined changes in the prevalence of autopsy-detected PCa over time in an American population [53]. They found a 3-fold decrease in the prevalence of autopsy-detected latent PCa during the 1991–2001 period as compared to the earlier, pre-PSA 1955–1960 period. This decrease in prevalence was associated with a downward stage and grade migration of the latent cancers. The adoption of early detection of PCa in a population even affects the grade and stage distribution of the latent, autopsy-detected PCa instances. It is therefore likely that the proportion of Ins-PCa among the latent cancers would increase in PSA-tested populations. The frequency of small latent carcinomas has been estimated at about 12% in the 1970s and did not vary with age [54]. Rates for larger latent carcinomas increased sharply with age and showed an area-to-area variation resembling that of clinical carcinoma of prostate.

3.3. Pretreatment tools for predicting insignificant prostate cancer

3.3.1. Epstein criteria

In 1994, Epstein et al. published pretreatment criteria significantly predictive of Ins-PCa identified in RP specimens.

Table 1 – Reported incidences of insignificant prostate cancer in radical prostatectomy specimens in the literature

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Cohort</th>
<th>Setting</th>
<th>Definition of Ins-PCa</th>
<th>Percent of Ins-PCa, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein et al, 1994 [1]</td>
<td>157</td>
<td>T1c</td>
<td>Clinical</td>
<td>OC + GS &lt;7 + &lt;0.5 cm³</td>
<td>26</td>
</tr>
<tr>
<td>Irwin and Trapasso, 1994 [23]</td>
<td>28</td>
<td>T1c–T2</td>
<td>Clinical</td>
<td>&lt;0.5 cm³</td>
<td>12</td>
</tr>
<tr>
<td>Terris et al, 1995 [24]</td>
<td>92</td>
<td>T1c–T2</td>
<td>Clinical</td>
<td>&lt;1 cm³</td>
<td>16</td>
</tr>
<tr>
<td>Cugo et al, 1995 [25]</td>
<td>130</td>
<td>Overall</td>
<td>Clinical</td>
<td>&lt;0.5 cm³</td>
<td>2.3</td>
</tr>
<tr>
<td>Goto et al, 1996 [26]</td>
<td>170</td>
<td>Overall</td>
<td>Clinical</td>
<td>OC + GS &lt;7 + &lt;0.5 cm³</td>
<td>10</td>
</tr>
<tr>
<td>Elgamal et al, 1997 [27]</td>
<td>90</td>
<td>T1c</td>
<td>Clinical</td>
<td>GS &lt;7 + &lt;0.5 cm³</td>
<td>20</td>
</tr>
<tr>
<td>Carter et al, 1997 [28]</td>
<td>240</td>
<td>T1c</td>
<td>Clinical</td>
<td>OC + GS &lt;7 + &lt;0.5 cm³</td>
<td>29</td>
</tr>
<tr>
<td>Epstein et al, 1998 [10]</td>
<td>163</td>
<td>T1c</td>
<td>Clinical</td>
<td>GS &lt;7 + &lt;0.5 cm³</td>
<td>31</td>
</tr>
<tr>
<td>Noguchi et al, 2001 [29]</td>
<td>222</td>
<td>T1c</td>
<td>Clinical</td>
<td>&lt;0.5 cm³</td>
<td>10</td>
</tr>
<tr>
<td>Grossklaus et al, 2001 [30]</td>
<td>135</td>
<td>Overall</td>
<td>Clinical</td>
<td>&lt;0.5 cm³</td>
<td>25</td>
</tr>
<tr>
<td>Chan et al, 2001 [31]</td>
<td>217</td>
<td>Overall</td>
<td>Clinical</td>
<td>OC + GS &lt;7 + &lt;0.5 cm³</td>
<td>24.4</td>
</tr>
<tr>
