VOLUME 27 · NUMBER 26 · SEPTEMBER 10 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Three-Dimensional Prostate Mapping Biopsy Has a Potentially Significant Impact on Prostate Cancer Management

Gary Onik, Matthew Miessau, and David G. Bostwick

From the Department of Radiology, Florida Hospital Celebration Health, Celebration; and Bostwick Laboratories, Orlando, FL.

Submitted October 27, 2008; accepted March 4, 2009; published online ahead of print at www.jco.org on August 3, 2009.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Gary Onik, MD, Department of Radiology, 400 Celebration Pl, Celebration Health/Florida, Celebration FL 34747; e-mail: onikcryo@aol.com.

0732-183X/09/2726-4321/$20.00

DOI: 10.1200/JCO.2008.20.3497

ABSTRACT

Purpose
To compare a new staging, three-dimensional prostate mapping biopsy (3D-PMB) method with traditional transrectal ultrasound (TRUS) biopsy and assess its possible impact on patient management.

Patients and Methods
One hundred eighty patients with unilateral cancer on TRUS biopsy, who were considering conservative management, underwent restaging with 3D-PMB. The 3D-PMB was carried out transperineally using a brachytherapy grid under TRUS guidance. Biopsies were taken every 5 mm throughout the volume of the prostate, and labeling of the specimen coordinates allowed accurate reconstruction of the location and extent of a patient's cancer.

Results
3D-PMB obtained a median of 50 cores (standard deviation, ± 20.61). One hundred ten patients (61.1%) were positive bilaterally, and 41 patients (22.7%) had Gleason scores increased to 7 or higher. Thirty-six patients had negative results on 3D-PMB. Complications of 3D-PMB were self-limited and included 14 patients (7.7%) who required short-term indwelling catheter drainage and two patients with hematuria, one of whom required overnight bladder irrigation.

Conclusion
3D-PMB is a transperineal biopsy that can be safely used to accurately stage prostate cancer patients. At the present time, when patient management is increasingly based on the extent and characteristics of prostate cancer, 3D-PMB could have a profound effect on patient management.

J Clin Oncol 27:4321-4326. © 2009 by American Society of Clinical Oncology

INTRODUCTION

Over the last decade, the management of prostate cancer has evolved to the point at which the grade, stage, and location of a patient's cancer often dictate the type and extent of treatment. Examples include watchful waiting in patients who are thought to have clinically insignificant cancer,[1] brachytherapy monotherapy in low-risk patients,[2] adjuvant hormone therapy in high-risk patients undergoing radiation therapy,[3] and focal therapy in patients with unifocal cancer.[4] Appropriate patient selection for the various therapies requires accurate knowledge of the extent, location, and grade of the patient's cancer. Unfortunately, the preoperative staging of prostate cancer by both imaging and transrectal ultrasound (TRUS) biopsy is inaccurate and inadequate and does not reflect the final pathology as demonstrated on radical prostatectomy (RP) specimens.[5,6] Recent studies indicate that a new transperineal three-dimensional prostate mapping biopsy (3D-PMB) provides more accurate determination of the extent and location of cancer before definitive therapy.[7] In this article, we report our 5-year experience with transperineal 3D-PMB, compare our data with data obtained with traditional TRUS biopsy, and discuss the possible impact of 3D-PMB on patient management.

PATIENTS AND METHODS

All patients previously underwent TRUS-guided biopsy at other institutions and were then restaged at our center using 3D-PMB before definitive cancer management. Patients signed a consent form that had been approved by the Florida Hospital Institutional Review Board for this study.

The result of the previous TRUS biopsy on patients dictated whether one half or the whole prostate gland was rebiopsied using the transperineal method. If only one half of the gland was biopsied, it was performed on the side that had shown no cancer on the TRUS biopsy. The transperineal biopsy was performed under general anesthesia or heavy intravenous sedation using a similar method to that described by Barzell and Whitmore[8] and Crawford et al.[9]

