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Sono-elastography for Differentiating Benign and Malignant Cervical Lymph Nodes: A Systematic Review and Meta-Analysis

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Review Article

ABSTRACT

We did this systematic review to determine diagnostic accuracy of sono-elastography in evaluating cervical lymph nodes (LNs). A highly sensitive search for sono-elastography and LNs was performed in MEDLINE, Cochrane Library, ACP Journal Club, EMBASE, Health Technology assessment, and ISI web of knowledge for studies published prior to December 2012. SPSS version 18 (SPSS Inc., Chicago, IL, USA) used for descriptive analysis and meta-disk version 1.4 applied for meta-analysis. Forest plots for pooled estimates and summery of receiver operating characteristic plots for different cut-offs were produced. The literature and manual search yielded 69 articles, of which 10 were eligible to include. A total of 578 individuals with a total number of 936 cervical LNs was evaluated (502 malignant and 434 benign). The summary sensitivity of the scoring and strain ratio (SR) measurements for the differentiation of benign and malignant LNs were 0.76 (95% CI: 0.71–0.8) and 0.83 (95% CI: 0.78–0.87). The summary specificities were 0.8 (95% confidence interval [CI]: 0.75–0.84) and 0.84 (95% CI: 0.79–0.88), respectively. Area under the curve for scoring system was 0.86 (standard error [SE] = 0.03) and 0.95 (SE = 0.02) for SR measurement. Sono-elastograohy has high accuracy in differentiating benign and malignant cervical LNs.

Keywords: Cervical, diagnostic accuracy, lymph nodes, sono-elastography

INTRODUCTION

Evaluation of lymph nodes (LNs) in patients with different underlying diseases is important to decide current status, proper treatment and prognosis of the patients.[1] It is crucial to differentiate malignant LNs from benign LNs to follow appropriate treatment.

The gold standard for evaluating enlarged LNs is pathologic examination of obtained tissue. Although fine-needle aspiration (FNA) is considered as the most efficient method for differentiating benign and malignant LNs, it is considered as an invasive method which is prone to sampling errors and analytic uncertainty.[2] Its false negative rate has been reported to be between 12.5% and 25%.[3-5]

Different modalities such as ultrasound computed tomography, and magnetic resonance imaging are currently used as imaging techniques for differentiating benign and malignant LNs, but their ability to differentiate malignant and benign LNs is limited.[6]

Sono-elastography is a recently developed ultrasound modality which is based on tissue displacement in response to external forces. Soft tissues show more displacement than stiff ones. It has been applied in the evaluation of different organs such as breast, thyroid, pancreas, liver and LNs.[7-12]

Series of previous studies had evaluated accuracy of this modality in differentiating benign and malignant LNs. Its sensitivity and specificity ranged from 79% to 100% and 50–96%, respectively.[13-18]

The goal of this study was to perform a meta-analysis of published information to evaluate the overall accuracy of sono-elastography for differentiation of benign and malignant cervical LNs.

METHODS

We searched MEDLINE, Cochrane Library, EMBASE, ACP Journal Club, Health Technology Assessment, and ISI web of knowledge for studies published prior to December 10, 2012 using these search terms: "Elastography," "sono-elastography," "real-time tissue elastography," "elasticity," "elastogram," "elasticity imaging techniques," "LN." A manual search was performed to include additional studies from references of the retrieved articles. Two independent reviewers evaluated articles for eligibility. The criteria for eligibility were:

1. Studies evaluated diagnostic accuracy of sono-elastography in differentiating malignant and benign cervical LN

   Systematic review articles, narrative review articles, letter to editors and editorial articles were excluded.
2. Using appropriate reference standard test such as FNA, histological assessment of specimens obtained by surgery or dissection
3. Diagnostic measures on sonoelstographic evaluation results such as sensitivity, specificity, positive and negative predictive values.

