Circular RNAs Serve as Prognostic, Diagnostic and Clinicopathological Markers in Lung Cancer: An Updated Meta-Analysis

CURRENT STATUS: UNDER REVISION

BMC Cancer BMC Series

Zhuozheng Liang

Third Affiliated Hospital of Sun Yat-Sen University

Cui Chen

Guangdong Medical University

Cheng Guo

Third Affiliated Hospital of Sun Yat-Sen University Department of Otorhinolaryngology Head and Neck Surgery

Ping Meng

Third Affiliated Hospital of Sun Yat-Sen University

Manman Zou

Third Affiliated Hospital of Sun Yat-Sen University

Liyi Zhang

Third Affiliated Hospital of Sun Yat-Sen University

Hui Liu

Third Affiliated Hospital of Sun Yat-Sen University

Tiantuo Zhang

Third Affiliated Hospital of Sun Yat-Sen University

hitcinmatalzz@163.com Corresponding Author

ORCID: <https://orcid.org/0000-0001-7496-8135>

DOI:

10.21203/rs.2.24261/v1

SUBJECT AREAS

Cancer Biology *Oncology*

KEYWORDS

Lung cancer, Circular RNA, Diagnosis, Prognosis, Meta-analysis

Abstract

In recent years, the roles of circular RNAs (circRNAs) in the biogenesis and clinical application have gradually garnered much interest in the field of cancer research. However, high-quality studies evaluating the roles of circRNAs in clinicopathological feature and clinical application of lung cancer are still unrevealed. Herein, we aimed to elucidate the functions of circRNAs in the association with prognosis, diagnosis and clinicopathology in lung cancer. Comprehensive and reasonable search strategies were used in four databases up to Nov. 24th 2019. A total of 50 studies with 3815 patients were incorporated into our meta-analysis, in which 42 focused on clinical characteristics, 10 related with diagnosis (16 items were eligible), and 31 were aimed at prognosis. In terms of clinical characteristics, both odds ratio (OR) and 95% confidence interval (95%CI) were shown that circRNAs were significantly associated with TNM, tumor differentiation, lymph node metastasis, distal metastasis and tumor size in lung cancer. For diagnosis, both upregulated and downregulated circRNAs distinguished patients with lung cancer from healthy people with pooled sensitivity (Sen), specificity (Spe) and area under curve (AUC), of which the values were 0.78, 0.76 and 0.81 respectively. In the section of prognosis, circRNAs can better predict the survival time of patients with lung cancer (overall survival, OS: HR=0.46, 95%CI: 0.33-0.65 in downregulated circRNAs; HR=2.23, 95%CI :1.97-2.53 in upregulated circRNAs). In summary, the results presented here suggested that circRNAs were the potent cancer biomarkers in clinicopathology, diagnosis and prognosis of lung cancer patients, which deserve further application in clinical practice.

Full Text

Due to technical limitations, full-text HTML conversion of this manuscript could not be completed. However, the manuscript can be downloaded and accessed as a PDF.

Tables

Figures

Table 1. The summary of clinicopathological features of circRNAs in lung cancer.						
Clinical characteristics	Tumor promoter			Tumor suppressor		
	OR	95%CI	P-value	OR	95%CI	P-value
TNM	2.74	1.81-4.15	<0.001	0.41	0.21-0.80	0.009
III-IV vs I-II	2.90	1.90-4.42	<0.001	0.32	0.18-0.59	<0.001
II-IV vs I	1.71	0.26-11.38	0.580	1.12	0.53-2.38	0.762
Differentiation	2.22	1.73-2.85	<0.001	1.82	1.05-3.15	0.032
Modulate/poor vs high	2.32	1.77-3.04	<0.001	1.39	0.60-3.21	0.436
Poor vs high/modulate	1.77	0.95-3.32	0.073	2.23	1.08-4.64	0.031
Lymph node metastasis	1.92	1.27-2.90	0.002	0.32	0.17-0.61	0.001
Distal metastasis (M1 vs M0)	2.86	1.29-6.30	0.009	0.89	0.30-2.59	0.826
Tumor size	1.72	1.08-2.46	0.022	0.50	0.27-0.94	0.032
	1.42	0.39-5.20	0.599	—	—	—
	1.51	0.86-2.64	0.154	0.40	0.14-1.13	0.083
	2.27	0.92-5.62	0.076	0.66	0.34-1.27	0.217
Age	0.87	0.73-1.04	0.119	0.77	0.54-1.10	0.157
	1.40	0.65-2.99	0.391	—	—	—
	1.25	0.66-2.38	0.500	—	—	—
	0.84	0.69-1.03	0.095	0.77	0.54-1.10	0.157
	0.70	0.42-1.15	0.160	—	—	—
Gender	0.94	0.78-1.12	0.474	0.94	0.62-1.42	0.760
Smoking	1.03	0.81-1.30	0.836	1.17	0.60-2.30	0.641
Histological type (LSCC vs LAC)	1.12	0.85-1.49	0.424	0.73	0.40-1.31	0.287
Note: LSCC, lung squamous cell carcinoma; LAC, lung adenocarcinoma; OR, odds ratio; CI, confidence interval.						