The location of the urethra was marked using a Foley catheter, and the catheter was left in place after the procedure to assess the patient for hematuria. The biopsy used a

standard brachytherapy grid with 5-mm spacing, with *x*-axis coordinates A through M and *y*-axis coordinates from 1 through 12, using G as the midline urethral plane. An 18-gauge automated biopsy gun with a specimen of 2 cm in size (Boston Scientific, Boston, MA) was used to take biopsies every 5 mm throughout the volume of the prostate as guided by a biplane TRUS. The number of biopsies in each procedure was dependent on the volume of the prostate gland. Additional biopsies were taken at coordinates where required by the length of the prostate to fully sample the gland. Midline biopsies were taken posterior to the urethra with effort made to avoid puncturing the urethra. The longitudinal ultrasound view was used to monitor the depth of the needle placement while avoiding multiple penetrations of the bladder and to allow sampling of the entire length of the gland. The axial view was checked throughout the biopsy to maintain the correct vertical and horizontal coordinates for the biopsies. The cores were marked at their proximal end with ink to later determine correct orientation. Cores were placed in separate jars and labeled with their coordinates.

The procedure was carried out under real-time ultrasound guidance. Gross prostate movement caused by respiration could be detected, and the biopsies were obtained in the same phase of respiration for each core. At the start of each case, the ultrasound probe was aligned to the midline of the prostate while fixed in the center position of the brachytherapy stand's probe holder. During the procedure, the ultrasound probe was periodically brought back to the original midline position to check for prostate misalignment. If misalignment was noted, the probe was repositioned into the midline by the brachytherapy stand fine positioning controls.

Exact time between the biopsies was not recorded but, for practical reasons, was generally within a few months. Data on patients who were placed on any hormone therapy at an outside institution are not available. All patients were placed on reductase inhibitor therapy 2 weeks before 3D-PMB because it was previously reported that this regimen could reduce Doppler demonstrable intraprostatic blood flow to the prostate. The regimen was applied to reduce the chances for prostatic bleeding.

Each patient served as his own control. The 3D-PMB information was compared with the previous TRUS biopsy. 3D-PMB results were also assessed as to whether the new information obtained might change the patient management. Criteria for possible change in patient management included bilateral cancer when previously only unilateral cancer had been identified on TRUS biopsy, increase of Gleason score to ≥ 7, or cancer on 3D-PMB within 5 mm of the neurovascular bundle(s).

RESULTS

A total of 218 patients underwent the 3D-PMB between March 2002 and May 2008. Of these, prior TRUS biopsy revealed unilateral cancer in 180 patients and bilateral cancer in 38 patients; the 180 patients with unilateral cancer were included in this study (Table 1).

3D-PMB obtained a mean of 52.2 cores per patient, with a median of 50 cores (standard deviation, ± 20.61). Of the 180 patients, 36 had negative 3D-PMB, yielding a false-negative rate of 20%. A total of 35 of these patients had cancer measuring less than 5 mm in greatest dimension; one additional patient had a TRUS-detected tumor larger than 5 mm. A total of 110 patients (61.1%) had bilateral cancer (Table 1). Gleason score increased to 7 or higher in 41 patients (22.7%). Cancer was found within 5 mm of the neurovascular bundle in 35 (19.4%) of 180 patients. Using the previously outlined criteria for a patient in whom a change in management might have occurred because of the results of the 3D-PMB, 125 (69.44%) of 180 patients had at least one criterion that might have changed their management.

The differences between the number of biopsy cores taken, number of positive biopsy cores, and mean Gleason score between TRUS-guided biopsy and 3D-PMB were compared using a paired *t* test. The resulting values indicate a difference between the sets of data for each biopsy method (Table 2).

One hundred patients had combined characteristics of prostate-specific antigen less than 10, Gleason score ≤ 6, and stage ≤ T2a, indicating low-risk disease[10] and possible candidacy for active surveillance. The results for this group are listed in Table 1.

Of the 180 patients, 77 patients had ≤ nine cores taken on TRUS biopsy, and 84 patients had ≥ 10 cores taken on TRUS biopsy. The remaining 19 patients did not have information regarding the number

