Original Article

Diagnostic accuracy of contrast-enhanced dual-energy computed tomography for detecting metastatic lymph nodes in patients with malignant tumors: a systematic review and meta-analysis

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Background: This meta-analysis evaluated the diagnostic accuracy of contrast-enhanced dual-energy computed tomography (DECT) for detecting metastatic lymph nodes in patients with cancer.

Methods: PubMed, Embase and Cochrane Library databases were searched for literature published from database inception until September 2022. Only studies that investigated the diagnostic accuracy of DECT for metastatic lymph nodes in patients with malignant tumors and surgically removed metastatic lymph nodes for pathological confirmation were included. The quality of the included studies was evaluated using the Quality Assessment of Diagnostic Accuracy Studies tool. The threshold effect was determined by calculating Spearman correlation coefficients and summary receiver operating characteristic (SROC) curve patterns. Deeks test was used to assess publication bias.

Results: All of the included studies were observational studies. A total of 16 articles involving 984 patients were included (2,577 lymph nodes) in this review. A total of 15 variables were included in the meta-analysis, including 6 individual parameters and 9 combined parameters. Normalized iodine concentration (NIC) in the arterial phase combined with the slope in the arterial phase showed better identification of metastatic lymph nodes. The spearman correlation coefficient was –0.371 (P=0.468), and the SROC curve did not show a "shoulder-arm" shape, suggesting that there was no threshold effect and that heterogeneity was present. The combined sensitivity was 94% [95% confidence interval (CI): 86–98%], the specificity was 74% (95% CI: 52–88%), and the area under the curve was 0.94. The Deeks test suggested no significant publication bias in the included studies (P=0.06).

Conclusions: NIC in arterial phase combined with the slope in the arterial phase has some diagnostic value in differentiating between metastatic and benign lymph nodes, but this should be further evaluated in additional studies with rigorous design and high homogeneity.

Keywords: Radiography; dual-energy computed tomography (DECT); metastatic lymph nodes; cancer

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Introduction

In most countries, cancer is the primary cause of mortality before the age of 70 years and a major impediment to extending life expectancy. According to figures from the International Agency for Research on Cancer (IARC), 19.3 million new cancer cases and approximately 10 million deaths were estimated to occur globally in 2020 (1). The main purpose of lymph node assessment is the staging of the cancer, which is important in the choice of treatment options. Lymph nodes serve as conduits for the spread of cancer to other organs in many different forms of cancer. Lymph node metastasis is an essential prognostic characteristic and one of the most important determinants impacting patient survival (2). Therefore, accurate detection of lymph node metastases is critical for cancer staging and treatment planning (3).

In recent years, dual-energy computed tomography (DECT) has been widely used for the prediction of various types of cancer and other diseases such as lung cancer (4), gastrointestinal tumors (5), breast cancer (6), biliary tract cancer (7), adherent perinephric fat (8), microthrombosis associated with COVID-19 pneumonia (9), pulmonary emboli (10), and lumbar disk herniation (11). DECT is a CT technique that uses two different X-ray energies, and it can accurately determine the composition of objects, thereby substantially increasing the capabilities of traditional CT single-energy scanning (12).

The difference between contrast-enhanced CT and traditional CT is that contrast-enhanced CT uses intravenous iodine contrast to assess whether there is blood perfusion. When the contrast is injected in the blood stream and shows perfusion, this is crucial since perfusion is a hallmark of cancer. Contrast-enhanced DECT can provide an iodine map to assess the iodine content of the tissue and indirectly reflect the blood supply to the tissue (13). In addition to traditional CT images, DECT can provide monochromatic images at 40–200 keV energy levels (14), iodine concentration (IC) mapping, effective atomic number (effc-z) images, and many other quantitative parameters, making it a significant milestone for CT diagnosis (4-11,15). DECT has shown promise in the diagnosis of preoperative metastatic lymph nodes in recent years (16), and DECT characteristics may help to distinguish metastatic from benign lymph nodes (17).

Different manufacturers often apply different DECT imaging techniques, which can be broadly divided into two categories: (I) one based on the detector side of the approach, such as detector-based DECT, which has 2 layers of detectors that detect low versus high energy photons and (II) another based on the tube sphere side of the approach, such as dual-source DECT, single-source DECT with rapid kilovoltage switching, and split-beam DECT (18). The differences of these technologies mainly stem from the product characteristics of different manufacturers and the different implementation forms of energy scanning (19). Each of these techniques has its own characteristics. To date, there is no consensus on which manufacturer and which technique provides the best diagnostic performance (20).

Furthermore, no systematic assessments or meta-analyses have been conducted on the usefulness of DECT in the detection of metastatic lymph nodes. Therefore, this review includes a large number of studies relevant to the topic. This allowed for an assessment of the sensitivity and specificity of DECT for lymph node metastasis. The following article is presented in accordance with the PRISMA-DTA reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-22-527/rc).

Methods

The PRISMA-DTA standards were used to conduct this systematic review and meta-analysis, which follows current best practices (21). Prior to the start of the review, the systematic review was prospectively registered and submitted to the PROSPERO database (CRD42022303023). This meta-analysis was not subject to ethical approval.

Search strategy

A comprehensive search of the PubMed, Embase, and Cochrane Library databases was performed for literature published in the English language from the inception of each database to September 30, 2022. Preliminary keywords and medical subject headings (MeSH) terms, including lymph nodes, metastatic lymph nodes, spectral CT, dual energy, and CT, were combined to generate a list of studies. The search strategy is shown in Appendix 1.