Data extraction and quality assessment

Two independent reviewers extracted data from included studies. Extracted data included: First author name, study publication year, country, reference standard, number of patients, number of malignant and benign LNs, mean patient age in each study, number of male and female patients, classification method, cut-off values of qualitative elasticity scoring (ES) method or strain ratio (SR) method.

The quality of included studies was evaluated by means of quality assessment of diagnostic accuracy studies (QUADAS) questionnaire which consists of 14, four option questions (yes, no, unclear, not applicable [N/A]). The same two independent reviewers evaluated the quality of studies and in discord cases, disagreement solved by consensus of reviewers.

Statistical analysis and data synthesis

Accuracy of scoring system and SR method was assessed by pooled estimates of sensitivity, specificity, positive and negative predictive values, and diagnostic odds ratio (DOR). If the case of homogeneity, fixed-effect model applied for pooled estimate calculation and if significant heterogeneity was present, the random-effect model was used [Appendix 1]. The Cochran Q-test was estimated to detect the heterogeneity among studies. Inconsistency (I^2) was calculated to describe the percentage of the variability attributable to heterogeneity.

Summary receiver operating characteristic curves were constructed, by means of Moses–Shapiro–Littenberg method and the area under the curve was calculated. $P < 0.05$ was considered significant.

RESULTS

Figure 1 describes the fellow of study selection in this systematic review. The literature and manual search yielded 69 articles, of which, 10 were eligible to include in this study that were published between 2007 and 2012. The studies were conducted in Japan ($n = 3$), Italy ($n = 1$), China ($n = 5$) and Japan-China Union ($n = 1$).

The characteristics of included articles are listed in Table 1.

A total of 578 individuals with a total number of 936 cervical LNs was evaluated. Five hundred and tow LNs were malignant while 434 were benign.

In five studies, only qualitative scoring system (in three articles scoring 1–4 and in 2 scoring 1–5) was used. In one study, only SRs applied for classification and in remaining four studies both SR and ES system were applied.

In two studies, histopathological evaluation along with imaging techniques was used for LNs classification.

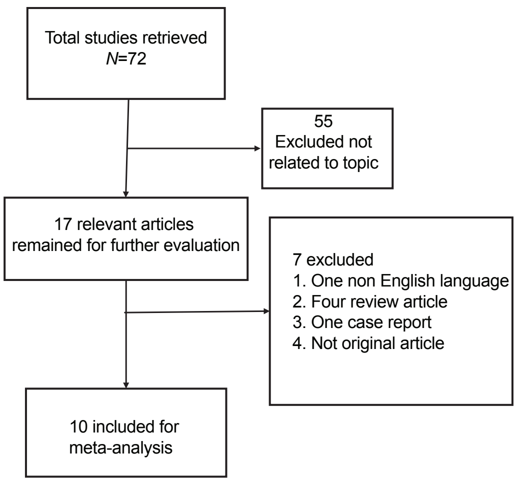

Figure 1: Flow chart of selecting studies

Area under the curve for scoring system was 0.86 (standard error [SE] = 0.03) and 0.95 (SE = 0.02) for SR measurement.

Quality assessment of included studies

Quality of included studies was evaluated by means of QUADAS questionnaire and information is present in Table 2. It could be conclude that all included studies except two studies that were conducted by Rubaltelli and Zhang had high quality [Figure 2].

Accuracy of scoring and strain ratio for the differentiation of benign and malignant lymph nodes

The summary sensitivity of the scoring and SR measurements for the differentiation of benign and malignant LNs were 0.76 (95% confidence interval [CI]: 0.71–0.8) and 0.83 (95% CI: 0.78–0.87). The summary specificities were 0.8 (95% CI: 0.75–0.84) and 0.84 (95% CI: 0.79–0.88), respectively [Table 3].

Test of heterogeneity

All measurements of both methods showed heterogeneity ($I^2 > 50\%$) in differentiating benign and malignant LNs.