Table 1. Biopsy Characteristics

Characteristic	No. of Patients	%
TRUS biopsy results		
Patients previously unilateral	180	
Gleason score		
Range	3-9	
Score of 6	120	
Preoperative stage T1c	132	
PSA, ng/mL		
Mean	7	
Median	5.1	
SD	8.56	
TRUS cores taken, No.		
Mean	9.9	
Median	10.0	
SD	4.81	
TRUS cores positive, No.		
Mean	1.79	
Median	1.0	
SD	1.31	
Preoperative gland volume, mL		
Mean	37.38	
Median	33.0	
SD	19.84	
3D-PMB results	180	
Bilateral positive	110	61
Unilateral positive	34	
Negative biopsy	36	
Positive biopsy	144	
No. of total cores		
Mean	52.17	
Median	50	
SD	20.61	
No. of positive cores		
Mean	5.6	
Median	4.0	
SD	5.4	
Increase in Gleason score ≥ 7	41	22.7
Potential change in management		
Bilateral cancer	110	61.1
Gleason score increased to ≥ 7	45	25
Potential NVB	35	19.4
At least one of the criteria present	125	69.4
Potential active surveillance patients 3D-PMB results	100	
Increase Gleason score ≥ 7	26	26
Positive biopsy	74	74
Bilateral disease	50	50

Abbreviations: TRUS, transrectal ultrasound; PSA, prostate-specific antigen; SD, standard deviation; 3D-PMB, three-dimensional prostate mapping biopsy; NVB, neurovascular bundle.

Table 2. Differences in Biopsy Methods

Factor	TRUS Biopsy		3D-PMB		
	Mean	SD	Mean	SD	*P*
Total biopsy cores, No.	9.93	4.81	52.17	20.61	< .0001
Positive biopsy cores, No.	1.79	1.31	5.67	5.46	< .0001
Gleason score	6.27	0.81	6.61	0.84	< .0001

Abbreviations: TRUS, transrectal ultrasound; 3D-PMB, three-dimensional prostate mapping biopsy; SD, standard deviation.

of cores taken. The results for these two separate groups are listed in Table 3. Differences in the biopsy results were assessed using a *t* test for correlated samples and are listed in Tables 4 and 5, along with χ^2 tests of the relationship between previous TRUS biopsy size and unilateral or bilateral disease on 3D-PMB, as well as previous TRUS biopsy size and Gleason score upgrade potential.

Seventy-seven patients had ≤ nine biopsy cores taken from the previous biopsy. The previous biopsy was not dependent on gland size. The average prostate volume of these 77 patients (≤ nine cores) was 36.36 mL, with a median of 30 mL (standard deviation, ± 21.24 mL). Complications of 3D-PMB were self-limited and included 14 patients (7.7%) who required short-term indwelling catheter drainage and two patients with hematuria, one of whom started bleeding after restarting aspirin therapy and required overnight bladder irrigation.

Table 3. Biopsy Results for Low-Core and High-Core Groups

Biopsy Results	≤ 9 Cores on TRUS (n = 77)	≥ 10 Cores on TRUS (n = 84)
Previous TRUS biopsy results		
PSA, ng/mL		
Mean	6.71	7.04
Median	5.0	5.0
SD	9.29	8.06
Preoperative stage T1c, No. of patients	54	63
No. of TRUS cores taken		
Mean	6.38	13.19
Median	6.0	12.0
SD	1.34	4.51
No. of positive TRUS cores		
Mean	1.41	2.16
Median	1.0	2.0
SD	0.82	1.53
3D-PMB results		
No. of cores taken		
Mean	50.96	53.13
Median	48.0	50.5
SD	22.79	16.69
No. of positive cores		
Mean	5.68	5.94
Median	4.5	4.0
SD	5.09	6.81
Bilateral disease		
No. of patients	18	51
%	23	60
Gleason upgrade		
No. of patients	25	19
%	32	22
Gleason upgrade from ≤ 6 to ≥ 7		
No. of patients	17	15
%	22	17

Abbreviations: TRUS, transrectal ultrasound; PSA, prostate-specific antigen; SD, standard deviation; 3D-PMB, three-dimensional prostate mapping biopsy.

DISCUSSION

Watchful waiting or active surveillance, radiation with adjuvant hormonal therapy, and brachytherapy monotherapy and focal therapy are all new management strategies for prostate cancer. All of these new evolving management strategies for prostate cancer have, as their basis, selection of the appropriate patient. Therefore, it is imperative that pathologic grade and disease stage be identified as accurately as possible in order for the correct treatment option to be selected. Unfortunately, the ability to stage and grade patients through imaging (magnetic resonance imaging and color Doppler ultrasound) still has not met with enough success to make it a standard for patient selection.[5]

The gold standard for patient staging at this point is TRUS biopsy. Once again, however, TRUS biopsy does not seem to accurately reflect the extent and grade of disease when compared with RP specimens.

