International Journal of Impotence Research (2012) 24, 161 – 164

www.nature.com/ijir

ORIGINAL ARTICLE

The impact of multiple biopsies on outcomes of nerve-sparing robotic-assisted radical prostatectomy

P Sooriakumaran[1], A Calaway[1], D Sagalovich[1], S Roy[1], A Srivastava[1], J Joneja[1], M Shevchuk[1] and AK Tewari[1]

Active surveillance of prostate cancer patients involves subjecting them to multiple prostate biopsies, and we sought to investigate the effects of this on functional outcomes after robotic-assisted radical prostatectomy (RARP). Between May 2009 and December 2009, 367 patients who consecutively underwent RARP by a single surgeon were divided into two groups, one that had single prostate biopsy and another multiple biopsies before RARP. The groups were matched for significant clinicopathologic preoperative variables, and only premorbidly potent low-risk cases that underwent nerve sparing were included. This left 50 and 23 patients for analysis in the single and multiple biopsy groups, respectively. The primary endpoint was potency and continence at 3 and 6 months after surgery. We found continence rates of 84% (83%) and 94% (96%) for single (multiple) biopsy groups at 3 and 6 months, respectively ($P = 0.88$, $P = 0.77$). Multiple biopsy patients had worse postoperative erectile function at 6 months (57% versus 80%, $P = 0.03$). Men subject to multiple preoperative biopsies are more likely to become impotent postoperatively than those who undergo surgery after a single biopsy. This should be borne in mind when counseling men regarding repeat biopsy as part of an active surveillance strategy.

International Journal of Impotence Research (2012) **24,** 161–164; doi:10.1038/ijir.2012.9; published online 26 April 2012

Keywords: multiple biopsy; outcome; prostatectomy; robotic; potency

INTRODUCTION

There has been a stage during migration of prostate cancer in recent years, with more and more localized disease being diagnosed.[1] With this, there has been a rise in the proportion of low grade, low stage, low-tumor volume (so-called 'low risk') prostate cancer presenting to urologists. The gold standard of radical prostatectomy may thus be an overtreatment for a number of these patients destined never to suffer as a result of their disease. The problem is that we do not know which 'low-risk' patients will progress and which will not. This dilemma has provided the rationale for active surveillance, a treatment strategy aimed at not causing harm by subjecting the patient to radical treatment, but rather regular monitoring of the patient's disease and intervening with radical therapy as necessary. However, most active surveillance protocols require a prostate biopsy at baseline and at regular intervals, and thus there are concerns of morbidity resulting from multiple biopsies. One of the less well-studied adverse effects of biopsy is its impact on erectile function. Some authors have suggested that multiple biopsies *per se* can cause nerve damage and subsequent ED.[2,3] The other, even less investigated event, is the impact of multiple biopsies on the operative ability to perform nerve sparing if such patients end up having surgery in the future. To our knowledge, there have been no studies investigating these effects of multiple biopsies on patients undergoing robotic-assisted radical prostatectomy (RARP). To answer that question, we retrospectively evaluated our cohort of 367 patients who underwent RARP by a single surgeon at our institution over an eight-month period.

PATIENTS AND METHODS

Patient selection

This is a retrospective study of 367 consecutive men with prostate cancer who underwent RARP by a single surgeon (AK Tewari) between May 2009 and December 2009. The patients were consented for this IRB approved study during their preoperative clinic visit. We identified patients who had undergone surgery after a single preoperative biopsy ($n = 317$) and those who had multiple biopsies who then underwent surgery due to multiple initially negative biopsies, or progression of disease or patient choice after enrollment on an active surveillance regimen ($n = 50$); 170/317 (53.6%) and 30/50 (60%) of the single and multiple biopsy groups respectively were potent before RARP, as determined by an International Index of Erectile Function (IIEF-5) score of > 21, and were included in our study. All of these patients were also continent preoperatively defined by use of no pads or one pad as a security liner per day. We then excluded the patients who did not have bilateral nerve sparing and who were not D'Amico low risk (defined as Gleason biopsy $\leqslant 6$, PSA < 10, stage $\leqslant$ T2a) leaving 93 and 23 patients in the two groups (it is our practice not to perform bilateral nerve sparing in intermediate or high-risk patients). Finally, we matched the patients for PSA, leaving 50 and 23 patients in the single and multiple biopsy groups, respectively.

