European Review for Medical and Pharmacological Sciences 2013; 17: 2383-2389

Diagnostic accuracy of Cyfra 21-1 for head and neck squamous cell carcinoma: a meta-analysis

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Abstract. – BACKGROUND AND OBJECTIVES: The role of Cyfra 21-1 in diagnosing squamous cell carcinoma of head and neck is not yet clear. The present meta-analysis aimed to establish the overall diagnostic accuracy of Cyfra 21-1 for head and neck squamous cell carcinoma.

METHODS: After a systematic literature review and selection of English language studies, sensitivity, specificity and other measures of accuracy of Cyfra 21-1 in the diagnosis of head and neck squamous cell carcinoma were pooled using random effects models. Summary receiver operating characteristic curve was used to summarize overall diagnostic performance. Publication bias was examined by Deeks' funnel plot.

RESULTS: Thirteen studies with 2269 subjects met the inclusion criteria for the analysis. The pooled sensitivity and specificity of Cyfra 21-1 for diagnosing head and neck squamous cell carcinoma were 0.51 (95%CI: 0.48-0.54) and 0.97 (95%CI: 0.95-0.98), respectively. The positive likelihood ratio was 10.11 (95%CI: 6.50-15.71), negative likelihood ratio was 0.52 (95%CI: 0.41-0.66) and diagnostic odds ratio was 25.60 (95%CI: 13.39-48.96). The area under the summary receiver operating characteristic curve was 0.94.

CONCLUSIONS: The evidence from current meta-analysis suggests Cyfra 21-1 plays a valuable role in the diagnosis of head and neck squamous cell carcinoma with high specificity. The results of tumor marker assays should be interpreted in parallel with clinical findings and the results of conventional tests.

Key Words:

Cyfra 21-1, Meta-analysis, Squamous cell carcinoma.

Introduction

The incidence of head and neck cancer is increasing in the industrialized world and places a great health burden[1]. Head and neck squamous cell carcinoma (HNSCC) is the most common type of head and neck cancer, and arises in the oral cavity, oropharynx, larynx, and hypopharynx. HNSCC places a heavy burden on patients because it reduces life quality, and ability to work, in addition to increasing disability[2,3]. In addition, the prognosis of HNSCC is poor, with only 40-50% of patients are expected to survive for 5 years, and in patients with un-resectable advanced disease, a 5-year survival rate o was less than 10%, However, patients presenting with carcinomas that are confined at the time of early diagnosis (T1/2N0M0) have an excellent cure rate[2]. Thus, the early detection of HNSCC plays critical role in the management of HNSCC patients. The diagnosis of HNSCC remains a clinical challenge, although morphology, histology, and immunohistochemistry are still the major methods of diagnosis HNSCC. These procedures are time-consuming and with low sensitivities, and options for using imaging analysis for early screening of HNSCC remains limited[4,5]. So, it is imperative to find cost-effective, non-invasive, and reliable diagnostic markers to facilitate the diagnostic accuracy. And among them, cytokeratin fraction 21-1 (Cyfra 21-1) is highlighted.

Cyfra 21-1 is a well-accepted tumor marker with high sensitivity and specificity in non-small cell lung cancer, especially squamous cell carcinoma. A number of studies have reported that increased serum level of Cyfra 21-1 was detected in HNSCC patients[6] and, in fact, several studies have been published and suggested the possibility of using Cyfra 21-1 to diagnose HNSCC, but they have given varying results. Therefore, we undertook this meta-analysis of the research literature to establish the overall accuracy of using Cyfra 21-1 as diagnostic marker of HNSCC.

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Methods

Literature search and study selection

We searched in Medline (Pubmed), Embase, Web of Science, and the Cochrane database to identify studies that evaluating the use of Cyfra 21-1 to diagnose HNSCC, up to May 20, 2013. The search terms were "Head and neck *or* oral *or* oropharynx *or* larynx *or* hypopharynx", "squamous cell carcinoma", "Cytokeratin fraction 21-1 *or* Cyfra 21-1", "sensitivity" and "specificity". Reference lists of eligible studies were also manually searched from the databases. Although no language restrictions were imposed on the search criteria, only english-language publications were included in the present meta-analysis.

