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Original Article

Elastography for the differentiation of benign and malignant cervical lymph node: a meta-analysis

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Abstract: Objectives: To assess the diagnostic efficacy of elastography in diagnosis of benign and malignant cervical lymph node. Methods: After comprehensive search and study selection, a meta-analysis was performed on data from 548 patients pooled from 14 studies for evaluating FLT accuracy, in which data from 351 patients pooled from ten double-tracer studies were used for direct comparison with FDG. Weighted sensitivity and specificity were used as main indicators of test performance. The data from individual study were extracted and patient subgroup analyses were performed. Results: Elastography had a pooled sensitivity (random effect model) of 85% (95% CI, 0.76-0.90) in the differential diagnosis of benign and malignant LNs (lymph nodes). The pooled specificity (random-effect model) was 86% (95% CI, 0.77-0.91) which were showed in Figures 2 and 3. The summary positive LR and negative LR were 5.86 (95% CI, 3.62-9.50) and 0.18 (95% CI, 0.12-0.28), respectively. The summary diagnostic odds ratio (DOR) used to examine the elastography accuracy is 32.641 (95% CI, 16.772-63.525) and the area under the SROC was 0.92 (95% CI, 0.89-0.94). Significant heterogeneity was found in sensitivity (heterogeneity, chi-square = 95.68, P = 0.00, I-square = 86.41), specificity (heterogeneity, chi-square = 109.23, P = 0.00, I-square = 88.10), indicating that more than 80% of variance across studies is attributed to heterogeneity rather than chance. Conclusion: Elastograohy has high accuracy in differentiating benign and malignant cervical LNs.

Keywords: Cervical lymph node, elastography, meta-analysis, accuracy

Introduction

A lymph node (LN) is an oval-shaped organ of the lymphatic system, distributed widely throughout the body including the armpit and stomach and linked by lymphatic vessels [1-3]. Lymph nodes are major sites of B, T, and other immune cells. Lymph nodes are important for the proper functioning of the immune system, acting as filters for foreign particles and cancer cells. Lymph nodes do not deal with toxicity, which is primarily dealt with by the liver and kidneys. Lymph nodes also have clinical significance. They become inflamed or enlarged in various infections and diseases which may range from trivial throat infections, to life-threatening cancers [4-6]. The condition of the lymph nodes is very important in cancer staging, which decides the treatment to be used, and determines the prognosis. When swollen, inflamed or enlarged, lymph nodes can be hard, firm or tender [7].

Evaluation of LN in patients with various underlying diseases is important to detect current status, suitable treatment and prognosis of the patients [8]. It is crucial to distinguish malignant LNs from benign LNs to follow appropriate therapy. 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 [9]. Its false negative rate has been reported to be between 12.5% and 25% [10, 11].

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 [12]. Because malignant tissues are generally harder than normal surrounding tissues, measurement of tissue elasticity might be useful for the differential diagnosis of different pathologic changes. Elastography, or sono-elastography, is an imaging technique that provides information on tissue elasticity. Its use in clinical practice is based on the premise that pathological processes like cancer modify the physical characteristics of diseased tissues. This principle has already been exploited for diagnostic purposes, but interest in elastography has been increased by the recent development of integrated systems that facilitate the inclusion of sonoelastographic studies in routine practice. 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 [13-16].

Several 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 [17-21]. The aim of present study was to perform a meta-analysis of published information to investigate the overall accuracy of elastography for differentiation of benign and malignant cervical LNs.

Materials and methods

Literature search

A systematic search was conducted for the studies on association between the elastography and cervical lymph nodes published before October, 2015 in PubMed, Web of Science Embase, Cochrane Central Trials and CNKI (China National Knowledge Infrastructure) databases. The search was performed without any restrictions on language. The search terms were as follows: “lymph nodes” in combination with “strain imaging”, “elasticity imaging techniques”, “elasticity” or “elasticity”. To identify additional relevant publications and missing data, the reference lists of identified studies and review articles were manually searched and study authors were contacted. Two investigators (A and B) searched and assessed studies for eligibility independently, and disagreements were resolved by discussion. If any clarification of data was necessary, we contacted the authors for detailed information.

Study selection

The inclusion criteria were as following: (1) assessing the accuracy of the elastography for the differentiation of benign and malignant cervical lymph nodes; (2) all cervical lymph nodes were confirmed histologically by means of histological pathology results or fine needle aspiration for cytology (FNAC); (3) the outcome data available to reconstruct a diagnostic 2×2 contingency table for true positives (TP), false positives (FP), false negatives (FN) and true negatives (TN).

