

QUANTIFYING THE IMPACT OF PROSTATE VOLUMES, NUMBERS OF BIOPSY CORES, AND 5 α -REDUCTASE INHIBITOR THERAPY ON THE PROBABILITY OF PROSTATE CANCER DETECTION USING MATHEMATICAL MODELING

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Running head: Modeling prostate cancer detection probability by varying gland and tumor volume

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Abstract

Purpose: Previous studies have demonstrated a negative correlation between prostate volume and biopsy yield. By decreasing prostate volume, 5 α -reductase inhibitors may enhance cancer detection, which may explain the greater detection of high-grade tumors in the finasteride arm of the Prostate Cancer Prevention Trial (PCPT). **Materials and Methods:** A mathematical model was constructed analyzing the effects of prostate and tumor volumes, and biopsy core numbers, on cancer detection. The effects of volume reduction observed with finasteride in the PCPT were also modeled, as was the potential reduction in tumor volume needed to explain the observed difference in prostate cancer detection. The model was also applied to the REduction by DUtasteride of prostate Cancer Events (REDUCE) study. **Results:** A higher number of biopsies are required to ensure a ≥ 0.90 detection probability in larger glands or with smaller tumors. In the PCPT, for a tumor volume of 1 cc, an increase in detection rate of 17% in the finasteride arm would be predicted, if there was no change in tumor volume; likewise 11–17% for the dutasteride arm of the REDUCE study. The calculated reduction in tumor volume needed to explain the difference in cancer detection between the finasteride and placebo arms of the PCPT is 51–66%. **Conclusions:** This model provides guidance on the optimal number of biopsy cores that accords with an earlier model. These findings also suggest that if there were no reduction in tumor volume, 5 α -reductase inhibitor therapy could lead to excess detection of cancer including high-grade tumors.

Introduction

It would seem intuitive that total prostate volume influences the probability of successfully biopsying a prostate tumor contained within the gland. This hypothesis is supported by studies demonstrating a negative correlation between total prostate volume and biopsy yield,^{1, 2} and those where larger prostate volume was a predictor of positivity of a repeat biopsy as well as negativity of the initial biopsy.^{3, 4} These findings have led to the suggestion that biopsy core number should be adjusted according to patient age and prostate volume to optimize sampling.⁵ Mathematical models have also been constructed to advise on biopsy strategies for men with different ages and prostate volumes.⁶⁻⁸ Such models are of use because a cumbersome study would be needed to assess the many different potential core numbers and location combinations with different prostate volumes.

5 α -Reductase inhibitor treatment results in reductions in total prostate volume, which could in theory enhance prostate cancer detection by reducing the benign component of the gland, thus increasing the likelihood of a biopsy core sampling tumor. This hypothesis was cast into sharp relief with the findings of the Prostate Cancer Prevention Trial (PCPT).⁹ Over the course of the trial, prostate cancer prevalence was 24.8% lower in the finasteride *versus* the placebo arm, as detected in for-cause biopsies triggered by an abnormal PSA and/or digital rectal examination, or on a mandatory end-of-study biopsy. However, tumors of Gleason grade 7–10 were significantly more common in the finasteride group than in the placebo group over the study duration, raising the concern that finasteride might promote the growth of more

aggressive tumors. However, an over-detection bias due to reductions in benign prostate volume has been hypothesized to account for the proportions of high-grade tumors.¹⁰

The aim of the current study was to construct a mathematical model to predict the likelihood of a positive biopsy based on input variables of tumor volume, peripheral and transition zone volumes, and number of biopsy cores, to better inform the optimal biopsy protocol for a given subject. A secondary aim was to examine how the reduction in prostate volume observed with finasteride in the PCPT could alter detection of tumors, including those of high-Gleason grade. Finally, the potential impact of this model on prostate cancer detection in the ongoing REduction by DUtasteride of prostate Cancer Events (REDUCE) trial, a chemoprevention study designed to determine if dutasteride 0.5 mg daily over 4 years reduces the risk of biopsy-detectable prostate cancer,¹¹ was examined, to understand how observations made from the PCPT may apply to the REDUCE study.