Inclusion criteria

A study was included in the present meta-analysis if it met the following selection criteria: (1) it was a diagnostic study using Cyfra 21-1 for HNSCC; (2) the diagnosis of HNSCC was confirmed by histopathological examinations; (3) sufficient data were reported to allow the generation of a 2×2 table for calculating sensitivity and specificity. Studies with less than 20 patients or without a control group were excluded to avoid selection bias. A study was excluded if it included other type of cancer other than squamous cell carcinoma. Meeting abstracts and letters were excluded because they reported insufficient data. Two authors independently screened the articles for inclusion. Disagreements between authors were resolved by discussion.

Data extraction and quality assessment

Two reviewers independently assessed the final set of articles. The following data were retrieved from the reports: author, publication year, diagnostic standard, sensitivity and specificity data. The methodological quality of included studies was evaluated using the Quality Assessment for Studies of Diagnostic Accuracy (QUADAS) Tool, which is an evidence-based approach to quality assessment intended for use in systematic reviews of diagnostic accuracy studies. A quality index is generated, with a maximum value of 14[7].

Statistical analyses

The current study was performed according to standard methods recommended for meta-analyses of diagnostic accuracy studies[8]. The following indexes of test accuracy, together with 95% confidence intervals (95%CIs) were calculated for each

Table I. Clinical summary of included studies.

Study (Ref)	Year	Sample size		Method	Cut off value	TP	FP	FN	TN	QUADAS
		HNSCC	non-HNSCC							
Ayude et al (10)	2003	40	101	ECLIA	1.7 ng/ml	20	4	20	97	10
Céruse et al (11)	2005	300	71	Immunoradiometric assay	1 ng/ml	216	4	84	67	10
Deng et al (12)	2003	142	118	ECILA	3.3 ng/ml	88	0	54	118	11
Doweck et al (13)	1995	20	29	Immunoradiometric assay	1.3 ng/ml	12	2	8	27	8
Eleftheriadou et al (14)	2006	79	77	ECLIA	3.3 ng/ml	21	0	58	77	10
Goumas et al (15)	1997	42	80	Immunoradiometric assay	3.3 ug/L	12	4	30	76	9
Inal et al (16)	2004	28	20	Immunoradiometric assay	NA	4	0	24	20	10
Kandiloros et al (17)	2006	136	125	ECLIA	3.3 ng/ml	44	0	92	125	11
Lee et al (18)	2001	58	77	Immunoradiometric assay	2.48 ng/ml	35	4	23	73	10
Nagler et al (19)	1999	38	30	Immunoradiometric assay	0.7 ng/ml	36	4	2	26	10
Wollenberg et al (20)	1996	163	94	ELISA	2.9 ng/ml	28	5	135	89	9
Yen et al (21)	1998	168	77	Immunoradiometric assay	2.48 ng/ml	98	4	70	73	9
Zhong et al (22)	2007	100	56	ELISA	0.65 ug/L	57	2	43	54	12

HNSCC: Head and neck squamous cell carcinoma; ECLIA: electrochemiluminescent immunoassay; NA: Not available; TP: true positive; FP: false positive; FN: false negative; TN: true negative; QUADAS: Quality Assessment for Studies of Diagnostic Accuracy

study: sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR). The sensitivity and specificity for the single test threshold identified for each study was used to plot a summary receiver operating characteristic (SROC) curve. Spearman rank correlation was used to test for threshold effects. Chi-square and Fisher's exact tests were used to assess heterogeneity across studies. A random-effects meta-analysis was carried out to take into account inter-study variability, otherwise, the fixed-model was chosen. Since publication bias is a concern in meta-analyses of diagnostic studies, we tested for it using Deeks' funnel plots[9]. All analyses were performed using two statistical software programs: Meta-DiSc for Windows (XI, Cochrane Colloquium, Barcelona, Spain) and Stata (version 12, Stata Corporation, College Station, TX, USA). All statistical tests were two-sided, and significance was set at $p < 0.05$.

Results

After a systematic databases search and manual review of reference lists in eligible studies, a total of 13 publications on the diagnostic accuracy of Cyfra 21-1 in HNSCC patients were considered eligible for inclusion in present study[10-22]. Studies were excluded for primarily the following considerations: they were not diagnostic studies, they did not report sufficient data to construct a 2 × 2 table, they used the same case series or overlapping case series, or they mixed other cancer types.