The exclusion criteria were as following: (1) not related to the topic or cannot get the full texts; (2) incomplete data available; (3) publication types such as reviews, editorials, letters, animal experiments and case reports; (4) when publications involved the overlapping data sets, only the study with the largest number of participants was included, and updated data were excluded directly.

Data extraction and quality assessment

Two authors (A and B) reviewed and extracted data independently. The following data were extracted: the name of the first author, year of publication, country, description of the study population (number of patients, median age), number of cervical LNs, malignant LN rate, reference, method and a cutoff value. Additionally, direct data of TP, FP, FN, TN and indirect data of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy for the 2×2 table could be extracted. Once the data they obtained were different, the third author (C) would check the data. Finally, disagreements were resolved through discussion among the authors.

Statistical analysis

The summary sensitivity and specificity were calculated for each study included by using the bivariate mixed-effects regression model, as well as negative likehood rations (NLR), positive likehood rations (PLR) and diagnostic odds ratio (DOR). Moreover, the summary receiver operating characteristic (SROC) curve was conducted to show the results graphically, and the areas under the curve (AUC) were also calculated to present a relative perfect accuracy of the elastography for the differentiation of

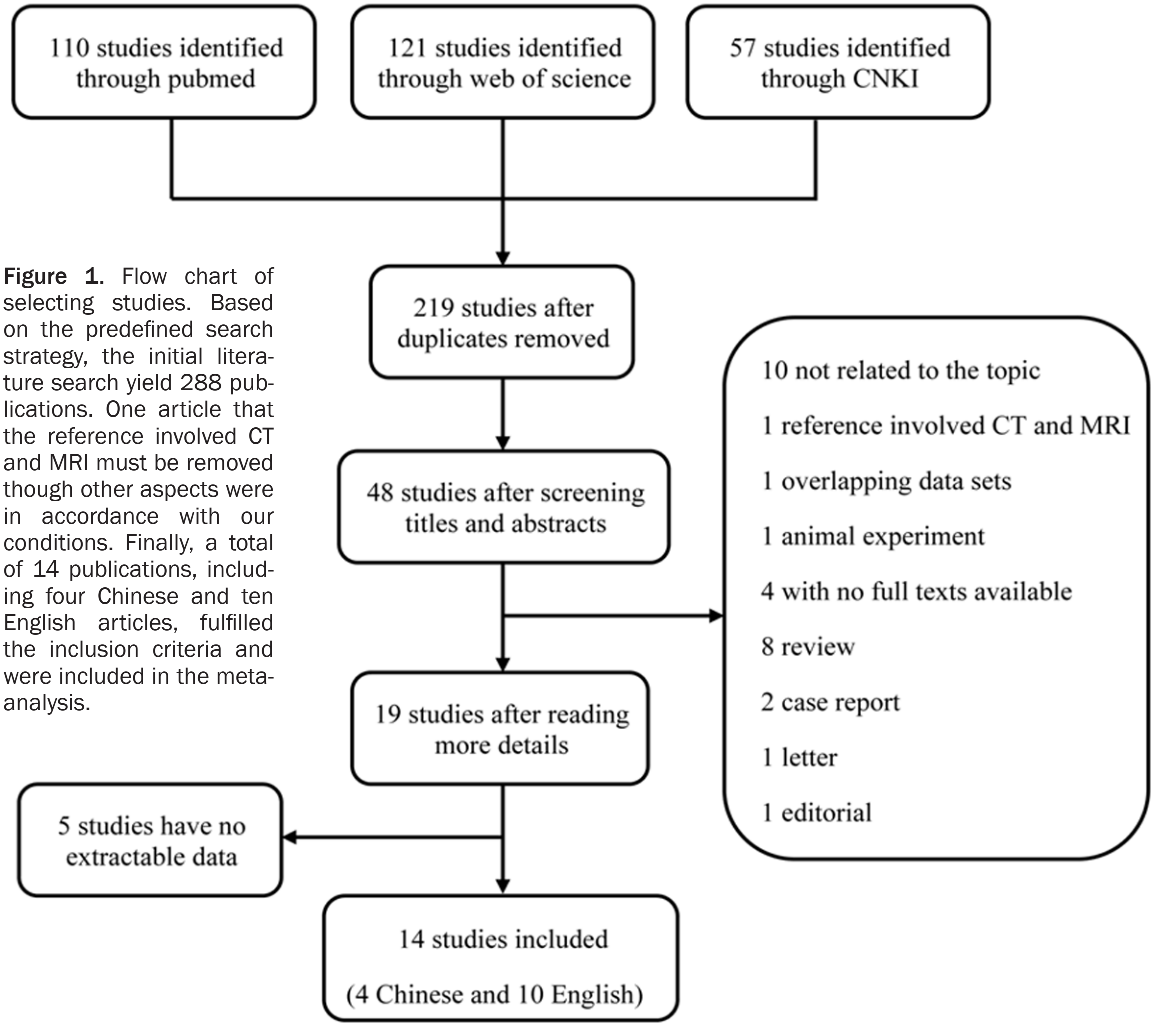

Figure 1. Flow chart of selecting studies. Based on the predefined search strategy, the initial literature search yield 288 publications. One article that the reference involved CT and MRI must be removed though other aspects were in accordance with our conditions. Finally, a total of 14 publications, including four Chinese and ten English articles, fulfilled the inclusion criteria and were included in the meta-analysis.

benign and malignant cervical lymph nodes if AUC approached to 1 approximately.

Heterogeneity was evaluated based Q statistic and I^2 test, with $P < 0.10$ or $I^2 > 50\%$ considered statistically significant. Funnel plots are the most common used tool to detect publication bias. With the drawbacks of funnel plots, a wide range of studies of different sizes and subjective judgments, publication bias was detected by Egger's test. We calculated indirect data using SPSS version 20.0 for constructing contingency table. Other analyses were done using STATA 12.0 and meta-DISC. Two-sided $P < 0.05$ was considered indicative of statistically significant.