<td>Kattan et al, 2003 [7]</td>
<td>409</td>
<td>T1c–T2a</td>
<td>Clinical</td>
<td>OC + GS &lt;7 + &lt;0.5 cm³</td>
<td>20</td>
</tr>
<tr>
<td>DiMarco et al, 2003 [32]</td>
<td>274</td>
<td>bGS 6</td>
<td>Clinical</td>
<td>OC + GS &lt;7 + &lt;0.5 cm³</td>
<td>28</td>
</tr>
<tr>
<td>Augustin et al, 2003 [33]</td>
<td>1254</td>
<td>Overall</td>
<td>Clinical</td>
<td>GS &lt;7 + &lt;0.5 cm³</td>
<td>5.8</td>
</tr>
<tr>
<td>Anast et al, 2004 [34]</td>
<td>152</td>
<td>T1c</td>
<td>Clinical</td>
<td>OC + GS &lt;7 + &lt;0.5 cm³</td>
<td>25.7</td>
</tr>
<tr>
<td>Miyake et al, 2005 [35]</td>
<td>195</td>
<td>Overall</td>
<td>Clinical</td>
<td>&lt;0.5 cm³</td>
<td>14.4</td>
</tr>
<tr>
<td>Ochiai et al, 2005 [36]</td>
<td>207</td>
<td>Overall</td>
<td>Clinical</td>
<td>&lt;0.5 cm³</td>
<td>21.7</td>
</tr>
<tr>
<td>Loeb et al, 2006 [37]</td>
<td>1410</td>
<td>Overall</td>
<td>Screening</td>
<td>OC + GS &lt;7 + &lt;0.5 cm³</td>
<td>6.6</td>
</tr>
<tr>
<td>Steyerberg et al, 2007 [6]</td>
<td>247</td>
<td>T1c–T2a</td>
<td>Screening</td>
<td>OC + GS &lt;7 + &lt;0.5 cm³</td>
<td>49</td>
</tr>
<tr>
<td>Shukla-Dave et al, 2007 [38]</td>
<td>220</td>
<td>T1c–T2a, bGS 6, PSA &lt;20</td>
<td>Clinical</td>
<td>OC + GS &lt;7 + &lt;0.5 cm³</td>
<td>41</td>
</tr>
<tr>
<td>Nakaniishi et al, 2007 [39]</td>
<td>258</td>
<td>1 positive core</td>
<td>Clinical</td>
<td>OC + GS &lt;7 + &lt;0.5 cm³</td>
<td>51.6</td>
</tr>
<tr>
<td>Postma et al, 2007 [40]</td>
<td>550</td>
<td>Overall</td>
<td>Screening</td>
<td>OC + GS &lt;7 + &lt;0.5 cm³</td>
<td>Round 1: 32%</td>
</tr>
<tr>
<td>Van Oort et al, 2009 [41]</td>
<td>502</td>
<td>Overall</td>
<td>Clinical</td>
<td>GS &lt;7 + &lt;0.5 cm³</td>
<td>12.8</td>
</tr>
<tr>
<td>Capitanio et al, 2008 [42]</td>
<td>1358</td>
<td>Overall</td>
<td>Clinical</td>
<td>GS &lt;7 + &lt;0.5 cm³</td>
<td>5</td>
</tr>
<tr>
<td>Chun et al, 2008 [43]</td>
<td>1132</td>
<td>Overall</td>
<td>Clinical</td>
<td>OC + GS &lt;7 + &lt;0.5 cm³</td>
<td>5.7</td>
</tr>
<tr>
<td>Sengupta et al, 2008 [44]</td>
<td>6496</td>
<td>Overall</td>
<td>Clinical</td>
<td>PSA &lt;10 + OC + GS &lt;7 + &lt;0.5 cm³</td>
<td>5.5</td>
</tr>
<tr>
<td>Dong et al, 2008 [3]</td>
<td>296</td>
<td>T1c–T2a, bGS 6</td>
<td>Clinical</td>
<td>OC + GS &lt;7 + &lt;0.5 cm³</td>
<td>27.4</td>
</tr>
<tr>
<td>Lee et al, 2010 [45]</td>
<td>746</td>
<td>bGS 6</td>
<td>Clinical</td>
<td>OC + GS &lt;7 + &lt;0.5 cm³</td>
<td>25.3</td>
</tr>
<tr>
<td>Loeb et al, 2010 [46]</td>
<td>1073</td>
<td>Overall</td>
<td>Screening</td>
<td>OC + GS &lt;7 + &lt;0.5 cm³</td>
<td>6</td>
</tr>
<tr>
<td>Raventós et al, 2010 [47]</td>
<td>280</td>
<td>Overall</td>
<td>Clinical</td>
<td>GS &lt;7 + &lt;0.5 cm³</td>
<td>11.8</td>
</tr>
<tr>
<td>Helfand et al, 2010 [48]</td>
<td>629</td>
<td>Overall</td>
<td>Clinical</td>
<td>OC + GS &lt;7 + &lt;0.5 cm³</td>
<td>6</td>
</tr>
</tbody>
</table>

