Published in final edited form as:

Int Urol Nephrol. 2016 September ; 48(9): 1445–1452. doi:10.1007/s11255-016-1336-6.

Midline lesions of the prostate: role of MRI/TRUS fusion biopsy and implications in Gleason risk stratification

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Abstract

Purpose—MRI-TRUS fusion biopsy (FBx) has proven efficacy in targeting suspicious areas that are traditionally missed by systematic 12-core biopsy (SBx). Midline prostate lesions are undersampled during SBx, as traditional approaches aim laterally during TRUS biopsy. The aim of our study was to determine the utility of FBx for targeting midline lesions identified on multiparametric MRI (mpMRI).

Methods—A review was performed of a prospectively maintained database of patients undergoing mpMRI followed by FBx and SBx from 2007 to 2015. Midline location was defined as any lesion crossing the midline on axial imaging and involving both prostatic lobes. Index lesion was defined as lesion with highest Gleason score on biopsy. Patient demographic, imaging, and histopathologic data were collected. Multivariate logistic regression was conducted to determine independent predictors of having clinically significant (CS) cancer (Gleason ≥ 7) in midline lesions.

Results—Out of 1266 patients, we identified 202 suspicious midline lesions in 190 patients [median (IQR) age 63 (10) years; PSA 7.6 (6.6)]. Eighty-eight (46.3 %) patients had cancer detection on FBx of midline lesion. A midline target represented the index lesion of the prostate in 63/190 (33.2 %) patients. Risk category upgrading based on FBx of a midline lesion compared to

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of interest NIH and Philips Healthcare have a cooperative research and development agreement. NIH and Philips share intellectual property in the field.

SBx occurred in 45/190 patients (23.7 %). On multivariate analysis, higher PSA ($p = .001$), lower MRI-derived prostate volume ($p < .001$), and moderate–high or high suspicion on mpMRI ($p = .014$) predicted CS cancer in midline lesions.

Conclusions—MRI-TRUS FBx facilitates sampling of midline lesions. Integration of mpMRI and FBx for targeting of midline lesions improves detection of CS prostate cancer.

Keywords

Prostate cancer; Multiparametric MRI; Fusion biopsy; Midline

Introduction

The current prostate cancer (PCa) evaluation paradigm involving PSA screening followed by systemic 12-core biopsy has been criticized for both overdiagnosis of low-risk cancers and underdiagnosis of clinically significant cancers, leading to potentially inappropriate treatments and adverse outcomes. Over the last several years, various extended and saturation biopsy schemes have been studied with respect to improving prostate cancer detection [1, 2]; however, the optimal number and location of prostate biopsies is still debated. Current standard of care in patients with prostate cancer suspicion, defined as an elevated serum PSA and/or abnormal digital rectal exam (DRE), is to perform transrectal ultrasound (TRUS)-guided systematic 12-core biopsy (SBx). This approach is designed to primarily diagnose peripheral zone lesions based on the standard biopsy template [3]. During SBx, urologists typically aim laterally within the prostate in order to maximize peripheral zone sampling and to avoid risk of urethral injury. Therefore, in this routine protocol, cores sampling the midline peripheral zone are not acquired. Several studies have assessed the efficacy of adding midline cores to the standard scheme, yet most demonstrate little to no benefit of randomly sampling the midline prostate routinely [4–6].

Recent advances in prostate imaging techniques and technology, such as development of multiparametric MRI (mpMRI), have allowed for the precise identification of prostatic lesions [7]. This, in turn, has led to the development of novel MR-based strategies such as MRI/TRUS fusion-guided biopsy to target and sample specific areas within the prostate suspicious for cancer as opposed to performing unguided systematic biopsies throughout the prostate [8–10]. Several preliminary studies have shown that MRI/TRUS fusion-guided biopsy tends to outperform systematic 12-core biopsy in the detection of clinically significant high-risk cancers [11–13]. Furthermore, MRI/TRUS fusion-guided biopsy has proven to be effective in accurately targeting lesions in regions of the prostate that are traditionally missed or hard to reach with systematic 12-core biopsy, such as the anterior prostate, transition zone, distal apical, and posterior subcapsular regions [14–17].