Quality of reporting and study design

The final set of 13 studies involved 2269 subjects, including 1314 HNSCC patients and 955 controls. In all included studies, HNSCC was diagnosed based on histopathological examination, which was considered the gold standard for diagnosis. Among included studies, seven used immunoradiometric assay to determine Cyfra 21-1 levels, four used electrochemiluminescent immunoassay (ECLIA), two used enzyme-linked immunosorbent assay (ELISA), and all the studies used serum as analysis matrix. Of the 13 included publications, eight had QUADAS scores ≥10, suggested the qualities of included studies were generally high. Thus, the results of our meta-analysis are reliable. Clinical summary of included studies and the QUADAS scores for each publication is listed in Table I.

Diagnostic accuracy

Heterogeneity examinations plays an important role in the selection of appropriate calculate model. Four performance indices showed high χ^2-values: sensitivity, 250.30; specificity 33.40; NLR, 266.62; and DOR, 29.00, ($p < 0.05$ in all cases), suggesting substantial heterogeneity among the studies; thus, we choose the random-effect model to synthesize the data. Forest plots of the sensitivity and specificity of Cyfra 21-1 assays for diagnosing HNSCC are shown, respectively, in Figures 1 and 2. The following pooled parameters were calculated over all 13 studies: sensitivity, 0.51 (95%CI: 0.48-0.54); specificity, 0.97 (95%CI: 0.95-0.98); PLR, 10.11 (95%CI: 6.50-15.71); NLR, 0.52 (95%CI: 0.41-0.66); and DOR, 25.60 (95%CI: 13.39-48.96).

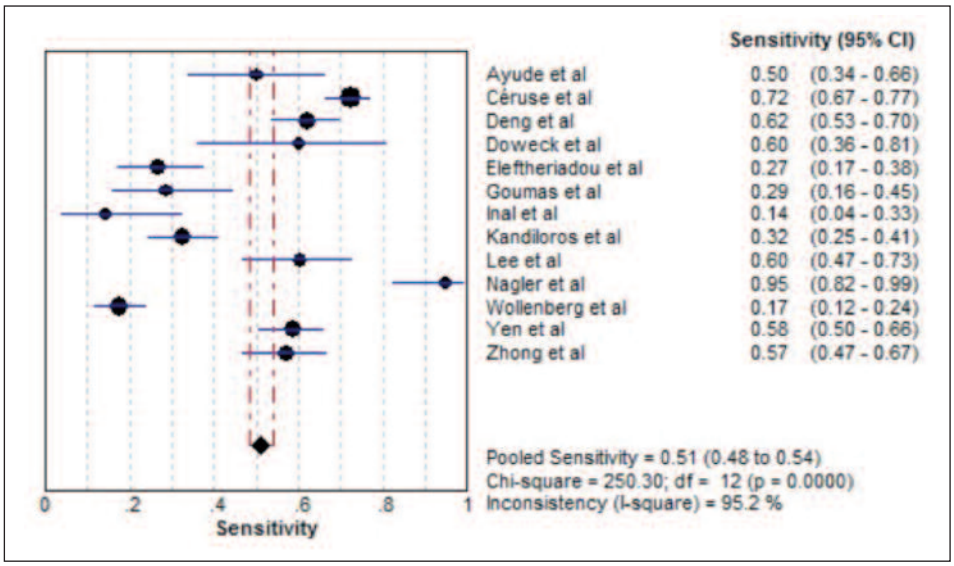

Figure 1. Forest plot of sensitivity of Cyfra 21-1 for the diagnosis of HNSCC. The point estimates of sensitivity from each study are shown as solid circles. Error bars