Selection of studies

After eliminating duplicates, the abstract and title of the remaining articles were independently screened by two investigators according to the inclusion and exclusion criteria. When a study was deemed eligible, the full text

was obtained, and further screening was performed. Once agreement between the two investigators (ZKX and ZC) was reached, the final list of studies underwent full-text analysis and data extraction. When there was disagreement between raters, a consensus was reached through discussion or consultation with a third investigator (KDR).

Full-text articles were thoroughly selected according to the following inclusion criteria: (I) inclusion of patients with malignant neoplasms; (II) the application of DECT in the detection of metastatic lymph nodes; (III) surgical removal of metastatic lymph nodes for pathological confirmation; and (IV) the assessment of the diagnostic accuracy of lymphatic metastasis with DECT, with the data permitting the construction of a 2×2 table for calculating the diagnostic accuracy of DECT, including true positive (TP), false positive (FP), false negative (FN), and true negative (TN) results. Publications were excluded if they met any of the following criteria: (I) a lack of blood supply for the primary tumor; (II) inability to obtain the full text and extract data or the diagnostic indicators for individual parameters; (III) lack of reporting for the outcome of tumor recurrence; (IV) non-English language literature; and (V) reviews, retrospective studies, conference abstracts, case report/case series, and meta-analyses.

Data extraction

Two investigators (KDR and CXY) independently extracted data from the identified studies. When the data information in the original articles was unclear or the two investigators had different opinions, differences were resolved through discussion.

The following characteristics were extracted: study characteristics, including first author, year of publication, prospective versus retrospective study design, total number of patients, mean age, number and percentage of males, type of disease, total number of lymph nodes, and number of metastatic lymph nodes; and DECT characteristics, including machine brand, DECT type, tube voltage, tube current, slice thickness (mm), collimation (mm), rotation time (s), and contrast time (s). Finally, the true-positive, false-positive, true-negative, and false-negative rates (%), as well as sensitivity and specificity of identifying metastatic lymph nodes were reported. If they were not explicitly stated in the original research, data on TPs, FPs, TNs, and FNs were estimated based on the number, sensitivity, and specificity of lymph nodes described in the literature.

Assessment of methodological quality

Two investigators (GPH and ZHW) independently assessed the methodological quality of the included studies using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool (22), and differences were addressed by consensus. If no consensus was achieved between the 2 raters, a third rater (KDR) was consulted.

Statistical analysis and data synthesis

If the parameters included in this analysis had different degrees of heterogeneity, different cutoff values could have led to different sensitivities and specificities of diagnostic tests, and a threshold effect would be generated. Therefore, we first tested whether there was a threshold effect for the diagnostic test. To determine whether there was a threshold effect, Spearman correlation coefficient and summary receiver operating characteristic (SROC) curves were used. If there was a positive correlation between sensitivity and specificity ($P<0.05$) or the scatter points in the SROC curve showed a "shoulder-arm" distribution, heterogeneity caused by a threshold effect was considered. Conversely, if there was no positive correlation between sensitivity and specificity ($P>0.05$) or the scatter points in the SROC curve showed a "non-shoulder arm" distribution, there was considered to be was no threshold effect leading to heterogeneity. If there was a threshold effect, the best method to merge data was to fit the SROC curve and to calculate the area under the ROC curve, or not to merge the data. If there was no threshold effect, the effect values were combined. The effect model depended on whether there was heterogeneity between the studies.

The I^2 test [$I^2=100\% \times (Q-df)/Q$] was used to assess heterogeneity of the studies that were included in the meta-analysis. Each parameter was statistically assessed using Stata 15.0 (StataCorp LLC, College Station, TX, USA) and Meta-Disc 14.0 (https://meta-disc.software.informer.com/1.4/). The effect size included sensitivity, specificity, positive likelihood ratio, negative likelihood ratio (NLR), diagnostic advantage ratio, and area under the SROC curve (AUC). If $I^2 \leq 50\%$ or $P>0.05$ showed that there was no substantial heterogeneity, the fixed effects model was employed to combine the effect indicators. If $I^2>50\%$ or $P<0.05$, a random effects model was used to combine effect indicators, and sensitivity and heterogeneity tests were performed. A forest plot was also generated to show the

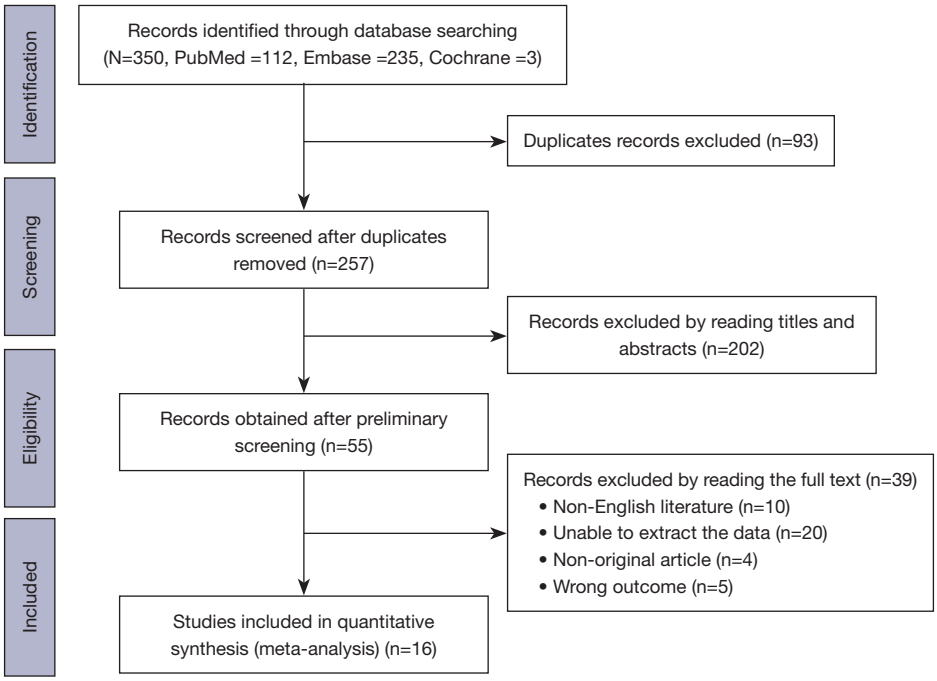

Figure 1 Flow diagram showing the study selection process for the meta-analysis.

results of the data synthesis.

