Chapter 4: Management of an elevated PSA and biopsy strategies in the large prostate

Joana B Neves[1], Mark Emberton[2], Veeru Kasivisvanathan[3]

Position, affiliation, email:

[1]Clinical Research Fellow in Prostate Cancer, Division of Surgery and Interventional Science, University College London
joana.b.neves@ucl.ac.uk

[2]Dean, Faculty of Medical Sciences, University College London;
Honorary Consultant Urologist, Department of Urology, University College London Hospitals
Professor of Interventional Oncology, Division of Surgery and Interventional Sciences, University College London
m.emberton@ucl.ac.uk

[3]NIHR Doctoral Fellow and SpR in Urology;
Division of Surgery and Interventional Science, University College London;
Department of Urology, University College London Hospitals
veeru.kasi@ucl.ac.uk

Abstract (250 words)

An abnormally high serum PSA is still the most frequent trigger for men to enter a suspected prostate cancer diagnostic pathway. Large prostates, especially the ones with a volume over 100cc, are usually associated with elevated PSA levels. Similarly, in men with benign prostatic hyperplasia (BPH), PSA tends to increase over time, something that also occurs in men with untreated progressive prostate cancer. These two factors lead to frequent and unnecessary referrals of men with large prostates to suspected prostate cancer pathways. Many PSA derivatives and risk stratification tools have been developed in an attempt to overcome the limitations of total serum PSA and more accurately predict which men should have prostate biopsies, but translation into clinical practice has been hindered.
Thus, many men with large prostates are referred for prostate biopsy. However, biopsy strategies may need to be adapted in the setting of a 100cc prostate. Higher sampling density schemes have been advocated for these men to ensure the diagnosis of clinically significant cancer but this can be accompanied by increased side effects. mpMRI is increasingly done prior to biopsy and can aid in the selection of men who can safely avoid biopsies. Likewise, they can help target biopsies to suspicious areas, which may represent an avenue to balance adequate sampling of large prostates and adverse events.

Keywords (up to 6)

Diagnosis, prostate, prostatic hyperplasia, prostatic neoplasms, prostate-specific antigen, biopsy

4.1 Large prostates and elevated PSA

Prostate-specific antigen (PSA) is a glycoproteic enzyme produced almost exclusively by the prostate. PSA is secreted into prostatic gland ducts and is responsible for hydrolysing the seminal clot, enabling sperm motility. In physiological conditions, only a small amount of PSA reaches intravascular circulation (1). However, serum PSA levels can increase due to a rise in PSA production, to increase in vascular permeability, and/or to disruption of tissue architecture. Thus, both benign and malignant prostatic diseases, such as benign prostatic hyperplasia (BPH), prostatitis, and prostate cancer, can be associated with increased PSA serum levels (1-3).

In a large proportion of men, aging is associated with hyperplasia of the stromal and glandular components of the transition zone leading to prostatic enlargement, also known as BPH (4-6). Men with BPH not only have a higher baseline PSA before 50 years old, but are also more likely to see their PSA increase over time (2, 7-9). Additionally, BPH and higher prostate volumes correlate with the presence of prostate inflammation (10), a factor known to also lead to increased PSA readings (3).

An abnormally high serum PSA (above 3 ng/ml) is still the most frequent trigger for men to enter a suspected prostate cancer diagnostic pathway. Thus, if BPH is associated with increased PSA levels, a significant proportion of men with large prostates will be lead to have additional tests, such as a prostate multiparametric MRI (mpMRI) and/or prostate biopsy. This represents a source of anxiety for those men as well as a burden for health care systems. However, to complicate things further, relying solely on prostate volume to deny further diagnostic testing may be unwise as BPH and prostate cancer can co-exist and large-scale epidemiologic studies have shown that men with BPH may even be more likely to have prostate cancer (11). Consequently, to achieve a balance between appropriate testing to identify clinically significant cancer and unnecessary testing which can lead directly and indirectly to harm, PSA readings need to be put into context and prostate volume is one of the factors to take into account.

Aiming to correctly distinguish between BPH and prostate cancer in men with elevated serum PSA, urologists and researchers have studied a number of PSA derivatives that incorporate prostate volume, such as PSA density or PSA transition

zone density, have analysed PSA trends over time (PSA kinetics), have looked at different PSA isoforms, such as free PSA, and have incorporated a multitude of clinical factors, including prostate volume, into risk stratification tools. A closer look at all of these variables is warranted to assess how they can benefit clinical decision making in men with large prostates.