Ins-PCa = insignificant prostate cancer; OC = organ confined; GS = Gleason score; bGS = biopsy Gleason score; PSA = prostate-specific antigen.
using PSA and needle biopsy findings [1]: no Gleason pattern 4 or 5, less than three core samples involved of a sextant biopsy, and no core sample >50% involved. The best model for predicting Ins-PCa in RP specimens was obtained by the two following preoperative criteria combinations: (1) PSA density <0.1 ng/ml per gram, no Gleason pattern 4 or 5, less than three positives cores, and <50% of cancer involvement per core; and (2) PSA density between 0.1 and 0.15 ng/ml per gram and <3 mm of cancer in one core (Table 2). The positive and negative predictive values of this model were 95% and 66%, respectively. These two current preoperative definitions of Ins-PCa have been extensively evaluated in the literature. It is noteworthy to emphasise that analyses from Epstein et al. only 37% of men who fulfilled the preoperative Epstein biopsy criteria had Ins-PCa as defined by the current definition of Ins-PCa at diagnosis on biopsies was 84% to 42% in selected series (Table 2). In the study by Lee et al, only 37% of men who fulfilled the preoperative Epstein biopsy criteria had Ins-PCa as defined by the current definition of Ins-PCa in RP specimens [45]. Nevertheless, the authors emphasised that the preoperative contemporary Epstein criteria were highly predictive for favourable disease (58% of organ-confined and Gleason 6 PCa) and cure by RP. The European study by Jeldres et al. demonstrated a rate of organ-confined disease of 91.7% when the updated Epstein criteria were used. Conversely, the rate of Gleason 7–10 cancers was substantially higher in this study cohort compared with the rate found in the reference cohort from Bastian et al. (24% vs 9%), which yielded a substantially lower overall accuracy (76%) than the one reported by Bastian et al. (84%). These discrepancies can be explained by several factors, such as grade misclassification, number of cores obtained at biopsy, or ethnical considerations.

However, it is noteworthy that predicting favourable disease at RP should not be the main end point of interest, because most definitions of Ins-PCa will result in low-risk disease at surgery, and the main aim of insignificance definition is to avoid surgery or other treatment modalities.

### Table 2 – Percent of insignificant prostate cancer (Ins-PCa) in radical prostatectomy specimens in patients with suspected Ins-PCa according to the preoperative Epstein criteria

| No. of patients | Percent of Ins-PCa at RP | PSAdensity <0.1 | PSA density <0.1–0.15 | Updated Epstein criteria
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No grade 4 or 5</td>
<td>&lt;3 mm of cancer in one core</td>
<td>Updated Epstein criteria</td>
</tr>
<tr>
<td>Epstein et al., 1994 [1]</td>
<td>157</td>
<td>73</td>
<td>73</td>
<td>–</td>
</tr>
<tr>
<td>Carter et al., 1997 [28]</td>
<td>64</td>
<td>–</td>
<td>–</td>
<td>75</td>
</tr>
<tr>
<td>Bastian et al., 2004 [55]</td>
<td>237</td>
<td>–</td>
<td>–</td>
<td>84</td>
</tr>
<tr>
<td>Jeldres et al., 2008 [56]</td>
<td>366</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Lee et al., 2010 [45]</td>
<td>136</td>
<td>–</td>
<td>–</td>
<td>76</td>
</tr>
<tr>
<td>Lee et al., 2010 [57]</td>
<td>131</td>
<td>–</td>
<td>–</td>
<td>37.58***</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PSA density &lt;0.1–0.15</td>
<td>PSA density &lt;0.1–0.15</td>
<td>Updated Epstein criteria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No grade 4 or 5</td>
<td>&lt;3 mm of cancer in one core</td>
<td>Updated Epstein criteria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;50% cancer per core</td>
<td>PSA density &lt;0.1–0.15</td>
<td>Updated Epstein criteria</td>
</tr>
</tbody>
</table>

Ins-PCa = insignificant prostate cancer; RP = radical prostatectomy; PSA = prostate-specific antigen.

* Updated Epstein criteria: PSA density <0.15 ng/ml per gram, Gleason score ≤6, fewer than three positive cores, <50% of cancer involvement in any core.

** Gleason score ≤6 and organ-confined disease in RP specimen.

*** Organ-confined disease in RP specimen.

3.3.2. Other predictive models

Several authors have put forward alternative preoperative models to better predict Ins-PCa [23–27,29,34,36,47,58]. Ochiai et al. found that the combination of a tumour length <2 mm, a Gleason score ≤3 + 3, and a prostate volume >50 ml best predicted Ins-PCa [36]. Overall, the sensitivity and the specificity of these predictive models ranged from 23% to 77% and from 75% to 98%, respectively. These findings underline the need for developing more accurate models to identify Ins-PCa.

