ORIGINAL PAPER

TRAUMA AND RECONSTRUCTIVE UROLOGY

'Real-time sonoelastography' in anterior urethral strictures: A novel technique for assessment of *spongiofibrosis*

Shyam Manoharlal Talreja, Sher Singh Yadav, Vinay Tomar, Neeraj Agarwal, Usha Jaipal, Shivam Priyadarshi

Department of Urology, SMS Medical College and Hospital, Jaipur, India

Citation: Talreja SM, Yadav SS, Tomar V, Agarwal N, Jaipal U, Priyadarshi S. Real-time Sonoelastography' in anterior urethral strictures: A Novel technique for assessment of *Spongiofibrosis*. Cent European J Urol. 2016; 69: 417-424.

Article history
Submitted: March 6, 2016
Accepted: Sept. 26, 2016
Published online: Nov. 30, 2016

Corresponding author
Shyam Manoharlal Talreja
SMS Medical College
and Hospital
Department of Urology
RD Hostel, SMS Campus
302004 Jaipur, India
phone: +91 141 0810 733 0833
alrejashyam@gmail.com

Introduction Spongiofibrosis assessment is critically important in the evaluation of anterior urethral strictures as its severity is directly proportional to stricture recurrence and thus affects management. Retrograde urethrography (RGU) is ineffective in the evaluation of spongiofibrosis. Sonourethrography (SUG) delineates it but does not accurately estimate its depth. Real-time elastography (RTE), a newer technique that not only attempts a qualitative but also quantitative estimation of spongiofibrosis (tissue stiffness) which results due to underlying pathological processes.

Material and methods In the present study, various elastographic patterns and strain ratios in anterior urethral stricture patients were studied and compared to operative and histopathological findings. Sixty-three RGU diagnosed anterior urethral stricture cases were taken and re-evaluated by SUG and SE by another radiologist who was blinded to the findings of the RGU. Strain patterns and ratios of spongiofibrotic segments were documented and compared with operative findings as gold standard.

Results Blue pattern on RTE showed 100% concordance with severe fibrosis as evaluated against histopathological findings whereas green pattern showed 87.5% concordance with moderate degree of fibrosis. Severe degree of fibrosis cases, confirmed on histopathology had a significantly higher mean strain ratio (10.51 ±2.297) as compared to moderate degree (6.33 ±2.353) ($p < 0.001$ S).

Conclusions Real time sonoelastography in the evaluation of spongiofibrosis not only assesses it qualitatively but also quantifies it. Strain ratios are statistically better indicators for estimating spongiofibrosis.

Key Words: anterior urethral strictures ‹› elastography ‹› retrograde urethrography strain pattern strain ratio

INTRODUCTION

Assessment of spongiofibrosis is crucial in the evaluation of stricture urethra as its severity is proportional to the frequency of stricture recurrence and may dictate management [1–4]. Retrograde urethrography (RGU) is the most commonly used imaging modality, but it fails to delineate spongiofibrosis. Sonourethrography (SUG) introduced by McAninch et al. [5] in 1988 provides a good estimation of spongiofibrosis but it lacks in providing quantitative information on tissue elastic properties and does not accurately estimate the depth of spongiofibrosis [1, 6, 9].

Elasticity of a tissue is an important characteristic and is deeply related with the pathological changes associated with fibrosis, inflammation, ageing and neoplastic process. The affected tissues are harder than their normal counterpart [10–13]. Therefore, for proper assessment of spongiofibrosis, not only horizontal extent but depth and density of the tissue is also important.

Real-time sonoelastography (RTE) is a non-invasive technique which aims at imaging tissue stiffness both qualitatively and quantitatively [7, 14–17]. This is the first study describing strain patterns and ratios on elastography in the evaluation of anterior stricture urethral diseases which provides such detailed findings. Hence in the present study, we aim to study various elastography patterns and strain ratios in patients of anterior stricture urethra and also

doi: 10.5173/ceju.2016.808

to compare the above parameters with endoscopic or histopathological findings.

MATERIAL AND METHODS

This study is a hospital based descriptive, observational, comparative study based on Post hoc data, done from August 2014 to February 2015.

