# Role of circular RNAs in the diagnosis, regulation of drug resistance and prognosis of lung cancer (Review)

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**Abstract.** Lung cancer is one of the most common malignant tumors in China and is the highest cause of mortality among male and female patients, both in urban and rural areas. A subset of patients with lung cancer only display chest tightness without any other obvious symptoms. This is because most symptoms do not manifest during the early stages of disease development. Consequently, most patients with lung cancer are diagnosed when the disease is in the advanced stages, when they are already unfit for surgical treatment. Furthermore, the prognosis of patients with lung cancer is poor. The 5-year survival rate of patients with stage IA lung cancer is 85%, compared with 6% in those with stage IV. This requires the development of strategies for early diagnosis, treatment and prognosis to improve the management of lung cancer. Circular RNAs (circRNAs) belong to a class of closed circular non-coding RNAs formed by reverse splicing of a precursor mRNA. These RNAs are highly stable, ubiquitously expressed, conserved, and show high specificity. CircRNAs regulate biological processes, such as the proliferation, differentiation and invasion of lung cancer cells. Therefore, they can be used as biomarkers for the early diagnosis and prognosis prediction of lung cancer, as well as novel targets for therapy design. In the present review, the biological characteristics and functions of circRNAs, as well as their application in the diagnosis, control of drug resistance and effect on the prognosis of patients with lung cancer, will be discussed.

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**Contents**



## 1. Introduction

Lung cancer [World Health Organization (WHO)/International Classification of Diseases 10th revision (ICD-10) code of cancer, C34.901] is one of the leading causes of cancer-associated morbidity and mortality worldwide. It is the second most prevalent type of cancer (11.4%) after breast cancer (WHO/ICD-10 C50.902; 11.7%). Globally, lung cancer contributes to ~1.8 million deaths per year (18%), which makes it the number one cause of cancer-related deaths (1). Non-small cell lung cancer (NSCLC) accounts for 80-85% of all lung cancers (2). The 5-year survival rate for patients with stage IA lung cancer is 73%, while that for patients with stage IV is only 13% (3). Based on these statistics, it is imperative to develop efficient tools for the early screening, diagnosis and treatment of lung cancer, to lower the magnitude of lung cancer-related deaths and prolong patient survival.

Circular RNAs (circRNAs) are non-coding RNAs that differ from linear RNAs due to the presence of a special structure that contains neither a 5'-cap structure nor a 3'-adenosine tail (4). This closed loop structure is formed by the reverse splicing of precursor mRNAs, and not only confers resistance to hydrolysis by exonucleases, but also makes the molecule more stable (5). CircRNAs were first identified in the 1970s in an RNA virus. Since then, they have been regarded as erroneous transcriptional products of RNA, and have thus far been ignored by researchers (6). The

development and advancement in high-throughput sequencing and bioinformatics technologies have led to the identification of multiple circRNAs in human tissues, blood, urine and saliva (7), where they regulate a multitude of biological processes. For example, they have been shown to participate in the occurrence and development of lung cancer, by regulating proliferation, differentiation, metastasis and apoptosis of tumor cells (8). Consequently, researchers have employed circRNAs in the screening, diagnosis, treatment and prognosis of lung cancer (9).

Several adjuvant treatments for advanced unresectable lung cancer have been developed, including radiotherapy, chemotherapy, targeted therapy and immunotherapy (10). Antitumor drugs targeting epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase, proto-oncogene tyrosine-protein kinase ROS, programmed cell death protein 1/programmed death-ligand 1 (PD-L1) and proton therapy have been shown to prolong the survival of patients, but the efficacy of these interventions is reduced by the emergence of resistance in advanced lung cancer (11). In the present study, the biological characteristics, biological functions, diagnostic and prognostic value of circRNAs in lung cancer are reviewed, and the relationship between circRNAs and resistance against adjuvant drugs (such as chemotherapy resistance, targeted drug resistance, immunotherapy resistance and radiation resistance) is discussed.