More stringent biopsy criteria have also been tested in the literature, especially the “minute” or “microfocal” PCa that was defined by a single neoplastic microfocus at biopsies involving ≤5% or ≤1 mm in one core. Unfortunately, the diagnosis of “minute” PCa did not completely eliminate the risk of misclassification of a significant PCa, and the smallest focus of cancer on needle biopsy is not a guarantee of clinically insignificant PCa. In their systematic review and meta-analysis, Harn den et al. observed that between 33% and 84% of patients with minute PCa on biopsies had at least one adverse pathologic feature in the RP specimen and were considered to have a significant and potentially progressive PCa [59].
3.3.3. **Nomograms based on clinicopathologic variables**

Several authors have generated preoperative predictive models to better identify potentially insignificant PCa. The main nomograms that have been reported and validated in predicting Ins-PCa are listed in Table 3.

The first nomogram for the prediction of Ins-PCa was reported by Kattan et al. [7]. The study cohort included patients who underwent RP for clinical T1c–T2a PCa. The authors developed three different nomograms (base, medium, and full models) by integrating additional biopsy features. The full model predicted the presence of an Ins-PCa with an area under the curve (AUC) of 0.79. This good discriminatory ability has been externally validated in two medium, and full models) by integrating additional biopsy features. The full model predicted the presence of an Ins-PCa in the RP specimens (Gleason score 7–10, non–organ-confined disease). This study also provided an external validation of the Kattan nomogram. However, 45% of patients who were considered to have Ins-PCa using the Kattan nomogram had an “aggressive” PCa in the final pathologic assessment. Thus, the study showed that regardless of which nomogram is used to predict Ins-PCa, a significant number of patients remain understaged.

3.3.4. **Impact of various factors on predictive models**

3.3.4.1. **Study population and prostate-specific antigen screening**

Differences in study population are likely the predominant factor responsible for variability in predictive values among nomograms [4,6]. Some of the variations in the prediction of Ins-PCa may be attributable to patient selection. For example, the nomogram developed by Nakanishi et al. was restrictive and incorporated only those patients with a single positive core at biopsy [39]. Stage and grade distribution at biopsy as well as the rate of Ins-PCa in RP specimens observed in European men differs from their North American counterparts. It has been shown that the Epstein criteria defined from an American cohort perform less well in European men [60].

PSA screening has resulted in an increase in low-risk PCa at diagnosis. Several authors found an increasing trend of low-risk and insignificant PCa in the past decades [33,61,62]. Earlier studies evaluating the prediction of Ins-PCa are characterised by different clinical profiles of PCa compared with those noted to date. PCa diagnosed in a screening setting has a substantially higher likelihood of being indolent than those identified in a clinical setting (Tables 1 and 3). As emphasised by the ERSPC study data, a calibration factor may correct differences among patients from different settings or regions that are not captured by the characteristics in the reference model [5,6].

3.3.4.2. **Biopsy core number**

One of the reasons for the lack of correlation between preoperative potentially and definitive Ins-PCa may be sampling error or bias when biopsy findings are not representative of the overall tumour burden. This consideration argues for the need for more extensive sampling to exclude undersampled, significant cancer.

Table 3 – Predictive accuracy of published nomograms for the prediction of insignificant prostate cancer in the literature

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Setting</th>
<th>No cores</th>
<th>Predictive accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kattan</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steyerberg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nakanishi</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chun</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kattan et al, 2003 [7]</td>
<td>409</td>
<td>Clinical</td>
<td>≤6</td>
</tr>
<tr>
<td>Steyerberg et al, 2007 [6]</td>
<td>490</td>
<td>Screening</td>
<td>6</td>
</tr>
<tr>
<td>Nakanishi et al, 2007 [39]</td>
<td>258</td>
<td>Clinical</td>
<td>10–13</td>
</tr>
<tr>
<td>Roemeling et al, 2007 [5]</td>
<td>825</td>
<td>Screening</td>
<td>6</td>
</tr>
<tr>
<td>Dong et al, 2008 [3]</td>
<td>296</td>
<td>Clinical</td>
<td>5–34</td>
</tr>
<tr>
<td>Median: 11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chun et al, 2008 [43]</td>
<td>1132</td>
<td>Clinical</td>
<td>6–10</td>
</tr>
</tbody>
</table>

PSA = prostate-specific antigen; bGS = biopsy Gleason score.

