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Review Article

Serum cross-linked N-telopeptide of type I collagen as a biomarker of bone metastases for patients with lung cancer: a meta-analysis

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Abstract: Objective: Bone metastasis is one of the most common events for lung cancer patients. The aim of this study was to investigate serum cross-linked N-telopeptide of type I collagen (NTx) as a biomarker for bone metastases in patients with lung cancer by pooling published studies. Methods: Open published studies about serum cross-linked N-telopeptide of type I collagen (NTx), as a biomarker of bone metastases for patients with lung cancer, were electronically searched in databases of Pubmed, Embase, and CNKI by two reviewers (Yanjun Su and Hui Chen), independently. Relevant studies were included in this met-analysis and data of each included study were extracted. Mean NTx levels of bone metastases lung cancer (case group) and non-bone metastases lung cancer (control group) of each individual publication was compared. Using serum NTx as a biomarker, diagnostic sensitivity (sen), specificity (sep), positive likelihood ratio (+lr), negative likelihood ratio (-lr), diagnosis odds ratio (dor), and area under the received operative curve (AUC) for bone metastases were pooled by a meta-analysis method, through random or fixed effects models. Results: Eleven studies were included for quantitative analysis and 9 studies for meta-analysis. Serum levels of NTx for bone metastases lung cancer and non-bone metastases lung cancer were 28.82 ± 7.74 nmol/L and 17.11 ± 5.26 nmol/L, respectively, indicating that serum level of NTx in the metastases disease group was significant higher than non-metastases disease group (t=3.34, P=0.003). Combined data showed pooled sensitivity and specificity were 0.79 (95% CI: 0.73-0.83), respectively. Pooled +lr, -lr, and dor were 2.83 (95% CI: 1.98-4.06), 0.28 (95% CI: 0.18-0.45), and 11.60 (95% CI: 6.26-21.49), respectively, through a random effects model. Systematic area under ROC curve (AUC) was calculated using data from each individual study. Pooled AUC was 0.84. Conclusion: Serum NTx levels were significant elevated in bone metastases lung cancer. This could be a potential biomarker for bone metastases diagnosis with relative high sensitivity and specificity.

Keywords: Meta-analysis, lung cancer, diagnosis, NTx

Introduction

According to recent published cancer epidemiology studies, lung cancer has become the most frequently diagnosed malignant carcinoma in males and second most in females [1]. Furthermore, it is the leading cause of cancer related deaths worldwide for both men and women. For lung cancer, the skeletal system is one of the most common metastatic sites, accounting for more than 30% of metastases lesions [2]. Generally, bone metastases disease is often diagnosed by magnetic resonance imaging (MRI), emission computed tomography (E-CT), and positron emission computerized tomography PET-CT [3, 4]. However, these examination procedures are complex and cannot be performed repeatedly in a short period of time.

NTx can be released from bone into the blood when the bone is destroyed by metastatic disease [5, 6]. Previous published studies have found that serum NTx concentration was elevated in patients with bone metastatic lesions [7-9]. However, because of the small simple size, the statistical power was limited and the conclusion was not powerful. A meta-analysis, pooling all published data about NTx as a biomarker of bone metastases for patients with