To perform sensitivity analyses, Stata software was used. The software examined the effect of a single study on the pooled effect size by observing whether the results changed significantly after removal of a particular study. Finally, Deeks test was employed to examine publication bias, with $P<0.05$ indicating the presence of publication bias.

Results

Literature search

A total of 350 relevant papers were obtained by searching the databases, and after deduplication, 257 original studies were identified. After a reading of the titles and abstracts of these 257 original studies, 202 papers were excluded. Then, full texts were read in detail, and a rescreening was performed based on the inclusion and exclusion criteria, resulting in a final sample of 16 eligible studies for inclusion in this meta-analysis (16,23-37). The flowchart outlining the screening process is shown in *Figure 1*. The specific reasons for exclusion at the full-text screening stage are described in the Appendix 2.

Study characteristics

This meta-analysis included 16 original investigations, totaling 2,577 lymph nodes from 984 individuals. The papers included were published between 2015 and 2022, with 11 studies having been published in the last 5 years (16,23-32). The mean age of patients in the 16 included studies varied from 34.0±7.8 to 59.5±8.7 years, while the percentage of males ranged from around 0.0% to 70.9%. Moreover, 7 of the 16 studies included patients with thyroid cancer (16,23,24,29,30,33,36), 4 studies included patients with colorectal cancer (25,28,35,37), and the remaining 5 studies included patients with esophageal cancer, liver cancer, breast cancer, squamous cell carcinoma of the oropharynx, or lung cancer (26,27,31,32,34). *Table 1* details the patient characteristics of the included studies. *Table 2* details the DECT characteristics of the listed studies. Regarding manufacturer type, 6 studies used Siemens equipment, 9 nine studies used General Electric Company equipment. The majority of studies used dual-energy X-rays at energies of 80 to 140 kV. Of the studies included, 4 used single-energy DECT while 9 used dual-energy DECT, and the technology employed in the remaining 3 studies was not

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

Reference	Year	Study type	Number of patients	Age (years)	Sex (% male)	Cancer type	Total number of LNs	Total number of MLNs
Zou *et al.* 2021	2021	Retrospective study	52	43.00±15.22	11 (21.2)	Papillary thyroid carcinoma	359	139
Zhuo *et al.* 2021	2021	Retrospective study	74	N	40 (54.1)	Papillary thyroid carcinoma	216	92
Wu *et al.* 2021	2021	Controlled study	35	39.79±13.58	6 (17.1)	Papillary thyroid carcinoma	206	80
Qiu *et al.* 2021	2021	Prospective study	71	59.3±14.1	41 (57.7)	Colorectal cancer	150	84
Sun *et al.* 2020	2020	Retrospective study	26	N	N	Esophageal cancer	51	34
Zeng *et al.* 2019	2019	Retrospective study	43	N	N	Hepatocellular carcinoma	156	52
Yang *et al.* 2019	2019	Prospective study	178	55.59±12.87	119 (66.9)	Colorectal cancer	178	72
Li *et al.* 2019	2019	Retrospective study	30	41.6±14.8	13 (43.3)	Papillary thyroid carcinoma	99	70
He *et al.* 2019	2019	Prospective study	51	N	16 (31.4)	Papillary thyroid carcinoma	212	124
Zhang *et al.* 2018	2018	Prospective study	193	47.6±10.1	0 (0.0)	Breast cancer	337	76
Foust *et al.* 2018	2018	Retrospective study	8	N	N	Squamous cell carcinoma of the oropharynx	29	13
Zhao *et al.*2017	2017	Retrospective study	34	42.24±14.65	16 (47.1)	Papillary carcinoma and medullary carcinoma	136	102
Li *et al.* 2016	2016	Retrospective study	61	59.5±8.7	37 (60.7)	Lung cancer	40	20
Liu *et al.* 2015	2015	Prospective study	45	34.0±7.8	11 (24.4)	Papillary thyroid carcinoma	175	63
Liu *et al.* 2015	2015	Prospective study	55	N	39 (70.9)	Colorectal cancer	152	60
Kato *et al.* 2015	2015	Retrospective study	28	N	N	Colorectal cancer	81	35

The data of age are expressed as mean ± standard deviation. N, not reported; LN, lymph node; MLN, metastatic lymph node.

specified.

Methodological quality

We used the QUADAS-2 tool to evaluate the quality of primary diagnostic accuracy studies, and *Figure 2* summarizes the overall risk of bias and applicability concerns for this research.

For the diagnostic experiments to be evaluated (whether or not predetermined thresholds were used in the original studies), we judged the risk of bias for diagnostic experiments to be evaluated (QUADAS-2, domain 2) to be high in all studies. We assessed the risk of bias by determining whether there was a time interval between the diagnostic experiment and the gold standard (QUADAS-2, domain 4). In 11 of the 16 studies included, the time interval between the DECT examination and the pathological gold standard was not clearly stated, and, therefore, the risk of bias was considered to be unclear for these 11 articles. The evaluation of clinical applicability included the selection of cases, the implementation and interpretation of the experiments, and the evaluation of the applicability of the gold standard.

Results of data synthesis

Value of each parameter of DECT in the diagnosis of metastatic lymph nodes

Due to the small amount of studies on some parameters, the diagnostic performance of only 15 indicators was analyzed.