Results

Characteristics of included studies

Based on the predefined search strategy, the initial literature search yield 288 publications. One article that the reference involved CT and MRI must be removed though other aspects were in accordance with our conditions. Finally, a total of 14 publications, including four Chinese and ten English articles, fulfilled the inclusion criteria and were included in the meta-analysis [21-26]. The flow chart that displays the study selection process was shown in **Figure 1**. 1606 cervical lymph nodes from 1036 patients were diagnosed by histological pathology results and FNAC. In general, the number of cervical lymph nodes had a significant change in the included studies (**Table 1**). The median number was 115 nodes, ranging from 42 to 376. The proportion of malignant lymph nodes was 52.96% (range 41.2 to 67.02). The mean age of the included patients was 51.37 years (range 40.8 to 69.9). 52.72 percent of the patients were male. In Addition, there existed some variation of the type of elastography used in these fourteen studies. Two studies used the Acoustic radiation force

Table 1. Characteristics of the fourteen studies included in this meta-analysis

Study/Year	Country	No. of patients	No. of cervical LNs	Malignant LN rate%	Reference	Method
Takashi Fujiwara (2013)	Japan	19	42	47.62	histopathologic results	ARFI
Andrej Lyshchik (2007)	Japan	43	141	42.55	histological nodal findings	elastography
Wei Meng (2013)	China	123	181	51.93	histological findings	ARFI
Young Jun Choi (2012)	Korea	15	67	50.75	histopathologic examination	SWE
Kunwar S.S.Bhatia (2010)	China	74	74	50	fine needle aspiration for cytology	RTE
Naomi Ishibashi (2012)	Japan	19	71	43.7	histologic examination	RTE
Wu-Chia Lo (2013)	China	131	131	41.2	cytopathological or histopathological findings	RTE
Kunwar S.S.Bhatia (2012)	China	46	55	56.36	fine needle aspiration for cytology (FNAC)	SWE
L. Rubaltelli (2009)	Italy	53	53	52.83	histological diagnosis	elastography
Rong Tan (2010)	China	107	128	54.69	histopathologic analysis	elastography
Yong-Mei Sun (2013)	China	92	92	57.61	histological pathology results and fine needle aspiration for cytology (FNAC)	elastography
Xi-Lin Shen (2012)	China	144	376	67.02	histological pathology results and fine needle aspiration for cytology (FNAC)	elastography
Ya-Hui Yao (2012)	China	96	96	66.67	histological pathology results	elastography
Deng-Ke Teng (2012)	China	74	99	58.59	histological pathology results	elastography

Note: LN = lymph node; ARFI = Acoustic radiation force impulse elastography; RTE = real-time elastography; SWE = shear wave elastography.