To further study the utility of MRI/TRUS fusion-guided biopsy, we hypothesized that midline lesions may be undersampled with systematic 12-core biopsy, and that MRI/TRUS fusion-guided biopsy has added value in patients with midline lesions identified on mpMRI.

Materials and methods

Study population

Retrospective review was performed of 1266 consecutive patients from August 2007 to January 2015 who underwent initial mpMRI followed by MRI/TRUS fusion-guided biopsy and systematic 12-core biopsy for prostate cancer suspicion. These patients had been enrolled in an institutional review board-approved prospective trial of mpMRI and fusion biopsy ([NCT00102544](#)). All patients were seen at the National Cancer Institute, National Institutes of Health for elevated PSA or abnormal DRE. If patient received multiple mpMRIs and/or fusion biopsies during this time period, only the first session was included for analysis.

Image acquisition and interpretation

Scans were acquired using a 3 Tesla scanner (Achieva, Philips Healthcare, Best, The Netherlands). An endorectal coil (BPX-30, Medrad, Pittsburgh, Pennsylvania, USA) tuned to 127.8 MHz and a 16-channel surface/cardiac coil (SENSE, Philips Medical Systems, Best, The Netherlands) were utilized during the procedure. IV Gadolinium contrast (Magnevist 46.9 %) was administered at a dose of .1 mmol/kg. The mpMRI included triplanar T2-weighted turbo spin echo (T2 W MRI), diffusion-weighted MRI (DW MRI) with apparent diffusion coefficient (ADC) mapping, high b value DW MRI ($b = 2000 \text{ s/mm}^2$), and axial dynamic contrast-enhanced imaging (DCE MRI). Each prostate mpMRI was evaluated by two genitourinary radiologists (P.L.C. and B.T. with 16 and 8 years of experience in prostate MRI, respectively), and each detected lesion was assigned a suspicion score according to a modified version of the previously validated NIH suspicion scoring system [1 = low, 2 = low-moderate, 3 = moderate, 4 = moderate-high, 5 = high] [18]. PIRADSv2, which currently stands as the recommendation for prostate MRI interpretation, was not utilized since prospective data acquisition for this study began in 2007; PIRADSv2 was not instituted until January 2015 and is currently being validated [19].

Biopsy protocol

Patients who had suspicious areas identified on mpMRI underwent both MRI/TRUS fusion-guided biopsy and systematic 12-core biopsy in the same session utilizing an office-based platform (UroNav, Philips/In Vivo Corp, Gainesville, FL, USA) [20]. In addition to the systematic 12-core biopsy, two targeted cores were obtained per lesion (axial/sagittal plane) pre-identified on mpMRI [21]. An $18 \times 25 \text{ cm}$ spring-loaded core needle biopsy instrument (Bard Max-Core) was utilized to obtain biopsy specimens. Biopsy specimens were evaluated and assigned with Gleason scores by a senior genitourinary pathologist (M.J.M.) with 26 years of experience.

Study design

Patients with midline lesions found on mpMRI in the peripheral zone or transition zone were identified. Midline location was defined as any lesion crossing the midline on axial imaging and involving both prostatic lobes. Lesion location, MRI suspicion score (NIH SS), tumor diameter, Gleason scores, and percent core involvement were recorded. For per-patient

predictive analysis, only the midline lesion with the highest Gleason score and percent core involvement was included for patients with multiple midline lesions found on mpMRI. All patient data, including age, race, pre-biopsy serum PSA, prior biopsy history, and MRI-calculated prostate volume, were similarly collected for per-patient analyses.

Cancer detection rate (CDR) for midline lesions was tabulated on a per-lesion and per-patient basis. Index lesion was defined as the highest Gleason score lesion among all biopsy-proven specimens identified by either systematic or targeted biopsy. When Gleason scores were equal, the lesion with highest percent core involvement was considered as the index lesion. For disease risk categorization, low-risk disease was defined as Gleason 6, intermediate risk as Gleason 7, and high risk as Gleason 8. Clinically significant disease was defined as intermediate- or high-risk disease.

Statistical analysis

Statistical analysis was performed using STATA version 13.0 (StataCorp LP, College Station, TX, USA). Wilcoxon rank sum test was used to compare distribution of continuous variables. Pearson Chi-square and Fisher's exact test were used to compare proportions of categorical variables. Spearman rank correlation coefficient was utilized to describe the association between two variables. Univariate and multivariate logistic regression analyses were performed to identify the predictors of presence of a suspicious midline lesion on mpMRI and cancer detection. Statistical significance was defined as two-sided p value of less than .05.