Study design and outcomes measurement

Patients were asked to provide demographic information and to complete self-administered versions of IIEF-5 questionnaire. In addition, presurgical clinical data such as number of biopsies, PSA, clinical stage and biopsy Gleason score were abstracted from medical records.

[1]LeFrak Center of Robotic Surgery, and Prostate Cancer, James Buchanan Brady Foundation Department of Urology, Weill Cornell Medical College of Cornell University, New York Presbyterian Hospital, New York, NY, USA. Correspondence: Dr P Sooriakumaran or Professor AK Tewari, Ronald P. Lynch Professor of Urologic Oncology, Director, LeFrak Institute of Robotic Surgery, and Institute of Prostate Cancer Institute, James Buchanan Brady Foundation Department of Urology, Weill Cornell Medical College of Cornell University, New York Presbyterian Hospital, 525 East 68th Street, Starr 900, New York, NY 10065, USA.
E-mail: sooriakumaran@gmail.com or ashtewarimd@gmail.com
Received 30 August 2011; revised 21 February 2012; accepted 25 March 2012; published online 26 April 2012

Patients completed outcomes questionnaires at postoperative follow-up appointments at 3 months and 6 months. Those who were unable to present for the follow-up had questionnaires dispatched via postal or electronic mail. Nonresponsive subjects were then contacted via telephone by a member of the research team at each of the above follow-up intervals to ensure receipt of the questionnaire in an attempt to minimize missing data. Patients were asked to report if they used any pads for urinary incontinence. Potency questionnaires consisted of questions two and three of the IIEF-5. A score of $\geqslant 3$ on both of these questions was considered necessary to fulfill our definition of potency. Data collection and follow-up correspondence was performed in compliance with the Health Insurance Portability and Accountability Act.

The primary endpoint for our analysis was postoperative functional outcomes, including potency and continence, at our previously mentioned follow-up intervals. Secondary endpoints were postoperative variables including console time, hematocrit drop, and surgical margins.

Statistical methods

Statistical analysis was performed using PASW version 17.0. (SPSS, Chicago, IL, USA), with statistical significance considered at $P<0.05$. χ^2 and Fisher's exact tests were used to compare baseline, postoperative and follow-up categorical variables, whereas Kruskal-Wallis tests were used to compare continuous variables between the two groups.

RESULTS

There were no significant differences between the two groups in age, body mass index, prostate volume, preoperative PSA, total cores during last biopsy and maximum percent cancer on core biopsy. The median number of biopsies in the multiple biopsy group was two, which was statistically significantly different when compared with the single biopsy group ($P<0.001$). The median interval between (last) biopsy date and date of surgery was 78 days and 82 days for the multiple and single biopsy groups, respectively ($P=0.897$) (Table 1).

We found no effect on postoperative continence as a result of multiple biopsies, with rates of 84% (83%) and 94% (96%) for the single (multiple) biopsy groups at 3 and 6 months, respectively ($P=0.88$; $P=0.77$) (Table 2). However, multiple biopsy patients had worse postoperative erectile function at 3 months, though this was not statistically significant, with 43% of such patients being potent compared with 64% of single biopsy patients ($P=0.25$). Potency recovery at 6 months was significantly worse in the multiple biopsy group (57% versus 80%, $P=0.03$) (Table 3).

There were very few patients with positive surgical margins to compare whether oncologic outcomes varied based on whether multiple biopsies were taken preoperatively or not. Console time was not significantly different between the multiple and single biopsy groups (103 min versus 96 min, $P=0.4$). Hematocrit drop (on postoperative day 1 compared with time of surgery) showed nonstatistically significant less bleeding in the single biopsy group (3.4% versus 1.7%, $P=0.82$) (Table 4).

DISCUSSION

Most studies of complications associated with prostate biopsy have focused on pain, hematuria, rectal bleeding and prostatitis.[4] Recently, there have been studies investigating urinary and erectile function after prostate biopsy.[2,3,5] There are few publications on preoperative and postoperative impact of serial prostate biopsies on active surveillance patients who ultimately undergo RARP. [5] This is especially relevant as one-third of men enrolled in AS may eventually require definitive surgical treatment.