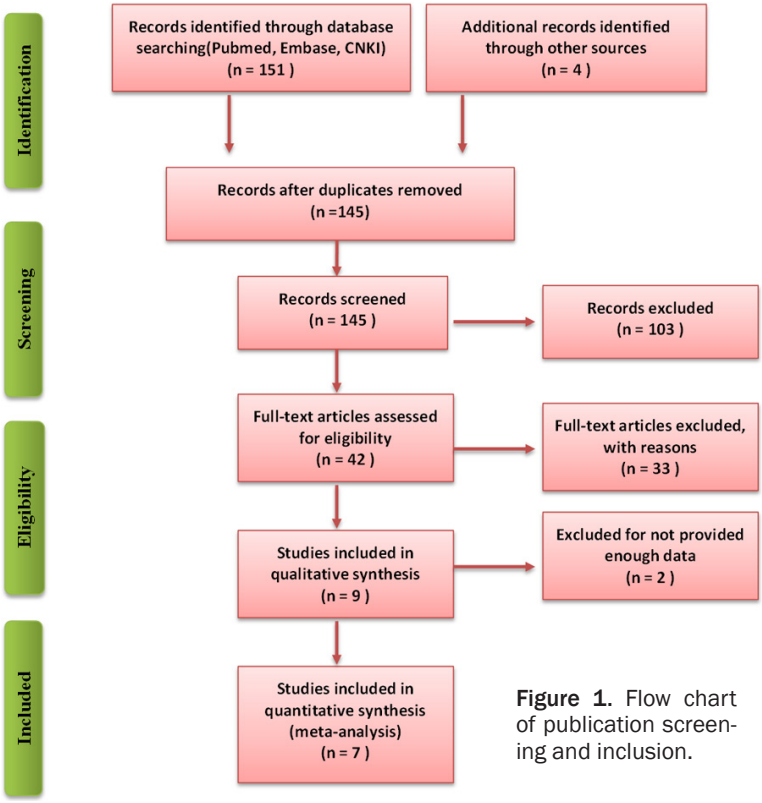

Figure 1. Flow chart of publication screening and inclusion.

lung cancer, was performed to further evaluate its diagnostic clinical practices.

Methods

Publication search

Open published studies, concerning serum cross-linked N-telopeptide of type I collagen as a biomarker of bone metastases for patients with lung cancer, were electronically searched in databases of Pubmed, Embase, and CNKI by two reviewers (Yanjun Su and Hui Chen), independently. Publication search terms were as follows: lung cancer, non-small cell lung cancer, NTx, cross-linked N-telopeptide of type I collagen, and metastasis/metastases. References of included studies were carefully examined to find potential applicable studies.

Study inclusion and exclusion criteria

Publication inclusion criteria included: (1) Clinical studies about serum NTx in lung cancer patients as biomarker for diagnosis of bone metastases; (2) Patients diagnosed with lung cancer (including non-small cell lung cancer and small cell lung cancer) with pathology or cytology confirmation; (3) Data of true positive (tp), false positive (fp), false negative (fn), and true negative (tn) could be extracted or calculated from each individual publication; (4) Study was published in English or Chinese. Study exclusion criteria included: (1) Studies published in other languages; (2) Lung cancer was not confirmed by pathology or cytology; (3) Not enough data could be extracted or calculated from the original studies.

Data extraction

The data and information of each included study was extracted by two reviewers (Yanjun Su and Hui Chen), independently. First/corresponding authors, year of study publication, country, sample size, serum NTx measurement methods, median/mean age of the cases, and cut off value for serum NTx were extracted and recorded. Data of tp, fp, fn, and tn for meta-analysis were also extracted or calculated from each study. All information and data were crossed checked by Yanjun Su and Hui Chen. If there was disagreement, a third reviewer (Lei Zhang) was consulted to make a decision.

Statistics analysis

STATA/SE 11.0 (StataCorp LP, http://www.stata.com), GraphPad Prism 6, and MetaDiSc 1.4 software were used for dealing with data. Statistical heterogeneity among the 9 included studies was evaluated by Chi-square test [10] and inconsistency was calculated by I^2 [11]. Diagnostic sensitivity and specificity were calculated by the equations of sensitivity = true positive/(true positive+ false negative) and specificity = true negative/(true negative+ false positive). Area under receiver operating characteristic (ROC) curve was used to evaluate the diagnostic value of bone metastases by serum NTx. Sensitivity and specificity were pooled by fixed or random effects model, according to the statistical heterogeneity.

Table 1. General characteristics of included trials

Author	Year	Country	NTx		Sample size	Age (mean/median)	TP	FP	FN	TN	Cutoff value	Detection methods
			Case	Control								
Pectasides D	2005	Greece	37.0 ± 36.9	23.5 ± 21.0	64	61.0 (mean)	27	15	4	18	29.7 nM	ELISA
Wang Wei	2008	China	24.06 ± 10.67	13.16 ± 9.52	105	58.4 (median)	45	18	5	37	NA	ELISA
Chen Weisheng	2010	China	25.97 ± 11.25	13.02 ± 8.76	76	58.3 (mean)	NA	NA	NA	NA	NA	ELISA
Lumachi F	2011	Italy	33.5 ± 7.2	25.6 ± 3.1	35	63 (median)	9	7	7	12	30 nM	ELISA
Zhang Shiqiang	2011	China	25.36 ± 11.07	12.16 ± 7.62	106	NA	55	7	6	38	NA	ELISA
Xie Weiguo	2011	China	25.01 ± 11.67	13.21 ± 7.59	67	53.2 (mean	NA	NA	NA	NA	NA	ELISA
Bayrak SB	2012	Turkey	22.69 ± 7.98	18.67 ± 6.85		64.07 (mean)	20	18	3	24	25.69	ELISA
Tamiya M	2012	Japan	27.8	17.1	166	NA	45	10	28	83	22.0	ELISA
Sun Hui	2013	China	46.18 ± 24.22	23.99 ± 9.05	100	NA	40	11	13	36	26.75	ELISA