* Only one positive core in all patients included.

** Calculated probability of indolent cancer.

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Studies have demonstrated that the increase in biopsy core number from sextant biopsies to extended schemes, including additional far lateral biopsies (10–12 cores), improved the PCA detection rate but does not detect more Ins-PCa [63]. The majority of PCs detected in these lateral cores were clinically significant. The percent of positive cores has been shown to predict extraprostatic extension, recurrence, and death after RP. Tumour volume as assessed by extended biopsy does predict outcome [64]. Saturation biopsies have been evaluated as a staging tool to improve the characterisation of low-volume and well-differentiated PCs, but whether they improve prediction of tumour insignificance remains open to debate. It is also noteworthy that insufficient prostate sampling increases the chance of undergrading the tumour, leading to a false increase in Ins-PCa prevalence. Grossklaus et al. suggested in a small series of PCa patients that the prediction of Ins-PCa was not improved by an extended biopsy scheme versus sextant biopsies [30].

Epstein et al. have emphasised the benefit of saturation biopsies in the measurement of tumour extent and grade and thus in the evaluation of Ins-PCa [65]. Using a saturation biopsy scheme, the false-positive rate for the diagnosis of Ins-PCa only ranged from 8% to 11.5% according to the algorithm chosen. However, this was an ex vivo study, and transfer to clinical practice might have limitations. An autopsy series from 164 prostates found that taking additional cores in cases of microfocal PCs identified on sextant biopsies helped differentiate significant from insignificant PCs [50]. However, results of autopsy series based on the true prevalence of PCs suggested that 40% of PCs would stay undetected regardless of the number of locations from which biopsies were taken. In men with a diagnosis of microfocal and potentially insignificant PCs on primary biopsy, authors found that the reevaluation by an extended 32-core biopsy scheme was helpful in identifying 70% of men who had significant tumours based on the repeat saturation biopsy findings [66]. Cancers originating in the transition zone are more likely to behave in an indolent fashion and therefore could more easily be defined as insignificant. Thus, extended biopsy schemes, including cores in the transition zone, might increase the prevalence of diagnosed Ins-PCa. However, to date, no published series has confirmed this statement.

3.4. Impact of the dichotomy of significant vs insignificant prostate cancer in clinical practice

3.4.1. Diagnosis of potentially insignificant prostate cancer before definitive therapy

Stage and grade migration of PCa increases the proportion of men undergoing overtreatment, which can place them at unnecessary risk for complications. In the ERSPC, PSA screening has been shown to reduce specific mortality by 20%, and it was estimated that 48 men needed to be treated to prevent one death [67]. The number needed to treat (NNT) has recently been estimated at 29 and 18 by extrapolating the follow-up to 10 and 12 yr, respectively [68]. In the Göteborg randomised, population-based PCa screening trial, authors have shown that PCa mortality was reduced almost by half over 14 yr and that the NNT was at least as high as in breast cancer screening programmes [69].

The ability to identify Ins-PCa prior to definitive therapy and patients harbouring tumours that pose no risk to life and health is critically needed. Although clinical and pathologic predictors of Ins-PCa can be identified, it remains to be established whether such patients can be safely managed conservatively. Despite the imperfection of predictive tools, the preoperative definition of a potentially insignificant PCa provides a starting point in identifying patients eligible for active surveillance or organ-sparing therapies. Thus, it remains difficult to select the optimal active surveillance candidate, and cancer characteristics are only part of the story, which must also factor in patients’ age and life expectancy irrespective of PCa.

Although the Epstein definition of Ins-PCa is the most widely used tool in defining potentially insignificant PCa, this definition has not been thoroughly incorporated as an active surveillance selection criterion in most active surveillance protocols. Only the active surveillance programme from the Johns Hopkins Hospital included it as an entry criterion. Midterm follow-up from this institution has recently been reported [70]. Overall, 102 (35%) of 290 men developed unfavourable findings on surveillance biopsy at last follow-up and were recommended to undergo treatment (median follow-up: 3 yr). Of men who underwent treatment, 45 (44%) elected to undergo RP. The authors emphasised that most events with more unfavourable findings on repeat biopsy after active surveillance occurred 1 to 2 yr after diagnosis, suggesting undersampling of more aggressive tumours rather than progression of indolent tumours [71]. Even with more unfavourable findings on repeat biopsy, 27% of PCa instances were Ins-PCa at RP. However, one-third of these PCa instances were non–organ-confined disease with adverse pathology. Patients enrolled in active surveillance programmes should be informed that they may harbour more aggressive disease, with a risk of non–organ-confined PCa [72].