## 2. Classification and characteristics of circRNAs

Based on their origin, circRNAs can be divided into four types, namely intron circRNAs (ciRNAs), exon circRNAs (EcircRNAs), exon-intron circRNAs (EIciRNAs) and intergenic circRNAs (12), among which EcircRNAs is the most extensively studied group. Mechanistically, circRNAs actions include lasso-driven cyclization, intron pair-driven cyclization and RNA binding protein (RBP)-driven cyclization. Based on these, the actions of circRNAs can be divided into two main modes, direct reverse splicing and exon jump (13). Lasso-driven cyclization is a mechanism of exon jump in which the 5' end of one exon connects to the 3' end of another exon to form an exon jump. At this point, it represents an RNA lasso composed of exons and introns. However, intron removal leads to EcircRNA formation, while exon-intron circRNAs (EIciRNAs) are formed when introns are cycled between exons and exons are also retained. Direct reverse splicing mechanisms include intron pairing-driven cyclization and RBP driven cyclization (14). Notably, ciRNAs depend on introns with conserved motifs at both ends, namely, the GU-rich element near the 5' splice site and the C-rich element near the 3' branch site. Additionally, intron lasso is cyclized by connecting free hydroxyl terminal groups to 5' splicing sites after releasing the 3' exon (15) (Fig. 1).

## 3. Biological characteristics of circRNAs

*Stability*. CircRNAs are resistant to degradation by RNase R enzymes, which is attributed to their circular configurations that are a result of special 5'-3' phosphodiester bonds (16). One study comparing the stability of circRNAs and their related linear mRNAs revealed that the half-life of circRNAs is >48 h, while the half-life of related mRNAs is only 20 h, indicating that circRNAs are more stable than mRNAs (5).

*Universality*. CircRNAs are abundant in human tissues, serum, saliva and urine. Therefore, they are ideal diagnostic markers for malignant tumors (17). For instance, Jeck *et al* (5) extracted total RNA from immortalized human fibroblast cell lines and prepared cDNA using RNase R-treated samples and untreated samples. The results showed that cANRIL (low-copy RNA) in RNase R treated samples was higher than that in untreated samples Circle >10-fold enrichment. CircRNAs are more abundant than linear mRNAs (18).

*Conservativeness*. At the sequence level, circRNAs are highly conserved between species, such as between species of the *Drosophila* genus. Furthermore, certain circRNAs in *Drosophila* brains are also expressed in mammalian brains (19). An estimated 5-10% of circRNAs are homologous in human and porcine brains (20).

*Specificity*. Generally, circRNAs exhibit cell, tissue and developmental stage-specific expression patterns (21). For example, circRNAs are expressed at increased levels in developing organs, such as the heart, lungs and brain (22).

## 4. Biological functions of circRNAs

Various studies have been performed on the biological functions of circRNAs. Firstly, the indirect regulation of downstream target gene expression has been studied using microRNA (miRNA/miR) 'sponges'. miRNAs are non-coding RNAs that complement and pair with mRNA bases to indirectly regulate gene expression by inhibiting mRNA translation or promoting their degradation at the transcriptional level. For instance, miR-330-5p exerts anti-tumor effects in lung and prostate cancer (International Classification of Diseases code C61), while circ_0000517 targets miR-330-5p, thereby attenuating the inhibitory effect on the expression of the downstream target protein YY1. This results in promoting the proliferation, glycolysis and glutamine decomposition of NSCLC cells (23).

Secondly, the role of circRNAs has been studied in parental gene transcription regulation. EIciRNAs and ciRNAs are largely localized in the nucleus, where they regulate transcription. For example, EIciRNAs interact with U1 small nuclear ribonucleoprotein to promote the transcription of their parent genes (24).

Thirdly, protein translation has been studied in relation to circRNAs. Endogenous circRNAs can be translated into proteins or peptides. For example, circ_FAM188B is a stable circRNA that is differentially expressed in skeletal muscles during the development of broiler and layer embryos. Circ_FAM188B encodes the novel protein, circ_FAM188B-103AA, as well as several other peptides. Circ_FAM188B-103AA promotes the proliferation of satellite cells in the skeletal muscles of chickens, as well as inhibiting their differentiation (25).