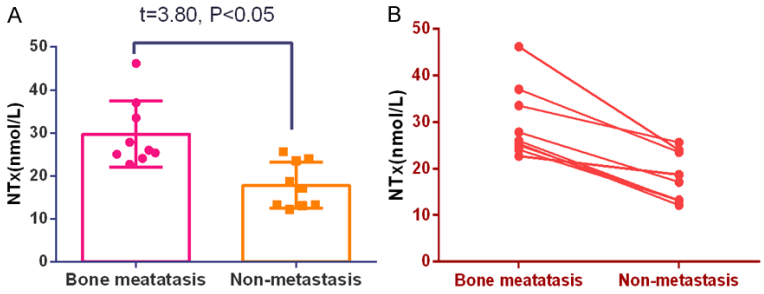

Figure 2. Bar plot of serum NTx of metastases and non-metastases group.

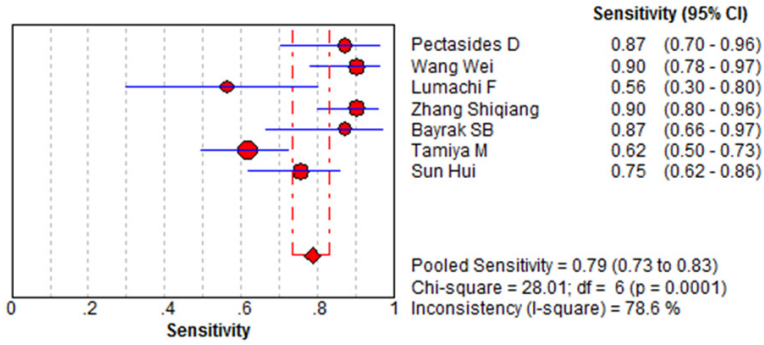

Figure 3. Forest plot of sensitivity for bone metastases disease detection by serum NTx.

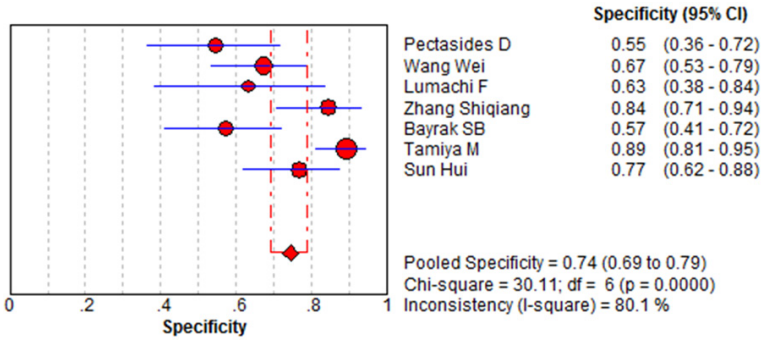

Figure 4. Forest plot of specificity for bone metastases disease detection by serum NTx.

Results

Study search and inclusion

Databases including Pubmed, Embase, and CNKI were electronically searched through endnote software. Initially, 155 publications were identified and 10 studies were excluded for duplicated publication or data. Subsequently, 103 studies were further excluded after reading the title and abstract, obviously not suitable for our inclusion criteria. 42 publications were reviewed for full text and 33 studies were excluded. Finally, 9 studies [7-9, 12-17] were included for quantitative analysis and 7 studies for meta-analysis, **Figure 1**.

General characteristics of included publications

Of the 9 included studies, 5 were performed in Chinese population and the other 4 studies were performed in Greece, Italy, Japan, and Turkey. Sample size ranged from 35 to 166 and all detection methods for serum NTx was ELISA assay. General information of the 9 included studies is shown in **Table 1**.