3.4.2. The risk of clinical progression in men with insignificant prostate cancer in radical prostatectomy specimens

Patients treated by surgery for Ins-PCa pathologically defined in an RP specimen should be at zero risk of systemic progression or death from cancer in the postoperative course. If this were true, they might require less intense postoperative surveillance. However, the oncologic follow-up of men with pathologically confirmed Ins-PCa after RP has not been thoroughly investigated [41,42,44] (Table 4). One of the explanations of this shortcoming in the current literature may be the fact that the stringency of criteria results in small cohorts of patients. Yet this analysis is critically important before considering active surveillance in patients with potentially insignificant PCa at diagnosis. The absence of a strong difference between oncologic outcomes of clinical PCs and Ins-PCa or poor rates of PSA failure after RP in Ins-PCa patients would cast a shadow of doubt on the validity of the clinical definition of insignificant PCa. In one of the first reports of Epstein et al, the authors
reported that no patients with a tumour volume <0.5 cm$^3$ demonstrated progression following RP [10].

In line with this finding, from a series of 1358 PCa patients who underwent RP, Capitanio et al. found Ins-PCa in only 65 patients. None of them developed PSA failure after a relatively short follow-up of 3 yr [42]. Analysis of PSA follow-up in a larger cohort of Ins-PCa patients (354 cases) by Sengupta et al. [44] revealed that patients with Ins-PCa have a 13% risk of PSA failure at 10 yr after surgery. The risks of metastatic progression (0.3%) or specific death (0%) after RP were negligible over a follow-up approaching 10 yr. Although these low-risk and low-volume PCa patients were at low risk for progression, this risk was comparable to that faced by men with low-risk PCa as defined by the d'Amico criteria. In a smaller cohort of Ins-PCa patients, van Oort at al also reported a 10% 5-yr risk of BCR [41]. Pathologic criteria. In a smaller cohort of Ins-PCa patients, van Oort at

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Percent of Ins-PCa at RP, % (n)</th>
<th>Follow-up, yr</th>
<th>5-yr RFS, %</th>
<th>Rate of metastatic disease during follow-up, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postma et al, 2007 [40]</td>
<td>550</td>
<td>33 (182)</td>
<td>5.6</td>
<td>94</td>
</tr>
<tr>
<td>Sengupta et al, 2008 [44]</td>
<td>6496</td>
<td>5.5 (354)</td>
<td>9.2</td>
<td>87</td>
</tr>
<tr>
<td>Capitanio et al, 2008 [42]</td>
<td>1358</td>
<td>5 (89)</td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>Van Oort et al, 2009 [41]</td>
<td>502</td>
<td>12.8 (64)</td>
<td>3.3</td>
<td>90</td>
</tr>
</tbody>
</table>

Ins-PCa = insignificant prostate cancer; RP = radical prostatectomy; RFS = recurrence-free survival.

### 3.5. Improving the prediction of truly insignificant prostate cancer

The lack of perfect performance in models predictive for Ins-PCa justifies the assessment of novel tools. There is an ongoing need for identifying truly biologically significant PCa that cannot be accurately predicted by the currently available tools. The aim of such extended diagnostic strategies in initial management would be to reduce the risk of misclassification of a clinically significant disease.

#### 3.5.1. Urinary prostate cancer antigen 3 score

Some studies have evaluated the correlation between prostate cancer antigen 3 (PCA3) score and RP findings [75,77]. A significant association between PCA3 score and tumour volume has also been emphasised [75,76,78,79]. Whitman et al. also found an association between PCA3 and extraprostatic extension, whereas Nakanishi et al. demonstrated a significant link between PCA3 and high Gleason score. Hessels et al. did not confirm the latter findings in their recent study [77], but their patient cohort included few men with favourable features: 40% had pT3 disease, and only 10 cancers had a volume <0.5 cm$^3$. In a 160-case series, Auprich et al. confirmed PCA3 score as a valuable predictor of pathologically confirmed Ins-PCa. PCA3 scores were significantly lower in Ins-PCa, and the addition of the PCA3 score in multivariable models increased the accuracy of Ins-PCa prediction [78].