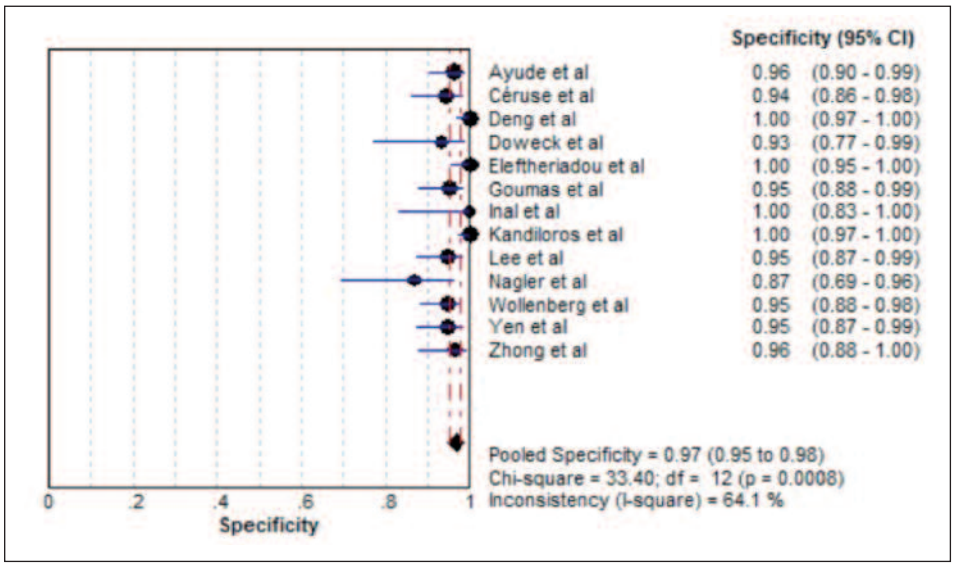

Figure 2. Forest plot of specificity of Cyfra 21-1 for the diagnosis of HNSCC. The point estimates of specificity from each study are shown as solid circles. Error bars indicate 95% confidence intervals.

Figure 3 shows a plot of the rate of true positives as a function of the rate of false positives of individual studies, as well as the corresponding SROC curve. As a global measure of test efficacy across all studies, we determined the Q-value, defined as the point of intersection of the SROC curve with a diagonal line extending from the left upper corner to the right lower corner of the ROC space. The Q-value corresponds to the highest joint value of sensitivity and specificity for the diagnostic test. This point does not indicate the only or even the best combination of sensitivity and specificity for a particular clinical setting, but it does provide an overall measure of the discriminatory power of the diagnostic test. The Q-value for the studies in our meta-analysis was 0.87. The area under the curve (AUC) was 0.94, indicating high overall accuracy.

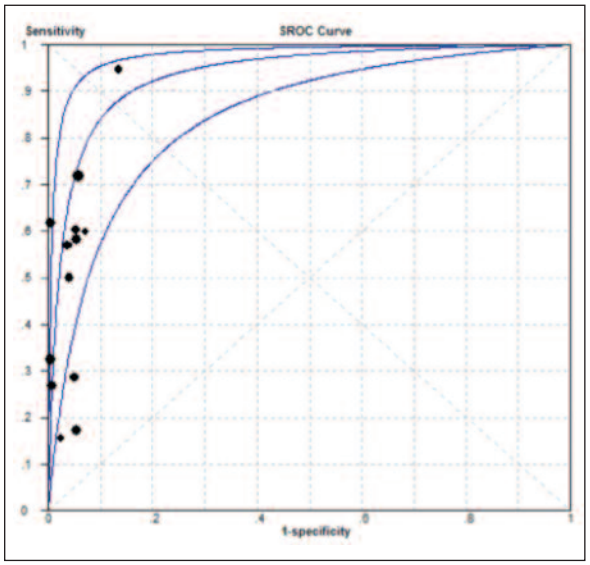

Figure 3. Summary receiver operating characteristic (SROC) curve of Cyfra 21-1 for the diagnosis of HNSCC. The size of each solid circle represents the size of each study in the meta-analysis. The regression SROC curve indicates the overall diagnostic accuracy.

Subgroup analysis: assay method

Of the 13 studies, 7 tested Cyfra 21-1 by immunoradiometric assay, while 4 tested Cyfra 21-1 by ECLIA. We conducted subgroup analysis to identify whether one type of assay gave better diagnostic accuracy than the other. The pooled sensitivity, specificity, PLR, NLR, and DOR for the two groups are listed in Table II. For immunoradiometric assay, the maximum joint sensitivity and specificity were 0.91, and AUC was 0.96; for ECLIA, the corresponding values were 0.68 and 0.74. These results suggest that immunoradiometric assay is a better method for diagnostic performance of Cyfra 21-1 in HNSCC.