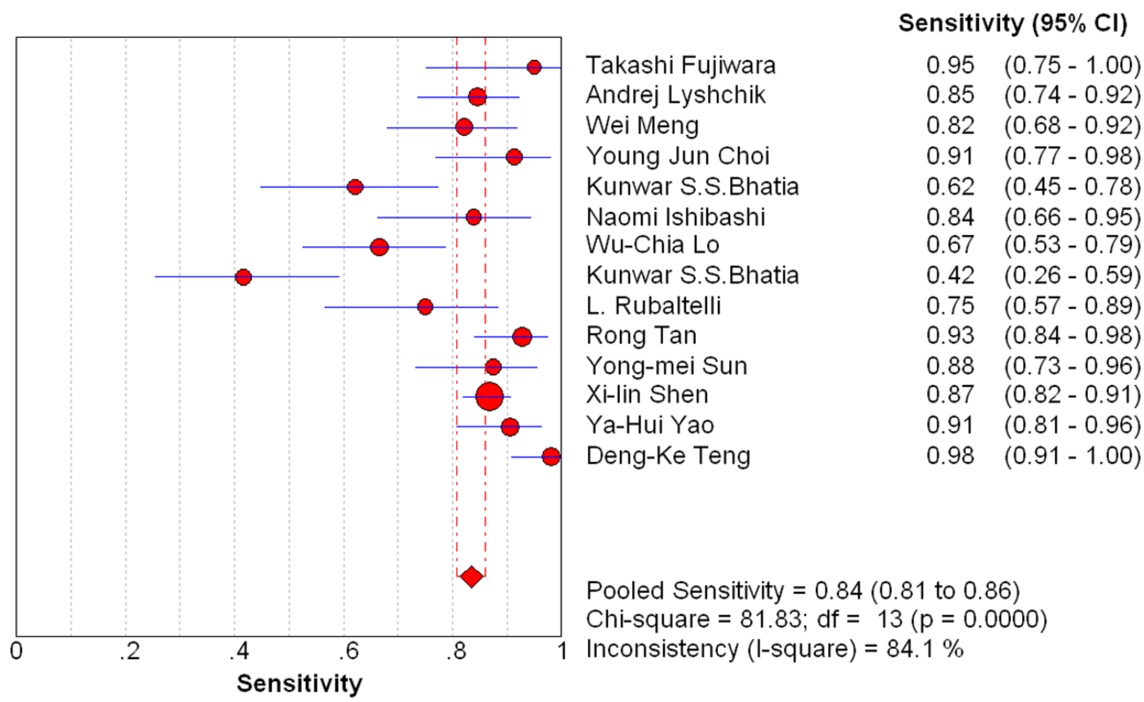

Figure 2. Forest plot (random-effect model) of the meta-analysis of sensitivity for the differentiation of benign and malignant lymph nodes.

impulse elastography (ARFI), while three performed ultrasound real-time elastography (RTE). Two applied the technique of shear wave elastography (SWE) for checking nodes, and the remaining seven articles did not show readers the type of elastography. Missing data that were modeled from the given factors using stochastic regression analysis included the mean age (one study), male percentage (one study) and the cutoff value (one study).

Meta-analysis results

Diagnostic accuracy: We display the test results for elastography in differentiating benign and malignant cervical lymph nodes. Elastography had a pooled sensitivity (random effect model) of 85% (95% CI, 0.76-0.90) in the differential diagnosis of benign and malignant LNs. The pooled specificity (random-effect model) was 86% (95% CI, 0.77-0.91) which were showed in **Figures 2** and **3**. The summary positive LR and negative LR were 5.86 (95% CI, 3.62-9.50) and 0.18 (95% CI, 0.12-0.28), respectively. The summary diagnostic odds ratio (DOR) used to examine the elastography accuracy is 32.641 (95% CI, 16.772-63.525) and the area under the SROC was 0.92 (95% CI, 0.89-0.94).

Heterogeneity study: Significant heterogeneity was found in sensitivity (heterogeneity, chi-square = 95.68, P = 0.00, I-square = 86.41), specificity (heterogeneity, chi-square = 109.23, P = 0.00, I-square = 88.10), indicating that more than 80% of variance across studies is attributed to heterogeneity rather than chance. To explore the sources of heterogeneity, meta-regression analysis was performed. The outcomes of meta-regression analysis are shown method were associated with a higher RDOR. The other characteristics were not statistically significant in the regression model.

Publication bias: Funnel spot and test results of the publication bias are shown that there was no statistically significant publication bias among the 14 included studies (P = 0.942).