Inclusion criteria:

(A) RGU proven anterior urethral stricture cases

Exclusion criteria:

(A) History of recent traumatic catheterization.
(B) Patients who are unable to void during RTE
(C) Active urinary tract infection.
(D) Meatal or sub meatal stricture.
(E) Patients who did not undergo or gave negative consent for treatment were excluded from the study.

A total of sixty-three patients (Post Hoc analysis) satisfying the inclusion and exclusion criteria were included in the study. Prior informed written consent was obtained.

These patients then underwent further evaluation by sonourethrography followed by real time sonoelastography (HITACHI HI-VISION PREIRUS) with a linear (L-74M) 5–13 MHz transducer, kept perpendicular to the skin surface. SUG was performed as described by McAninch et al. [5] using a 10 to 12 F Foleys catheter with an injection of saline. The SUG probe was 7–12 MHz linear array transducer kept on the ventral surface of the penis. The conventional ultrasound examination included B-mode images on which spongiofibrosis appeared as areas of hyperechogenicity.

Sonourethrography was followed by real-time sonoelastography and included documentation of strain patterns and calculations of strain ratios. The urethra was subjected to gentle compression and decompression by a specific probe. The adequacy of the compression was indicated by the RTE scale on the screen while scanning. Images were considered optimum when the adequacy criterion for compression was optimally attained.

The sonoelastographic pattern (elastograms) of urethral spongiofibrosis after optimum compression was evaluated and categorized into three groups according to the stiffness of the tissue. Tissue stiffness was depicted in a continuum of fundamental colours from red to green to blue designating soft (i.e high strain), intermediate (equal strain) and hard (no strain) tissue, respectively [14, 18]. To avoid spurious results, the procedure was repeated at least once. The strain ratio was calculated as an independent parameter irrespective of B mode or elastogram characteristics.

During RTE, the radiologist manually selected two regions of interests (ROI). One ROI was for the targeted lesion and the other was for the normal surrounding tissue also known as reference ROI. Both ROI were of the same size to enable the areas to be compared and strain ratio calculated [18, 19]. Strain ratio is the average strain in the reference area divided by the average strain in the targeted lesion and is automatically generated by the elastography software. The ROI needs to be set as such that it includes sufficient surrounding tissue because elasticity values are displayed relative to the average strain inside the ROI. To avoid strain decay, reference tissue was taken at the same depth as the lesion or with a difference in depth no more than 10 mm. For calculation of strain ratio, 5-6 images per patient were taken and the image with optimum compression was chosen for further evaluation. Thus spongiofibrosis was estimated via strain pattern and ratio for each patient and the data was documented and analysed.

All the cases were managed either by visual internal urethrotomy (VIU) or open surgery according to RGU findings. During VIU, the assessment of stricture severity was done according to the data elicited in Table 1 [1, 8]. It was graded as mild (involving <1/3rd of corpus spongiosum thickness), moderate (1/3–1/2 and severe (>1/2) [8]. In the remaining open surgery cases, elastography findings were compared with the operative and histopathological findings. Histopathological assessment of stricture segments for the degree of spongiofibrosis was performed on specimens obtained during open surgery cases, for validation of intra-operative grading. Haematoxylin and eosin, and Massons' trichome stained slides were evaluated for the same.

Statistical analysis was done using computer software Primer and MS Excel. The qualitative data were expressed in proportions and percentages and the quantitative data as mean and standard deviations. The difference in proportion was analysed by using chi square test and the difference in means was analysed by using the student T test and one way ANOVA, which were further analysed by using post hoc test (Tukey test). Concordance rate was used to evaluate the agreement between two different investigations. Level of significance

Table 1. *Parameters for assessing severity of spongiofibrosis*

	Mild	Moderate	Severe
SUG (degree of narrowing)	<33%	33-50%	>50%
Operative findings:			
Colour of mucosa	Pink	Grey	White
Difficulty in incision	Mild	Moderate	Severe

SUG – sonourethrography

Table 2. *Association of RTE colour patterns with cystoscopic findings*

			Cystoscopy finding					
			Colour of mucosa			Difficulty in incision		
Elastographic Patterns	Total no. of strictures on RTE	Total no. of strictures on Cystoscopy	Pink	Grey	White	Mild	Moderate	Severe
Blue	33	11	0	0	11	0	3	7
Green	25	17	0	15	2	8	8	0
Red	10	10	7	3	0	2	1	0
	68	38	7	18	13	10	12	7
Chi-square test				p <0.001 S			p <0.001 S	

no. – number, S – significant, RTE – real-time sonoelastography

for tests was determined at 95% confidence interval (p <0.05).

