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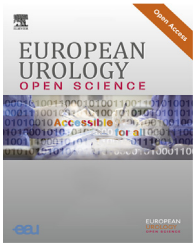


European Association of Urology

Opinion: Open Science

# Abandon the Label of Clinically Insignificant Prostate Cancer

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It has been shown that screening programs using prostate-specific antigen (PSA) are effective in reducing the incidence of prostate cancer metastases and mortality [1]. However, these programs have also resulted in unnecessary repeat tests, as well as overdiagnosis and overtreatment of asymptomatic men with indolent prostate cancer that would not have led to prostate cancer–related death. Therefore, a risk-adapted prostate cancer screening strategy has been developed that combines PSA testing with risk calculators and multiparametric magnetic resonance imaging (mpMRI) to differentiate "significant" from "insignificant" prostate cancer. The distinction between clinically significant and insignificant prostate cancer plays a pivotal role, as it allows a reduction in overtreatment. However, defining what is clinically significant versus insignificant prostate cancer is difficult and it is important to realize that the concept of clinical insignificance should not be confused with the absence of relevance of the disease. Here, we discuss our reflections on this misinterpretation and why we should avoid wildly labeling prostate tumors as clinically insignificant.

First, the lack of a clear definition creates confusion. A literature review of characteristics used to define clinically insignificant prostate cancer reveals significant variation over the years. Even the current European Association of Urology (EAU) guideline leaves room for flexibility; the term is mentioned three times in the 2021 edition [2], each time within the context of a different meaning. The criteria most frequently used for insignificant prostate cancer include clinical stage (organ-confined disease) and Gleason pattern (absence of Gleason pattern 4/5) with or without an arguable threshold for volume. Particularly in view of early diagnosis and potential deferral of treatment, the differential characteristics used to define clinically insignificant prostate cancer should not be up for interpretation. Therefore, the EAU must be encouraged to explore the heterogeneity of definitions, thresholds, and criteria for clinically insignificant prostate cancer before reintroducing the term in practice.

Besides the confusing content for the definition, the nomenclature is prone to semantic misunderstandings. Insignificant means "meaningless" or "too small or unimportant to be worth considering risk"—indicating a certain innocence of the situation—while, conversely, the word cancer generally leads to anxiety. In order to avoid disruption of concern, being intentionally concrete can be useful and help in preventing confusion. Aside from "clinically insignificant", other terms commonly used in prostate cancer include the following: indolent, latent, unimportant, low grade, and (very) low risk. From a linguistic point of view, it is important to use precise language and therefore it is better to avoid subjective words that suggest insignificance of a disease.

Furthermore, from an oncological point of view, clinical insignificance does not accurately describe the content of the disease. Currently, doctors tend to consider International Society of Urological Pathology (ISUP) grade 1 (Gleason 6) clinically insignificant, with the preferred management being active surveillance. This implies a strong probability that a man will never be bothered by the disease. However, given the recommendation to not ignore this type of cancer, but to safely observe it (within active surveillance programs, including frequent PSA testing and biopsies for many years), the term clinically insignificant is already a contradiction in terms here, as long as we cannot exclude patients with tumors with the lowest malignant potential.

Nevertheless, even though it is generally agreed that insignificant prostate cancer will not threaten survival, grade 1 disease may progress to higher grades over time. Up to one-third of patients on active surveillance are reclassified during follow-up, most of whom will undergo curative treatment because of disease upgrading or upstaging or patient preference [3]. Moreover, the risk of progression

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to metastases was 14% and prostate cancer–related death was 3% at 10 yr in a recent "active monitoring" cohort [4]. Owing to these implications, the uncertain oncological prospects, and long-term follow-up, it is hard to fathom why the diagnosis is clinically insignificant, even when active surveillance is followed.

Likewise, it can be called into question how a disease can be considered clinically insignificant when we do not yet know how to reliably select insignificant cancer. Disentanglement of true (overdiagnosed) Gleason 6 tumors from those with progressive potential will require determination of other biomarkers mediating clinically aggressive versus unaggressive phenotypes. For instance, men with germline pathogenic *BRCA2* mutations are more likely to be diagnosed with clinically significant prostate cancer [5]. This association was also found for *MSH2* mutation carriers [6]. Furthermore, genome-wide association studies suggest that single-nucleotide polymorphisms (SNPs), or interactions between SNPs, are linked to prostate cancer susceptibility and maybe also prostate cancer aggressiveness [7]. These examples illustrate that there are opportunities for more precise selection of clinically insignificant cancer, but this requires additional criteria that are not readily available.

One could sum up this situation by saying that calling all ISUP grade 1 prostate cancer clinically insignificant is reductive. And we have not even mentioned the "obvious" factors, such as age at diagnosis, ethnicity, and lead time, that also influence the significance of a tumor.

Finally, we would like to discuss the relevance of clinically insignificant prostate cancer at a financial level. Overdiagnosis reduces the financial benefits of prostate cancer screening, particularly for older men [8]. Incorporation of mpMRI into active surveillance protocols increases costs, although decreasing the intensity of testing and biopsies may be cost-effective options for men opting for conservative management of low-risk disease [9]. From both an oncological and a macroeconomic point of view, a balanced discussion of the incremental costs of early diagnosis of prostate cancer versus the potential benefits should include ways to reduce overdiagnosis. Meanwhile, we must not overlook the financial toll of cancer on a personal level, as patients with a diagnosis of cancer are more likely than the average person to experience economic distress, such as problems with insurance and bankruptcy [10]. These consequences of a cancer diagnosis are undesirable and disproportionate for healthy men with clinically insignificant disease.

The EAU risk-adapted strategy facilitates identification of men at the highest risk of prostate cancer and will potentially save the lives of many each year by detecting significant cancer earlier. The success of this strategy depends on the ability to safely avoid any further diagnosis and, in particular, treatment in men with tumors with the lowest risk of progression. However, it would be better to avoid the term clinically insignificant for these cancers, simply because we cannot accurately estimate whether a tumor is significant for a patient or not. Instead, we would suggest to focus on the ([very] low) risk of a prostate cancer.

***Conflicts of interest:*** The authors have nothing to disclose.

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