
Quantifying the Impact of Prostate Volumes, Number of Biopsy Cores and 5 α -Reductase Inhibitor Therapy on the Probability of Prostate Cancer Detection Using Mathematical Modeling

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Purpose: Previous studies 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.

Materials and Methods: A mathematical model was constructed to analyze the effects of prostate and tumor volumes, and biopsy core number on cancer detection. The effects of the volume reduction observed with finasteride in the Prostate Cancer Prevention Trial 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 study.

Results: A higher number of biopsies are required to ensure a detection probability of 0.90 or greater in larger glands or with smaller tumors. In the Prostate Cancer Prevention Trial for a tumor volume of 1 cc a 17% increase in the detection rate in the finasteride arm would be predicted if there was no change in tumor volume, likewise the rate would be 11% to 17% for the dutasteride arm of the Reduction by Dutasteride of Prostate Cancer Events study. The calculated reduction in tumor volume needed to explain the difference in cancer detection between the finasteride and placebo arms of the Prostate Cancer Prevention Trial would be 51% to 66%.

Conclusions: This model provides guidance on the optimal number of biopsy cores that accord 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 cancer detection, including high grade tumors.

Key Words: prostate, prostatic neoplasms, biopsy, decision support techniques, androgens

It would seem intuitive that total prostate volume influences the probability of successfully biopsying a prostate tumor contained in the gland. This hypothesis is supported by studies demonstrating a negative correlation between total prostate volume and biopsy yield,^{1,2} and those in which larger prostate volume was a predictor of the positivity of repeat biopsy as well as the negativity of initial biopsy.^{3,4} These findings 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.

Treatment with 5 α -reductase inhibitor 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 by PCPT findings.⁹ During the course of the trial the prostate cancer prevalence was 24.8% lower in the finasteride vs the placebo arm, as detected in for cause biopsies triggered by abnormal PSA and/or digital rectal examination, or on mandatory end of study biopsy. However, Gleason grade 7–10 tumors were significantly more common in the finasteride group than in the placebo group throughout 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 was hypothesized to account for the proportions of high grade tumors.¹⁰

We constructed a mathematical model to predict the likelihood of positive biopsy based on the input variables of tumor volume, PZ and TZ volumes, and the 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

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PCPT could alter tumor detection, including those of high Gleason grade. Finally, the potential impact of this model on prostate cancer detection in the ongoing REDUCE trial, a chemoprevention study designed to determine whether 0.5 mg dutasteride daily for 4 years decreases the risk of biopsy detectable prostate cancer,¹¹ was examined to understand how observations made from PCPT may apply to the REDUCE study.

MATERIALS AND METHODS

Model Construction

A mathematical model was constructed to analyze the effects of tumor size, PZ and TZ gland volumes, and the number 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 a probability of 0.90 or greater a specified tumor configuration of 4 nodules, representing the median number of tumor foci from previous data.¹² Total tumor volume represents the combined volume of all 4 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 nodule volumes are 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 to construct the current model (Appendix 1). Appendix 2 shows the details of model construction.

Modeling the Influence of Prostate Volume and Tumor Size Reduction on Prostate Cancer Detection

To study the effects of the prostate volume reduction observed with finasteride in PCPT (24.1% vs placebo) and the effect that this may have on REDUCE study findings prostate volumes of 20 to 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, 0.75, 1.0, 1.5, 2.0 and 3.0 cc was also used. Four biopsy patterns were examined, including a standard sextant of 6 cores (greater than 80% of men in PCPT underwent 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 in the PZ (10-core biopsies are a protocol requirement for the REDUCE study). For the majority of calculations an assumption was made that 5 α -reductase

inhibitor use did not result in a reduction in tumor size. Although the effects of 5 α -reductase inhibitors on known tumors, as opposed to the prevention of new tumors, are unclear, some data suggest that treatment can result in tumor volume reductions.¹³ Therefore, the scenario in which an equal reduction in tumor and prostate volume size occurred was also modeled.