Table 2. The characteristics of included circRNAs in lung cancer for diagnosis analysis.										
Study	Year	CircRNA	Cancer Type	Sample		Regulation	Sample Type	Diagnosis power		
				Case	Control			SEN	SPE	AUC
Xiaoxia Liu [6]	2019	hsa_circ_0005962	LAC	153	54	Up	Plasma	0.72	0.72	0.73
Lijian Chen [7]	2019	hsa_circ_100146	NSCLC	40	40	Up	Tissue	0.76	0.58	0.64
Jipeng Li [8]	2018	hsa_circ_0079530	NSCLC	92	92	Up	Tissue	0.76	0.72	0.76
Liang Zong [9]	2018	hsa_circ_102231	LAC	57	57	Up	Tissue	0.81	0.89	0.90
Shaoyan Zhang [10]	2018	hsa_circ_0014130	NSCLC	46	46	Up	Tissue	0.87	0.85	0.88
Xiuyuan Li [11]	2018	circ-PVT1	NSCLC	45	45	Up	Tissue	0.83	0.68	0.80
Xiuyuan Li [11]	2018	circ-PVT1	NSCLC	45	45	Up	Serum	0.71	0.80	0.79
Xiaoli Zhu [12]	2017	hsa_circ_0013958	LAC	49	49	Up	Tissue	0.76	0.80	0.82
Xiaoli Zhu [12]	2017	hsa_circ_0013958	LAC	30	30	Up	Plasma	0.67	0.93	0.80
Chunmei Fan [13]	2019	circ-MAN1A2	LC	45	121	Up	Serum	0.51	0.79	0.65
Xiaoxia Liu [6]	2019	hsa_circ_0086414	LAC	153	54	Down	Plasma	0.77	0.67	0.78
Yanni Zhang [14]	2018	circ-FOXO3	NSCLC	45	45	Down	Tissue	0.8	0.73	0.78
Fei Xu [15]	2018	hsa_circ_0072309	LSCC	43	43	Down	Tissue	0.88	0.74	0.87
Fei Xu [15]	2018	hsa_circ_0006114	LSCC	43	43	Down	Tissue	0.86	0.72	0.82
Fei Xu [15]	2018	hsa_circ_0006460	LSCC	43	43	Down	Tissue	0.81	0.70	0.78
Fei Xu [15]	2018	hsa_circ_0077837	LSCC	43	43	Down	Tissue	0.86	0.81	0.86
Note: NSCLC, non-small cell lung cancer; LC, lung cancer; LAC, lung adenocarcinoma; LSCC, lung squamous cell carcinoma; SEN, sensitivity; SPE, specificity, AUC, area under curve.										