Results

Descriptive analysis

Of 1266 patients who underwent mpMRI and fusion biopsy during the study period, 202 suspicious midline lesions were identified on mpMRI in 190 (15.0 %) patients. Patient demographics are displayed in Table 1. Median age (IQR) and PSA (IQR) for patients with midline lesions were 63 (10) years and 7.6 (6.6) ng/ml, respectively. A negative family history of prostate cancer ($p = .021$) and high PSA ($p = .028$) predicted identification of a suspicious midline prostate lesion on mpMRI. Midline lesion characteristics are summarized in Table 2. Overall cancer detection rate (CDR) for midline lesions was 44.1 % (89/202) [CDR 26/100 (26 %) in peripheral zone; CDR 63/102 (61.8 %) in transition zone], with 69/89 midline lesions (77.5 %) harboring intermediate- or high-risk disease. On a per-patient basis, the CDR was 46.3 % (88/190), with a midline lesion representing the index lesion of the prostate in 33.2 % of patients (63/190). Targeted fusion biopsy of a midline lesion yielded higher-risk disease relative to systematic 12-core biopsy in 23.7 % (45/190) of patients, with 40 of these 45 patients (88.9 %) upgraded to intermediate- or high-risk disease. In these 40 patients, 34 clinically significant cancers (Gleason sum ≥ 7) found on targeted biopsy of a midline lesion would have been missed with systematic 12-core biopsy alone (Figs. 1, 2). Furthermore, only five total low-risk cancers (Gleason 6) were identified by targeted biopsy of a midline lesion when 12-core random biopsy yielded no disease. Therefore, 6.8 clinically significant cancers were found for every one additional low-risk cancer detected by targeted biopsy of a midline lesion.

Predictive analysis

Multivariate logistic regression was performed to identify predictors for presence of cancer on biopsy of midline lesions (Table 3). High PSA (1.130 [1.04–1.22], $p = .003$), low MRI-derived prostate volume (.817 [.74–.91], $p < .001$), high MRI suspicion score (NIH SS 3; 7.931 [1.54–40.76], $p = .013$; NIH SS 4,5; 11.029 [1.68–72.23], $p = .012$), and anterior lesion location (4.045 [1.68–9.76], $p = .002$) remained independent predictors for having a positive midline lesion.

In addition, multivariate logistic regression analysis was performed to determine predictors for presence of clinically significant (Gleason score ≥ 7) midline lesions (Table 4). Higher PSA (1.164 [1.07–1.27], $p = .001$), lower MRI-derived prostate volume (.801 [.71–.90], $p < .001$), and NIH suspicion score 4,5 (19.055 [1.80–201.31], $p = .014$) predicted presence of clinically significant cancer in midline lesions. NIH SS and anterior lesion location were significantly correlated in our cohort ($r = .4103$, $p < .0001$); Similarly, NIH SS and tumor diameter were also significantly correlated ($r = .7024$, $p < .0001$). The confounding between NIH SS and these two variables (anterior lesion location, tumor diameter) was controlled through multivariate analysis with NIH SS remaining the independent predictor out of two for clinically significant disease in both cases.

Discussion

The indications for use of imaging and targeted biopsy for prostate cancer have expanded to include diagnosis, staging, and surveillance [22–24]. The current study aims to expand on its potential role in the detection and sampling of midline lesions where SBx may be inadequate. Several studies have assessed the utility of adding midline prostate cores to the standard systematic 12-core biopsy template in order to increase yield of cancer detection and improve sensitivity. One study reported that only 10 additional cancers among 425 patients (2.3 %) were diagnosed on the sole basis of midline biopsies in the context of a 21-sample needle biopsy protocol [5]. While evaluating the role of additional biopsies, Epstein et al. [6] demonstrated that while posterolateral needle biopsies added benefit, midline biopsies did not appreciably increase the detection of cancer. Another study evaluated the utility of adding one midline peripheral zone core to the standard 12-core biopsy protocol and found no appreciable benefit in detecting occult midline prostate cancer [4]. Consequently, the authors concluded that adding indiscriminate TRUS biopsy cores may be limited in sensitivity and posited that biopsy under the guidance of mpMRI may be more beneficial.