Materials and methods

Model construction

A mathematical model was constructed to analyze the effects of tumor size, peripheral zone (PZ) and transition zone (TZ) gland volumes, and the numbers of biopsy cores taken in the PZ and TZ, on prostate cancer detection. A key output of the model was the number of PZ and TZ cores needed to detect with probability ≥ 0.90 a specified tumor configuration of 4 nodules, the median number of tumor foci from previous data.¹² The total

tumor volume represents the combined volume of all four nodules, with the second nodule half the size of the first, the third half the size of the second, and the fourth half the size of the third. For example, for a tumor volume of 3.00 cc, the nodules are of volume 1.59, 0.81, 0.39 and 0.21 cc respectively. In common with other mathematical models for prostate cancer detection probability, a number of assumptions were used in the construction of the current model (Table 1). Details of the construction of the model are provided in the Appendix.

Modeling of the influence of prostate volume and tumor size reduction on prostate cancer detection

In order to study the effects of the prostate volume reduction observed with finasteride in the PCPT (24.1% *versus* placebo), and the effect this may have on the findings of the REDUCE study, prostate volumes of 20–80 cc in 10 cc increments were entered into the model along with a prostate volume reduction of 25%. A range of tumor volumes of 0.5 cc, 0.75 cc, 1.0 cc, 1.5 cc, 2.0 cc, and 3.0 cc was also utilized. Four biopsy patterns were examined: a standard sextant (6 cores: in excess of 80% of men in the PCPT had a 6-core biopsy); 10 cores with 6 in the PZ and 4 in the TZ; 10 cores with 8 in the PZ and 2 in the TZ; and 10 cores all in the PZ (10-core biopsies are a protocol requirement for the REDUCE study). For the majority of calculations an assumption was made that the use of a 5 α -reductase inhibitor did not result in a decrease in tumor size. Although the effects of 5 α -reductase inhibitors on known tumors, as opposed to prevention of new tumors, are unclear, there are some data to suggest that treatment can result in reductions in tumor

volume.¹³ The scenario where an equal reduction in tumor and prostate volume size occurred was therefore also modeled.

A further scenario explored the potential reduction in tumor volume needed to explain the observed difference in prostate cancer detection of 25% between the finasteride and placebo arms of the PCPT. In order to examine this scenario, two different methods were employed. Firstly, the probability of detecting a tumor of volume 1.5 cc in a prostate volume of 30 cc was derived for a sextant biopsy. This probability was then multiplied by 0.75 (representing a 25% reduction in detection probability) and the resulting probability used to determine the corresponding tumor volume. Secondly, the 'true' detection rate from the PCPT was calculated for the finasteride and placebo groups, assuming that the false negative rate was 18% for both treatment arms (an average figure based on the literature).^{14, 15} Division of the detection rates from the PCPT by these calculated 'true' detection rates provided a detection probability, which was then applied to the model using average prostate volumes of 34 cc (placebo group) and 26 cc (finasteride group), the median prostate volumes at the end-of-study biopsy.⁹

Results

Minimum biopsy core number for cancer detection

The minimum number of PZ and TZ biopsy cores needed for ≥ 0.90 probability of cancer detection for a total tumor volume of 1.0 cc and 3.0 cc, by prostate volume, are shown in Table 2. As would be expected, an increasing number of biopsies are required to ensure a probability of ≥ 0.90 as prostate volume

rises and as tumor volume falls. A comparison of the findings of this study and those of the model of Vashi *et al*⁸ are also presented in Table 2.

Modeling of the influence of prostate volume and tumor size reduction on prostate cancer detection

Table 3 outlines the increases in prostate cancer detection as a result of a 25% difference in prostate volume by baseline prostate volume prior to treatment. For a typical tumor volume of 1.0 cc, an increase in the detection rate of approximately 17% would be predicted for the PCPT.