Table 2 Dual-energy CT characteristics of the individual included studies

Reference	DECT brand	DECT type	kV1	kV2	Tube current	Slice thickness (mm)	Collimation	Rotation time (s)	Contrast	Dose	Flow rate	Arterial phase (s)	Venous phase (s)
Zou *et al.* 2021	Siemens	Dual source	N	N	600 mA	1	64 mm ×0.6 mm	N	Iohexol	1 mL/kg	3 mL/s	25	45
Zhuo *et al.* 2021	Siemens	Dual source	90	150	250 mA, 125 mA	0.75	2 mm ×192 mm ×0.6 mm	0.5	Iopromide	N	4 mL/s	N	50
Wu *et al.* 2021	GE	Single source fast switching kV	80	140	260 mA	1.25	N	N	Iohexol 350	1.2 mL/kg	3.1 mL/s	N	50
Qiu *et al.* 2021	Canon	Single source fast switching kV	80	135	112–187 mA	0.5	N	N	Ultravist 300	1.0 mL/kg	3 mL/s	40	70
Sun *et al.* 2020	Siemens	N	90	150	N	1	N	0.25	Iohexol	N	23 mgI/kg/s	N	N
Zeng *et al.* 2019	GE	Single source fast switching kV	80	140	600 mA	1.25	N	0.8	Ioversol 320	1.0 mL/kg	3.0 mL/s	25	65
Yang *et al.* 2019	GE	Single source fast switching kV	80	140	375 mA	1.25	N	N	Iohexol	1.5 mL/kg	4ml/s	N	N
Li *et al.* 2019	GE	Single source fast switching kV	80	140	260 mA	5	N	0.7	N	N	3.0 mL/s	N	45
He *et al.* 2019	Siemens	Dual source	80	150	130 mA, 65 mA	1.5	128 mm ×0.6 mm	1	Ioversol 370	85 mL	3.0 mL/s	N	30
Zhang *et al.* 2018	GE	N	N	N	275 mA	1.25	N	N	Iohexol	1.5 mL/kg	4 mL/s	N	N
Foust *et al.* 2018	Siemens	Dual source	80	140	302 mA, 157 mA	0.75	0.6 mm	0.28	N	50 mL	3 mL/s	N	35
Zhao *et al.*2017	GE	Single source fast switching kV	80	140	260 mA	5	N	0.7	N	90 mL	3.0 mL/s	N	45
Li *et al.* 2016	GE	Single source fast switching kV	80	140	N	1.25	N	N	Iohexol	1.2 mL/kg	2.5mL/s	N	N

Table 2 (*continued*)

Table 2 (*continued*)

Reference	DECT brand	DECT type	kV1	kV2	Tube current	Slice thickness (mm)	Collimation	Rotation time (s)	Contrast	Dose	Flow rate	Arterial phase (s)	Venous phase (s)
Liu *et al.* 2015	GE	Single source fast switching kV	N	N	550 mA	1.25	0.625 mm	N	Iopamidol 300	N	4 mL/s	25	50
Liu *et al.* 2015	GE	Single source fast switching kV	80	140	600 mA	1.25	N	0.6	Ultravist	1.5 mL/kg	3 mL/s	N	N
Kato *et al.* 2015	Siemens	N	N	N	N	N	N	N	N	N	N	44	70

CT, computed tomography; DECT, dual-energy computed tomography; GE, GE Healthcare; kV, kilovoltage; N, not reported.

The data on the TPs, FPs, TNs, FNs, sensitivities, and specificities of each parameter, as well as main characteristics, are shown in Appendix 3. Each parameter included in the analysis had varying degrees of heterogeneity (available online: https://cdn.amegroups.cn/static/public/qims-22-527-1.pdf). The effect sizes of the diagnostic sensitivity, specificity, positive likelihood ratio, NLR, diagnostic ratio, and area under the SROC curve (AUC) are summarized for each parameter of DECT in *Table 3*.

As can be seen from the summary in *Table 3*, of the 15 parameters, 4 had relatively large AUC values of 90% or more. These were normalized iodine concentration (NIC) in the arterial phase combined with the slope in the arterial phase, NIC in the arterial phase combined with NIC in the venous phase, NIC in the arterial phase combined with the slope in the venous phase, and the slope in the arterial phase combined with the slope in the venous phase, and their corresponding AUC values were 0.94, 0.90, 0.93, and 0.93, respectively. The sensitivity and specificity of NIC in the arterial phase combined with the slope in the arterial phase were 94% (95% CI: 86–98%) and 74% (95% CI: 52–88%) (*Figure 3*), respectively, with a large amount of heterogeneity in sensitivity (I^2=88.96%) and specificity (I^2=97.36%). The combined positive likelihood ratio (PLR) was 3.39 (95% CI: 2.22–5.18) (*Figure 4A*), the combined NLR was 0.10 (95% CI: 0.04–0.27) (*Figure 4B*), and the combined diagnostic odds ratio (DOR) was 38.86 (95% CI: 9.00–167.66) (*Figure 4C*). Among all the parameters, the AUC of NIC in the arterial phase combined with the slope in the arterial phase was the largest, with a value of 0.94 (*Figure 4D*).

Threshold effect

The results are shown in *Table 3*; the SROC curve lacked a shoulder-arm structure, suggesting that no threshold effect existed. After excluding the effect of threshold effects, we also considered the heterogeneity caused by non-threshold effects.

Since there was no threshold effect in this study, the presence of heterogeneity was deemed not to be related to the threshold effect. Therefore, this study used a random effects model to combine effect sizes and analyze the sources of heterogeneity.