In an effort to improve the detection and staging of prostate cancer by biopsy, a number of strategies involving biopsy location optimization and increasing number of biopsy cores taken have been developed. The accepted TRUS biopsy protocol, as defined by the National Comprehensive Cancer Network (NCCN), is now an extended biopsy protocol that consists of the sextant cores plus an additional four cores taken from the lateral peripheral zones, for a total of 10 cores.

The data obtained from 3D-PMB confirm that TRUS biopsy, as it is currently practiced, even if optimized by the extended biopsy as suggested by the NCCN, gives an inaccurate assessment of a patient's extent and grade of disease. Our data indicate that, overall, 23% of patients are undergraded, with a Gleason score increasing from 6 to 7 or greater by TRUS biopsy when compared with 3D-PMB. In addition, more than 60% of patients who had unilateral disease on their TRUS biopsy ultimately actually had bilateral disease demonstrated by 3D-PMB.

Because all of the patients were biopsied outside of our institution, there is no uniformity in TRUS biopsy protocol used in the initial diagnosis of these patients. The data indicate that nearly half of the biopsies performed did meet the standard of an extended biopsy of ≥ 10 cores advocated by the NCCN. To remove the bias of what might be considered inadequate TRUS biopsies, the data were evaluated with respect to two groups—those who had ≥ 10 or ≤ nine cores on TRUS biopsy (Table 1). When confined to a presumably optimized biopsy of

Table 4. Group Statistics Separated by Biopsy Number

Statistic	Standard TRUS Biopsy Mean	Standard TRUS Biopsy SD	3D-PMB Mean	3D-PMB SD	*P*
≥ 10 previous cores taken					
Total No. of biopsy cores	13.19	4.51	53.13	16.69	< .0001
No. of positive biopsy cores	2.16	1.53	5.94	6.81	< .0001
Gleason score	6.56	0.91	6.71	0.84	.2359
≤ 9 previous cores taken					
Total No. of biopsy cores	6.38	1.34	50.96	22.79	< .0001
No. of positive biopsy cores	1.41	0.82	5.68	5.09	< .0001
Gleason score	6.14	0.75	6.73	0.90	.00011

Abbreviations: TRUS, transrectal ultrasound; 3D-PMB, three-dimensional prostate mapping biopsy; SD, standard deviation.

at least 10 cores (mean, 13.19 cores), 60% of patients demonstrated bilateral disease on the 3D-PMB, and 17% increased their Gleason score to ≥ 7. Even when a presumably optimal protocol is used, information that could potentially have a great impact on patient management is still obtained from the 3D-PMB.

When all of these factors are taken into account, the information obtained from the 3D-PMB might have changed the management in 70% of patients who had at least one of these negative criteria discovered by the 3D-PMB. When the group of low-risk patients (n = 100), presumably suitable for active surveillance, were examined separately, 26% had an increase in Gleason score to ≥ 7, and 50% were noted to have gone from unilateral to bilateral disease (Fig 1). This gives clear indication that 3D-PMB could exclude a significant number of patients from the active surveillance management group.

We did not include patient stage in our analysis because the majority of our patients had low-risk disease and were stage T1c. By definition of palpability, any further information obtained by the 3D-PMB in T1c patients still would not change their stage, which is why we strongly emphasized bilaterality rather than stage in our analysis.

The data obtained by the 3D-PMB did not have all negative implications for the patients because 36 (20%) of the 180 patients who had unilateral disease demonstrated on their TRUS biopsy had negative biopsies on their 3D-PMB. In only one of these negative biopsies did the data indicate that the 3D-PMB missed what would be thought of as a significant tumor of ≥ 5 mm. 3D-PMB was designed so that biopsies obtained every 5 mm throughout the volume of the prostate would presumably diagnose significant tumors ≥ 5 mm. A significant tumor was missed in one (3%) of the 36 patients, which is consistent with the study by Crawford et al.[9] In this study where the 3D-PMB was simulated on RP and autopsy specimens, significant tumors were missed only 5% of the time.