Finally, circRNAs have been studied in relation to RNA-binding proteins. CircRNAs can bind Argonaute proteins, mannose-binding lectin, eukaryotic initiation factor 4A-III, RNA polymerases and other RNA-binding proteins to

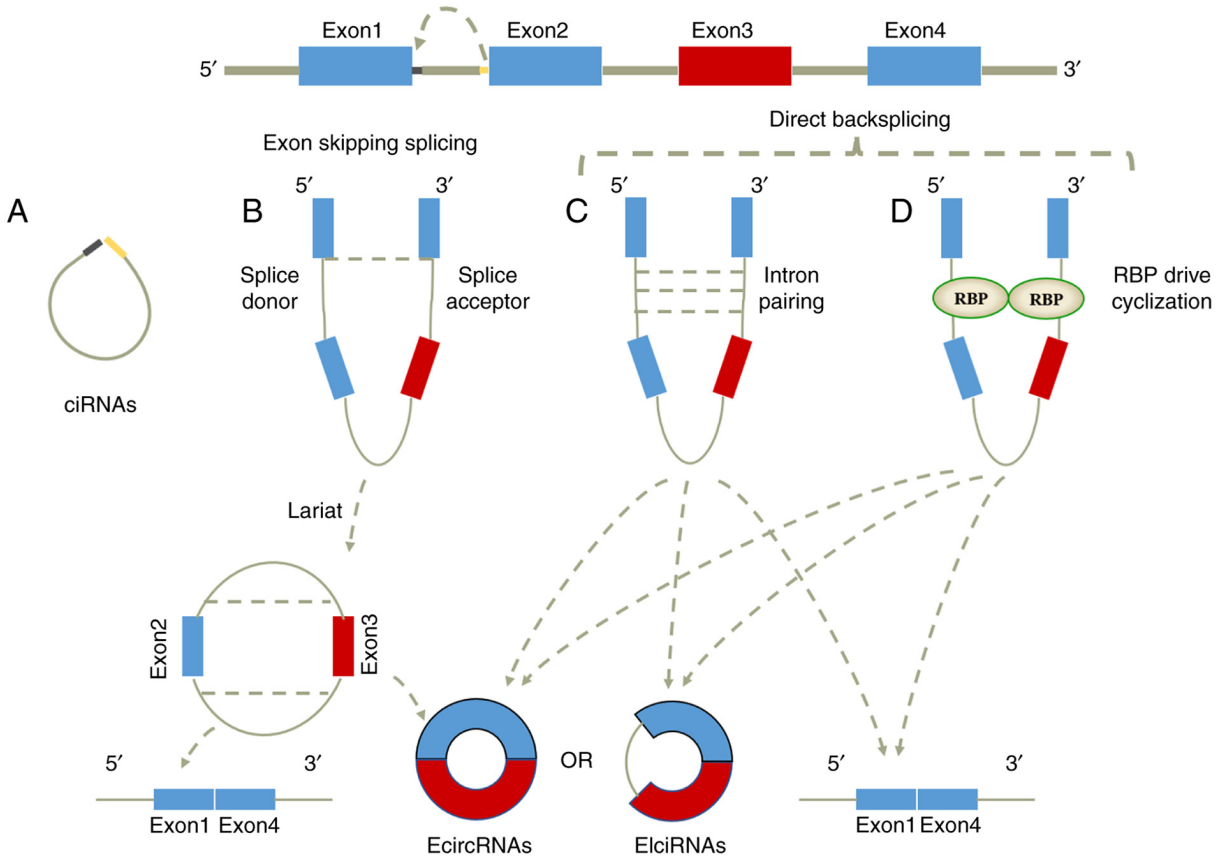



Figure 1. Loop formation mechanism of circRNAs. (A) ciRNA. (B) Lasso-driven cyclization. (C) Intron pairing-driven cyclization. (D) RBP-driven cyclization. CircRNA, circular RNA; ciRNA, intron circRNA; EcircRNAs, exon circRNAs; EIciRNAs, exon intron circRNAs; RBP, RNA binding protein.

form RNA-protein complexes that subsequently affect gene expression and participate in cell proliferation, differentiation and apoptosis (26) (Fig. 2).