Serum levels of NTx

Serum levels of NTx for bone metastases lung cancer and

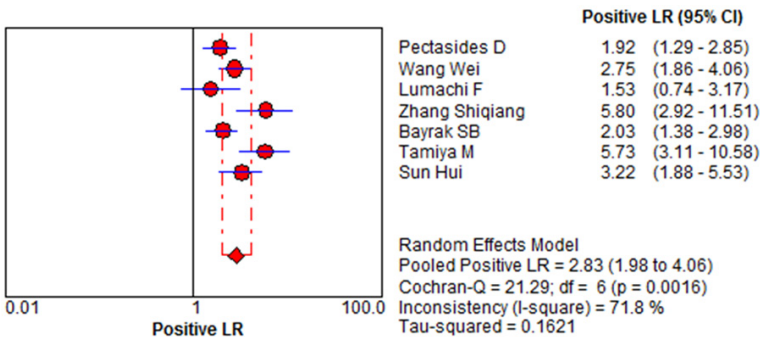

Figure 5. Forest plot of +lr for bone metastases disease detection by serum NTx.

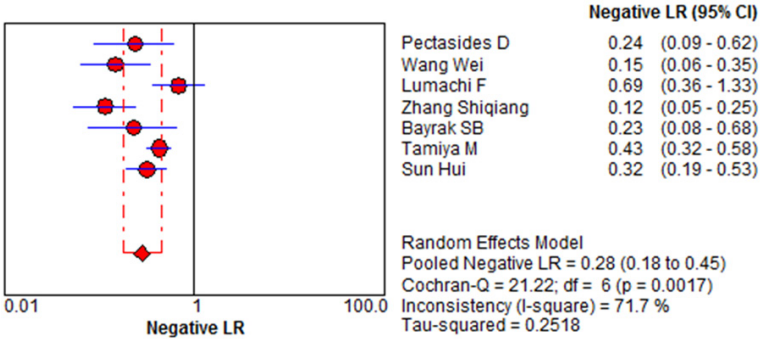

Figure 6. Forest plot of -lr for bone metastases disease detection by serum NTx.

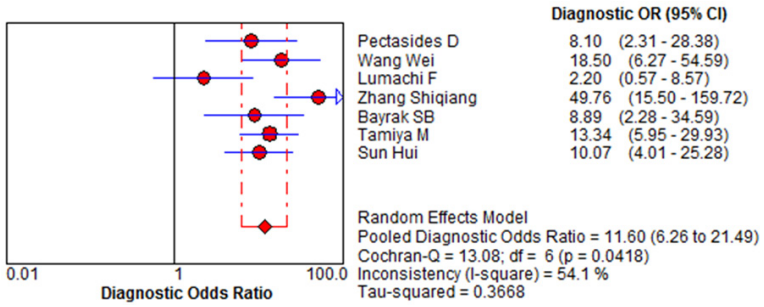

Figure 7. Forest plot of dor for bone metastases disease detection by serum NTx.

non-bone metastases lung cancer were 28.82 ± 7.74 nmol/L and 17.11 ± 5.26 nmol/L, respectively, indicating that serum levels of NTx in metastases disease group were significant higher than non-metastases disease group (t=3.34, P=0.003), **Figure 2A**. Correlation of serum NTx between metastases and non-metastases is demonstrated in **Figure 2B**.

Pooled sensitivity and specificity

Because of significant statistical heterogeneity, sensitivity (sen) and specificity (spe) were calculated through random effects model. Combined data showed that pooled sen and spe were 0.79 (95% CI: 0.73-0.83) (**Figure 3**) and 0.74 (95% CI: 0.69-0.79), respectively (**Figure 4**).

Pooled +lr and -lr

Statistical heterogeneity also existed in the aspects of +lr and -lr. Data was pooled by random effects model. Pooled +lr and -lr were 2.83 (95% CI: 1.98-4.06) (**Figure 5**) and 0.28 (95% CI: 0.18-0.45), respectively (**Figure 6**).

Pooled dor

Pooled dor was 11.60 (95% CI: 6.26-21.49) with random effects model, **Figure 7**.

Pooled SROC curve

Systematic area under curve (AUC) was calculated using data from each individual study. Pooled AUC was 0.84, **Figure 8**.

Publication bias evaluation

Publication bias was evaluated by Deeks funnel plot asymmetry test (**Figure 9**). No publication bias was found in our meta-analysis (t=-1.64, P=0.16).