Recently, another prospective study assessed the impact of the PCA3 assay in a cohort of low-risk PCa patients [79]. The findings suggested that the PCA3 score was strongly indicative of tumour volume and accordingly a determinant for significance of PCa according to the current Epstein definition. The risk of having a significant PCa was increased 3-fold in men with a PCA3 score $\geq$25 compared with men with a PCA3 score <25.

#### 3.5.2. Magnetic resonance imaging

Although magnetic resonance imaging (MRI) has become an increasing commonly used imaging tool for characterisation of low-volume PCa, its predictive value has not been thoroughly assessed among PCa patients eligible for active surveillance [80]. T2-weighted standard images have a low specificity, especially for detecting PCa in the transition zone. In addition, the use of routine T2-weighted images may underestimate the detection of low-risk or low-volume PCa [81].

Other MRI parameters may have greater prognostic importance than standard T2-weighted sequences, howev-
er. The diagnostic performance of MRI in PCa detection is improved by the addition of an apparent diffusion coefficient map to T2-weighted imaging [82]. Diffusion-weighted MRI has been shown to discriminate cancer tissue from benign peripheral tissue as well as low-risk PCa from high- or intermediate-risk PCa [83]. Recent data also suggest that MRI combined with magnetic resonance spectroscopic imaging (MRSI) could be relevant for assessment of low-risk patients [84].

Future studies should also investigate whether 3.0-T MRI provides greater predictive value and help to better assign patients to active surveillance. The 3.0-T MRI improves spectral resolutions of prostate imaging on T2-weighted sequences. One potential advantage is adequate imaging without endorectal coil. However, high additional value for cancer staging has to be proven. Recent recommendations from a European consensus meeting concluded that T2-weighted, dynamic, contrast-enhanced, and diffusion-weighted MRI were the key sequences incorporated into the minimum requirements, especially concerning the exclusion of clinically significant disease as defined by a lesion size >0.5 cm³ (approximately 10 mm) in the peripheral zone [85]. Shukla-Dave et al. found that new models that combined clinical and biopsy data with MRI and MRSI findings performed better than the clinical models for predicting the probability of Ins-PCa in RP specimens [38,86]. The reported accuracy of this combined model as measured by the AUC improved to 0.85 compared with 0.73 for the Kattan nomogram.

3.5.3. Prostate-specific antigen velocity
In a large retrospective study from 1073 RP specimens, Loeb et al. suggested PSA velocity as a useful additional tool in predicting Ins-PCa. Patients with a preoperative PSA velocity >0.4 ng/ml per year were 50% less likely to have Ins-PCa in RP specimens [46]. Sengupta et al. also reported that the PSA doubling time was an independent predictor of Ins-PCa in a multivariate model taking into account age, biopsy Gleason score, and clinical stage [44]. Unfortunately, findings from the ERSPC study failed to identify PSA velocity as an independent predictor of clinically significant PCa. In this screening trial, the use of PSA velocity led to appreciable numbers of missed indolent but also significant PCa [87,88]. In the active surveillance Johns Hopkins cohort, PSA kinetics during follow-up did not reliably predict biopsy progression in 290 men who were included in the active surveillance programme. In this study, PSA velocity was an unreliable trigger for differing treatment and a poor indicator of clinically significant PCa [70].

3.5.4. Genetic variants
The analysis of PCa risk alleles has been reported to be potentially interesting in identifying Ins-PCa [89,90]. Helfand et al. suggested that men with significant PCa had a greater frequency of any of five risk alleles studied (at chromosomes 8q24 and 17) than patients with Ins-PCa [89]. However, no single risk allele was able to distinguish an Ins-PCa instance, and only a cumulative effect was observed.

New research methods are also emerging, and high-throughput technologies will facilitate high-dimensional biomarker discovery. Future approaches will probably integrate proteomic, transcriptomic, and multiplex approaches to detect novel biomarkers and aim to identify combinations of multiple biomarkers to optimise the preoperative characterisation of PCa and better differentiate indolent from aggressive cancers.

3.6. Is the current definition of insignificant prostate cancer still timely in the era of active surveillance?

To date, there is a rationale for the debate about a more liberal definition of insignificant disease. In a large multicentre analysis of 24 414 patients, Stephenson et al. found that only 0.003% of men with organ-confined Gleason score-6 disease died from PCa within 15 yr of RP [91]. Other authors suggested that tumour volume did not independently influence the oncologic outcome in Gleason score-6 PCa [92]. It also should be noted that the proportion of men with pathologically confirmed Ins-PCa is relatively small and that the employment of the current strict definition of insignificant PCa will not critically decrease the rate of overtreatment. It is quite possible that using 0.5-cm³ cancer volume as a cut-off for clinically significant PCa is too small, and it is important to note that this cut-off is based on a single study [9].