Sensitivity analysis

The above effect size synthesis and data analysis found that the NIC in the arterial phase combined with slope in the arterial phase had the highest AUC. We focused on the sensitivity analysis of this combination. As shown in *Figure 5*, regardless of which study was excluded, the final combined result was not significantly affected, indicating that each study had little influence on the general results. As such, the results of this study were stable. We also examined sensitivity analysis results for other parameter combinations, which are shown in https://cdn.amegroups.cn/static/public/qims-22-527-2.pdf, and these results were all stable.

Figure 2 Risk of bias and applicability concerns for the studies included in the meta-analysis. (A) Risk of bias summary. (B) Risk of bias graph.

Investigation of heterogeneity

Sources of clinical variability were explored by meta-regression. Based on clinical practice, we then formally evaluated the effects of the following variables on sensitivity and specificity: DECT manufacturers (Siemens *vs.* General Electric Company), blood supply (abundant *vs.* insufficient), contrast flow rate (>3 *vs.* ≤3 mL/s), and study design (prospective *vs.* retrospective). The results of the meta-regression for each parameter are shown in *Table 4*. For the NIC in the arterial phase combined with the slope in the arterial phase, meta-regression analysis showed a significant effect of experimental design on the heterogeneity of sensitivity.

Table 3 Combined effect size of each parameter of dual-energy computed tomography

Parameter	Sensitivity	Specificity	PLR	NLR	DOR	AUC	Spearman correlation	P value
IC in AP	0.77 (0.70–0.83)	0.78 (0.70–0.84)	3.42 (2.32–5.04)	0.3 (0.22–0.43)	12.01 (5.73–25.16)	0.84	–0.429	0.397
NIC in AP	0.78 (0.69–0.86)	0.79 (0.66–0.88)	3.49 (2.19–5.57)	0.29 (0.19–0.46)	13.74 (5.48–34.45)	0.85	–0.042	0.907
Slope in AP	0.74 (0.65–0.82)	0.85 (0.72–0.93)	4.12 (2.50–6.77)	0.32 (0.22–0.47)	13.82 (6.46–25.96)	0.85	–1.017	0.819
IC in VP	0.80 (0.73–0.86)	0.84 (0.79–0.88)	4.58 (3.52–5.98)	0.23 (0.15–0.36)	21.89 (11.90–40.28)	0.86	–0.429	0.289
NIC in VP	0.83 (0.74–0.89)	0.78 (0.74–0.82)	3.54 (2.93–4.26)	0.24 (0.18–0.34)	15.85 (10.21–24.63)	0.85	0.098	0.762
Slope in VP	0.75 (0.66–0.83)	0.87 (0.79–0.92)	5.26 (3.59–7.72)	0.29 (0.22–0.39)	20.75 (11.63–37.04)	0.88	0.345	0.308
IC in AP + NIC in AP	0.95 (0.78–0.99)	0.66 (0.44–0.82)	2.59 (1.76–3.81)	0.11 (0.02–0.51)	21.00 (11.69–37.70)	0.88	0.7	0.188
NIC in AP + slope in AP	0.94 (0.86–0.98)	0.74 (0.52–0.88)	3.52 (1.99–6.24)	0.10 (0.04–0.27)	38.86 (9.00–167.66)	0.94	–0.371	0.468
NIC in AP + NIC in VP	0.95 (0.91–0.98)	0.60 (0.49–0.70)	2.4 (1.84–3.13)	0.09 (0.05–0.18)	29.54 (12.78–68.27)	0.9	0	1
NIC in AP + slope in VP	0.93 (0.88–0.97)	0.73 (0.57–0.84)	3.39 (2.22–5.18)	0.10 (0.05–0.21)	37.02 (13.05–105.02)	0.93	–0.086	0.872
Slope in AP + NIC in VP	0.95 (0.89–0.97)	0.66 (0.56–0.75)	2.75 (2.05–3.68)	0.09 (0.04–0.20)	31.89 (13.69–74.24)	0.88	0.029	0.957
Slope in AP + slope in VP	0.92 (0.88–0.95)	0.74 (0.61–0.83)	3.25 (2.40–4.41)	0.12 (0.07–0.19)	32.00 (15.04–68.09)	0.93	0.036	0.939
IC in VP + NIC in VP	0.97 (0.92–0.99)	0.69 (0.62–0.75)	2.97 (2.42–3.65)	0.05 (0.02–0.15)	53.29 (20.16–140.83)	0.82	–0.072	0.878
Slope in VP + slope in VP	0.96 (0.89–0.99)	0.68 (0.61–0.74)	2.85 (2.17–3.75)	0.07 (0.03–0.20)	41.03 (14.83–113.54)	0.77	–0.486	0.329
NIC in VP + slope in VP	0.95 (0.90–0.97)	0.68 (0.62–0.74)	2.94 (2.48–3.48)	0.10 (0.06–0.17)	31.23 (18.39–53.04)	0.85	0.433	0.244

PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratio; AUC, area under curve; IC, iodine concentration; AP, arterial phase; NIC, normalized iodine concentration; VP, venous phase.

Publication bias

The Deeks test with Stata software was used to examine publication bias; P>0.05 indicated that there was no substantial publication bias in the included papers. *Figure 6* shows the publication bias test for NIC in the arterial phase combined with the slope in the arterial phase. The publication bias tests for the remaining parameters are shown in https://cdn.amegroups.cn/static/public/qims-22-527-3.pdf.