Some smaller tumors presumably would fall between the grid points and be missed in our series. This happened approximately 20% of the time, although we cannot know for sure what the real sensitivity of the 3D-PMB is until it is compared to a series of RP specimens. It seems that in this 20% of patients, 3D-PMB may confirm that a patient's disease is truly low risk and active surveillance is a reasonable course of action. Only until a series of active surveillance patients staged by 3D-PMB is observed for a period of time will we know how many significant tumors are missed that will ultimately lead a patient to a more radical intervention. Studies have also shown that patients in active surveillance programs have a decreased quality of life as a result of the psychological stresses of remaining with cancer.[11,12] Although we have no formal measure of quality of life in this study, our experience has been that patients who receive a negative report from a 3D-PMB feel relieved and comfortable with active surveillance. The concept of using an extensive TRUS biopsy (32 cores) specifically for prostate cancer staging to determine whether a patient is a suitable candidate for active surveillance was introduced by Boccon-Gibod et al.[13] Although it provided useful information, the morbidity of this TRUS approach was unacceptable, with one patient having massive rectal bleeding and another patient having Gram-negative sepsis.[13]

Table 5. Group Statistics Separated by Biopsy Number

Statistic	≤ 9 Previous Biopsies Mean	≤ 9 Previous Biopsies SD	≥ 10 Previous Biopsies Mean	≥ 10 Previous Biopsies SD	*P*
No. of TRUS positive biopsy cores	1.41	0.82	2.16	1.53	.000215
No. of TRUS biopsies taken	6.38	1.34	13.19	4.51	< .0001
No. of 3D-PMB cores taken	50.96	22.79	53.13	16.69	.516
No. of positive 3D-PMB cores	5.68	5.09	5.94	6.81	.7269
3D-PMB results, No. of patients					< .0001
Unilateral positive	59		33		
Bilateral positive	18		51		
Gleason score, No. of patients					.1613
Upgrade	25		19		
No upgrade	52		65		

Abbreviations: SD, standard deviation; TRUS, transrectal ultrasound; 3D-PMB, three-dimensional prostate mapping biopsy.

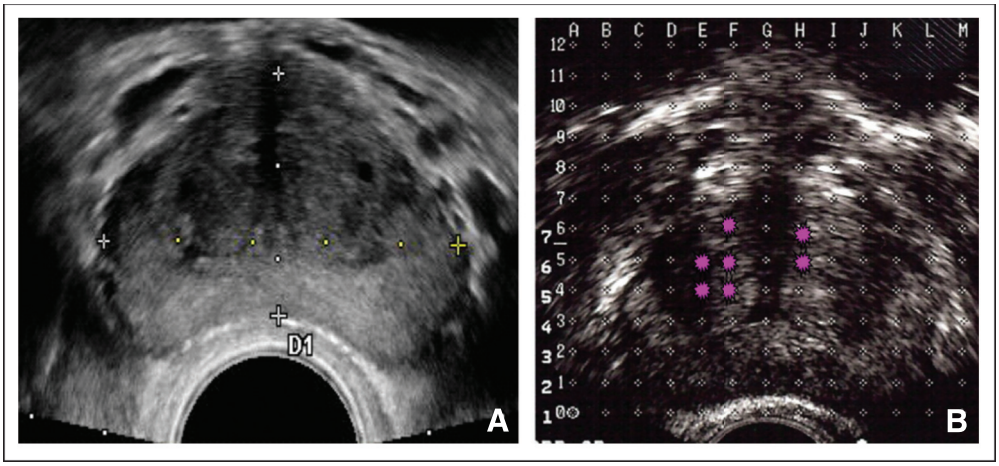

Fig 1. (A) Transrectal ultrasound (TRUS) in a 54-year-old patient. The ultrasound was normal. The patient had a TRUS biopsy, which revealed a 1-mm adenocarcinoma with a Gleason score of 6 on the right side of his gland. He underwent 1 year of watchful waiting and then had a three-dimensional prostate mapping biopsy (3D-PMB) for further staging. The ultrasound overshoots the anterior margin by 3 mm. (B) TRUS with a brachytherapy grid overlay. Where a grid dot overlays the prostate, a biopsy is taken. The starburst patterns in the anterior portion of both sides of his gland indicate where his 3D-PMB was positive for carcinoma with a Gleason score of 8. Obviously, this patient has to receive more definitive therapy.

An improvement in this approach to restaging patients was introduced by Barzell and Melamed,[7] where the biopsy method used was a transperineal approach using a brachytherapy grid as a guide with biopsies taken every 5 mm throughout the prostate, following the same protocol as simulated by Crawford et al.[9] For the first time, the density of biopsies obtained was the same for all prostate volumes. Results showed that the sensitivity and negative predictive value of the TRUS biopsies was only 54% and 49%, respectively, when compared with the 3D mapping procedure, which, again, is similar to the results we have reported here.