A further scenario explored the potential reduction in tumor volume needed to explain the observed 25% difference in prostate cancer detection between the finasteride and placebo arms in PCPT. To examine this scenario 2 methods were used. 1) The probability of detecting a 1.5 cc volume tumor in a prostate volume of 30 cc was derived for a sextant biopsy. This probability was then multiplied by 0.75, representing a 25% decrease in the detection probability, and the resulting probability was used to determine the corresponding tumor volume. 2) The true detection rate from PCPT was calculated for the finasteride and placebo groups, assuming that the false-negative rate was 18% for the 2 treatment arms, representing an average value based on the literature.^{14,15} Dividing the detection rates from PCPT by these calculated true detection rates provided a detection probability, which was then applied to the model using average prostate volumes of 34 (placebo group) and 26 cc (finasteride group), representing median prostate volumes at the end of study biopsy.⁹

RESULTS

Minimum Biopsy Core Number for Cancer Detection

Table 1 shows the minimum number of PZ and TZ biopsy cores needed for a 0.90 or greater probability of cancer detection for a total tumor volume of 1.0 and 3.0 cc by prostate volume. As would be expected, an increasing number of biopsies were required to ensure a probability of 0.90 or greater as prostate volume increased and tumor volume decreased. Table 1 also shows a comparison of the findings of this study and those of the model of Vashi et al.⁸

Modeling the Influence of Prostate Volume and Tumor Size Reduction on Prostate Cancer Detection

Table 2 lists increases in prostate cancer detection as a result of a 25% difference in prostate volume by baseline prostate volume before treatment. For a typical tumor vol-

TABLE 1. Minimum number of PZ and TZ biopsy cores needed for 0.90 or greater probability of cancer detection under randomization for total tumor volume of 1.0 and 3.0 cc by prostate volume

Prostate Vol (cc)	Tumor Vol 1.0 cc				Tumor Vol 3.0 cc			
	PZ Cores	TZ Cores	Totals	Vashi et al ⁸	PZ Cores	TZ Cores	Totals	Vashi et al ⁸
20	6	0	6	6	4	0	4	3
20	4	2						
30	8	0	8	9	4	0	4	5
40	12	0	12	12	6	0	6	6
40	10	2			4	2		
40	8	4						
50	14	0	14	15	8	0	8	7
50					6	2		
50					4	4		
60	16	0	16	17	8	0	8	9
70	20	0	20	—	10	0	10	—
70	18	2			8	2		
80	22	0	22	—	10	0	10	11

For each combination of prostate and tumor volume the biopsy schedule with the highest probability of cancer detection is listed first and, when only 1 is listed, only this schedule is associated with 0.90 or greater probability of detection.

TABLE 2. Percent increase in cancer detection probabilities under randomization with 25% decrease in prostate volume in men undergoing sextant biopsy by baseline prostate volume and tumor volume

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

ume of 1.0 cc an increase in the detection rate of approximately 17% would be predicted for PCPT.

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

The potential reduction in combined low and high grade tumor volume needed to explain the observed 25% difference in prostate cancer detection between the PCPT finasteride and placebo arms for a prostate volume of 30 cc and a tumor volume of 1.5 cc was also modeled. From the model the corresponding detection probability was 0.90 for men treated with placebo. In the finasteride arm overall cancer detection was decreased by 25%, resulting in a probability of $0.75 \times 0.90 = 0.68$. When the volume reduction of 25% was factored in, a 1.5 to 0.5 cc reduction in tumor volume was required to reach this detection rate, suggesting that a two-thirds reduction in tumor volume is required to produce a 25% decrease in the detection rate. Using the second approach and assuming an 18% false-negative rate the model estimated true prostate cancer detection probabilities of 0.642 for placebo and 0.557 for finasteride, corresponding to a tumor size of 0.80 and 0.39 cc, respectively, representing a 51% decrease in tumor volume.

Table 3 shows 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 before treatment. The data presented are for 10 cores in the PZ since data on the other variants of 10-core biopsy were similar. For a typical tumor volume of 1.0 cc an increase in the detection rate of between 11% and 17% for 10 cores would be predicted for the REDUCE study based on a mean prostate volume of 46 cc.

DISCUSSION

When 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 at a biopsy session. Under sampling may result in clinically significant tumors being missed, while it has been argued that over sampling increases the 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 developed a mathematical probability model.⁸ They incorporated knowledge of tumor volumes considered life threatening, coupled with an estimation of doubling time, to recommend the number 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 study are similar to those of Vashi et al⁸ but they differ in specifics. Each entails a multifocality model and each includes the total prostate volume and the number of biopsy cores as input variables. However, in the current model specific assumptions on PZ and TZ volumes, and the PZ and TZ number of biopsy cores were used and model randomization was 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 and, therefore, the current model did not include this possibility. Thus, the model predicts that, if the total number of cores remains the same, moving cores from the PZ to the TZ 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 we classified life threatening tumor volume by patient age (larger in older men). In the current model this adjustment was not made directly. Rather, the user may examine probabilities by different tumor volumes, which can be adjusted to account for age. Despite these differences in the modeling approach there is strong consistency between the results.