Discussion

Metastatic lymph nodes are the key to predicting the prognosis of cancer, and early detection of metastatic lymph nodes can help with the staging and treatment of cancer (38). DECT provides more quantitative parameters than does traditional CT, while also providing quantitative indicators, especially IC (39). This study focused on the influence of various parameters provided by an iodine map and the slope of the energy spectrum curve in the diagnosis of metastatic lymph nodes. IC and NIC can reflect the difference in iodine content between benign and malignant lymph nodes, and, thus, indirectly reflect the blood supply. Additionally, NIC avoids the effect of individual differences, and previous studies have found higher NIC values in metastatic lymph nodes than in benign lymph nodes. This is probably because tumor cells release a large number of regulatory factors before metastasis occurs, thus, stimulating the proliferation of blood vessels and lymphatic vessels in the lymph nodes

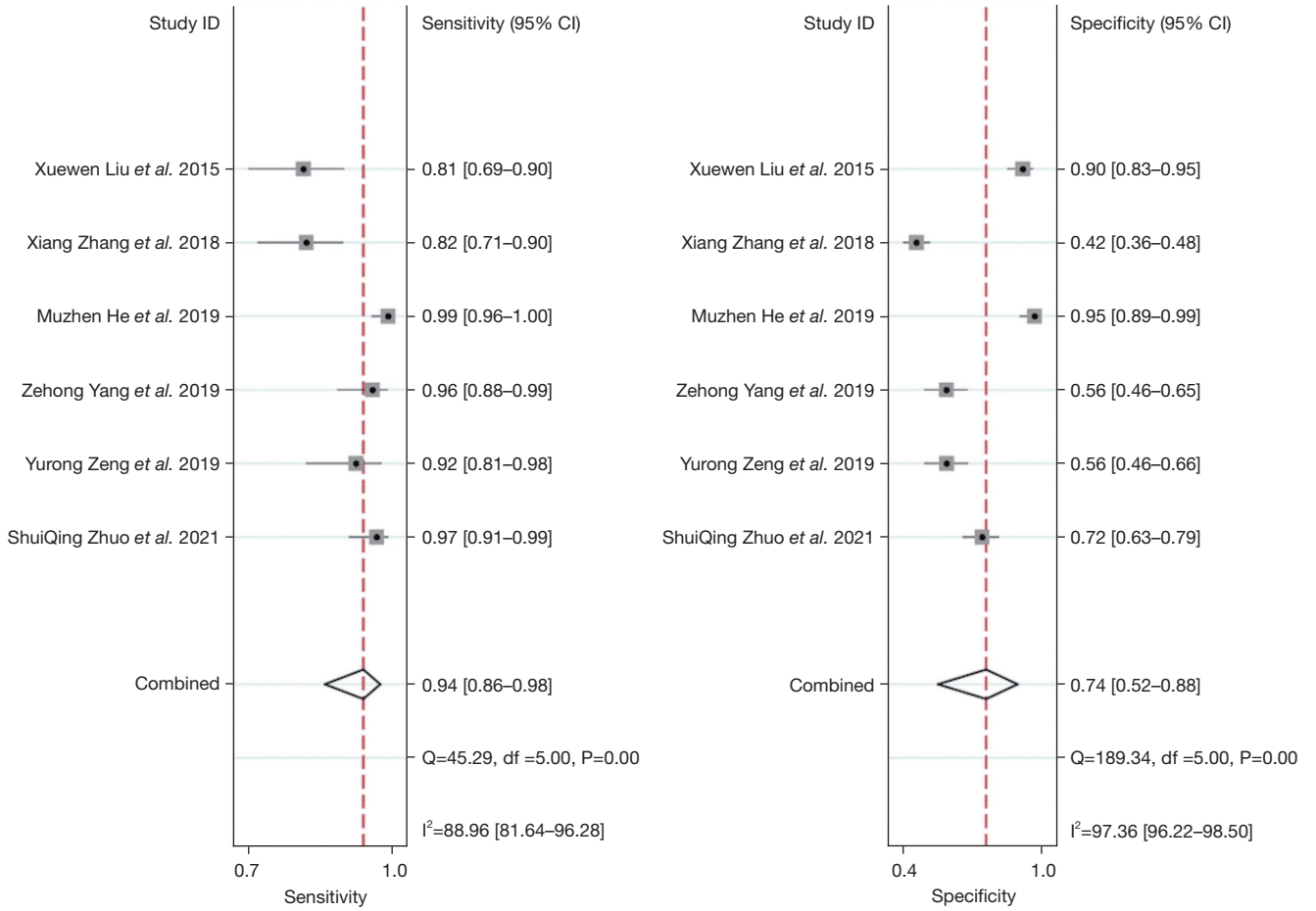

Figure 3 Forest plots of primary study sensitivity (left) and specificity (right) of the NIC in the arterial phase combined with the slope in the arterial phase for detecting metastatic lymph nodes. Each solid square represents an individual study. Error bars represent 95% CIs. Diamonds indicate the pooled sensitivity and specificity for all of the studies. NIC, normalized iodine concentration; CI, confidence interval.

which results in a widening of the microvasculature and an increase in blood flow (40). Both metastatic and no-metastatic lymph nodes follow a descending spectrum curve patterns, but the curve pattern of the metastatic nodes is much steeper, suggesting that the slope of the spectral Hounsfeld unit curve [λHU = (CT value (40 keV) – CT value (100 keV)]/(100–40). "CT value (40 keV)" and "CT value (100 keV)" are the CT attenuation measurements at 40 and 100 keV, respectively] could reflect the different statuses of lymph nodes (metastatic or non-metastatic) (37).

