

# CANCER DETECTION RATE AND GRADE SHIFT IN THE PCPT ARE REFLECTIONS OF FINASTERIDE-INDUCED CHANGES IN PROSTATE VOLUME AND TUMOR SHRINKAGE: RESULTS OF A MATHEMATICAL MODELING STUDY

Robert Serfling,<sup>1</sup> Michael Shulman,<sup>2</sup> G. L. Thompson,<sup>3</sup> Zhiyao Xiao,<sup>4</sup> Elie Benaim,<sup>2</sup> Claus G. Roehrborn,<sup>2</sup> and Roger Rittmaster<sup>5</sup>

<sup>1</sup>Department of Mathematical Sciences, University of Texas at Dallas, Richardson, TX, USA; <sup>2</sup>Department of Urology, University of Texas Southwest Medical Center at Dallas, Dallas, TX, USA; <sup>3</sup>Department of Chemistry, University of Texas at Dallas, Richardson, TX, USA; <sup>4</sup>Department of Mathematics and Statistics, University of North Carolina at Charlotte, Charlotte, NC, USA; <sup>5</sup>Urology Clinical Development and Medical Affairs Group, GlaxoSmithKline, Research Triangle Park, NC, USA

## INTRODUCTION AND OBJECTIVES

- Previous studies have demonstrated a negative correlation between total prostate volume and biopsy yield,<sup>1-10</sup> and that increasing prostate volume is a predictor of positivity of a repeat biopsy as well as negativity of the initial biopsy, demonstrating that a larger prostate volume is associated with a higher false negative biopsy rate if core numbers remain the same.<sup>11-14</sup>
- By decreasing total prostate volume, 5 $\alpha$ -reductase inhibitor treatment could in theory enhance prostate cancer detection, by reducing the benign component of the gland and therefore increasing the likelihood of a biopsy core sampling tumor.
- Over the 7-year course of the Prostate Cancer Prevention Trial (PCPT), prostate cancer prevalence was 24.8% lower in the finasteride *versus* the placebo arm, but tumors of Gleason grade 7–10 were significantly more common in the finasteride group than in the placebo group.<sup>15</sup> A detection bias related to reductions in benign prostate volume (i.e. under-detection for larger prostates) was hypothesized to account for the proportions of high-grade tumors.<sup>16</sup>
- 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) clinical trial, a chemoprevention study designed to determine if dutasteride 0.5 mg daily over 4 years reduces the risk of biopsy-detectable prostate cancer,<sup>17</sup> was examined.

## METHODS

### Model construction

- A mathematical model was constructed, utilizing geometric considerations similar to those used by Vashi *et al.*<sup>18</sup> to analyze the effects of tumor size (determined by using different PSA values), 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 is 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,<sup>19</sup> based on two ranges of PSA values translated into tumor volumes, as shown in Table 1.

Table 1. Tumor nodule volumes derived from two different PSA ranges of 4–10 ng/mL and >10 ng/mL.

PSA range	Nodule number				Total tumor volume
	V <sub>1</sub>	V <sub>2</sub>	V <sub>3</sub>	V <sub>4</sub>	
4–10 ng/mL	0.53 cc	0.27 cc	0.13 cc	0.07 cc	1.00 cc
>10 ng/mL	1.59 cc	0.81 cc	0.39 cc	0.21 cc	3.00 cc

- 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. In order for the probability of different nodule distribution in the TZ and PZ to be accounted for, probabilities of each nodule being distributed in the PZ and TZ were utilized as outlined below:
  - 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

### 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, prostate volumes of 20–80 cc in 10 cc increments were entered into the model along with a prostate volume reduction of 25%.

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 given.<sup>18</sup>

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 4	0 2	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. 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.

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%

- 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, and 4 biopsy patterns, namely a standard sextant (6 cores); 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, to match the protocols used in the PCPT and the REDUCE study.
- The scenario where an equal reduction in tumor and prostate volume size occurred was also modeled, and 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 was also examined.

## RESULTS

### Model construction

- 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.
- 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* are also presented in Table 2.

### Modeling of the influence of prostate volume and tumor size reduction on prostate cancer detection in the PCPT and REDUCE study

- Table 3 outlines the increases in prostate cancer detection for sextant biopsy as a result of a 25% difference in prostate volume, by baseline prostate volume prior to treatment.
- For a typical tumor volume of 1 cc, an increase in the detection rate of approximately 17% would be predicted for the PCPT.
- For a 1.0 cc tumor and an initial prostate volume of 30 cc, the detection probability increases by a lower figure of 6% if tumor volume is also reduced by 25%.
- 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 for a prostate volume of 30 cc and a tumor volume of 1.5 cc determined by two methods was 51–66%.
- Table 4 outlines the increases in prostate cancer detection as a result of a putative 25% difference in prostate volume between dutasteride- and placebo-treated men, by baseline prostate volume prior to treatment.
- For a typical tumor volume of 1 cc, an increase in detection rate of 11–17% for 10 cores would be predicted for the REDUCE study based on a mean prostate volume of 46 cc.<sup>20</sup>

Table 4. Percent increase in cancer detection probabilities under randomization 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.

