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Research Article

Serum Prostate-Specific Antigen (PSA) Level is a Biomarker for Prostate Adenocarcinoma Grade, Tumour Volume and Histologic Prognostic Indicators

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Abstract

While serum PSA has limited specificity for prostate cancer detection, and its appropriate clinical application remains a topic of debate, it has been shown to correlate with cancer grade and some measures of tumour volume. We sought to replicate these findings and also establish the utility of PSA as a potential biomarker for prognostic indicators in patients with needle biopsies positive for prostate adenocarcinoma. Following clinical audit CoPath electronic archive search using keywords 'prostate' and 'adenocarcinoma,' anonymized reports from 43 clinical audit needle biopsies positive for prostate adenocarcinoma from 2015 through 2022 were reviewed. Data on primary and secondary tumour grade, histologic Gleason score, Grade group, tumour volume, perineural invasion and extraprostatic extension were reviewed with associated PSA levels. Patients with cancers that fell into Grade groups 1 and 2 (Gleason 3+3 and 3+4), had an average PSA level of 10.55 ng/ml, while those in higher Grade groups 3, 4 and 5 (Gleason 4+3, 4+4, 4+5, 5+4 and 5+5), had an average PSA of 26.09 ng/ml. Patients with higher tumour volume (> = 60% of biopsy tissue containing tumour) had an average PSA level of 22.98 ng/ml, while patients with lower tumour volume (<or = 40% of biopsy tissue containing tumour) had an average PSA level of 8.60 ng/ml. In patients with perineural invasion their average PSA level was 16.34 ng/ml, while those without had an average of 12.30 ng/ml. Similarly, patients with extraprostatic extension had an average PSA of 20.50 ng/ml, while those without had an average of 12.90 ng/ml.

Keywords: Prostate Cancer; Tumor Volume; Grade Groups; Perineural Invasion; Extraprostatic Extension

Abbreviation

PSA: Prostate Specific Antigen

Introduction

Prostate cancer is the second most common cancer and the fifth leading cause of cancer death in men worldwide. Localized prostate cancer is asymptomatic; however, the onset of symptoms often correlates with advanced incurable disease. Before PSA testing a digital rectal examination was the only screening tool available and 30–35% of men had bone metastasis at the time of diagnosis. One of every 2–3 patients with prostate cancer died of disease [1]. After the PSA test was introduced into clinical practice as a tumour marker [2-4] the number of newly diagnosed prostate cancers rose rapidly. The serum PSA test was first used for monitoring patients with prostate cancer in in 1981 [5]. It was originally designed for monitoring the progression of prostate cancer and the

response to therapy, not as a screening tool. In 1987, the serum PSA test was introduced into clinical practice as a tumour marker to confirm diagnosis and follow the course of the disease and effect of treatment [3]. In an attempt to mitigate that prostate cancer was often beyond cure at time of diagnosis, serum PSA testing was reported as a screening tool for prostate cancer in 1991 [6]. Although it is prostate-specific rather than disease-specific, PSA, a glycoprotein normally expressed by prostate tissue, is now a biomarker of choice for early detection and follow up of patients with prostate cancer [2-6]. Stamey., *et al*. reported that PSA was elevated in 122 of 127 patients with newly diagnosed, untreated prostatic cancer, including 7 of 12 patients with unsuspected early disease and all of 115 with more advanced disease [3]. The PSA level increased with advancing clinical stage and was proportional to the estimated volume of the tumor. Catalona., *et al*. showed that the combination of measurement of the serum PSA concentration and rectal examination, with ultrasonography performed in patients with abnormal findings, provides a better method of detecting prostate cancer than rectal examination alone [6]. Similarly, Cooner., *et al*. found that among 1,807 men a 13% increase in prostate cancer detection rate was achieved in a clinical urological practice by physician-conducted prostate ultrasonography, digital rectal examination in conjunction with serum prostate specific antigen [7]. Since increased PSA serum levels can be found in other benign conditions, including prostate hypertrophy, urinary tract infections, or after instrumentation, and is also vulnerable to false-negatives [8-10], it has limited specificity alone for prostate cancer detection, and its appropriate clinical application remains a topic of debate [11-13]. We sought to establish the utility of PSA as a potential biomarker for cancer grade, tumour volume and prognostic indicators in patients with needle biopsies positive for prostate adenocarcinoma.