Publication bias

We used Deeks' funnel plot asymmetry test to evaluate the final set of studies for potential publication bias. The slope coefficient was associated with a p value of 0.38, indicating symmetry in the data and a low likelihood of publication bias (Figure 4).

Table II. Comparison of different assay methods for diagnosing HNSCC

Index	Summary	Immunoradiometric assay	ECLIA
Sensitivity	0.51 (95%CI 0.48-0.54)	0.63 (95%CI 0.59-0.67)	0.44 (95%CI 0.39-0.49)
Specificity	0.97 (95%CI 0.95-0.98)	0.94 (95%CI 0.91-0.96)	0.99 (95%CI 0.98-1.00)
PLR	10.11 (95%CI 6.50-15.71)	10.06 (95%CI 6.52-15.51)	45.00 (95%CI 16.64-121.67)
NLR	0.52 (95%CI 0.41-0.66)	0.44 (95%CI 0.39-0.48)	0.57 (95%CI 0.52-0.63)
DOR	25.60 (95%CI 13.39-48.96)	26.54 (95%CI 16.36-43.04)	82.88 (95%CI 31.25-219.86)
Q vaule	0.87	0.91	0.68
AUC	0.94	0.96	0.74

Discussion

HNSCC remains a clinical challenge, it is a relatively common malignancy, and is currently accounting for 5% of all malignancies worldwide[5]. In recent years, great attention has been paid to the early detection of HNSCC, because patients presenting with tumors that are confined at the time of early diagnosis have an well clinical prognosis after timely intervention. However, the current morphology, histology, and immunohistochemistry remain with low sensitivity, and its invasive procedure makes it is not be available in all level hospitals and well tolerated. For imaging examinations, although PET/CT (Positron Emission Tomography-Computed Tomography) plays a role in the diagnosis of HNSCC, its cost-effectiveness is not so satisfied[5]. The present meta-analysis suggests that Cyfra 21-1 may serve as diagnostic indicators of high specificity 0.97 (95%CI: 0.95-0.98), and Cyfra 21-1 may represent a useful diagnostic marker in HNSCC diagnosis.

The present meta-analysis uses SROC curve to summarize the overall test performance of Cyfra 21-1, and it shows the trade-off between sensitivity and specificity[23]. Our SROC analysis showed a maximum joint sensitivity and specificity of 0.87, and an AUC of 0.94, suggesting high overall accuracy. DOR, defined as defined as the ratio of the odds of a true positive to the odds of a false positive, is a single indicator of diagnostic test accuracy that combines sensitivity and specificity data into a single number. The value of a DOR ranges

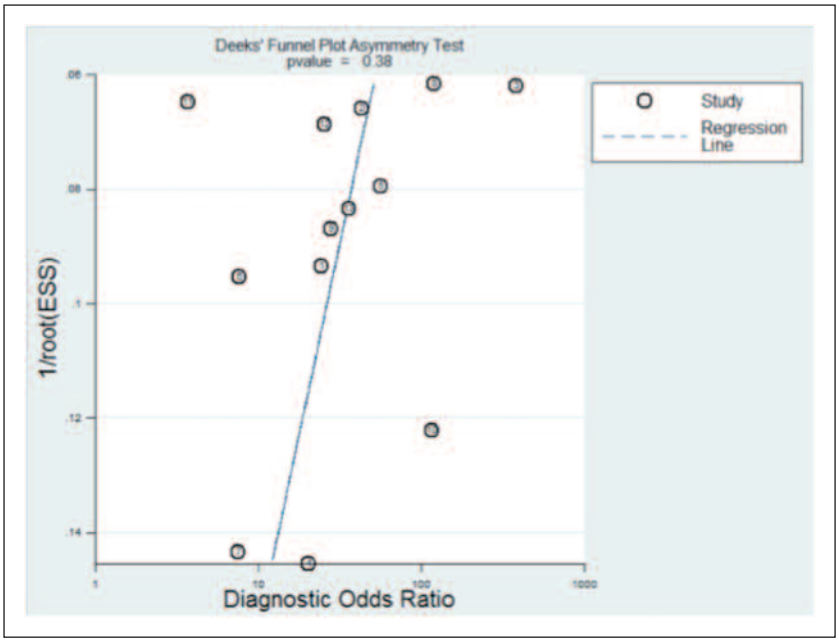

Figure 4. Linear regression test of funnel plot asymmetry. The statistically non-significant *p* value of 0.38 for the slope coefficient suggests symmetry in the data and a low likelihood of publication bias.