RESULTS

Mean age of patients was 35.10 ±9.3 (ranging from 21 to 56 years). The most common presentation was poor urine stream (61.9%) followed by dysuria (22.2%) and strain during voiding (15.87%). The most common aetiology for strictures was post catheterization (44.44%) followed by idiopathic (28.57%) and trauma (9.52%).

Sixty-eight anterior urethral strictures were observed on evaluation of sixty-three patients by different investigatory modalities (RGU, SUG and RTE). Of the 63 patients, 29 underwent VIU (46.03%), 27 open surgery (42.86%) and 7 patients didn't require any operative intervention. Of the 68 strictures observed, 29 were managed by VIU, 30 by open surgery (excision and primary anastomosis and substitution urethroplasty) and the remaining nine strictures were not found on cystoscopy. Therefore, the total number of strictures observed intra-operatively was 59. RGU detected 65 strictures while SUG and RTE detected 61 strictures.

Spongiofibrosis was evaluated based on three colour pattern viz. red, green and blue. The most common strain pattern observed on RTE was blue (48.53%) followed by green (36.76%) and red (14.71%).

Blue colour pattern on RTE was observed in 33/68 (48.53%) strictures. Of these, white colour mucosa on cystoscopy was observed in 11/11 (100%) strictures and 7/11 (64%) had severe difficulty during incision on cystoscopy (Table 2).

Green colour pattern on RTE was observed in 25/68 (36.7%) strictures. Most of them had grey colour mucosa on cystoscopy i.e 15/17 (88.2%) while the remaining 2/17 (11.8%) had white colour mucosa. Mild and moderate difficulty in incision during cystoscopy was observed in 8/17 (47%) strictures each (Table 2).

Red colour pattern on RTE was observed in only 10/68 (14.07%) strictures. Most of them 7/10 (70%) had pink colour mucosa with normal appearance on cystoscopy and the remaining 3/10 (30%) had grey colour mucosa. Moderate difficulty in incision was observed in 12/38 (31.58%) strictures while mild difficulty in incision was observed in 10/68 (14.07%) during cystoscopy (Table 2).

Table 3. *Association of elastography patterns with degree of fibrosis on histopathology (of strictures treated by open surgery)*

	Degree of fibrosis on HPE		
Elastography patterns	Moderate	Severe	Total
Blue	0	22	22
Green	7	1	8
Red	0	0	0
Total	7	23	30
	Chi-square p <0.001 S		

HPE – histopathological evaluation, S – significant

Table 4. *Association of strain ratio with degree of fibrosis on histopathology*

Degree of fibrosis (HPE)	Number of strictures	Mean strain ratio	Stdandard deviation
Moderate	7	6.33	2.353
Severe	23	10.51	2.297

HPE – histopathological evaluation

This association of RTE colour patterns with cystoscopic findings was statistically significant i.e blue colour pattern on RTE corresponded to white colour mucosa and mostly, severe difficulty in incision during cystoscopy; and green colour pattern was more often associated with grey colour mucosa and mild to moderate difficulty in incision during cystoscopy (Table 2).

Histopathological evaluation of the remaining 22 strictures having a blue colour pattern on RTE showed severe fibrosis 22/22 (100%) and the association was statistically significant. Green colour pattern corresponded mostly to a moderate degree of fibrosis 7/8 (87.5%) on histopathology. Thus, blue colour pattern was 100% concordant with a severe degree of fibrosis and green colour pattern was 87.5% concordant with a moderate degree of fibrosis (Table 3).

Strain ratio is statistically a stronger parameter than strain pattern (colour patterns) as it is a quantitative parameter in contrast to the qualitative colour pattern. As the tissue stiffness i.e fibrosis increased, the strain ratio of that spongifibrotic segment also increased and was statistically significant ($p < 0.001$ S). Strain ratio was observed to be highest in white colour mucosa (9.59 ±3.23) compared to the grey colour mucosa (6.50 ±1.85) and pink colour mucosa (0.99 ±0.13) (Figure 1).