The main difference in our approach is that we send each core with its exact grid location and inked to show the orientation of the core so that more exact apical and base location of any cancer is known. Barzell groups his cores into 26 locations, with the midline biopsies separated and the octants divided into three zones each. We found this approach inferior for our purposes because we feel that knowing the exact location of a positive core better reflects the patients' chances for extracapsular penetration and seminal vesicle involvement. A recently published consensus on the optimal method of 3D-PMB endorsed the concept of having only a single biopsy core in each specimen jar to facilitate better locating of the tumor and to optimize pathologic examination of the specimen.[14]

As already indicated, focal therapy of prostate cancer (ie, male lumpectomy) is gaining a great deal of attention as a way of providing local cancer control and minimal morbidity and is basically being thought of as a middle ground between watchful waiting and radical whole-gland treatments. Given the data presented here, reliance on TRUS biopsy to select patients for focal therapy will lead to an unacceptable failure rate. Thus, 3D-PMB is an essential component of any program in focal therapy.

We have alluded to the possible advantages of having a better idea of a patient's cancer location in relation to treating patients with RP. We believe having more accurate knowledge of the extent of cancer and the cancer grade could also have an impact on patient management and a patient's informed choice of treatment options. Certainly, the upgrading of a patient's Gleason score and demonstration of bilateral disease in a T2a patient (changing stage to T2c or even T3) significantly change a patient's chance of extracapsular penetration and seminal vesicle involvement based on nomograms that currently estimate such risks.[15,16] Patients faced with such increased risk of positive margins might reasonably choose a different form of therapy. A further issue associated with 3D-PMB in potential RP patients is whether the extensive biopsies would make the subsequent RP procedure more difficult as a result of scarring associated with the biopsy. In the study by Barzell and Melamed,[7] with a limited number of patients undergoing RP after 3D-PMB, this difficulty was not encountered.

Our series of 218 patients demonstrated an acceptable level of morbidity even with the large number of specimens taken. The only significant complication was hematuria, which required overnight admission for bladder irrigation. The transperineal approach also allows for a relatively sterile procedure that limits the chance of sepsis seen with the TRUS biopsy approach.

Because 3D-PMB is carried out in an outpatient surgical setting under general anesthesia or heavy intravenous sedation, its cost is going to be greater than a TRUS biopsy carried out in an office setting. In addition, obtaining many specimens markedly increases pathology costs associated with a biopsy. When the issue of cost is ultimately raised about 3D-PMB and its utilization, we feel it needs to be looked at in the wider context of the costs of multiple biopsies associated with active surveillance programs and the cost of additional salvage treatments in those patients inadequately treated as a result of the understaging of their disease.

Lastly, we think it has to be realized that the utilization of TRUS biopsies and the inadequate information they provide, if used as the standard for a true negative in research studies, may adversely impose a bias on our basic knowledge of prostate cancer and its screening and diagnosis. Future investigators will have to carefully consider whether TRUS biopsy can be reasonably used for important studies regarding our basic knowledge of prostate cancer and its management.

In conclusion, 3D-PMB is an extensive volume-based transperineal biopsy that can be safely used to more accurately stage prostate cancer patients. At the present time, when tailoring of patient treatment is increasingly being based on the extent and characteristics of a patient's cancer, 3D-PMB could have a profound effect on patient outcomes. We feel that the results presented here warrant the initiation of large-scale, prospective, multi-institutional trials to fully elucidate the role of 3D-PMB.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** None **Stock Ownership:** None **Honoraria:** None **Research Funding:** None **Expert Testimony:** None **Other Remuneration:** Gary Onik, Bostwick Laboratory; David G. Bostwick, Bostwick Laboratories

AUTHOR CONTRIBUTIONS

Conception and design: Gary Onik
Financial support: Gary Onik
Administrative support: Gary Onik
Provision of study materials or patients: Gary Onik
Collection and assembly of data: Gary Onik, Matthew Miessau, David G. Bostwick
Data analysis and interpretation: Gary Onik, David G. Bostwick
Manuscript writing: Gary Onik, Matthew Miessau, David G. Bostwick
Final approval of manuscript: Gary Onik, David G. Bostwick

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