MpMRI and targeted fusion biopsy have demonstrated efficacy in targeting areas of the prostate that can typically be missed with systematic 12-core biopsy. Baco et al. [25] demonstrated in 211 patients that targeted biopsy significantly enhanced accuracy in diagnosing clinically significant anterior prostate cancer. The utility of targeted fusion biopsy has also been demonstrated in difficult-to-biopsy subcapsular regions and distal apical prostate lesions [15, 16].

During standard 12-core TRUS biopsy, urologists typically aim laterally to target the regions of the prostate with highest peripheral zone density as well as avoid unintentional injury to

the urethra. The sampling of midline targets under MRI/TRUS fusion potentially allows better needle guidance due to improved visualization of the urethra and may limit post-biopsy complications such as hematuria, which is an area currently under investigation. We surmised that midline lesions of the prostate, both in the peripheral zone and transition zone, may be undersampled with conventional TRUS biopsy. Therefore, we sought to assess the importance of midline prostatic lesions identified by mpMRI and the ability of fusion biopsy to target midline lesions.

Midline lesions seem to be fairly prevalent in our cohort, as a suspicious midline lesion was detected on mpMRI in 15 % of patients. Importantly, midline lesions are not only often positive on fusion biopsy (88/190, 46 %), but also are likely to harbor clinically significant disease (69/88; 78 %). Furthermore, such lesions represented the index lesion of the prostate in 33 % of patients who harbor midline lesions.

On multivariate analysis, higher PSA, lower MRI-calculated prostate volume, and higher MRI suspicion score remained independent predictors for having a clinically significant positive midline lesion. Higher PSA implies more aggressive cancer, which in turn leads to greater likelihood of having an intermediate- or high-risk midline lesion. The connection of prostate volumes with yield of targeted fusion biopsy is interesting and largely unexplored from a mechanistic standpoint. A study by Walton-Diaz et al. [26] illustrated that overall cancer detection rate with fusion biopsy was inversely correlated with prostate size. Prostates under 40 mL in volume yielded a cancer detection rate of 71 %, whereas the detection rates for prostates 55–69.9 mL (where our patient cohort falls) was 46.9 %. It is possible that imaging and/or fusion technology accuracy is impacted with enlarged prostate glands, leading to lower yields. For instance, larger prostates may make co-registration of MR and US more challenging due to presence of an intravesical lobe, intraprostatic calcifications, or a large heterogeneous transition zone. Furthermore, presence of high PSA and low prostate volume in these patients implies that a higher PSA density might play a role in detection of cancer in the midline lesions.

We found a consistent positive trend between MRI suspicion score and cancer detection rates in midline lesions; as NIH SS increased, the likelihood of having a clinically significant positive midline lesion increased. Importantly, this adds value to use of mpMRI parameters in predicting the final biopsy pathology of prostatic lesions, including midline lesions, as a consistent relationship has been repeatedly demonstrated.

Interestingly, both anterior lesion location and tumor diameter were associated with having a CS midline lesion on univariate analysis, yet did not meet statistical significance on multivariate analysis. These findings are in concordance with prior studies that demonstrated anterior location and larger target diameter to be associated with a higher targeted biopsy positivity rate [27, 28]. Yet, in both of the aforementioned studies, degree of suspicion on MRI remained the most powerful predictor of significant cancer on multivariate analysis. Therefore, mpMRI-assigned lesion suspicion score, relative to lesion location or lesion size, may be the most influential variable with respect to predicting the positivity and grade of a suspicious lesion.

The strengths of this study include a large patient cohort and standardized mpMRI and biopsy protocols. However, a number of limitations exist. The population from which these patients were identified consists of a large referral population with elevated PSA and prior biopsy history. A significant proportion (43 %) of our patients had prior negative prostate biopsy, which might have enriched our cohort with prostate cancer lesions likely to be missed by systematic biopsy. However, prior biopsy history did not predict the presence of midline lesion in our cohort, potentially increasing the generalizability of our results to both biopsy-naïve and prior biopsy populations. Finally, our institution represents one with considerable experience with this technology, but such results have been found to be reproducible in other settings [29].