## 5. Lab/experimental protocols for the detection of circRNAs

The detection conditions of circRNAs are similar to those of conventional RNA. At present, the detection process adopted by several studies is as follows: Total RNA extraction, RNA quality inspection and finally reverse transcription (RT) into cDNA. Primers are designed according to the circRNAs requiring to be detected and the expression level of circRNAs are detected by RT-quantitative PCR (27).

## 6. Diagnostic significance of circRNAs in lung cancer

Patients with stage IA and IV lung cancer have 5-year survival rates of 85 and 6%, respectively. Therefore, early lung cancer diagnosis is crucial for effective patient prognosis and treatment. If the presence of pulmonary nodules is confirmed by imaging techniques, such as CT or chest radiography, pathological results will lead to the next step of diagnosis and treatment. However, CT-guided percutaneous lung puncture and electronic bronchoscopy biopsy are invasive examinations. Thus, they are not suitable as a common means of screening for pulmonary nodules (28). Therefore, it is important to identify efficient detection methods with low invasiveness, fewer risks, improved cost effectiveness, improved support, strong operability and easy acceptance by patients. The conservativeness and stability of circRNAs make them promising biomarkers for tumor diagnosis. In addition, most of the studies on the diagnostic value of circRNAs in lung cancer have focused on tissues, with only a small number of studies performed using blood (29).

*Diagnostic value of circRNAs in lung cancer tissues.* Lin *et al* (30) demonstrated that hsa_circ_0007385 is significantly upregulated in cancerous tissues compared with paracancerous tissues (P<0.001), while receiver operating characteristic (ROC) curve analysis revealed an area under the curve (AUC) of 0.922 (95% CI, 0.890-0.953), suggesting that hsa_circ_0007385 expression in tissues has a high value in cancer diagnosis. Fu *et al* (31) sequenced three cancerous tissues alongside paracancerous tissues and validated the expression using smaller and larger sample sizes comprising 20 and 60 cases of cancerous and paracancerous tissues, respectively. They found that hsa_circ_012515 was significantly upregulated in NSCLC and was positively correlated with late-stage tumor development. The AUC value of the ROC curve was 0.89 (P<0.0001), suggesting that hsa_circ_012515 also has a high diagnostic value. Therefore, it can be used as a specific, sensitive diagnostic biomarker for patients with NSCLC (31). Geng *et al* (32) performed RNA sequencing of NSCLC cases and found that circ-MTHFD2 was significantly elevated in cancerous tissues compared with paracancerous tissues (P<0.001). ROC curves revealed a critical value