4.1.1 PSA density and PSA transition zone density in large prostates

Early studies suggested that BPH is associated with lower levels of serum PSA per volume unit of prostate than prostate cancer (0.3 ng/mL/g versus 3.5 ng/mL/g)(12). While increased serum PSA in BPH is associated with prostatic growth and higher PSA production, in prostate cancer this is related to disruption of tissue architecture (namely the basal cell layer) rather than to changes in PSA production (1). Thus, it was hypothesised that the quotient between total serum PSA and prostate volume, known as PSA density, and the quotient between total serum PSA and prostatic transition zone volume, could be useful tools to discriminate men with high PSA readings who need further investigations for suspected prostate cancer from those who could avoid it.

In the early 90's, studies based on transrectal ultrasound (TRUS) prostate volume assessment set a threshold of PSA density above 0.15 to advise men with serum PSA between 4 and 20 ng/ml to have a prostate biopsy (13, 14). Likewise, it has been suggested that in men with raised PSA (up to 10ng/ml), even if it is above the age-adjusted cut-off levels, a PSA density below 0.15 can lead to avoidance of unnecessary prostate biopsies (15). However, the utility of PSA density has been undermined by further reports stating that this threshold is inadequate (16) or may only be valid for men with prostate volumes below 35g (17), that PSA density increases with age (2), and that in men with prostatic inflammation, a feature very commonly associated with BPH(10), PSA density may also be higher (3, 18). Similarly, while some studies have proposed that PSA transition zone density has a better predictive value than PSA density alone (19-22), others have not confirmed this (23-25).

To date, neither PSA density and PSA transition zone density alone have translated into routine clinical practice or clinical guidelines to definitively distinguish men with BPH from men with prostate cancer. However, they can be useful

information when considered alongside a full clinical picture to make management decisions.

Many studies looking at PSA density and PSA transition zone density have excluded men with PSA levels above 10ng/ml. As men with very large prostates (>100cc) are more likely to have serum PSA values well above the 3ng/ml threshold and often at or above 10ng/ml, the ability to draw conclusions on the role of these derivatives in the very large prostate is less than ideal.

Notwithstanding, with the increasing use of prostate mpMRI, the two biomarkers may see a resurgence since PSA levels interpreted adjusting for MRI volume information appear to improve the diagnosis of high grade prostate cancer (26) and PSA density seems to increase the diagnostic accuracy of MRI when images are equivocal (27). An example would be a man with a raised PSA (e.g. 4ng/ml) who has a multi-parametric MRI that reveals no suspicious areas in a 120cc prostate. In the context of the negative MRI carried out at an expert centre, knowledge that the PSA density is very low (0.03ng/ml) may influence the clinician to counsel the patient to avoid a prostate biopsy.

4.1.2 PSA kinetics in large prostates

In both BPH and prostate cancer, serial measurement of PSA can show increased readings over time, a phenomenon known as increased PSA velocity (28). While PSA velocity tends to be higher in men with prostate cancer (28, 29), a trend towards a similar pattern may also be seen in men with benign prostates over 60cc in volume (30). Additionally, inflammation can lead to both dramatic PSA rises, and thus to very high PSA velocities (31), and to PSA fluctuation, whereby consecutive PSA readings oscillate between a range of values over time (for example, between 3 and 5). PSA fluctuation, possibly due to the connection between BPH and subclinical inflammation, is a feature frequently seen in men with BPH (28) and prostate volumes over 100cc (32). Therefore, PSA velocity may be a misleading marker in BPH, particularly in the very large prostate over 100cc, and longitudinal assessment of PSA readings is essential to distinguish between increased PSA velocity and PSA fluctuation.

Many different formulas have been used to calculate PSA velocity (33, 34)

and attempts have been made to simplify the concept by using alternative definitions, such as PSA doubling time (i.e. the time interval it takes for PSA to reach double its initial value) (28). PSA sampling frequency and overall time period of observation have an effect on PSA velocity assessment (35), and a definitive cut off is yet to be defined. Similarly, controversy regarding the clinical value of using PSA kinetics has built up. While a systematic review concluded that PSA velocity is outperformed by elevated PSA as a trigger to decide whether a men should enter a prostate cancer diagnostic pathway (33), a more recent screening series with over 18,000 patients indicated that men have an increased risk of harbouring prostate cancer if they have two consecutive PSA velocity calculations above 0.4 ng/mL/year (29). Despite the difference in opinions, experts seem to agree that longitudinal monitoring of PSA can aid clinical decision making and that, while PSA velocity should not be considered as a standalone marker, it can be a useful tool to tailor PSA surveillance in men without prostate cancer (i.e. men with higher PSA velocities should have a closer PSA follow up) (29, 34).