It is not known whether serial prostate biopsies impact functional outcomes over time. Biopsies are now being performed with increased needle cores (typically 10–12 per session) and are more laterally directed toward the neurovascular bundles.[6,7] Thus, it is not unreasonable to postulate that repeat prostate biopsy may eventually compromise urinary and/or erectile function. However, this should not be a limitation in our study as both groups had comparable IIEF scores before surgery.

Additionally, transrectal needle biopsy results in peri-prostatic inflammation, and has the potential for bleeding and hematoma. Ikonen *et al*.[8] showed that 77% of the patients had visible hemorrhage on endorectal magnetic resonance imaging after a single biopsy, and found that it took 28 days for a radiologically obvious decrease in the amount of blood. This postbiopsy hemorrhage can lead to periprostatic inflammation and fibrosis, obliterating surgical planes of dissection, and making a future operation more technically challenging. A more difficult operation could result in inadvertent neural and vascular injury. It is reasonable to speculate that these factors may lead to decreased functional outcomes.

An article by Lavery *et al*.[9] addressed the impact of whether the functional outcomes of RARP candidates who would have been eligible for active surveillance were improved compared with RARP candidates who were not suitable for conservative management. These authors showed that active surveillance candidates could expect excellent functional outcomes after the surgery, and thus the added benefit of enrolling in a conservative management protocol may be minimal. However, as none of the patients actually underwent active surveillance, conclusions regarding any impact of multiple biopsies as part of an active surveillance protocol could not be made.

Other investigators have recently begun to delineate the short-term impact of prostate biopsies on ED. Tuncel *et al*.[10] analyzed erectile function in patients undergoing 10-core prostate biopsy at 1 month and 6 months post procedure. Results indicated a statistically significant difference between the prebiopsy IIEF-5 scores and postbiopsy scores at 1 and 6 months ($P<0.001$). The authors postulated that ED in their cohort could be attributed to

Table 1. Preoperative variables, baseline demographics and biopsy data

Variable (IQR)	*Multiple biopsy (n = 23)*	*Single biopsy (n = 50)*	P-*value*
Median age	60 (53, 65)	58 (53, 62)	0.30
Median BMI	26 (24, 29)	26 (24, 28)	0.46
Median PSA	5.5 (4, 8.3)	5.1 (4.6, 6.7)	0.77
Median number of biopsies	2 (2, 2)	1 (1, 1)	<0.001
Median cores of last biopsy	12 (12, 15)	12 (12–15)	0.58
Median total positive cores on last biopsy	1 (1, 1.3)	2 (1–3)	0.02
Median max percent cancer on last biopsy	10 (5, 23)	10 (5–25)	0.78
Median interval (days) between last biopsy and surgery	78 (54, 112)	82 (59, 98)	0.90

Abbreviations: BMI, body mass index; IQR, interquartile range.

Table 2. Continence outcomes in the two groups at each follow-up interval

Variable	*Multiple biopsy (n = 23)*	*Single biopsy (n = 50)*	P-*value*[a]
No. of patients continent (%)			
12 weeks follow-up	19 (83)	42 (84)	0.88
26 weeks follow-up	22 (96)	47 (94)	0.77

[a] χ^2 test.

Table 3. Potency outcomes in the two groups at each follow-up interval

Variable	*Multiple biopsy (n = 23)*	*Single biopsy (n = 50)*	P-*value*[a]
No. of patients with potency (%)			
12 weeks follow-up	10 (43)	32 (64)	0.25
26 weeks follow-up	13 (57)	40 (80)	0.03

[a] χ^2 test.

Table 4. Postoperative variables, pathologic and intraoperative data

Variable	*Multiple biopsy (n = 23)*	*Single biopsy (n = 50)*	P-*value*
Pathology Gleason (%)			0.68
6 or less	5 (23)	16 (33)	
3+4	13 (59)	25 (52)	
4+3	4 (18)	6 (13)	
8, 9, 10	0	1 (2)	
Path stage (%)			0.90
T2	20 (95)	47 (96)	
T3	1 (5)	2 (4)	
Positive surgical margin (%)	1 (4)	1 (2)	0.56
Median prostate volume (IQR)	45.9 (36, 69)	45 (37, 61)	0.73
Percentage cancer (IQR)	2 (1, 5)	3 (1, 5)	0.69
Median console time (IQR)	103 (87, 136)	96 (86, 116)	0.40
Median hematocrit drop	3.36	1.71	0.82
Estimated blood loss	150	150	0.91