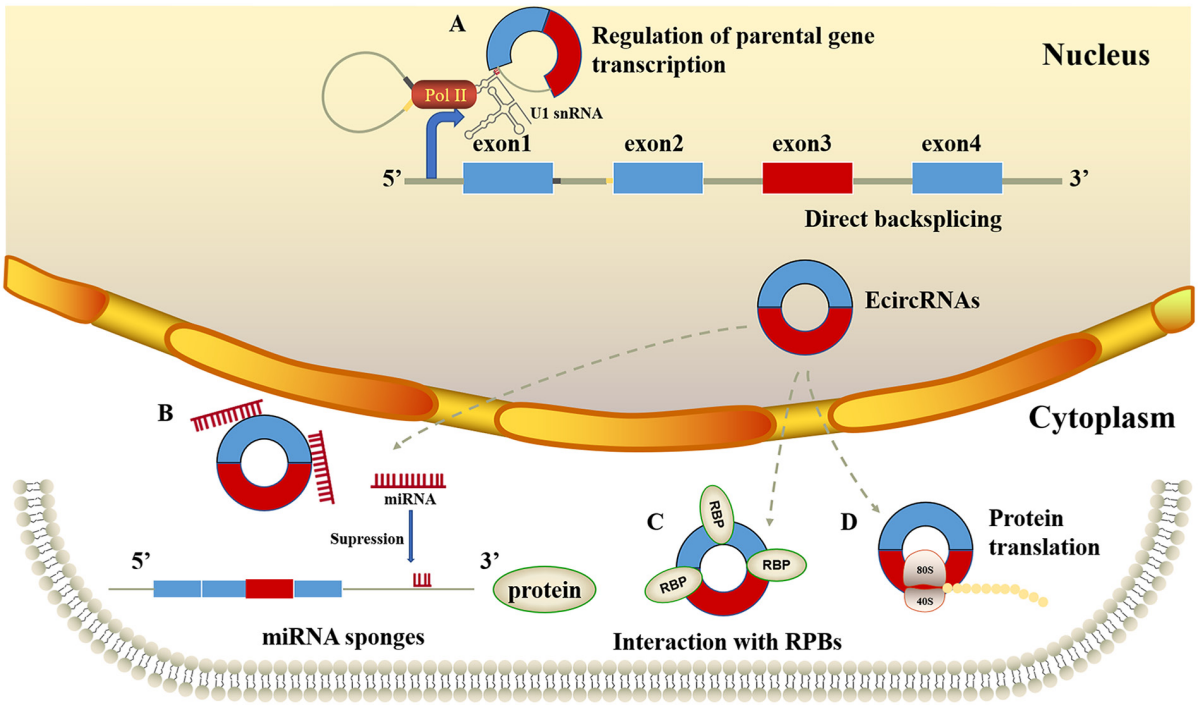



Figure 2. Biological functions of circRNAs. (A) Regulation of the transcription of parental genes. (B) Function as miRNA 'sponge'. (C) Interaction with RBPs. (D) Protein translation. CircRNA, circular RNA; Pol II, RNA polymerase II; snRNA, small nuclear RNA; EcircRNAs, exon circRNAs; miRNA, microRNA; RBP, RNA binding protein.

of 3.534 (for the relative expression of the circ-MTHFD2 gene), with a sensitivity and specificity of 90 and 71%, respectively. Furthermore, Li *et al* (33) found that hsa_circ_0000729 was upregulated in cancerous, relative to paracancerous tissues, with further analysis revealing an AUC value of 0.815 (95% CI, 0.805-0.862), which indicated a high accuracy and confirmed its value as a diagnostic marker for lung adenocarcinoma. The diagnostic accuracy of circRNAs in lung cancer could be associated with the disease stage. For example, Zhu *et al* (34) sequenced 49 cancerous samples alongside paracancerous samples, including 12 stage I (24.49%), 16 stage II (32.65%), 20 stage III patients (40.82%) and 1 stage IV (2.04%) patients. They found that hsa_circ_0013958 was significantly upregulated in cancerous relative to paracancerous tissues (P<0.001), with AUC values of 0.750, 0.766 and 0.874 for patients at stage I, II and III + IV, respectively. This demonstrated that hsa_circ_0013958 has an excellent diagnostic value in advanced lung adenocarcinoma (34).

*Diagnostic value of blood circRNAs for lung cancer.* In clinical diagnosis, plasma is the most easily accessible material. Plasma samples can be obtained via less invasive approaches than tissue samples and are, therefore, most widely used for prospecting for potential diagnostic markers in lung cancer. Due to their high stability and wide distribution, the significance of circRNAs as diagnostic markers in lung cancer has been evaluated. Exosomes, which contain proteins, RNAs and other components, are widely distributed in blood, saliva, milk and urine (35). Exosome-derived circRNAs have attracted widespread attention as potential diagnostic markers (36). Using high-throughput sequencing, Wang *et al* (37) analyzed the expression patterns of circRNAs in plasma exosomes from six pairs of patients with lung squamous cell carcinoma and obtained 252 differentially expressed circRNAs. Validation of expression via RT-qPCR confirmed that hsa_circ_0014235 and hsa_circ_0025580 were significantly upregulated in lung squamous cell carcinoma compared with the normal control group. ROC curves revealed that hsa_circ_0014235 (AUC=0.8254; 95% CI, 0.762-0.889) and hsa_circ_0025580 (AUC=0.8003; 95% CI, 0.741-0.862) have good diagnostic value for lung squamous cell carcinoma (37). CircRNA_002178 has also been reported to be significantly upregulated in plasma exosomes from patients with lung adenocarcinoma, compared with healthy controls (P<0.001), with an AUC of 0.9956 affirming its excellent diagnostic value (38). Ding *et al* (39) isolated exosomes from the serum of patients with NSCLC (n=30) and healthy subjects (n=25). They established that circ_MEMO1 was significantly upregulated in diseased relative to healthy controls (P<0.05), with an AUC value of 56.67 and specificity of 96%, suggesting the potential for serum circ_MEMO1 to be a new biomarker for NSCLC diagnosis.