Table 1: Main characteristics of all studies included in the meta-analysis

Author	Publication year	Reference standard	Mean age	Total number of patients	Male/ female	Total number of lymph nodes	Malignant/ benign LNs	Method of classification	Cut off point
Teng *et al.*[12]	2012	Fine core biopsy	N/A	89	33/56	89	52/37	SR/scoring system (1-4)	1.78 2/3
Ishibashi *et al.*[19]	2012	Surgery	69.9	19	13/6	71	71/40	Scoring system (1-5)	2/3
Tan *et al.*[20]	2010	Surgery	53.4	107	57/50	128	70/58	SR/scoring system (1-4)	1.5 2/3
Bhatia *et al.*[21]	2010	FNA	50	74	31/43	74	37/37	Scoring system (1-4)	2/3
Lyshchik *et al.*[22]	2007	Surgery	58	43	22/21	141	60/81	SR/scoring system (1-4)	1.5 2/3
Alam *et al.*[23]	2008	Histopathology/ imaging	55	37	25/12	85	53/32	Scoring system (1-5)	2/3
Bhatia *et al.*[24]	2012	FNA	58.5	46	23/23	55	31/24	SR	30.2 kPa
Zhang *et al.*[25]	2009	Histopathology/ imaging	38.2	82	N/A	155	87/68	SR/scoring system (1-4)	2.39 2/3
Rubaltelli *et al.*[26]	2009	FNA	N/A	53	N/A	53	28/25	Scoring system (1-4)	2/3

FNA=Fine-needle aspiration, N/A=Not applicable, LN=Lymph node, SR=Strain ratio

Table 2: Quality assessment of included studies

Author	Q1 Spectrum composition	Q2 Selection criteria	Q3 Appropriate reference standard	Q4 Disease progression bias	Q5 Partial verification bias	Q6 Differential verification bias	Q7 Incorporation bias	Q8 Test execution details	Q9 Reference execution details	Q10 Test review bias	Q11 Diagnostic review bias	Q12 Clinical review bias	Q13 Intermediate results	Q14 Withdrawals
Teng	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Ishibashi	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Tan	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bhatia 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
lyshchik	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Alam	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bhatia 2012	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Zhang	Yes	Yes	No	Unclear	No	No	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
Rubaltelli	Unclear	No	Yes	Unclear	Yes	Yes	Yes	Yes	No	Unclear	Unclear	No	Unclear	Yes

Table 3: Diagnostic accuracy of scoring system and SR

	Scoring system	SR
Sensitivity	0.76 (95% CI: 0.71-0.8)	0.83 (95% CI: 0.78-0.87)
Specificity	0.80 (95% CI: 0.75-.84)	0.84 (95% CI: 0.79-0.88)
DOR	17.16 (95% CI: 7.8-37.75)	72.77 (95% CI: 18.75-282.47)
Positive LR	4.43 (95% CI: 2.19-8.95)	8.72 (95% CI: 0.79-0.88)
Negative LR	0.28 (95% CI: 0.18-0.43)	0.19 (95% CI: 0.07-0.46)

DOR=Diagnostic odds ratio, LR=Likelihood ratio, CI=Confidence interval, SR=Strain ratio

DISCUSSION

In this meta-analysis, we evaluated accuracy of sono-elastography in differentiating benign and malignant cervical LNs. We detected high sensitivity and specificity for both elastography scoring system and SR.

Differentiating benign and malignant LNs is important to yield proper treatment. The status of LNs is important in staging of malignant diseases and considering the prognosis of the underlying disease. So, accurate differentiation of benign and malignant LNs is a crucial issue.

We also obtained high DORs for both scoring and SR evaluation (17.16 and 72.77). It can show that the odd of obtaining positive results in diseased rather than nondiseased individuals by means of sono-elastography is high.

Sono-elastography is a new technique of sonography that is noninvasive, available and easy to apply.[27]

It evaluates the stiffness of the lesions based on response to the compression and decompression. By applying a mechanical force to the target lesion, an elastogram will be obtained. The results of the response of the lesions to mechanical force will appear as red or green indicating softness or blue, indicating hardness of the tissue.[12]

Cell types of the lesion, the quantity of the entire types of cells and micro and macro pathological structures have roles in rate of stiffness.[12] So, sono-elastography, visualizes the hardness of the lesion by reflecting the biological characteristics.[25]

Two different methods could be obtained for sono-elastography evaluation.