Discussion

Differential diagnosis of LNs could help discriminate benign diseases and provide information for the staging of malignant diseases. The status of LNs is the single most important prognostic factor in malignant diseases and plays a critical role in the management of metastatic diseases [27]. Therefore, early and cor-

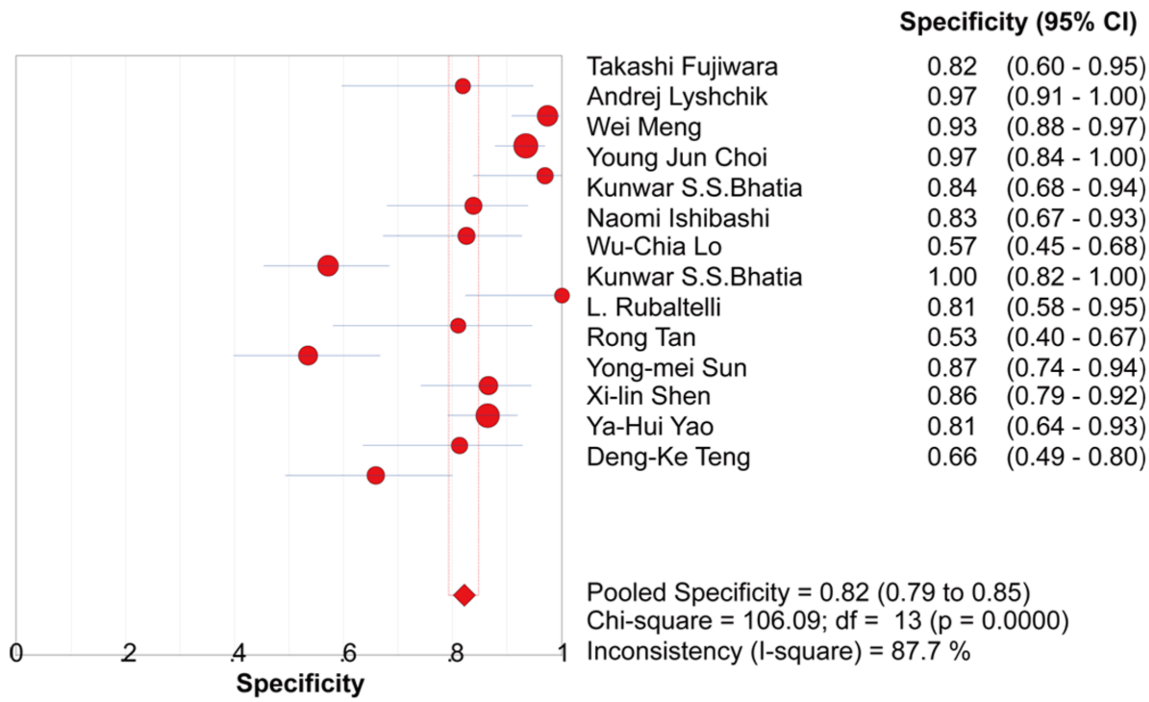

Figure 3. Forest plot (random-effect model) of the meta-analysis of specificity for the differentiation of benign and malignant lymph nodes.

rect differentiation of benign and malignant LNs is essential for clinical decision making.

Elastography is a new technique of sonography that is noninvasive, available and easy to apply. 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. 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. 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). Two different methods could be obtained for elastography evaluation. 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 [28]. 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. The nature of the tissue was analyzed either by a qualitative method or a quantitative method [18, 29, 30].

In this meta-analysis, we evaluated accuracy of elastography in differentiating benign and malignant cervical LNs. We detected high sensitivity and specificity for both elastography scoring system and SR. We also obtained high DORs for both scoring and SR evaluation. It can show that the odd of obtaining positive results in diseased rather than non-diseased individuals by means of elastography is high. The other included study by Giovannini et al. [18, 31] reported 84% sensitivity and 95% specificity. The variation may be produced during the subjective interpretation of the color pattern even if the same threshold was used. The reappraised pooled results still suggested a high accuracy of elastography for differentiating benign and malignant LNs. In a previous systematic review conducted by Ying et al. [32], 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. 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 [32]. Our meta-analysis results support conclusion Elastograohy has high accuracy in differentiating benign and malignant cervical LNs.

However, there were some limitations in this study. First, only 14 trials were included in the meta-analysis. As a result, the small number of studies might reduce the power of the tests on publication bias and source of heterogeneity. Second, different diagnostic standards for elastography were used in the selected studies.

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Disclosure of conflict of interest

None.

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