A total of 16 publications were included in this study comprising 2,577 lymph nodes, with disease types including thyroid cancer, lung cancer, colorectal cancer, oropharyngeal squamous cell carcinoma, breast cancer, esophageal cancer, and liver cancer,. Of the 15 indicators included in the analysis, 4 of the combined ones had a good diagnostic effect with an AUC greater than or equal to 0.90 (NIC in the arterial phase combined with slope in the arterial phase, NIC in the arterial phase combined with NIC in the venous phase, NIC in the arterial phase combined with slope in the venous phase, and slope in the arterial phase combined with slope in the venous phase). The combination of the two parameters of NIC in the arterial phase and the slope in the arterial phase not only increases the sensitivity but also has a high specificity. For this combination, the diagnostic energy efficiency analysis included 6 studies involving 1,274 lymph nodes. The sensitivity was 94%, the specificity was 74%, the AUC value of the included studies was 0.94, and the Q* value was 0.93, suggesting that the NIC in the arterial phase combined with the slope in the arterial phase has good diagnostic value for the diagnosis of metastatic lymph nodes. Moreover, to a certain extent, it avoids the missed

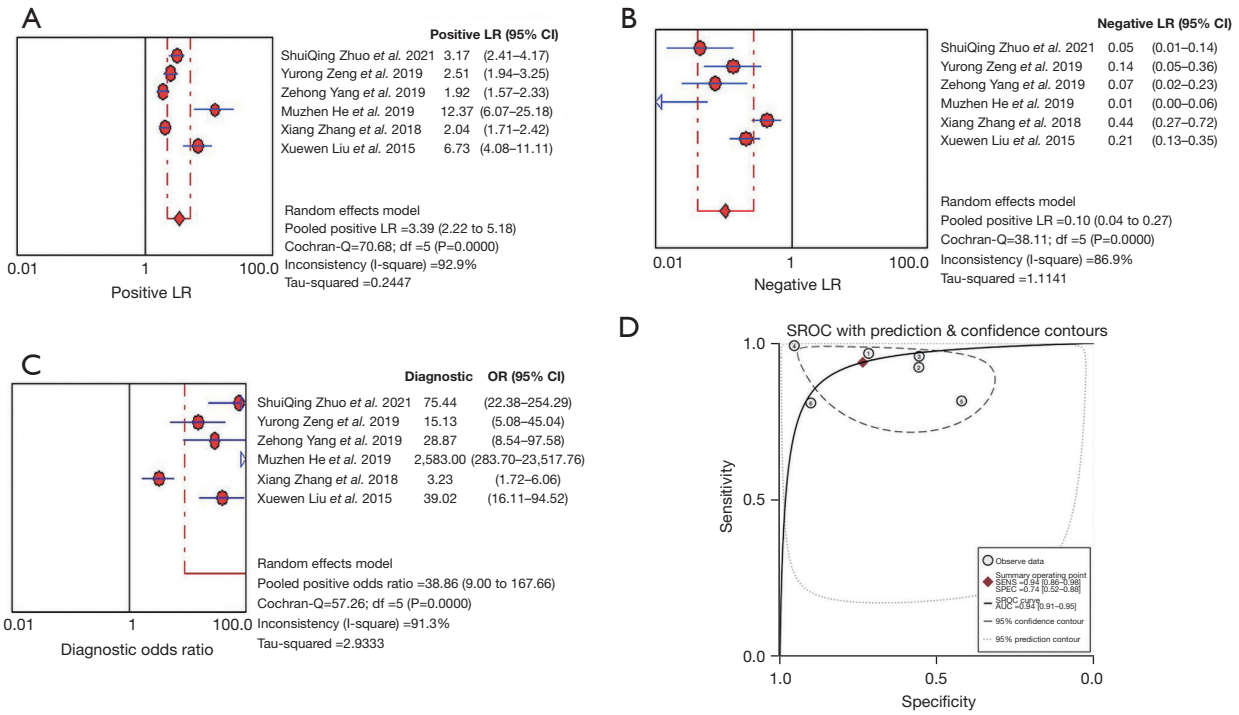

Figure 4 Forest plots of PLR (A), NLR (B), DOR (C), and AUC of SROC (D) for the NIC in the arterial phase combined with the slope in the arterial phase. (A) The combined PLR of NIC in the arterial phase combined with the slope in arterial phase for detecting metastatic lymph nodes was 3.39 (95% CI: 2.22–5.18). (B) The combined NLR of the NIC in the arterial phase combined with the slope in the arterial phase for detecting metastatic lymph nodes was 0.10 (95% CI: 0.04–0.27). (C) The combined DOR of NIC in the arterial phase combined with the slope in the arterial phase for detecting metastatic lymph nodes was 38.86 (95% CI: 9.00–167.66). (D) The AUC of the NIC in the arterial phase combined with the slope in the arterial phase was the largest, with a value of 0.94. LR, likelihood ratio; CI, confidence interval; PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratio; AUC, area under curve; SROC, summary receiver operating characteristic; NIC, normalized iodine concentration; SENS, sensitivity; SPEC, specificity.

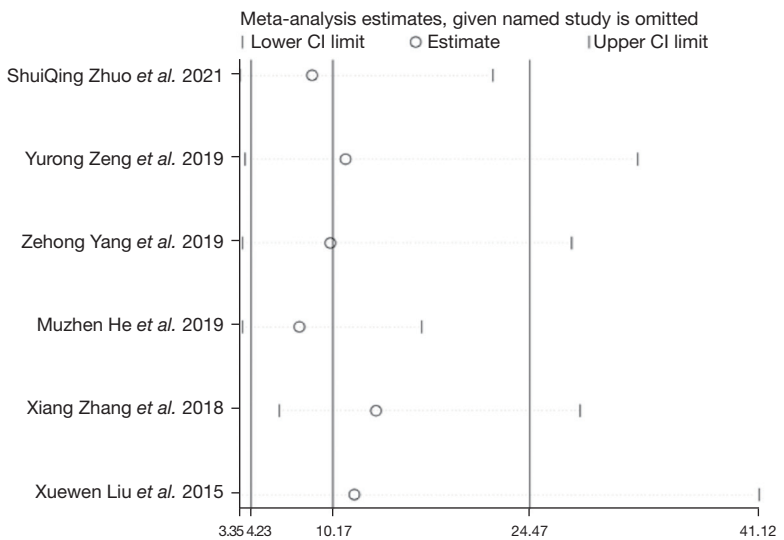

Figure 5 Sensitivity analysis for the NIC in the arterial phase combined with the slope in the arterial phase. CI, confidence interval; NIC, normalized iodine concentration.