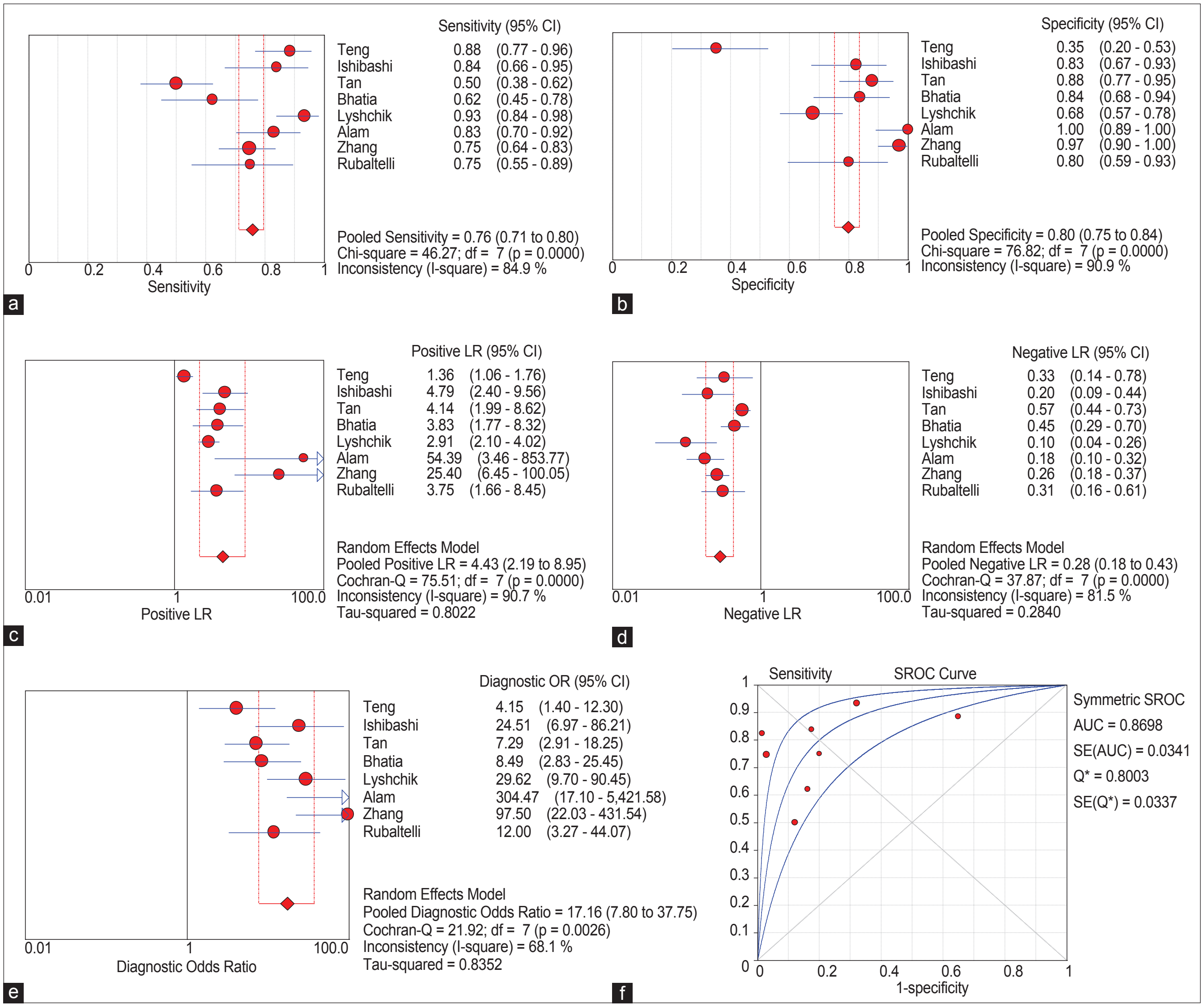

Figure 2: (a) Forest plot (random-effect model) of the meta-analysis of sensitivity of scoring systems. (b) Forest plot (random-effect model) of the meta-analysis of specificity of scoring systems. (c) Forest plot (random-effect model) of the meta-analysis of positive likelihood ratio of scoring systems. (d) Forest plot (random-effect model) of the meta-analysis of negative likelihood ratio of scoring systems. (e) Forest plot (random-effect model) of the meta-analysis of diagnostic odds ratio of scoring systems. (f) The summary receiver operating characteristics, with 95% confidence interval for differentiating benign and malignant lymph nodes by scoring systems

Qualitative elastography scoring method or SR measurement. By means of scoring system, operator should score the target lesion according to the proportion of blue areas in the lesions. It is semi-objective, and it depends on different factors such as the operator's experience and scoring system (5 or 4 point).

Strain ratio measurement has been considered to be more accurate that scoring method because it could estimate the difference between stiffness of the lesions and the surrounding tissue.[12] One of the advantages of the SR method is that as it is quantitative, in cases that the scores are the same visually, the SR could be different.

By pooled estimation, we found that the sensitivity, specificity, diagnostic OR and positive LR of the SR method is higher that scoring system. Which could show that SR method is more accurate than scoring system.

We should consider that SR method was not applied in all retrieved articles.

In five studies only, qualitative scoring system (in three articles scoring 1–4 and in 2 scoring 1–5) was used. In one studies, only SRs applied for