In plasma, circRNA levels are a potential diagnostic index for lung cancer and also tumor metastasis. Zhang *et al* (40) reported that circ_SATB2 is significantly upregulated in serum exosomes of patients with lung cancer, relative to non-cancerous controls (P<0.01), and these expression levels were significantly higher in serum exosomes of patients with metastatic lung cancer than in non-metastatic lung cancer counterparts (P<0.01). The respective AUC values were 0.660 and 0.797, suggesting that this circRNA has a potential diagnostic value. Other circRNAs have also shown potential as diagnostic markers for various cancers. For instance, hsa_circ_0001821 exhibited a diagnostic value in colorectal, liver and lung cancers, as evidenced by AUC values of 0.815

(95% CI, 0.751-0.869), 0.692 (95% CI, 0.617-0.760) and 0.792 (95% CI, 0.724-0.850), respectively (41). CircRNAs exhibit different diagnostic abilities across various stages of NSCLC development and expression. Hsa_circ_0102533 exhibited a higher diagnostic value (AUC=0.774; 95%, CI, 0.624-0.923) in stage I-II NSCLC than at stage III-IV (AUC=0.728; 95% CI, 0.588-0.869). This suggests that it has a higher diagnostic accuracy during early lung cancer stages and has potential as a blood-derived tumor marker for the early detection of NSCLC (42).

The significance of circRNAs in lung cancer diagnosis has not been fully elucidated, with associated studies exhibiting certain limitations. Firstly, sample sizes in most studies were insufficient, necessitating further expansion. In addition, most studies have only proven differential expression of certain circRNAs in cancer, relative to paracancerous tissues, without further clarifying the corresponding changes in expression across developmental stages. Thirdly, most studies on the diagnostic value of circular RNAs in both blood and lung cancer tissues have only revealed differential expression of certain circRNAs between patients with lung cancer and non-cancerous subjects, without a control group (namely, patients with benign tumors). Specifically, the levels of circRNAs in patients with benign lung tumors are unknown. If there are benign and malignant masses in the lung, the expression of corresponding circular RNAs have been found to be significantly high, relative to non-cancerous subjects. Further studies are required to elucidate the diagnostic value of circRNAs in lung cancer.

## 7. CircRNAs and resistance to adjuvant therapy in lung cancer

Common adjuvant therapies for lung cancer include chemotherapy, targeted therapy and immunotherapy. However, they are associated with drug resistance risks, which subsequently compromise their efficacies. CircRNAs regulate cancer cell invasion as well as proliferation, and play an important role in chemotherapy, immunity and targeted drug resistance (Table I) (43-65).

*Upregulated circRNAs in tumor tissues and cells are associated with drug resistance*. CircRNAs can influence NSCLC drug resistance through the 'sponge' miRNA model, binding to RBPs and/or regulating the translation of their parental genes (66).