Table 3. The summary of included circRNAs in lung cancer for prognosis.							
Author/Year	circRNA	Up Down	Cancer type	Expression		HR (95%CI)	Follow-up (months)
				High	Low		
Jingquan Han[16]	circ-BANP	Up	LC	28	31	2.54(0.38-5.68)	60
Liang Zong[9]	has_circRNA_102231	Up	LC	29	28	1.04(0.36-2.97)	60
Mantang Qiu[17]	circPRKCI	Up	LAC	55	34	1.98(1.15-3.58)	90
Yuanshan Yao[18]	has_circ_0001946	Up	LAC	38	34	1.70(0.8-3.62)	60
Bai-Quan Qiu[19]	circ-FGFR3	Up	NSCLC	34	29	2.53(1.16-5.48)	80
Liuxin Wang[20]	circ-VANGL1	Up	NSCLC	49	46	1.66(0.82-3.37)	60
Qi Huang[21]	circ-ATXN7	Up	NSCLC	45	12	1.09(0.48-2.45)	42
Guohua Liu[22]	circ-FOXN1	Up	NSCLC	44	36	2.05(1.24-3.37)	60
Jingchun An[23]	has_circ_0003645	Up	NSCLC	32	27	2.67(1.48-4.81)	60
Wei Han[24]	circ-RAD23B	Up	NSCLC	20	20	1.91(0.70-5.18)	60
Si Qin[25]	circ-PVT1	Up	NSCLC	43	47	1.68(0.65-4.31)	60
You Zhou[26]	hsa_circ_0004015	Up	NSCLC	16	19	1.57(0.37-5.26)	60
B. YAN[27]	ciRS-7	Up	NSCLC	NG		2.03(1.35-3.06)	100
Qinguang Zou[28]	has_circ_0067934	Up	NSCLC	41	38	2.68(1.89-4.00)	80
Yi Qi[29]	hsa_circ_0007534	Up	NSCLC	56	42	2.10(1.29-3.42)	60
Fucheng Zhao[30]	circ-FADS2	Up	NSCLC	22	21	2.77(0.97-7.93)	60
Yongsheng Li[31]	has_circ_0016760	Up	NSCLC	45	38	2.24(1.36-3.69)	60
Wei Liu[32]	hsa_circRNA_103809	Up	NSCLC	44	44	1.29(0.43-3.86)	80
Chongyu Su[33]	ciRS-7	Up	NSCLC	77	55	2.14(1.44-3.20)	60
J. WANG[34]	has_circ_0067934	Up	NSCLC	79	80	3.77(1.50-6.67)	60
Danhua Qu[35]	hsa_circ_0020123	Up	NSCLC	40	40	1.45(0.43-4.79)	80
Xiaofei Zhang[36]	ciRS-7	Up	NSCLC	41	19	3.58(1.69-4.83)	80
Jingru Wan[37]	has_circ_0020123	Up	NSCLC	28	27	2.50(1.35-4.64)	60
X.-Y. LI[38]	hsa_circ_000984	Up	NSCLC	80	75	3.33(1.26-4.45)	60
Lingchi Ding[39]	has_circ_001569	Up	NSCLC	29	27	2.17(1.11-4.26)	60
Xiuyuan Chen[40]	circ-HIPK3	Up	NSCLC	25	51	2.27(0.76-6.85)	60
Liu Yang[41]	hsa_circ_0046264	Down	LC	55	44	0.53(0.27-1.03)	20
Daishi Chen[42]	hsa_circ_100395	Down	LC	35	34	0.44(0.20-1.02)	150
Yuanshan Yao[43]	has_circ_0006427	Down	LAC	54	40	0.44(0.21-0.93)	60
Binbin Zhang[44]	circ-MTO1	Down	LAC	31	32	0.57(0.15-2.21)	100
Tongmiao Liu[45]	has_circ_0001649	Down	NSCLC	22	31	0.41(0.22-0.77)	60

Note: NSCLC, non-small cell lung cancer; LC, lung cancer; LAC, lung adenocarcinoma.

Figure 1

The flowchart showed the algorithm how to perform the exclusion and inclusion of the eligible studies in our meta-analysis.

Figure 2

The clinical application of circRNAs in lung cancer. (A) The ability of circRNAs to differentiate patients with lung cancer from normal people was calculated from the Summary receiver operating characteristic (SROC) curve. (B) Fagan's nomogram was shown to estimate the clinical utility of overall circRNAs to differentiate patients with lung cancer from normal people. (C) Likelihood ratio diagram showed the clinical diagnosis value of circRNAs in lung cancer.

Figure 3

Forest plot by subgroup analysis of diagnosis value in the application of circRNAs in lung cancer. (A) Upregulated circRNAs; (B) Downregulated circRNAs.

Figure 4

Forest plot of overall survival for prognosis of circRNAs in lung cancer. (A) Upregulated circRNAs; (B) Downregulated circRNAs.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.
supplementary.rar