Discussion

The skeletal system is one of the most common metastatic sites of lung cancer. It has been reported that about 30% to 40% of lung cancer patients have bone metastases lesions throughout the course of the disease. Bone metastasis lesions often cause lot of related complications and symptoms such as severe bone pain, pathological fractures, spinal cord compression syndrome, hypercalcemia, etc [18]. The above bone metastatic symptoms or complications are generally called skeletal-related events (SREs). Publications have demonstrated that uncontrolled SREs significantly decrease medi-

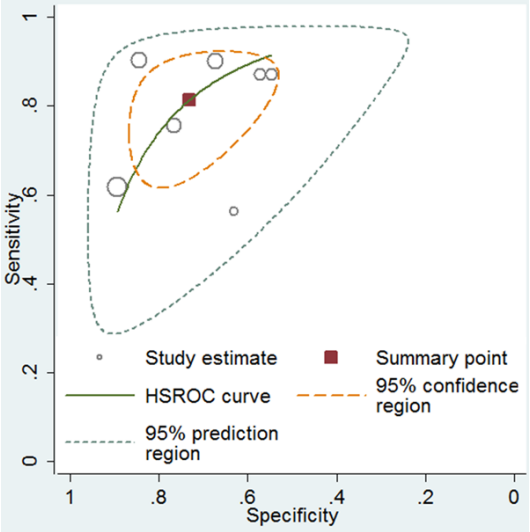

Figure 8. AUC of ROC curve for bone metastases disease detection by serum NTx.

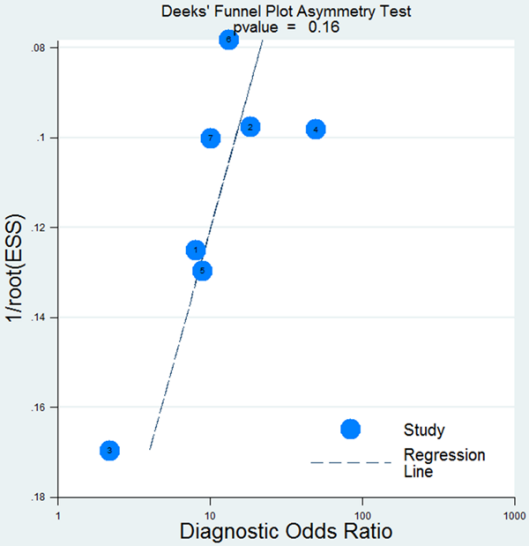

Figure 9. AUC of ROC curve for bone metastases disease detection by serum NTx.

an survival time and life quality of lung cancer patients with bone metastatic disease. Therefore, early detection and appropriate treatment is important for lung cancer patients with bone metastasis disease. At present, the most used methods for bone metastatic lesion detection include magnetic resonance imaging (MRI), emission computed tomography (E-CT), and positron emission computerized tomography PET-CT. These diagnostic methods, however, often require exposure of the patient to a radioisotope and cannot be performed repeatedly in a short period of time. Furthermore, these methods are often expensive and time-consuming.

Serum biomarkers for bone metastasis lesion detection are an ideal method for patients with suspected bone metastasis. Serum markers can be detected easily with or without min-invasion and can also be measured repeatedly in a short period of time.

NTx is an important collagen degradation product during the process of osteoclast degradation. Urinary NTx concentration can be used as biomarker for detection of bone metastatic disease in patients with malignancy [19]. It also can be used for evaluation of bone metastatic disease severity. Recently, several studies [9, 14, 15] have investigated the association between serum NTx levels and bone metastases in patients with lung cancer. Conclusions, however, have not been consistent.

In our present study, we pooled all open published studies related to NTx as biomarker for bone metastases detection in patients with lung cancer. The pooled results indicated that serum levels of NTx were significantly elevated in metastasis patients compared to non-metastases diseases (28.82 ± 7.74 nmol/L vs 17.11 ± 5.26 nmol/L). This finding suggests that serum concentration of NTx could be a potential biomarker for bone metastasis lesion detection. Furthermore, we performed system diagnostic analysis for serum NTx as biomarker in detection bone metastatic diseases in lung cancer patients. The combined data indicated that pooled sensitivity and specificity were 0.79 (95% CI: 0.73-0.83) and 0.74 (95% CI: 0.69-0.79), respectively, via our random effects method. Pooled AUC was 0.84, indicating that the diagnostic power of NTx for lung cancer bone metastasis is good with high clinical application value.

The pooled results demonstrated that serum NTx can be a biomarker with relative high sensitivity and specificity for metastatic disease detection in patients with lung cancer. The conclusion of this meta-analysis, however, is weak due to small sample size, statistical heterogeneity, and language restrictions. Therefore, our conclusion should be further tested and proven by a prospectively designed diagnostic study with a larger sample size.

Disclosure of conflict of interest

None.

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