*CircRNAs and lung cancer targeted therapy resistance*. Gefitinib, an inhibitor of EGFR tyrosine kinase (EGFR-TK), is commonly used to treat NSCLC. However, most patients develop acquired drug resistance after using gefitinib for 9-11 months (67). The ATP-binding cassette (ABC) transporters (ABCB1 and ABCG2) are a class of drug resistance-related proteins that hydrolyze ATP to generate energy and pump out endogenous as well as exogenous substances, including antineoplastic drugs, against a concentration gradient (68). Circ_SETD3, which is localized in the cytoplasm and overexpressed in drug-resistant tumor tissues, downregulates miR-520h expression, inhibits transporter ABCG2 degradation, pumps gefitinib out of cells, and promotes tumor drug resistance through the circ_SETD3/miR-520h/ABCG2 axis (51). Wen *et al* (69) found that hsa_circ_0000567 and hsa_circ_0006867 were upregulated and downregulated, respectively, in two drug-resistant gefitinib cell lines, suggesting that changes in circRNA expression play an important role in the development of NSCLC-acquired resistance to EGFR-TK inhibitors (EGFR-TKI). Exosomes, which are messengers of intercellular communication and signal transduction, contain biological macromolecules, such as proteins and nucleic acids (70). Yang *et al* (71) found that circ_102481 was significantly upregulated in EGFR-TKIs drug-resistant exosomes, relative to sensitive ones. Notably, its overexpression promoted the proliferation of EGFR-TKIs-sensitive cells, thereby making them resistant to drugs and inhibiting cell apoptosis (71).

*CircRNAs and chemotherapeutic resistance in lung cancer*. CircRNAs are associated with both targeted and chemotherapeutic drug resistance. For instance, circ_PIP5K1A was indicated to be upregulated in the exosomes of NSCLC tissues, serum and cells, and was also associated with inhibition of NSCLC cell proliferation, migration and invasion, as well as the promotion of cell sensitivity to cisplatin and elevated apoptosis (49). Epithelial-mesenchymal transition (EMT), which plays an important role in embryogenesis, wound healing, tumor progression and endogeneity of tumor cells with invasion and metastasis potential, is closely associated with tumor cell drug resistance (72). Circ_CCDC66 knockout downregulated the expression and invasive abilities of EMT markers, and significantly increased the resistance of human H23 cells to cisplatin (52). Besides, circ_0003998 (64), circ_ZFR (54), circ_0001821 (43) and circ_0011292 (44) were significantly upregulated in paclitaxel (PTX)-resistant NSCLC tissues and cells, and their silencing promoted the sensitivity of NSCLC to PTX. These findings indicate that circRNAs play a role in tumor drug resistance.

*CircRNAs and immunotherapeutic resistance in lung cancer*. Lung cancer immunotherapy is currently a popular research topic. Although circRNAs are associated with immune escape, only a handful of studies have described this phenomenon. Luo *et al* (73) found upregulated plasma hsa_circ_0000190 levels in lung cancer patients compared with healthy subjects ($P<0.0001$), which were significantly associated with higher expression of PD-L1 in tumor tissues ($P=0.0283$). Long-term follow-up of immunotherapy cases showed that upregulation of hsa_circ_0000190 was significantly associated with systemic and immunotherapeutic adverse reactions ($P=0.0002$ and $P=0.0058$, respectively) (73). miR-155-5p and miR-194-5p in circ_CHST15 (hsa_circ_0109320) 'sponges' have been indicated to upregulate PD-L1 expression, thereby promoting PD-L1-mediated immune escape from lung cancer and increasing drug resistance to PD-L1 inhibitors. The significance of circ_CHST15 in promoting immune escape was indicated by inhibiting $CD8^+$ T cell activities and inducing $CD8^+$ T cell apoptosis (60). Patterns of PD-L1 expression are not necessarily associated with lung cancer drug resistance. Findings from a previous clinical trial, comprising 305 patients with advanced NSCLC showed that upregulated PD-L1 levels enhanced the sensitivity of NSCLC

Table I. CircRNAs and lung cancer drug resistance.