4.1.3 Free PSA in large prostates

PSA is produced by as a proenzyme. Thus, the molecule needs to be cleaved to become active. As PSA enters blood vessels, proteins bind to it in an effort to reduce its proteolytic activity (complexed PSA). ProPSA and inactive forms of PSA can circulate unbound (free PSA)(36). Both complexed and free PSA can be accounted for when measuring total serum PSA but free PSA can also be read on its own. A low ratio between free and total PSA (free/total PSA) has been associated with prostate cancer due to mechanisms still to be thoroughly explained. A cut-off of 0.12 was initially defined (37, 38) but subsequent studies have proposed cut-offs around 0.25 (39-41). At present, free/total PSA should only be used as a complement to total PSA (42), as different cut offs for the first may be needed in view of the magnitude of the second (43). Similarly, free PSA fluctuates over time (42), so repeat readings may be necessary for accurate assessment of the ratio. Finally, free PSA may be increased in the presence of prostatic inflammation (3) (a phenomenon not uncommonly associated with BPH) and, in men with prostates over 40cc in volume, free/total PSA may not help differentiate between BPH alone and prostate cancer (38), limiting the utility of this tool in men with large prostates and elevated

PSA.

4.1.4 Prostate cancer screening risk stratification tools that incorporate prostate volume

A multitude of risk stratification tools have been developed with the aim of improving prostate cancer screening. A recent meta-analysis reviewed the six more studied and validated models (44). Age, PSA and digital rectal examination (DRE) findings were factored into almost all tools and prostate volume (assessed using TRUS) was also taken into consideration in three of them: ProstataClass, the Finne model, and the European Randomized Study of Screening for Prostate Cancer (ERSPC) risk calculator (RC) 3 (44). In ProstataClass (45), the Finne model (46), and the ERSPC RC 3(47, 48), a higher prostate volume contributes to a lower likelihood of having prostate cancer. Conducting prostate volume assessments with TRUS may be burdensome, especially in primary care, but an additional analysis on the ERSPC model showed that estimating volume using DRE still increased predictive accuracy when compared to using only a combination of the other variables (48).

These three models were among the four that showed improved accuracy compared to either PSA, DRE, or prostate volume assessment alone, and ProstataClass and ERSPC RC 3 were the best performing models (44). Despite this fact, screening risk stratification tools are still not systematically used in clinical practice and elevated serum PSA remains the main indication for prostate biopsy (49). Given that these risk stratification tools were developed using cohorts with a median prostate volume between 30 and 50cc(45, 46, 48), further analysis is needed to assess if there is overwhelming benefit of using a risk stratification tool that incorporates prostate volume in special populations, such as men with large prostates (over 100cc in volume) and elevated serum PSA.

4.1.5 Summary

Evidence is either insufficient or contradictory regarding the benefit of using PSA density, PSA transition zone density, PSA kinetics, free PSA, and risk stratification tools to help differentiate between BPH and cancer-bearing prostates in men with

elevated serum PSA. To complicate things further, very limited data is available specifically for men with large prostates (over 100cc). Today, clinical decision cannot be based solely on these factors, but in men with large prostates and elevated PSA levels the following seem to point to a lower likelihood of harbouring prostate cancer: presence of acute or chronic inflammation in previous biopsy (10, 50), low PSA density, low PSA transition zone density, null or low PSA velocity, long PSA doubling time, and high free/total PSA. Future studies combining one or several of these variables with prostate mpMRI may lead to improved discrimination regarding which men are more likely to have prostate cancer and should proceed to prostate biopsy.

4.2 Biopsy strategies in men with large prostates

Men with large prostates are more likely to have increased PSA and thus, according to current guidelines, more prone to be offered a prostate biopsy to exclude prostate cancer (51). This is particularly the case with prostate over the 100cc volume threshold. Likewise, men with large prostates are more likely to have repeat prostate biopsies after a first negative result (52).