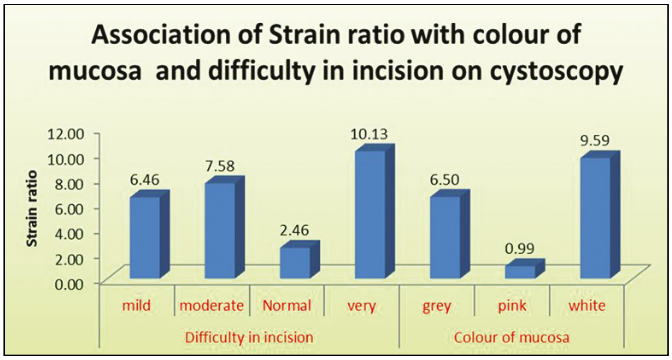

Figure 1. *Association of strain ratio with cystoscopic findings.*

A significant association between RTE strain pattern and mean RTE strain ratio was observed. The mean RTE strain ratio was significantly higher for blue colour (10.71 ±2.037) as compared to green colour (6.24 ±2.091) and red colour patterns (2.50 ±2.466), $p < 0.05$ S.

A significant association was observed between mean RTE strain ratio and degree of fibrosis on RTE. Mean strain ratio was significantly higher for severe degree of fibrosis (11.2 ±1.597) as compared to moderate (7.83 ±2.295) and mild degree of fibrosis (5.32 ±1.49), $p < 0.001$ S.

Mean strain ratio was significantly higher for severe degree of fibrosis (10.51 ±2.297) as compared to moderate degree (6.33 ±2.353) on histopathological evaluation $p < 0.001$ S (Table 4).

The above observations show that the diagnostic performance of real-time sonoelastography is significantly associated in the assessment of spongiofibrosis.