Comparisons with data from clinical practice studies are problematic since to our knowledge no group has systematically compared different numbers of biopsy cores against saturation biopsy techniques or, indeed, biopsies from radical prostatectomy specimens. Therefore, while almost all studies demonstrate that more cores tend to result in higher detection rates, such studies were not able to determine the optimal approach because tumor prevalence, rather than detection rates, remains unknown. The Vienna nomogram was also constructed to provide guidance on biopsy core number but based on clinical rather than modeled data.⁵ Although using the nomogram resulted in a 66.4% higher prostate cancer diagnosis rate compared with that in a control arm using octant biopsy, it was not determined whether

TABLE 3. Percent increase in cancer detection probabilities with 25% decrease in prostate volume by baseline prostate volume and tumor volume in men undergoing 10-core biopsy with all biopsies in PZ

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

Mean baseline prostate volume in the REDUCE study was 46 cc, corresponding to an 11% to 17% modeled increase in detection.

the nomogram was optimal per se. The nomogram tends to recommend fewer cores than the age/volume based model of Vashi et al⁸ and the current model.

The observation in PCPT that men treated with finasteride were more likely than those receiving placebo to be diagnosed with a Gleason score 7–10 prostate tumor⁹ 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 25% prostate volume reduction could significantly impact tumor detection using the sextant technique, which is the predominant number of cores used in PCPT.

The impact of 5 α -reductase inhibitor treatment 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 decreased in high vs 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 decreased. An inevitable conclusion from PCPT is that finasteride has a greater effect on low vs 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 PSA more than 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 PCPT was due in part to the effect of volume reductions on tumor detection and also to the usefulness of PSA as an indicator of high grade cancer.

Another important observation from PCPT data using this model is the potential 51% to 66% reduction in mean tumor volume required to account for the 25% difference in the overall prostate cancer detection rate between the finasteride and placebo arms. This difference could occur if finasteride prevented new tumors from developing or decreased the volume of existing tumors. Although 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 PCPT.⁹ Although the model is unable to shed further light on this topic, it appears possible that using finasteride resulted in a mixture of primary prevention and prevention of tumor progression in PCPT.

CONCLUSIONS

A model was 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 approximately 17% increase in tumor detection if tumor volume were unaltered by treatment. This detection bias should be considered when evaluating the results of PCPT and the REDUCE study.

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APPENDIX 1

Assumptions Used in Model Construction
The ratio of PZ to TZ volume is 3:1
The number of tumor nodules is specified as 4: the median number of tumor foci from previous data ¹²
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 tumor ⁸
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 core ¹⁶
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-to-TZ ratio of 3:1 ^{17,18}
The dominant nodule is in the PZ with a probability of 0.80 ^{18,19}
The second dominant nodule is in the TZ with a probability of 0.20 ²⁰
The probability of no tumor nodules in the TZ is 0.40 ¹⁸
The probability of the 4 tumor nodules being distributed in the PZ and TZ was chosen as follows: Nodules 1 to 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

APPENDIX 2

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 to 1.5 cc was considered, corresponding to radii of approximately 0.2 to 0.7 cm and volumes of approximately 0.4 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 Appendix 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: $P_1 = 1 - (1 - K_p V_c(r_1)/V_p)^+ \times (1 - K_t V_c(r_2)/V_t)^+ \times (1 - K_p V_c(r_3)/V_p)^+ \times (1 - K_p V_c(r_4)/V_p)^+$ $P_2 = 1 - (1 - K_p V_c(r_1)/V_p)^+ \times (1 - K_p V_c(r_2)/V_p)^+ \times (1 - K_p V_c(r_3)/V_p)^+ \times (1 - K_p V_c(r_4)/V_p)^+$ $P_3 = 1 - (1 - K_p V_c(r_1)/V_p)^+ \times (1 - K_p V_c(r_2)/V_p)^+ \times (1 - K_p V_c(r_3)/V_p)^+ \times (1 - K_p V_c(r_4)/V_p)^+$ $P_4 = 1 - (1 - K_p V_c(r_1)/V_p)^+ \times (1 - K_p V_c(r_2)/V_p)^+ \times (1 - K_p V_c(r_3)/V_p)^+ \times (1 - K_p V_c(r_4)/V_p)^+$
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 Appendix 1.

Abbreviations and Acronyms

PCPT	=	Prostate Cancer Prevention Trial
PSA	=	prostate specific antigen
PZ	=	peripheral zone
REDUCE	=	Reduction by Dutasteride of Prostate Cancer Events
TZ	=	transition zone

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