Abbreviation: IQR, interquartile range.

direct neurovascular-bundle damage or secondary trauma such as nerve compression caused by hematoma or edema, a previous theory offered by Zisman *et al*.[3] Studies by Akbal *et al*.[11] investigated ED after saturation prostate biopsy. The median number of cores taken during prostate biopsy was 22 (range: 20–30). Results indicated 11.6% of patients experienced ED in the initial time period after saturation biopsy, a significant difference from baseline ($P = 0.01$); however, unlike the above mentioned study by Tuncel *et al*,[10] this difference was no longer apparent 6 months after the procedure. It is unclear why this saturation group showed improvement in comparison to patients receiving 10-core biopsy, as one would expect an increased number of cores sampled would lead to worse potency outcomes based on Zisman's hypothesis.[3] It would be beneficial for a future study to evaluate whether the number of cores obtained during prostate biopsy affects potency outcomes.

Fujita *et al*.[2] retrospectively analyzed 231 active surveillance patients to compare whether there was a correlation between increased number of biopsies and ED. Increased biopsy number was associated with a decrease in Sexual Health Inventory for Men score ($P = 0.04$) and a history of three or more biopsies was associated with a greater decrease in sexual health inventory for men than after two or fewer biopsies ($P = 0.02$). This decline was presumed to be due to nerve injury, either directly or as a result of biopsy fibrosis. There was no significant difference noted in lower urinary tract symptoms (measured by International Prostate Symptom score) regardless of the number of prostate biopsies performed. Continence was not evaluated. Thus, multiple biopsies *per se* can lead to ED; what is less clear is the impact of multiple biopsies on men who subsequently undergo radical prostatectomy.

In our study we assessed a cohort of patients who had prior negative biopsies or who were on an active surveillance regimen for a varying period of time and ultimately underwent RARP. The number of cores taken on last biopsy was equivalent between the multiple and single biopsy group ($P = 0.58$). Additionally, there was not any statistically significant difference between the date of (last) biopsy and the date of surgery when compared between the two groups ($P = 0.9$). We found no effect on postoperative continence as a result of multiple biopsies, with rates of 84% (83%) and 94% (96%) for the single (multiple) biopsy groups at 3 and 6 months, respectively ($P = 0.88$, $P = 0.77$). However, multiple biopsy patients had worse postoperative erectile function with 43% of such patients being potent compared with 64% of single biopsy patients at 3 months ($P = 0.25$). Potency recovery at 6 months was also significantly worse in the multiple biopsy group (57% vs 80%, $P = 0.03$). Console time did not vary between the groups (103 min vs 96 min, $P = 0.4$). Hematocrit drop (on postoperative day 1 compared with time of surgery) was not statistically significantly greater in the multiple biopsy group when compared with the single biopsy group (3.4% vs 1.7%, $P = 0.82$).

Although data was not obtained concerning the number of cores on each previous biopsy owing to the fact that most of these patients were referred from outside institutions, we compared the total number of cores on last biopsy. We were able to make the assumption that as there was no difference in total cores obtained on last biopsy between these two groups, the multiple biopsy group must have had a greater total number of cores taken overall. The statistically significant difference between the median numbers of biopsies in the two groups further supports this assumption. Additionally, the fact that there was no difference between the groups with respect to the date of biopsy and date of surgery means that we can assume that immediate inflammatory changes occurring as a result of the biopsy did not confound our results.

A potential explanation for the potency findings might be that biopsies damage the periprostatic nerves due to direct injury. Another hypothesis is that following multiple biopsies there is thrombophlebitis and arterial thrombosis in the prostatic vasculature that can lead to vasculogenic impotence. This could be investigated by examining radical prostatectomy specimens from the multiple biopsy and single biopsy cohorts and comparing the vascular insult in both groups. Our group is currently performing this work. One of the limitations of our study was the insufficient biopsy data, in terms of overall number of cores taken and interval between biopsies. These variables may impact the degree of inflammation and fibrosis, thus making for a more difficult dissection and possible inadvertent injury to the neurovascular bundle. Additionally, biopsy specimens were obtained from numerous physicians creating variability in the data based on the physicians' experience and method. Further, whether differences in potency outcomes between single and multiple biopsy patients are still present in the longer term (for example, 12 months postoperatively) need investigation with longer patient

follow-up. It may also be that more biopsies' patients undergo before surgery the worse their potency outcomes. Unfortunately, most patients in our multiple biopsy cohort had two biopsies, and thus we were unable to investigate any 'dose-response' effect. Lastly, the retrospective nature of our study and small sample size make definitive conclusions difficult to draw.