Recently, Wolters et al. aimed to reassess the tumour volume threshold [93]. Using lifetime risk rates for the ERSPC population-based screened cohort, they found that the index tumour volume threshold of 0.5 ml reported by Stamey could be confirmed with a total tumour volume threshold of 0.7 ml. However, as grade and stage were the most important prognostic factors for PCa aggressiveness, they demonstrated that clinically insignificant PCa may include index tumours with volumes up to at least 1.3 ml (and a total tumour volume of 2.5 ml) for patients with low-grade, low-stage disease.

The criteria used in most active surveillance protocols are currently less stringent than those used to define an Ins-PCa, and most patients included in active surveillance protocols who were reclassified as higher risk over time remained curable by delayed therapy. Nevertheless, a non-negligible proportion of PCa continues to be classified as insignificant, where clinically significant and potentially life-threatening disease may be found at RP. In active surveillance protocols, studies comparing entry criteria have emphasised the risk of misclassification and the limitations of currently available active surveillance criteria [94]. Recent studies of repeat biopsies in men under active surveillance have also emphasised the risk of encountering upgraded and/or upstaged disease [95]. Long-term follow-up of active surveillance series might modify the definition of insignificant PCa with the identification of prognostic factors of disease progression.

As mentioned, most published active surveillance series have used entry criteria different from the current definition of insignificant PCa that were largely based on centre experiences with no hard data. The most current
active surveillance criteria are a Gleason score \( \leq 6 \), PSA \( \leq 10 \) ng/ml, and clinical stage T1–T2a disease, with additional biologic or biopsy criteria depending on institutional preferences. Other characteristics may include multiple pathologic biopsy parameters, such as \(<33\%\) of biopsy cores, fewer than two positive cores, and/or \(<50\%\) of cancer involvement [96,97]. This consideration argues for a more liberal definition of insignificant PCa. Only the Johns Hopkins active surveillance cohort required fulfilment of the Epstein criteria for eligibility, but the use of these criteria has not been validated in other active surveillance programmes, and their utility for this purpose may be questioned.

4. Conclusions

The exciting challenge of obtaining pretreatment diagnostic tools that can really distinguish insignificant from significant PCa should be one of the main objectives of urologists in the following years to decrease the risk of overtreatment of Ins-PCa. To date, the most commonly used criteria for defining Ins-PCa are based on the pathologic assessment of the RP specimen and include the well-established prognostic factors: (1) Gleason score \( \leq 6 \) without Gleason pattern 4 or 5, (2) organ-confined disease (no extraprostatic extension, no SVI, no LNI), and (3) tumour volume \(<0.5\, \text{cm}^3\). These criteria for Ins-PCa might be improved by incorporating factors other than the pathologic features alone, such as age, PSA level, and comorbidities.

Several preoperative criteria and prognostication tools for predicting Ins-PCa have been suggested. Nomograms are best placed to estimate the risk of progression on an individualised basis, but a substantial proportion of men with a high probability of harbouring Ins-PCa on the basis of current nomograms are at risk for pathologic understaging and/or undergrading, and to date, the literature fails to highlight a single predictive model as a gold standard. Ins-PCa cannot reliably be identified, and the risk of understaging remains not negligible. Thus, there is an ongoing need for identifying new prognostic tools (eg, MRI modalities, molecular markers) to improve the distinction between insignificant and significant disease and thus to promote the adequate management of PCa patients at low risk for progression.

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

Study concept and design: Bjartell, Montorsi.

Acquisition of data: Ploussard.

Analysis and interpretation of data: Ploussard, Epstein, Montironi, Carroll, Wirth, Grimm, Bjartell, Montorsi, Freedland, Erbersdobler, van der Kwast.

Drafting of the manuscript: Ploussard.

Critical revision of the manuscript for important intellectual content: Epstein, Montironi, Carroll, Wirth, Grimm, Bjartell, Montorsi, Freedland, Erbersdobler, van der Kwast.

Statistical analysis: Ploussard.

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Administrative, technical, or material support: None.

Supervision: Epstein, Montironi, Carroll, Wirth, Grimm, Bjartell, Montorsi, Freedland, Erbersdobler, van der Kwast.

Other (specify): None.

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