If the assumption is adopted that tumor volume is reduced along with the gland volume by 25%, the increase in detection probability is less than if tumor volume is unchanged. For a 1.0 cc tumor and an initial prostate volume of 30 cc, the detection probability increases by 6% if tumor volume is also reduced by 25%, compared with a 17% increase if there is no change in tumor volume.

The potential reduction in combined low- and high-grade tumor volume needed to explain the observed difference in prostate cancer detection of 25% between the finasteride and placebo arms of the PCPT for prostate volume of 30 cc and tumor volume of 1.5 cc was also modeled. From the model, the corresponding detection probability is 0.90 for men treated with placebo. In the finasteride arm, overall cancer detection was reduced by 25%, resulting in a probability of $0.75 \times 0.90 = 0.68$. When the volume reduction of 25% is factored in, a reduction in tumor volume from

1.5 cc to 0.5 cc is required to reach this detection rate, suggesting that a two-thirds reduction in tumor volume is required to produce a 25% reduction in detection rate. Using the second approach, and assuming an 18% false negative rate, the model estimated 'true' prostate cancer detection probabilities of 0.642 (placebo) and 0.557 (finasteride), corresponding to tumor sizes of 0.80 cc and 0.39 cc respectively, representing a 51% decrease in tumor volume.

Table 4 outlines the increases in prostate cancer detection in the REDUCE study as a result of a putative 25% difference in prostate volume between dutasteride- and placebo-treated men, by baseline prostate volume prior to treatment. The data presented are for 10 cores all in the PZ, as the data for other variants of a 10-core biopsy were similar. For a typical tumor volume of 1.0 cc, an increase in detection rate between 11% and 17% for 10 cores would be predicted for the REDUCE study based on a mean prostate volume of 46 cc.

Discussion

In seeking to detect prostate cancer using transrectal ultrasound-guided prostate biopsy, a significant issue is the optimal choice of the number of cores to take in a biopsy session. Undersampling may result in clinically significant tumors being missed, while it has been argued that oversampling increases detection of clinically "insignificant" tumors, especially those associated with low PSA, thereby unnecessarily burdening the patient.

To address the issue of the appropriate number of cores, Vashi *et al.*⁸ have developed a mathematical probability model. They incorporated knowledge of tumor volumes considered “life-threatening”, coupled with an estimation of doubling time, to recommend numbers of cores based on patient age and patient prostate volume. As would be expected, the recommended number of cores increases with prostate gland size, consistent with clinical study data.^{1,}

3, 4

The modeling approaches in this paper are similar to those of Vashi *et al.*, but differ in specifics. Each entails a multifocality model and each includes the total prostate volume and the number of biopsy cores as input variables. In the current model however, specific assumptions on the PZ and TZ volumes and the PZ and TZ numbers of biopsy cores are utilized, and the randomization in the model is designed to adhere to certain literature-based assumptions about the distribution of cancer in the PZ and TZ. One of these assumptions is that isolated or multiple tumor nodules confined to the TZ are rare: the current model did not therefore include this possibility. Thus the model predicts that, if the total number of cores remains the same, moving cores from the peripheral to the transition zone has a lower cancer detection probability than maintaining all cores in the PZ. The addition of TZ cores increases the detection probability, but to a lesser extent than adding PZ cores. Another point of difference from the model of Vashi *et al.* is that the authors classified life-threatening tumor volume by age (larger in older men). In the current model, this adjustment was not made directly; rather the user can examine probabilities by different tumor volumes, which can be adjusted

to account for age. Despite these differences in modeling approach there is strong consistency between the results.

Comparisons with data from clinical practice studies are problematic, as to our knowledge, no study has systematically compared different numbers of biopsy cores against saturation biopsy techniques, or indeed biopsies from radical prostatectomy specimens. Therefore, while almost all studies have demonstrated that more cores tend to result in higher detection rates, such studies are not able to determine the optimal approach, as tumor prevalences, rather than detection rates, remain unknown. The “Vienna nomogram” was also constructed to provide guidance on biopsy core number, but based on clinical rather than modeled data.⁵ Although the use of the nomogram resulted in a 66.4% higher prostate cancer diagnosis rate compared with a control arm using octant biopsy, it has not been determined whether the nomogram was optimal *per se*. The nomogram tends to recommend fewer cores than the age/volume-based model of Vashi *et al* and the current model.