Conclusion

MpMRI is able to accurately detect and characterize midline prostatic lesions, which were identified in 15 % of our patient cohort undergoing mpMRI with subsequent fusion biopsy. Midline lesions were often missed with systematic 12-core biopsy, and performing targeted fusion biopsy on an mpMRI-identified midline lesion yielded higher-risk disease than that obtained by systematic biopsy alone in 24 % of our patients. In our cohort, high PSA, low prostate volume, and higher MRI suspicion score predicted clinically significant cancer in these midline lesions. Our study demonstrates the utility of mpMRI and integrating targeted fusion biopsy in the workup of patients with midline lesions found on mpMRI.

Acknowledgments

This research was supported by the Intramural Research Program of the National Institutes of Health (NIH), National Cancer Institute, Center for Cancer Research, and the Center for Interventional Oncology. NIH and Philips Healthcare have a cooperative research and development agreement. NIH and Philips share intellectual property in the field. This research was also made possible through the National Institutes of Health Medical Research Scholars Program, a public-private partnership supported jointly by the NIH and generous contributions to the Foundation for the NIH from Pfizer Inc., The Doris Duke Charitable Foundation, The Alexandria Real Estate Equities, Inc. and Mr. and Mrs. Joel S. Marcus, and the Howard Hughes Medical Institute, as well as other private donors. For a complete list, please visit the Foundation Web site at: <http://fnih.org/work/education-training-0/medical-research-scholars-program>.

Abbreviations

FBx	MRI/TRUS fusion-guided biopsy
SBx	Systematic 12-core biopsy
mpMRI	Multiparametric magnetic resonance imaging
TRUS	Transrectal ultrasound
CS	Clinically significant
PSA	Prostate-specific antigen
DRE	Digital rectal exam
CDR	Cancer detection rate

NIH SS	NIH MRI suspicion score
PCa	Prostate cancer
IQR	Interquartile range
OR	Odds ratio
CI	95 % Confidence interval

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Fig. 1.

Patient is a 62-year-old male with PSA 6.12 ng/mL. Axial T2-weighted MR image shows a hypointense area in the midline to left apical peripheral zone (tumor diameter 1.7 cm; NIH SS 3) (**a**). The apparent diffusion coefficient (ADC) map shows a corresponding hypointense area (**b**), and the high $b = 2000$ diffusion-weighted MR image demonstrates hyperintensity (**c**). The permeability map for the dynamic contrast enhancement (DCE) sequence indicates early strong enhancement within the lesion (**d**). 3-D illustration of targeted fusion biopsy and systematic biopsy cores from biopsy session utilizing Uronav system; targeted fusion biopsy cores (1, 2) revealed Gleason 3 + 4 disease, while all 12 systematic biopsy cores were benign on pathology (**e**). Prostate whole-mount post-radical prostatectomy confirmed Gleason 3 + 4 cancer present in the midline to left apical peripheral zone region (**f**)

Fig. 2.

Patient is a 62-year-old male with PSA 9.79 ng/mL. Axial T2-weighted MR image shows a hypointense area in the midline mid-anterior central zone (tumor diameter 2.7 cm; NIH SS 4) (a). The apparent diffusion coefficient (ADC) map shows a corresponding hypointense area (b), and the high $b = 2000$ diffusion-weighted MR image demonstrates hyperintensity (c). The permeability map for the dynamic contrast enhancement (DCE) sequence indicates early strong enhancement within the lesion (d). 3-D illustration of targeted fusion biopsy and systematic biopsy cores from biopsy session utilizing Uronav system; targeted fusion biopsy cores (1, 2) revealed Gleason 4 + 3 disease, while all 12 systematic biopsy cores were benign on pathology (e). Prostate whole-mount post-radical prostatectomy confirmed Gleason 4 + 3 cancer present in the midline mid-anterior central zone (f)

Demographics and clinical characteristics of patients with midline prostatic lesions relative to patients without midline lesions identified on mpMRI