Table 4 Meta-regression analysis for each parameter

Parameter	Diagnostic indicators	DECT brand	Blood supply	Contrast flow rate	Study design
IC in AP	Sensitivity	–	–	+	–
	Specificity	–	–	–	–
NIC in AP	Sensitivity	–	–	–	+
	Specificity	–	–	–	–
Slope in AP	Sensitivity	–	–	–	+
	Specificity	–	–	–	–
IC in VP	Sensitivity	–	+	–	–
	Specificity	+	+	+	–
NIC in VP	Sensitivity	–	–	–	+
	Specificity	–	–	–	–
Slope in VP	Sensitivity	–	–	–	+
	Specificity	–	–	–	–
IC in AP + NIC in AP	Sensitivity	+	–	–	–
	Specificity	–	–	–	–
NIC in AP + slope in AP	Sensitivity	–	–	–	+
	Specificity	–	–	–	–
NIC in AP + NIC in VP	Sensitivity	–	+	–	+
	Specificity	–	–	–	–
NIC in AP + slope in VP	Sensitivity	–	–	–	+
	Specificity	–	–	–	–
Slope in AP + NIC in VP	Sensitivity	–	–	–	+
	Specificity	–	–	–	–
Slope in AP + slope in VP	Sensitivity	+	–	–	+
	Specificity	–	–	–	–
IC in VP + NIC in VP	Sensitivity	–	–	–	–
	Specificity	+	+	+	–
Slope in VP + slope in VP	Sensitivity	–	–	+	–
	Specificity	–	–	–	–
NIC in VP + slope in VP	Sensitivity	–	–	–	+
	Specificity	–	–	–	+

"+": significant effect on the heterogeneity; "–": nonsignificant effect on the heterogeneity. IC, iodine concentration; AP, arterial phase; NIC, normalized iodine concentration; VP, venous phase; DECT, dual-energy computed tomography.

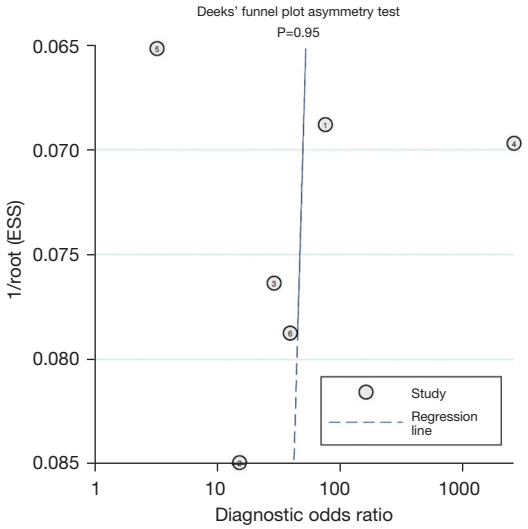

Figure 6 Publication bias. Deeks test was used to evaluate publication bias for NIC in the arterial phase combined with the slope in the arterial phase. ESS, effective sample size; NIC, normalized iodine concentration.

diagnosis of metastatic lymph nodes.

Diagnostic studies are usually more heterogeneous than are other types of studies because of differences in case selection, gold standard settings, and experimental procedures. Based on sensitivity analysis and clinical practice, we then formally evaluated the effect of the following variables on sensitivity and specificity: DECT brand (Siemens *vs.* General Electric Company); blood supply (abundant *vs.* insufficient), contrast flow rate (>3 *vs.* ≤3 mL/s), and study design (prospective *vs.* retrospective). For the NIC in the arterial phase combined with the slope in the arterial phase, meta-regression analysis showed a significant effect of the experimental design on the heterogeneity of sensitivity (P<0.00). These 4 variables also affected the sensitivity and specificity of the remaining partial parameters. In addition, the heterogeneity in this study may also be due to the different sizes of lymph nodes, the different blood supplies to lymph nodes during different periods, the different types of cancer, the different settings of machine parameters, and the different types and doses of contrast agents. In the studies by Li *et al.* (16), Zhao *et al.* (33) and Kato *et al.* (37), the contrast agents used were not described in the text, and the patients included in the study by Zhang *et al.* (31) were all female, which might have contributed to the large heterogeneity observed in these studies.

This meta-analysis had some limitations. While a very extensive literature search was conducted for this study, variables such as different types of cancer, lymph node sizes, machine characteristics, and DECT technologies might have affected diagnostic accuracy. However, this review did not evaluate the combined role of these variables.

Conclusions

With the development and refinement of various imaging techniques, DECT has great clinical significance and application prospects in detecting metastatic and benign lymph nodes. To make the best use of DECT in this respect, it is helpful to combine the two parameters of NIC in the arterial phase and slope in the arterial phase. To further investigate and validate the reliability of the results of this analysis, we need to design prospective cohort studies of high quality, with large sample sizes, homogeneous study populations, homogeneous control populations, and homogeneous detection methods and combine morphological features to model the best combination of parameters to provide clinical guidance for the differential diagnosis of benign and metastatic lymph nodes. In addition, DECT parameters with the best diagnostic performance for each tumor type and the best DECT techniques should also be sought to be able to provide individual guidance for the differentiation of benign and malignant lymph nodes in each patient with cancer, and this should be the focus of further clinical research.

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Footnote

Reporting Checklist: The authors have completed the PRISMA-DTA reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-22-527/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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