Traditionally, prostate biopsies involved sextant transrectal prostate sampling under TRUS guidance. Since 1995, multiple publications reported that this biopsy scheme lead to prostate undersampling and consequently underdiagnosis of prostate cancer in large prostates (from 40 to over 80cc in volume) (53-56). Despite some authors advocating that sampling density had no effect on diagnosis (51), in 2006 it was established that 10 to 12 core TRUS guided biopsies should be advised for all men due to higher malignancy detection rates than sextant biopsies (49, 57). In large prostates, the matter of sampling density is even more controversial. Some studies imply that 10 to 12 transrectal biopsy cores may not be enough for large prostates (58) and that more intensive biopsy protocols should be used as first or second-line prostate biopsy options – either using saturation techniques (59) or biopsy schemes adjusted to prostate volume (60, 61). Nevertheless, opposing evidence supports the concept that increasing the number of biopsy cores in large prostates may only contribute to higher diagnosis of clinically insignificant low volume Gleason 6 (52, 62) while carrying a higher adverse event rate (63). Biopsy of large volume prostates is associated with more frequent haematuria, haematospermia, urinary retention, and pain (63), and these risks could potentially increase with more sampling intensive procedures.

An alternative way of increasing sampling density of larger prostates is to carry out transperineal template prostate biopsies (TTPB) using a brachytherapy grid (64). This approach allows for a more systematic sampling of the prostate, with improved access to anterior and midline areas. Notwithstanding, it is resource intensive, requiring general or spinal anaesthetic (64), and, due to the increasing sampling, it is more prone to causing unwanted side effects (63). Additionally, this strategy does not negate the problem of overdiagnosing insignificant cancer, but may maximise the identification of clinically significant cancer(65), which can be of value when clinical doubt exists.

Using the transrectal approach, due to limitations in needle length, it is often difficult to sample the anterior zone of large prostates. While the transperineal route can aid in sampling this area, sometimes the prostate extends so much anteriorly that the biopsy needle hits the pubis as it is advanced through the perineum. Using this route, as opposed to the transrectal, allows the surgeon to perform certain manouvers that can help overcome this difficulty, such as flexing the hips by pushing the stirrups cranially, which helps raise the pubis. In addition, the biopsy needle can be inserted freehand at an angle into the perineum by removing the brachytherapy grid, facilitating access to the anterior prostate.

Another way of balancing out adequate diagnosis and adverse events in larger prostates would be to use mpMRI-targeted biopsies. In these biopsies, the information obtained using mpMRI is used to influence conduct and placement of the needles. Recent evidence supports the use of mpMRI prior to biopsy (66) and this is becoming increasingly common practice as a means to identify suspicious areas to that can then be biopsied. While evidence to prove that the diagnostic accuracy of mpMRI is independent of prostate volume is still lacking, in the very large prostate a strategy of sampling only suspicious areas could be particularly advantageous. For example, in average size prostates, pre-biopsy knowledge of the existence of a possible anterior tumour aids in the sampling of the anterior prostate, even using the transrectal route (67).

Overall, mpMRI-targeted biopsies appear to have better detection rates of clinically significant cancer than 12 core TRUS biopsy, with reduced diagnosis of clinically insignificant cancer (68). Similarly, a prospective study in men who had targeted biopsy cores in addition to 12 core TRUS biopsies indicated that prostate cancer may be more likely to be diagnosed using targeted cores than systematic 12 core sampling in prostates with a volume from 40 up to 160cc (69). Compared to TTPB, mpMRI-targeted biopsies may have similar clinically significant cancer detection rates and lower clinically insignificant cancer detection rates (64). They are also associated with fewer side effects (63).

Whilst early results would support the added value of mpMRI-targeted biopsies over systematic biopsies in large prostates, further research is needed to validate these findings. For example, a clear difference in detection rates between cognitive and software fusion targeted biopsies hasn’t been found (70). Targeting in

big prostates may be more difficult and software fusion may be advantageous in this setting so the comparison between the two methods also warrants more exploration.

4.3 Conclusions

Currently, the prostate cancer diagnostic pathway still puts more value on total PSA than on multifactorial individual risk stratification. Research on PSA derived markers and risk stratification tools has failed to translate into clinical practice. As a result, many men with large prostates and elevated serum PSA but without prostate cancer are still being offered first and repeat prostate biopsies. This is a particular problem in men with very large prostates (greater than 100cc), who are likely to have higher PSA levels independent of whether or not they harbour prostate cancer.

A more conservative approach that is sensitive enough not to miss clinically significant cancer is needed. The use of mpMRI alone or in combination with previously studied markers may impart that change and serve as a useful tool in the assessment of the very large prostate. mpMRI has the potential to screen out men, leading to fewer prostate biopsies, and to guide a more accurate and less intense sampling by means of targeted biopsies. This may decrease the healthcare burden of suspected prostate cancer diagnostic pathways not only in terms of direct biopsy costs but also in terms of indirect costs that result from reducing both biopsy complications and intensive surveillance regimes due to fear of misdiagnosis.

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