Nonetheless, despite its limitations, our study provides novel observations about a relatively unexplored hypothesis. Our results indicate a correlation between the number of biopsies performed in patients preoperatively and their post-RARP potency. These findings necessitate a higher powered, prospective study to further explore this hypothesis. Alternative strategies to diagnose prostate cancer in patients with initially negative biopsies and for monitoring disease in those on active surveillance should also be considered. Our group is investigating the role of magnetic resonance imaging in this capacity.

CONCLUSIONS

We have observed that patients subject to multiple preoperative biopsies are more likely to become impotent postoperatively than those who undergo surgery after a single biopsy. Patients should be counseled about the increased risk of impotence if they undergo multiple diagnostic biopsies or opt for active surveillance as initial management and end up undergoing surgery at a later date.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

Dr Prasanna Sooriakumaran is an Intuitive Surgical Clinical Fellow; Dr Ashutosh Tewari is the endowed Ronald P Lynch Professor of Urologic Oncology, the Director of the Prostate Cancer Institute, and Director of the Lefrak Center for Robotic Surgery, and has received grants in the past from Intuitive Surgical Inc. and the National Institute of Health. However, this work was not supported by such grants.

REFERENCES

1 Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin* 2010; **60**: 277–300.
2 Fujita K, Landis P, McNeil BK, Pavlovich CP. Serial prostate biopsies are associated with an increased risk of erectile dysfunction in men with prostate cancer on active surveillance. *J Urol* 2009; **182**: 2664–2669.
3 Zisman A, Leibovici D, Kleinmann J, Siegel YI, Lindner A. The impact of prostate biopsy on patient well-being: a prospective study of pain, anxiety and erectile dysfunction. *J Urol* 2001; **165**: 445–454.
4 Raaijmakers R, Kirkels WJ, Roobol MJ, Wildhagen MF, Schrder FH. Complication rates and risk factors of 5802 transrectal ultrasound-guided sextant biopsies of the prostate within a population-based screening program. *Urology* 2002; **60**: 826–830.
5 Zisman A, Leibovici D, Kleinmann J, Cooper A, Siegel Y, Lindner A. The impact of prostate biopsy on patient well-being: a prospective study of voiding impairment. *J Urol* 2001; **166**: 2242–2246.
6 Ochiai A, Babaian RJ. Update on prostate biopsy technique. *Curr Opin Urol* 2004; **14**: 157–162.
7 Eichler K, Hempel S, Wilby J, Myers L, Bachmann LM, Kleijnen J. Diagnostic value of systematic biopsy methods in the investigation of prostate cancer: a systematic review. *J Urol* 2006; **175**: 1605–1612.
8 Ikonen S, Karkkainen P, Kivisaari L, Salo JO, Taari K, Vehmas T *et al.* Endorectal magnetic resonance imaging of prostatic cancer: comparison between fat-suppressed T2-weighted fast spin echo and three-dimensional dual-echo, steady-state sequences. *Eur Radiol* 2001; **11**: 236–241.
9 Lavery HJ, Levinson AW, Brajtbord JS, Samadi DB. Candidacy for active surveillance may be associated with improved functional outcomes after prostatectomy. *Urol Oncol* 2011, e-pub ahead of print.
10 Tuncel A, Kirilmaz U, Nalcacioglu V, Aslan Y, Polat F, Atan A. The impact of transrectal prostate needle biopsy on sexuality in men and their female partners. *Urology* 2008; **71**: 1128–1131.
11 Akbal C, Turker P, Tavukcu HH, Simsek F, Turkeri L. Erectile function in prostate cancer-free patients who underwent prostate saturation biopsy. *Eur Urol* 2008; **53**: 540–544.