The observation in the PCPT that men treated with finasteride were more likely than those receiving placebo to be diagnosed with a prostate tumor of Gleason score 7–10⁹ has raised significant controversy and debate. The knowledge that finasteride reduces benign prostate gland volume led to the hypothesis that the increase in high-grade tumors in the finasteride arm was due to an ascertainment bias created by prostate volume reduction rather than by a true induction of more aggressive tumors. Data from the current model suggest that a prostate volume reduction of 25% could significantly

impact tumor detection using the sextant technique, the predominant number of cores used in the PCPT.

The impact that treatment with 5 α -reductase inhibitors has on the detection of high-grade tumors is potentially more complex. High-Gleason grade tumors are typically of greater volume than low-grade tumors, which suggests that any detection bias would be diminished in high- *versus* low-grade tumors. Furthermore, if 5 α -reductase inhibitors reduce tumor volume, as well as benign epithelial volume, the detection bias could also be further reduced. One inevitable conclusion from the PCPT is that finasteride had a greater effect on low- *versus* high-grade tumors. Therefore, it can be hypothesized that finasteride decreased serum PSA less in high-grade tumors compared with low-grade tumors. Because PSA was doubled in the finasteride group, and a PSA >4 ng/mL was used to trigger for-cause biopsies, a lesser effect of finasteride on high-grade tumors would lead to a greater likelihood of biopsy. Therefore it is likely that the increased detection of high-grade tumors in the finasteride arm of the PCPT was due in part to the effect of volume reductions on tumor detection, and also to the utility of PSA as an indicator of high-grade cancer.

Another important observation from the PCPT data using this model is the potential reduction in mean tumor volume (51–66%) required to account for the 25% difference in overall prostate cancer detection rate between the finasteride and placebo arms. This difference could occur if finasteride either prevented new tumors from developing or decreased the volume of existing

tumors. Although the PCPT was designed to examine the effect of finasteride on the development of new tumors, a proportion of men entering the study were likely to have a latent tumor undetected, because of the lack of prostate biopsy at baseline. The hypothesis that finasteride shrinks existing tumors is supported by the observation that the rates of prostate cancer in men treated with finasteride and placebo diverged early in the PCPT.⁹ Although the model is unable to shed further light on this topic, it appears possible that the use of finasteride resulted in a mixture of primary prevention and prevention of tumor progression in the PCPT.

Conclusions

A model has been constructed that provides guidance on the optimal number of biopsy cores for men with different prostate volumes. This model accords with an earlier model that used a different set of assumptions regarding tumor volume and prostate volume. The model also predicts that a 25% reduction in prostate volume as a result of 5 α -reductase inhibitor therapy would result in an approximate 17% increase in tumor detection if tumor volume was unaltered by treatment. This detection bias should be considered when evaluating the results of the PCPT and the REDUCE study.