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%

## CONCLUSIONS

- A model has been constructed that provides guidance on the optimal number of biopsy cores for men with different prostate volumes and PSA levels, which accords with an earlier model that utilized patient age, as opposed to PSA.<sup>18</sup>
- These data, supported by those of clinical studies,<sup>1-14</sup> strongly suggest that sextant biopsy suffices only for prostate sizes 20 cc for men with a PSA of 4–10 ng/mL, and for 40 cc for men with a PSA of >10 ng/mL. Similarly, a 12-core biopsy suffices only for prostate sizes 40 cc for those with a PSA of 4–10 ng/mL, and for 80 cc for those with a PSA >10 ng/mL.
- The understanding that reductions in tumor volume of 51–66% by finasteride would be needed to result in a 25% reduction in prostate cancer detection, add weight to the hypothesis that 5 $\alpha$ -reductase inhibitor therapy is likely not only to prevent new tumors but also to reduce the volume of existing cancer, as suggested in other studies.<sup>21</sup>
- These findings also suggest that a reduction in prostate volume from 5 $\alpha$ -reductase inhibitor therapy could lead to increased detection of prostate cancer including high-grade tumors, an observation that may define a role for these agents in assisting prostate cancer diagnosis.
- A similar detection bias can be expected in the dutasteride REDUCE study with the effect of the greater number of cores counterbalancing the larger baseline prostate volume.

## REFERENCES

- Stricker HJ, Ruddock LJ, Wan J, Belleville WD. Detection of non-palpable prostate cancer. A mathematical and laboratory model. *Br J Urol* 1993; **71**: 43–6.
- Uzzo RG, Wei JT, Waldbaum RS, et al. The influence of prostate size on cancer detection. *Urology* 1995; **46**: 831–6.
- Karakiewicz PI, Buzin M, Aprikian AG, et al. Outcome of sextant biopsy according to gland volume. *Urology* 1997; **49**: 55–9.
- de la Taille A, Antiphon P, Salomon L, et al. Prospective evaluation of a 21-sample needle biopsy procedure designed to improve the prostate cancer detection rate. *Urology* 2003; **61**: 1181–6.
- Ficarra V, Novella G, Novara 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* 2005; **48**: 932–7.
- Kobayashi T, Mitsumori K, Kawahara T, et al. Prostate gland volume is a strong predictor of biopsy results in men 70 years or older with prostate-specific antigen levels of 2.0–10.0 ng/mL. *Int J Urol* 2005; **12**: 969–75.
- Letran JL, Meyer GE, Loberiza FR, Brawer MK. The effect of prostate volume on the yield of needle biopsy. *J Urol* 1998; **160**: 1718–21.
- Mariappan P, Chong WL, Sundram M, Mohamed SR. Increasing prostate biopsy cores based on volume vs the sextant biopsy: a prospective randomized controlled clinical study on cancer detection rates and morbidity. *BJU Int* 2004; **94**: 307–10.
- Ung JO, San Francisco IF, Regan MM, DeWolf WC, Olumi AF. The relationship of prostate gland volume to extended needle biopsy on prostate cancer detection. *J Urol* 2003; **169**: 130–5.
- Eskicorapci SY, Guliyev F, Akdogan E, et al. Individualization of the biopsy protocol according to the prostate gland volume for prostate cancer detection. *J Urol* 2005; **173**: 1539–40.
- Rietbergen JB, Kruger AE, Hoedemaeker RF, et al. Repeat screening for prostate cancer after 1-year followup in 984 biopsied men: clinical and pathological features of detected cancer. *J Urol* 1998; **160**: 2121–5.
- Remzi M, Djavan B, Wammack R, et al. Can total and transition zone volume of the prostate determine whether to perform a repeat biopsy? *Urology* 2003; **61**: 161–6.
- Basiletti JB, Armenakas NA, Hochberg DA, Fracchia JA. Influence of prostate volume in the detection of prostate cancer. *Urology* 2003; **61**: 167–71.
- Abdel-Khalek M, El-Baz M, Ibrahim el H. Is extended 11-core biopsy valuable in benign prostatic hyperplasia patients with intermediate serum prostate-specific antigen (4.1–10 ng/ml) and prior negative sextant biopsy? *Scand J Urol Nephrol* 2004; **38**: 315–20.
- Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med* 2003; **349**: 215–24.
- Kukami GS, Al-Azab R, Lockwood G, et al. Evidence for a biopsy derived grade artifact among larger prostate glands. *J Urol* 2006; **175**: 505–9.
- Andriole G, Bostwick D, Brawley O, 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* 2004; **172**: 1314–7.
- Vashi AR, Wojno KJ, Gillespie B, Oesterling JE. A model for the number of cores per prostate biopsy based on patient age and prostate gland volume. *J Urol* 1998; **159**: 920–4.
- Gastucky SI, Wojno KJ, Walsh PC, Carmichael MJ, Epstein JI. Pathological features of hereditary prostate cancer. *J Urol* 1995; **153**: 987–92.
- Andriole G. Chemoprevention of prostate cancer: baseline characteristics of men in the REDUCE trial. Presented at the XXth Congress of the European Association of Urology, Istanbul, Turkey, March 2005.
- Andriole GL, Humphrey P, Ray P, et al. Effect of the dual 5 $\alpha$ -reductase inhibitor dutasteride on markers of tumor regression in prostate cancer. *J Urol* 2004; **172**: 915–9.