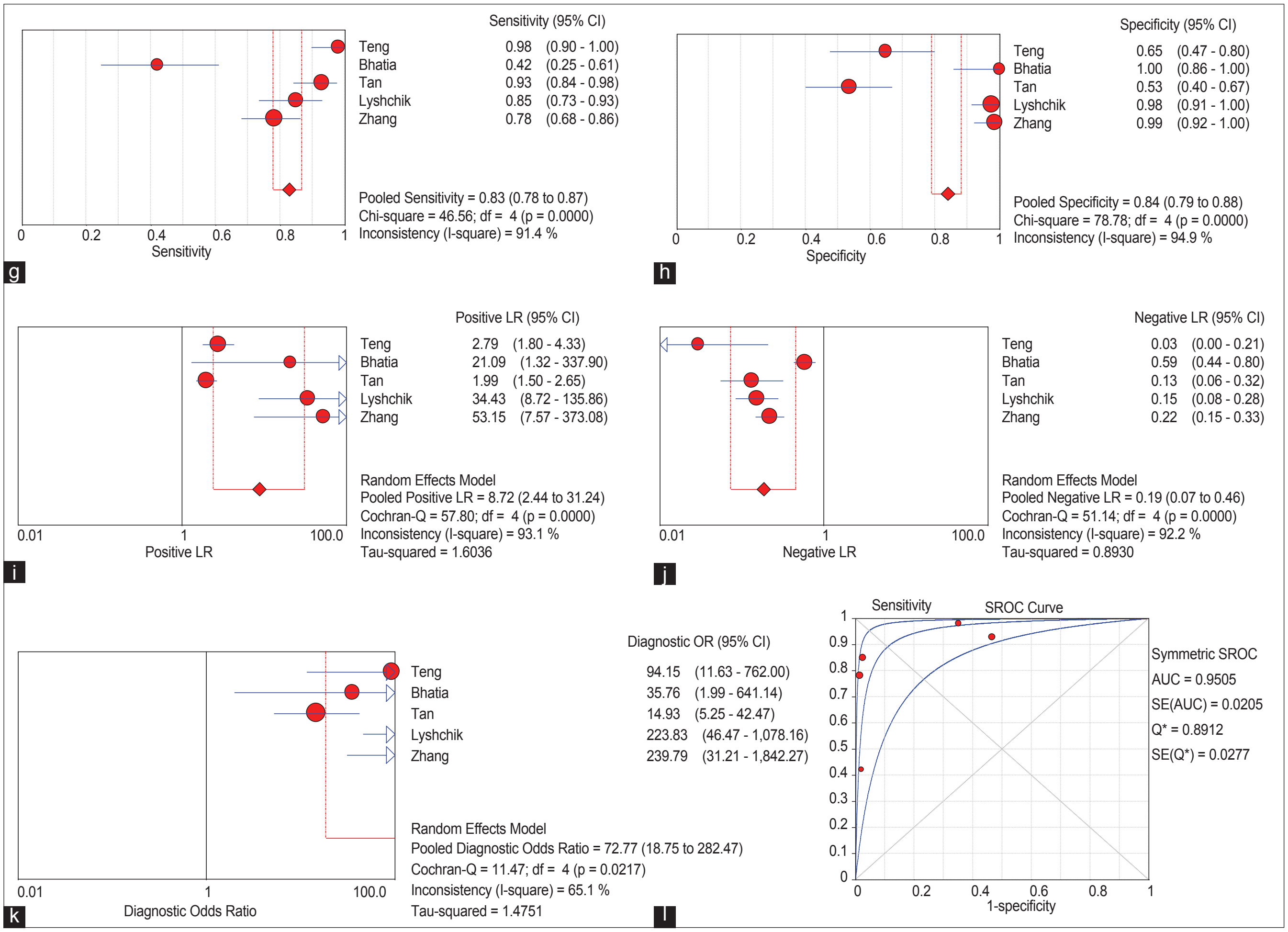

Figure 2: (g) Forest plot (random-effect model) of the meta-analysis of sensitivity of strain ratios. (h) Forest plot (random-effect model) of the meta-analysis of specificity of strain ratios. (i) Forest plot (random-effect model) of the meta-analysis of positive likelihood ratio of strain ratios. (j) Forest plot (random-effect model) of the meta-analysis of negative likelihood ratio of strain ratio. (k) Forest plot (random-effect model) of the meta-analysis of diagnostic odds ratio of strain ratios. (l) The summary receiver operating characteristics, with 95% confidence interval for differentiating benign and malignant lymph nodes by strain ratios

classification and in remaining four studies both SR and ES system were applied.

In a previous systematic review conducted by Ying *et al*., diagnostic accuracy of SR and scoring system method in differentiating benign and malignant cervical and axillary LNs had been evaluated. They found that sensitivity, specificity and diagnostic OR of SR method is significantly higher than scoring method.[27]

We found heterogeneity in all measurements of both methods ($I^2 > 50\%$) but as a limitation, we did not do meta-regression analysis to find the source of heterogeneity.

Ying *et al*. performed meta-regression analysis and evaluated 11 specific covariates of patient and study, but they did not find the source of heterogeneity in their study.[27]

Our study has some advantages

First we included studies that evaluated only cervical LNs, and we did not include studies that evaluated LNs in other locations such as axillary and sub-clavicular because the depth of the LNs could influence the stiffness value. Second, we analyzed scoring system and SR method separately and report measurements of each technique independently.

The limitations of the current study were absence of meta-regression analysis due to applying (Meta-DiSc; version 1.4; Zamora J, Abraira V, Muriel A, Khan KS, Coomarasamy A) software for analysis.

CONCLUSIONS

Sono-elastograohy has high accuracy in differentiating benign and malignant cervical LNs.

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APPENDIX 1

1. Exp elasticity imaging techniques/(2224)
2. Elasticity/(28093)
3. Elastogra $.mp. (2008)
4. Sono-elastography $.mp. (156)
5. 1 or 2 or 3 or 4 (30617)
6. Exp lymph nodes/(66016)
7. Lymph node.mp. (107833)
8. 6 or 7 (147810)
9. 5 and 8 (71)