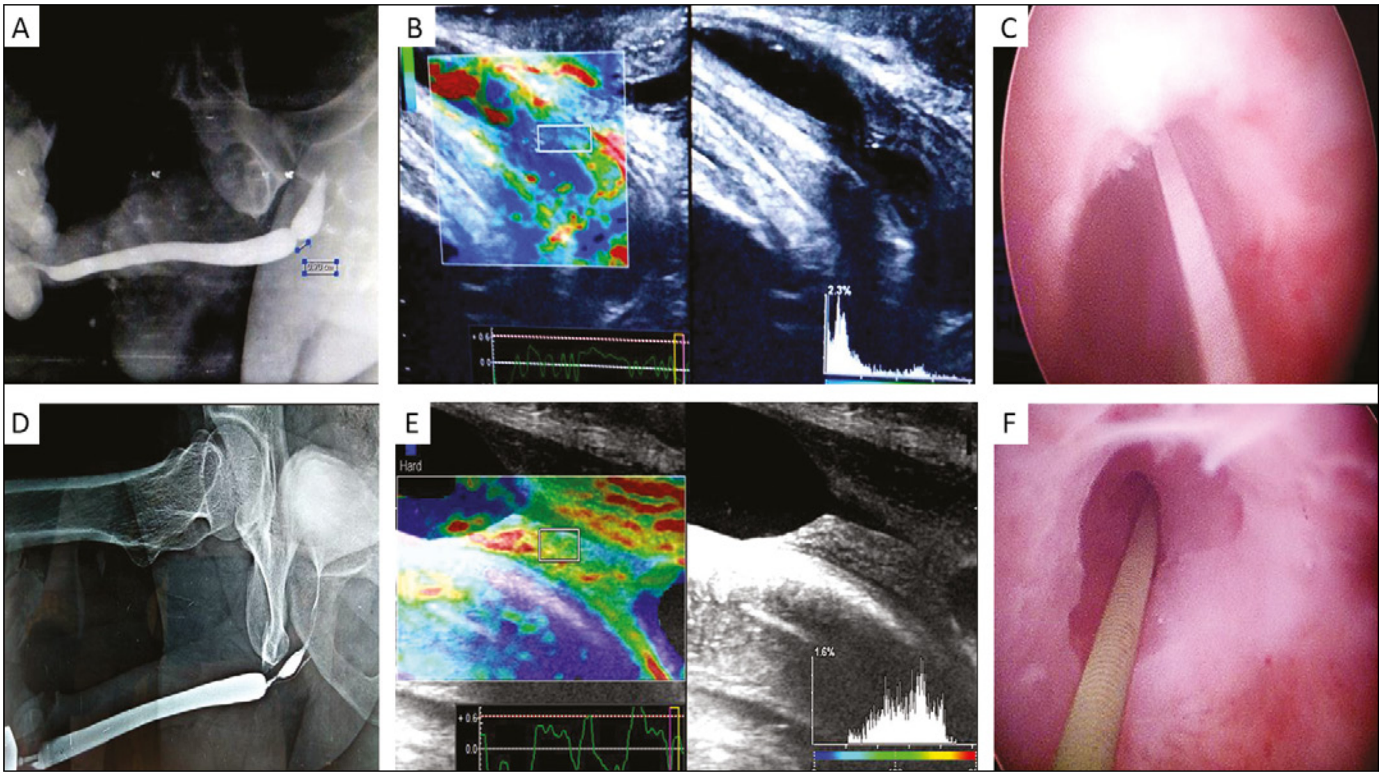

Figure 2. *A. RGU showing bulbar urethral stricture. B. Real time elastography on left showing blue pattern on elastogram while Sonourethrography on right revealing bulbar urethral narrowing. C. Cystoscopy finding showing same stricture appearing as white colour of mucosa. D. RGU showing another bulbar urethral stricture. E. Real time elastography on left showing green pattern on elastogram while Sonourethrography on right revealing bulbar urethral narrowing. F. Cystoscopy finding showing same stricture appearing as grey colour of mucosa.*