References

1. Ficarra, V., Novella, G., Novara, G., Galfano, A., Pea, M., Martignoni, G. et al.: The potential impact of prostate volume in the planning of optimal number of cores in the systematic transperineal prostate biopsy. *Eur Urol*, **48**: 932, 2005
2. Eskicorapci, S. Y., Guliyev, F., Akdogan, B., Dogan, H. S., Ergen, A., Ozen, H.: Individualization of the biopsy protocol according to the prostate gland volume for prostate cancer detection. *J Urol*, **173**: 1536, 2005
3. Remzi, M., Djavan, B., Wammack, R., Momeni, M., Seitz, C., Erne, B. et al.: Can total and transition zone volume of the prostate determine whether to perform a repeat biopsy? *Urology*, **61**: 161, 2003
4. Basillote, J. B., Armenakas, N. A., Hochberg, D. A., Fracchia, J. A.: Influence of prostate volume in the detection of prostate cancer. *Urology*, **61**: 167, 2003
5. Remzi, M., Fong, Y. K., Dobrovits, M., Anagnostou, T., Seitz, C., Waldert, M. et al.: The Vienna nomogram: validation of a novel biopsy strategy defining the optimal number of cores based on patient age and total prostate volume. *J Urol*, **174**: 1256, 2005
6. Daneshgari, F., Taylor, G. D., Miller, G. J., Crawford, E. D.: Computer simulation of the probability of detecting low volume carcinoma of the prostate with six random systematic core biopsies. *Urology*, **45**: 604, 1995
7. Chen, M. E., Troncoso, P., Johnston, D. A., Tang, K., Babaian, R. J.: Optimization of prostate biopsy strategy using computer based analysis. *J Urol*, **158**: 2168, 1997
8. Vashi, A. R., Wojno, K. J., Gillespie, B., Oesterling, J. E.: A model for the

- number of cores per prostate biopsy based on patient age and prostate gland volume. *J Urol*, **159**: 920, 1998
9. Thompson, I. M., Goodman, P. J., Tangen, C. M., Lucia, M. S., Miller, G. J., Ford, L. G. et al.: The influence of finasteride on the development of prostate cancer. *N Engl J Med*, **349**: 215, 2003
 10. Lotan, Y., Cadeddu, J. A., Lee, J. J., Roehrborn, C. G., Lippman, S. M.: Implications of the prostate cancer prevention trial: a decision analysis model of survival outcomes. *J Clin Oncol*, **23**: 1911, 2005
 11. Andriole, G., Bostwick, D., Brawley, O., Gomella, L., Marberger, M., Tindall, D. et al.: Chemoprevention of prostate cancer in men at high risk: rationale and design of the reduction by dutasteride of prostate cancer events (REDUCE) trial. *J Urol*, **172**: 1314, 2004
 12. Bastacky, S. I., Wojno, K. J., Walsh, P. C., Carmichael, M. J., Epstein, J. I.: Pathological features of hereditary prostate cancer. *J Urol*, **153**: 987, 1995
 13. Andriole, G. L., Humphrey, P., Ray, P., Gleave, M. E., Trachtenberg, J., Thomas, L. N. et al.: Effect of the dual 5alpha-reductase inhibitor dutasteride on markers of tumor regression in prostate cancer. *J Urol*, **172**: 915, 2004
 14. Djavan, B., Milani, S., Remzi, M.: Prostate biopsy: who, how and when. An update. *Can J Urol*, **12 Suppl 1**: 44, 2005
 15. Nam, R. K., Toi, A., Trachtenberg, J., Jewett, M. A., Klotz, L., Fleshner, N. et al.: Variation in patterns of practice in diagnosing screen-detected prostate cancer. *BJU Int*, **94**: 1239, 2004
 16. Uzzo, R. G., Wei, J. T., Waldbaum, R. S., Perlmutter, A. P., Byrne, J. C.,

- Vaughan, E. D., Jr.: The influence of prostate size on cancer detection.
Urology, **46**: 831, 1995
17. McNeal, J. E., Redwine, E. A., Freiha, F. S., Stamey, T. A.: Zonal distribution of prostatic adenocarcinoma. Correlation with histologic pattern and direction of spread. Am J Surg Pathol, **12**: 897, 1988
18. Chen, M. E., Johnston, D. A., Tang, K., Babaian, R. J., Troncoso, P.: Detailed mapping of prostate carcinoma foci: biopsy strategy implications. Cancer, **89**: 1800, 2000
19. Babaian, R. J.: Extended field prostate biopsy enhances cancer detection. Urology, **55**: 453, 2000
20. Esmat, A. Y., Refaie, F. M., Shaheen, M. H., Said, M. M.: Chemoprevention of prostate carcinogenesis by DFMO and/or finasteride treatment in male Wistar rats. Tumori, **88**: 513, 2002

Table 1.