Methods

Following clinical audit CoPath electronic archive search using keywords 'prostate' and 'adenocarcinoma,' anonymized reports from 43 clinical audit needle biopsies positive for prostate adenocarcinoma from 2015 through 2022 were reviewed. Data on primary and secondary tumour grade, histologic Gleason score, Grade group, tumour volume, perineural invasion and extraprostatic extension were reviewed with associated PSA levels. For initial diagnosis, hematoxylin and eosin-stained sections from 12 needle biopsies per case, 6 left and 6 right, anterior and posterior (3 histologic levels each), were available for each case along with p63 and p504s double stain, and evaluated by specialist consultant histopathologists.

Results and Discussion

Patients with cancers that fell into Grade groups 1 and 2 (comprising lower grade prostatic adenocarcinoma; Gleason 3+3 and 3+4), had an average PSA level of 10.55 ng/ml, while those in higher Grade groups 3, 4 and 5 (comprising higher grade adenocarcinomas, Gleason 4+3, 4+4, 4+5, 5+4 and 5+5), had an average PSA of 26.09 ng/ml. Patients with higher tumour volume (> = 60% of biopsy tissue containing tumour) had an average PSA level of 22.98 ng/ml, while patients with lower tumour volume (<or = 40% of biopsy tissue containing tumour) had an average PSA level of 8.60 ng/ml. Negative prognostic indicators of perineural invasion and extraprostatic extension also showed notable differences. In patients with perineural invasion their average PSA level was 16.34 ng/ml, while those without had an average of 12.30 ng/ml. Similarly, patients with extraprostatic extension had an average PSA of 20.50 ng/ml, while those without had an average of 12.90 ng/ml.

Although it is prostate-specific rather than disease-specific, serum PSA has been a biomarker of choice for early detection and follow up of patients with prostate cancer [2-6]. Since increased PSA serum levels can be found in other benign conditions, including prostate hypertrophy, urinary tract infections, or after instrumentation, and is also vulnerable to false-negatives [8-10], it has limited specificity for prostate cancer detection, and its appropriate clinical application has been assertively debated [11-13]. We sought to establish the utility of PSA as a potential biomarker for cancer grade, tumour volume and prognostic indicators in patients with needle biopsy-proven prostate adenocarcinoma.

Prostate specific antigen is a glycoprotein produced by the cells of the prostate gland and serum PSA screening for prostate cancer aims to detect prostate cancer at an early stage such that early treatment may reduce mortality [14]. However, PSA is clinically imprecise as both benign conditions including prostate hypertrophy, urinary tract infections, or instrumentation, as well as prostate cancer, can see elevations of this serum marker [8-10]. Despite its limited specificity, serum prostate specific antigen levels have proven useful in both the clinical and pathological context. Increasing prostate specific antigen values have been correlated with increasing biopsy-proven maximum cancer core lengths [15]. Prostate specific antigen density (PSA-D) has also been found to be directly associated with the new histologic prostate cancer grade groups [16]. Furthermore, patients with a prostate specific antigen doubling time of less than 12 months were shown to have

worse outcomes [17]. In the past, reduction in PSA screening has resulted in increased incidence of late-stage cancers with higher clinical stages and increased mortality [18]. In the past decade, new screening tools have been developed that make the classic PSA-only based screening an outdated strategy [18]. For example, the Stockholm3 (STHLM3) test combines five plasma protein markers (total PSA, free PSA, free hK2, prostatic secretory protein of 94 amino acids and growth/differentiation factor 15), >100 genetic markers, and clinical data (such as age, previous biopsy results and family history) to determine the risk of aggressive prostate cancer [18]. Improved use of PSA in combination with age, prostate volume and application of prostate cancer risk calculators allows a risk-adapted strategy with improved stratification of men with prostate cancer and avoidance of unnecessary diagnostic procedures. This combination used with MRI and targeted biopsy, can reduce overdiagnosis.

Figure 1: Serum Prostate-Specific Antigen (PSA) level and prostate adenocarcinoma grade, histologic prognostic indicators and tumour volume.

Figure 2: Perineural invasion (arrows), H&E stain, medium power.

Figure 3: Tumour (arrow) at level of adipose tissue (line), H&E, low power.

Conclusions

Similar to previous findings, we found that PSA is a useful biomarker and effective discriminator among cancer grades and estimates of tumour volume. We found that high PSA levels were also associated with presence of negative histologic prognostic indicators. Higher PSA levels between 16-30ng/ml prior to biopsy indicate patients at risk for high grade adenocarcinoma, higher tumour volume and presence of perineural invasion and extraprostatic extension. Based on our results, we propose that when biopsies from patients in the high PSA group (16-30 ng/ml) are positive, but without high grade tumour, high tumour volume or perineural invasion or extraprostatic extension, additional histologic levels may be useful to more definitively exclude these clinically useful prognostic parameters.

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Conflict of Interest

Authors have no financial interest or any conflict of interest to declare.

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