Table 1

Variable	Midline lesion present	No midline lesion	<i>p</i> value
<i>N</i>	190	1076	–
Age, median (IQR)	63 (10)	63 (11)	.1788
PSA, median (IQR) [ng/mL]	7.6 (6.6)	6.4 (5.8)	.0032
BMI, median (IQR) [kg/m ²]	27.5 (4.8)	27.8 (5.2)	.8974
Smoking history [<i>n</i> (%)]	24 (13.33)	161 (15.71)	.501
MRI prostate volume, median (IQR) [m ³]	47.5 (30)	49 (33)	.5269
Family history of PCa [<i>n</i> (%)]	41 (23.16)	326 (31.90)	.021
<i>Race</i>			
White/others [<i>n</i> (%)]	166 (87.37)	905 (84.11)	.277
Black [<i>n</i> (%)]	24 (12.63)	171 (15.89)	
History of prior negative biopsy [<i>n</i> (%)]	84 (44.21)	477 (44.33)	1.0
History of PCa [<i>n</i> (%)]	71 (45.81)	391 (45.05)	.861

Table 2

Midline lesion characteristics

Midline lesion characteristics	N (%)
<i>Location</i>	
Posterior prostate	119 (58.9)
Anterior prostate	83 (41.1)
<i>NIH suspicion score</i>	
Low	40 (19.8)
Low–moderate	4 (2.0)
Moderate	90 (44.6)
Moderate–high	24 (11.9)
High	36 (17.8)
Not reported	8 (4.0)
<i>Gleason distribution from fusion biopsy</i>	
No cancer	113 (55.9)
Gleason 6 (low risk)	20 (9.9)
Gleason 7 (intermediate risk)	37 (18.3)
Gleason 8 (high risk)	32 (15.8)

Table 3
Multivariate logistic regression for predicting the presence of biopsy-proven cancer in suspicious midline lesion

Variable	Univariate OR [CI]	p value	Multivariate OR [CI]	p value
Age	1.009 [.97–1.05]	.667		
PSA	1.099 [1.04–1.16]	<.001	1.130 [1.04–1.22]	.003
BMI	1.006 [.94–1.07]	.848		
Race (white/others)	.575 [.24–1.37]	.210		
Smoking history	1.310 [.55–3.10]	.540		
Family history of PCa	1.217 [.60–2.45]	.582		
Prior biopsy	.778 [.37–1.62]	.502		
Prior negative biopsy	.925 [.52–1.64]	.791		
History of PCa	.993 [.53–1.87]	.983		
MRI volume (per 5 ml)	.873 [.813–.937]	<.001	.817 [.74–.91]	<.001
Tumor diameter (mL)	1.171 [1.11–1.24]	<.001	1.053 [.98–1.13]	.153
NIH SS 1;2 (reference category)	1	–	–	–
NIH SS 3	11.077 [2.50–49.17]	.002	7.931 [1.54–40.76]	.013
NIH SS 4;5	80.182 [16.73–384.20]	<.001	11.029 [1.68–72.23]	.012
Anterior location	7.792 [4.06–14.94]	<.001	4.045 [1.68–9.76]	.002

OR odds ratio, CI 95 % confidence interval

Multivariate logistic regression for predicting the presence of biopsy-proven clinically significant cancer in suspicious midline lesion

Table 4

Variable	Univariate OR [CI]	p value	Multivariate OR [CI]	p value
Age	1.004 [.96–1.05]	.853		
PSA	1.123 [1.06–1.18]	<.001	1.164 [1.07–1.27]	.001
BMI	1.005 [.94–1.07]	.882		
Race (white/others)	.635 [.27–1.51]	.302		
Smoking history	.8 [.32–1.98]	.630		
Family history of PCa	1.136 [.55–2.33]	.727		
Prior biopsy	.957 [.48–2.05]	.910		
Prior negative biopsy	1.258 [.69–2.28]	.449		
History of PCa	.741 [.38–1.44]	.374		
MRI volume (per 5 ml)	.880 [.82–.95]	.001	.801 [.71–.90]	<.001
Tumor diameter (mL)	1.176 [1.11–1.24]	<.001	1.068 [.99–1.15]	.070
NIH SS 1;2 (reference category)	1	–	–	–
NIH SS 3	10.091 [1.29–78.66]	.027	6.892 [.77–61.92]	.085
NIH SS 4;5	121.571 [15.27–967.69]	<.001	19.055 [1.80–201.31]	.014
Anterior location	5.249 [2.77–9.96]	<.001	1.63 [.62–4.29]	.319

OR odds ratio, CI95 % confidence interval