- The ratio of peripheral zone (PZ) to transitional zone (TZ) volume is 3:1
- The number of tumor nodules is specified as 4: the median number of tumor foci from previous data¹²
- The sum of tumor nodules represents the overall tumor volume
- The volumes of the nodules within a tumor conform to the assumption that additional tumor nodules beyond the dominant tumor are approximately half the volume of the next higher tumor⁸
- The tumor nodules are spherical
- Each biopsy core is taken with a standard 18 gauge biopsy needle, with radius 0.06 cm and sample length 1.7 cm, for a total sample volume of 0.019 cc per core¹⁶
- The biopsy core regions for each nodule do not overlap, unless their total volume necessitates overlap
- The nodules are distributed in the PZ or TZ of the prostate as follows:
 - PZ : TZ ratio of 3:1^{17, 18}
 - The dominant nodule is in the PZ with probability 0.80^{18, 19}
 - The second dominant nodule is in the TZ with probability 0.20²⁰
 - The probability of no tumor nodules in the TZ is 0.40¹⁸
- The probability of the 4 tumor nodules being distributed in the PZ and TZ was chosen as follows:
 - Nodules 1–4 in the PZ: probability 0.40
 - Nodules 1 and 2 in the PZ; 3 and 4 in the TZ: probability 0.20
 - Nodules 1 and 3 in the PZ; 2 and 4 in the TZ: probability 0.20
 - Nodules 2, 3 and 4 in the PZ; 1 in the TZ: probability 0.20

Table 2.

Prostate volume	Tumor volume 1.0 cc				Tumor volume 3.0 cc			
	PZ cores	TZ cores	Total	Vashi <i>et al</i>	PZ cores	TZ cores	Total	Vashi <i>et al</i>
20 cc	6 4	0 2	6	6	4	0	4	3
30 cc	8	0	8	9	4	0	4	5
40 cc	12 10 8	0 2 4	12	12	6 4	0 2	6	6
50 cc	14	0	14	15	8 6 4	0 2 4	8	7
60 cc	16	0	16	17	8	0	8	9
70 cc	20 18	0 2	20	—	10 8	0 2	10	—
80 cc	22	0	22	—	10	0	10	11

Table 3.

Prostate volume	Tumor volume					
	0.50 cc	0.75 cc	1.00 cc	1.50 cc	2.00 cc	3.00 cc
20 cc	17%	12%	4%	1%	0%	0%
30 cc	23%	19%	17%	9%	2%	1%
40 cc	25%	23%	21%	17%	13%	3%
50 cc	27%	25%	23%	20%	18%	9%
60 cc	28%	26%	25%	23%	20%	16%
70 cc	29%	28%	26%	24%	22%	18%
80 cc	29%	28%	27%	25%	23%	20%

Table 4.

Prostate volume	Tumor volume					
	0.50 cc	0.75 cc	1.00 cc	1.50 cc	2.00 cc	3.00 cc
20 cc	2%	1%	0%	0%	0%	0%
30 cc	16%	7%	2%	1%	0%	0%
40 cc	20%	16%	11%	2%	1%	0%
50 cc	23%	19%	17%	9%	2%	1%
60 cc	25%	22%	20%	15%	8%	2%
70 cc	26%	24%	21%	18%	15%	3%
80 cc	26%	25%	23%	20%	17%	8%

Legends

Table 1. Assumptions used in the model construction

Table 2. Minimum number of PZ and TZ biopsy cores needed for ≥ 0.90 probability of cancer detection under randomization for a total tumor volume of 1.0 cc and 3.0 cc, by prostate volume. For each combination of prostate and tumor volume, the biopsy schedule with the highest probability of cancer detection is listed first. Where only one is listed, only this schedule is associated with a ≥ 0.90 probability of detection. A comparison with the data from the model of Vashi *et al* is also given⁸