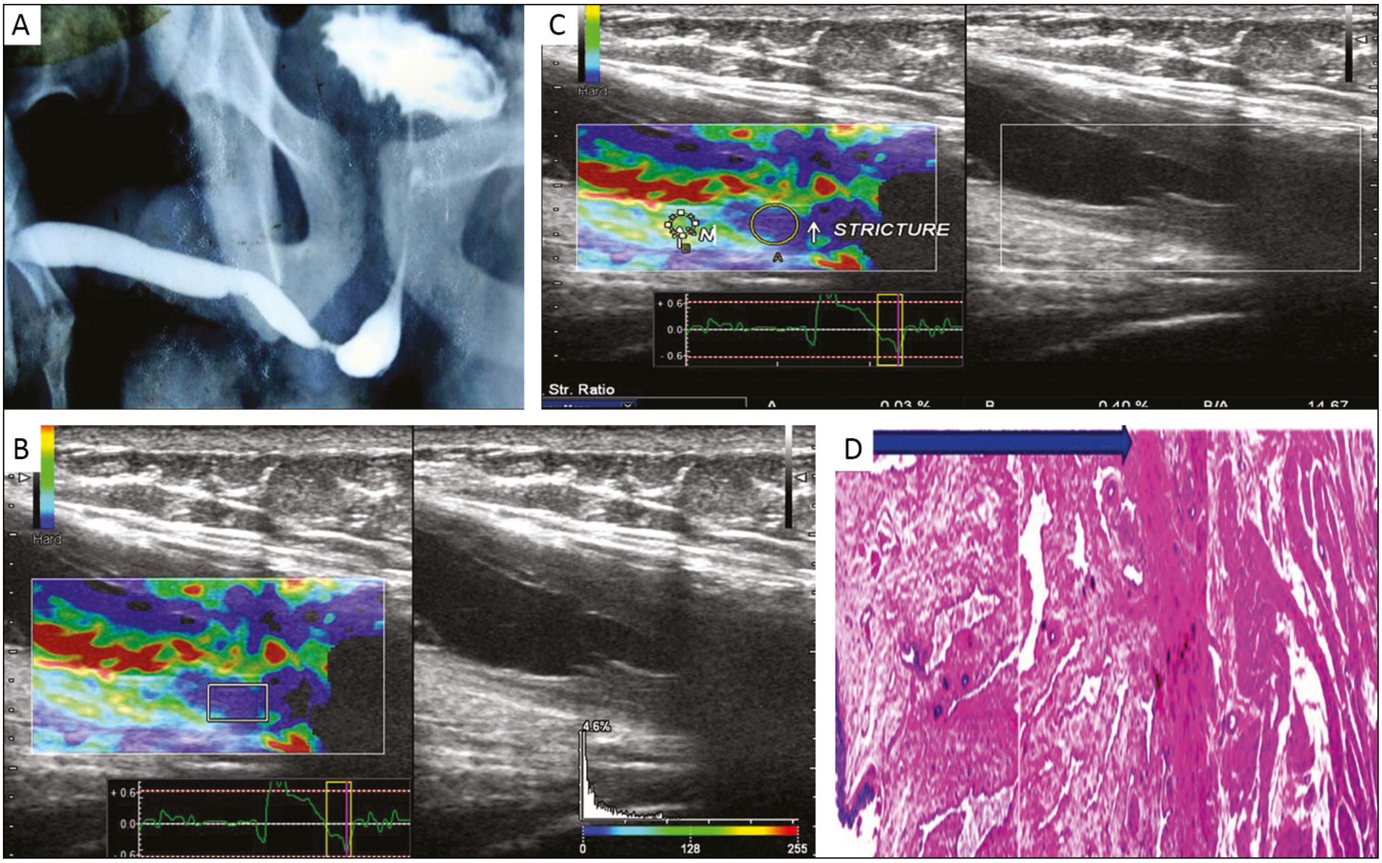

Figure 3. *A. RGU showing bulbar urethral stricture. B. Real time elastography on left showing blue pattern on elastogram while Sonourethrography on right revealing bulbar urethral narrowing. C. Real time elastography on left showing strain ratio of 14 over same stricture region. D. Micrograph showing fibrosis affecting full thickness of urethral segment (x100, H&E).*

DISCUSSION

Elasticity is an inherent property of a tissue to return to its initial shape after deformation [13, 17, 20]. This property is affected in various pathological conditions associated with fibrosis, inflammation and tumors and the affected tissue becomes stiffer or harder [10–13]. A spongiofibrotic segment of stricture urethra becomes stiffer and less distensible due to the underlying process of fibrosis. It is important to accurately estimate this spongiofibrosis for its severity is proportional to stricture recurrence [3]. Sometimes the size of the spongiofibrotic segment is very small or in early lesions, its detection is not possible. This is because the lesion may or may not possess echogenic properties that would be ultrasonically detectable as echogenicity and tissue stiffness are generally uncorrelated. Hence, imaging the tissue stiffness or strain provides information about the underlying pathological process i.e fibrosis [11, 18]. For this, an imaging modality also known as electronic palpation, elastography has been developed [7, 10, 12].

Currently, the most widely available elastography is based on the method of strain imaging (available on high end ultrasound equipment), and the other method being sheer wave imaging [7, 12, 14, 16]. Strain elastography, introduced in 2003 was the basis of the first practical system for ultrasound elastography and since then, has undergone formidable technological advancements [12, 21]. We have used strain elastography using a static elastographic approach where tissue stiffness was assessed by measuring deformation (i.e strain) in response to an applied force (i.e stress). The stress was applied by manual compression externally using a transducer and continuously compressing and decompressing the skin of the patient [11, 12, 14, 17, 21–24]. Tissue stiffness calculated by Young's modulus (E=stress/strain) is not directly measured by most elastography techniques as they measure only the strain [7, 14, 11, 12]. The resultant strain map is called an elastogram [7, 11, 17, 25]. Elastograms are displayed alongside the conventional B-mode images with the former being on the left and the later on the right side of screen [12, 14, 18].

Table 5. *Association of strain ratio with overall intra-operative degree of spongiofibrosis*

	Strain ratio					
Degree of spongiofibrosis	No.	Mean	Standard deviation	Minimum	Maximum	Median
Normal	9	2.46	2.97	0.8	8.7	1.1
Mild	10	6.46	2.43	4.5	11	5.6
Moderate	20	7.27	2.62	3.2	11.8	6.8
Severe	29	10.43	2.53	3.2	13.87	10.45
Total	68	7.86	3.69	0.8	13.87	7.98
ANOVA – analysis of variance	p <0.001 S					