from 0 to infinity, with higher values indicating better discriminatory test performance (higher accuracy). A DOR of 1.0 indicates that a test does not discriminate between patients with the disorder and those without it. In our meta-analysis, the mean DOR was 25.60, indicating that Cyfra 21-1 seemed to be helpful in the diagnosis of HNSCC. However, the SROC curve and the DOR are not easy to interpret and use in clinical practice, and likelihood ratios are considered more clinically meaningful. Therefore, we also determined the PLR and NLR of Cyfra 21-1 assays to obtain a more comprehensive picture of their diagnostic accuracy. A value of PLR greater than 10 is considered the threshold for reliability The PLR value of 10.11 suggests that patients with HNSCC have an approximately 10-fold higher chance of giving a positive Cyfra 21-1 test result than do subjects without HNSCC. At the same time the pooled NLR was found to be 0.52, indicating that a negative Cyfra 21-1 test result is 52% likely to be a false negative, which is not allowed to rule out HNSCC. Our data suggest that Cyfra 21-1 plays a role in the confirmation of HNSCC diagnosis, rather than to screen HNSCC patients, and the combination of Cyfra 21-1 with other tumor markers will increase the diagnostic accuracy[14,15,18,19].

In addition to providing diagnostic information, analysis of Cyfra 21-1 can provide detailed, personalized information about patients with HNSCC. The level of Cyfra-21-1 indicates a positive correlation with the grade of differentiation and nodal status in HNSCC patients, and has a role in monitoring the success of therapy and follow up of patients[24]. In addition, an abrupt increase of Cyfra 21-1 in serial measurements during follow-up would like to indicate impending disease progression and provide early prognostic information, particularly on tumor progression and metastatic formation in the individual HNSCC patient, regardless of the cut-off value[25]. Therefore, the Cyfra 21-1 serum level is a good marker for follow-up in patients with HNSCC. In this way, Cyfra 21-1 may turn out to be useful not only for diagnosing HNSCC but also for characterizing its prognosis, which will improve the comprehensive management of HNSCC patients.

The findings in this meta-analysis should be interpreted with caution because of several limitations. First, a relatively small number of studies with limited subjects were included in this meta-analysis, which may reduce the statistical power for determine the diagnostic role of Cyfra 21-1 for HNSCC. Second, we identified significant heterogeneity among included studies, which may be caused by different analysis method, different analysis time ranges from 1995 to 2007, or by patients from different country or areas, so future work should be well performed to determine the causes of heterogeneity. In addition, among the included 13 studies, the cut-off value of Cyfra 21-1 is quite different, further studies on a large scale of patients should be carried out to set up the standard cut-off value of Cyfra 21-1. Third, although we did not set any language restrictions during our literature searching, we included only English-language publications in this meta-analysis. It is possible that our results would be different if they included the findings of unpublished studies or of relevant studies published in other languages.

Conclusions

Cyfra 21-1 assays show significant process as diagnostic indicators in HNSCC. Cyfra 21-1 assay may prove useful as a cost-effective, non-invasive confirmatory test to complement current diagnosing procedures and as a rapid clinical test to guide the comprehensive management of patients with HNSCC.

Acknowledgements

This work was supported by grants from the Department of Science and Technology of Zhengzhou #112PPTSF299-2 to Dr Yunxia Wang. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

We are indebted to the authors of the primary studies included in this meta-analysis; without their contributions, this work would not have been possible. In addition, we are grateful to Yongchun Shen, MD for kindly giving suggestions on how to prepare and revise the manuscript.

Conflict of interest

The Authors declare that they have no conflict of interests.

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