Table 3. Percent increase in cancer detection probabilities under randomization with a 25% decrease in prostate volume in men undergoing sextant biopsy, by baseline prostate volume and tumor volume

Table 4. Percent increase in cancer detection probabilities with a 25% decrease in prostate volume, by baseline prostate volume and tumor volume, in men undergoing 10-core biopsy with all biopsies in the PZ. The mean baseline prostate volume in the REDUCE study is 46 cc, corresponding to a modeled increase in detection of 11–17%

Appendix

As with previous models,⁸ detection of a single spherical tumor nodule by a cylindrical biopsy core could occur if the center of the tumor nodule fell within an effective biopsy core region defined by extending the core cylinder in all directions by a distance equal to the radius of the tumor. If the tumor has volume v (cc), its radius is then $r = (3v/4\pi)^{1/3}$ (cm). Consequently, if the biopsy needle has length L and radius s , the effective core volume is given by $V_c(r) = V_1(r) + 2V_2(r)$, with $V_1(r) = L\pi(r + s)^2$, the volume of a cylinder of length L and radius $r + s$, and $V_2(r) = (2/3)\pi r^3 + (1/2)\pi^2 r^2 s + \pi r s^2$, the volume of the rounded cap extending the end of such a cylinder.

A range of tumor nodule volumes of approximately 0.03 cc to 1.5 cc was considered, corresponding to radii of approximately 0.2 cm to 0.7 cm and volumes of approximately 0.4 cc to 5.0 cc. If there are K biopsy cores each with effective core volume $V_c(r)$, we suppose that their effective core regions do not overlap unless their total volume exceeds that of the prostate. In this case, denoting the prostate gland volume by V_G , the probability that the tumor is not detected is $(1 - KV_c(r)/V_G)^+$, where x^+ denotes $\max(x, 0)$. If n tumor nodules with radii r_1, \dots, r_n are distributed independently and at random throughout the prostate, then the corresponding cancer detection probability is:

$$1 - (1 - KV_c(r_1)/V_G)^+ \times \dots \times (1 - KV_c(r_n)/V_G)^+$$

In order for the probability of different nodule distribution in the TZ and PZ to be accounted for, let $V_c(r_1)$, $V_c(r_2)$, $V_c(r_3)$, and $V_c(r_4)$ be the effective core

volumes of the 4 nodules (based on the nodule volumes outlined in Table 1), and put K_P for the number of cores in the PZ, K_T for the number of cores in the TZ, V_P for the volume of the PZ, and V_T for the volume of the TZ. The detection probabilities (P_1, P_2, P_3, P_4) are then:

$$P_1 = 1 - (1 - K_P V_c(r_1)/V_P)^+ \times (1 - K_P V_c(r_2)/V_P)^+ \times (1 - K_P V_c(r_3)/V_P)^+ \times (1 - K_P V_c(r_4)/V_P)^+,$$

$$P_2 = 1 - (1 - K_P V_c(r_1)/V_P)^+ \times (1 - K_P V_c(r_2)/V_P)^+ \times (1 - K_P V_c(r_3)/V_P)^+ \times (1 - K_P V_c(r_4)/V_P)^+,$$

$$P_3 = 1 - (1 - K_P V_c(r_1)/V_P)^+ \times (1 - K_P V_c(r_2)/V_P)^+ \times (1 - K_P V_c(r_3)/V_P)^+ \times (1 - K_P V_c(r_4)/V_P)^+,$$

$$P_4 = 1 - (1 - K_P V_c(r_1)/V_P)^+ \times (1 - K_P V_c(r_2)/V_P)^+ \times (1 - K_P V_c(r_3)/V_P)^+ \times (1 - K_P V_c(r_4)/V_P)^+,$$

The overall cancer detection probability is then given by:

$$P = 0.4P_1 + 0.2P_2 + 0.2P_3 + 0.2P_4$$

where the probability of detection of each of the 4 nodules is multiplied by the probability of each nodule being distributed in the PZ and TZ as outlined in Table 2.