Tissue stiffness is estimated by sonoelastography both qualitatively (strain pattern) and semi-quantitatively (strain ratio) [14, 15, 16]. Strain pattern depicts the relative difference in tissue elasticity between the abnormal foci (lesion) and the surrounding tissue [12, 15, 19, 21]. Tissue stiffness depicted by strain pattern is displayed on a continuum of fundamental colours ranging from red to green to blue, designating soft (high strain), intermediate (equal strain) and hard (no or less strain) tissue as in our study [14, 18, 19]. However, standardization of colour coding is yet to be established and few RTE-systems follow the inverse colour scale of the others [14]. Figures 2B & 2E shows some representative cases depicting RTE strain patterns.

There is a concordance of 100% between blue colour pattern and a severe degree of fibrosis; and 87.5% between green colour pattern and a moderate degree of fibrosis on histopathology was observed in our study, depicting the excellent diagnostic performance of RTE colour patterns in evaluation of strictures. (Table 3 & Figure 3) The association of RTE colour pattern with cystoscopic findings was also statistically significant (Table 2 & Figure 2)

Semi-quantification of tissue stiffness is achieved by the use of strain ratios (SR) [14, 21]. In our study, we sought SR's to numerically evaluate how many times stiffer a target lesion was compared to the surrounding normal tissue and provide a parameter which is statistically more powerful [21]. Strain ratio is the comparison of strains in two manually selected regions of interests (ROI); the former being the target lesion and the latter, reference ROI being in the surrounding normal tissue, at preferably the same level of depth or as close as possible, to avoid strain decay [14, 18, 19, 26]. Mousa et al. [15] have emphasized this point and we have taken care to avoid this strain decay in our study. Elastography software automatically provides the strain ratio which is the fraction of average strain in the reference area to average strain in the lesion. As the stiffness of the tissue increases, its strain ratio also increases [13, 14, 5]. Pastore et al. [13], Mousa et al. [15] and Zhi et al. [27] in their study observed that strain ratio based analysis was better than strain pattern analysis as it provided better statistical evidence. Our study results also supported their observations. Thus, SR contributes to the standardization of this technique [15].

In the present study an attempt to reduce the subjectivity in the interpretation of colour patterns in real time SE was done, by replacing it with a more reproducible, operator independent numerical parameter i.e strain ratio in concordance with the study of Pastore et al. [13]. To ensure the objectivity of the assessment, we tried calculating the mean value for mild, moderate and severe degree of spongiofibrosis which would give a pre-operative idea regarding the status of spongiofibrosis allowing treatment plans to be scheduled accordingly. The mean strain ratio for overall intra-operative mild, moderate and severe degree of spongiofibrosis was 6.46, 7.27 and 10.43 (p <0.001 S) (Table 5). The mean strain ratio was higher for blue colour pattern, white mucosa and severe degree of fibrosis as compared to green colour pattern, grey mucosa and moderate degree of fibrosis; and the latter set having a higher mean strain ratio as compared to red colour pattern, pink mucosa and mild degree of fibrosis. Figure 2 shows some representative cases depicting calculated strain ratios.

In one case, a green colour pattern was observed on RTE but on histopathology the stricture showed a severe degree of fibrosis (Table 3). Our hypothesis regarding this is that, even if the pattern on elastogram was green, it had a strain ratio ≥10; thus, the strain ratio contributed to standardization of this RTE as previously stated and was in agreement with previous studies [15, 28, 29, 30]. Ophir et al. [11] had reported that elastography could pick up a much smaller lesion which was missed on ultrasonography.

Sonoelastography is a rapid, easy to use, portable technique and does not use ionizing radiation. Therefore, it is safe for patients who have to repeatedly undergo the procedure [16, 17, 20]. The limitation of our study is it's relatively small study population, the technique is user dependent and requires a certain level of competence.

CONCLUSIONS

We observed that sonoelastography patterns and strain ratios gave a better estimation of spongiofibrosis. Strain ratio was a statistically stronger indicator as compared to strain pattern. The integration of this technique with the conventional B-mode ultrasound has made its application more feasible and allows for the fusion of information to strengthen the diagnostic performance. However, large prospective studies are needed for stronger statistical evidence and better delineation of its usefulness in evaluation of anterior urethral stricture disease.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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