| Effect on drug | Antitumor drug | CircRNA | Target molecule | Target gene/pathway | Expression level in tumor tissue | (Refs.) |
|---|---|---|---|---|---|---|
| Enhance resistance | PTX | circ_0001821 | miR-526b-5p | *GRK5* | Upregulated | (43) |
| Enhance resistance | PTX | circ_0011292 | miR-379-5p | *TRIM65* | Upregulated | (44) |
| Enhance resistance | Cisplatin | CDR1as | miR-641 | *HOXA9* | Upregulated | (45) |
| Enhance resistance | Cisplatin | circ_PVT1 | miR-145-5p | *ABCC1* | Upregulated | (46) |
| Enhance resistance | Cisplatin | circ_0076305 | miR-296-5p | *STAT3* | Upregulated | (47) |
| Enhance resistance | Osimertinib | circ_0002130 | miR-498 | *GLUT1*<br>*HK2*<br>*LDHA* | Upregulated | (48) |
| Enhance resistance | Gefitinib | circ_PIP5K1A | miR-101 | *ABCC1* | Upregulated | (49) |
| Enhance resistance | Gefitinib | circ_0004015 | miR-1183 | *PDPK1* | Upregulated | (50) |
| Enhance resistance | Gefitinib | circ_SETD3 | miR-520h | *ABCG2* | Upregulated | (51) |
| Enhance resistance | Cisplatin | circ_CCDC66 | - | EMT | Upregulated | (52) |
| Enhance resistance | Cisplatin | circ_RNF121 | miR-646 | *SOX4* | Upregulated | (53) |
| Enhance resistance | PTX, Cisplatin | circ_ZFR | miR-195-5p | *KPNA4* | Upregulated | (54) |
| Enhance resistance | Cisplatin | circRNA_103809 | miR-377-3p | *GOT1* | Upregulated | (55) |
| Enhance resistance | Cisplatin | circ_0007385 | miR-519d-3p | *HMGB1* | Upregulated | (56) |
| Enhance resistance | Anti-PD-1 | circUSP7 | miR-934 | *SHP2* | Upregulated | (57) |
| Enhance resistance | Anti-PD-1 | circ_CELF1 | miR-491-5p | *EGFR* | Upregulated | (58) |
| Enhance resistance | Anti-PD-1 | circIGF2BP3 | miR-328-3p,<br>miR-3173-5p | *PKP3* | Upregulated | (59) |
| Enhance resistance | Anti-PD-1 | circCHST15 | miR-155-5p,<br>miR-194-5p | *PD-L1* | Upregulate | (60) |
| Increase sensitivity | PTX | circ_0002483 | miR182-5p | *GrB2/*<br>*FOXO_1/*<br>*FOXO_3* | Downregulated | (61) |
| Increase sensitivity | Cisplatin | circ_SMARCA5 | miR-670-5p | *RBM24* | Downregulated | (62) |
| Increase sensitivity | Cisplatin | circ_cESRP1 | miR-93-5p | *CDKN1A* | Downregulated | (63) |
| Increase sensitivity | PTX | circ_003998 | miR-558 | *MMP1*<br>*MMP17* | Downregulated | (64) |
| Increase sensitivity | Cisplatin | circ_LDB2 | miR-346 | *LIMCH1* | Downregulated | (65) |

CircRNA, circular RNA; PTX, paclitaxel; PD-1, programmed cell death protein 1; PD-L1, PD-ligand 1; EMT, epithelial-mesenchymal transition.

cells to immunotherapy (74). These findings suggest that the relationship between PD-L1 levels and tumor drug resistance is not simply 'promotion' or 'inhibition', while the mechanism underlying the actions of circRNAs in tumor immune escape should be further evaluated.

A previous study demonstrated that other circRNAs are downregulated in drug-resistant tumor tissues and cells and have a role in enhancing the sensitivity of tumor drug-assisted therapy. For instance, circ_0002483 was downregulated in drug-resistant NSCLC tissues, and its overexpression was found to not only inhibit proliferation and invasion of NSCLC cells via the miR182-5p/growth factor receptor-bound protein 2/FOXO1/FOXO3 signaling pathway, but also promote their sensitivity to PTX chemotherapeutic drugs (61).

*CircRNAs and radioresistance in lung cancer.* Radiotherapy is clinically used as an adjunct therapy in the treatment of lung cancer. This therapy destroys the DNA of tumor cells leading to the death of cancer cells (75). The development of radioresistance, on the other hand, negates the benefits of radiotherapy (76). The mechanism leading to the development of tumor radioresistance is complex and heterogeneous. It involves cancer-associated fibroblasts, tumor stem cells, non-coding RNA, DNA damage response, proinflammatory cytokines and regulatory enzymes among other molecules (77). CircRNAs, as a type of non-coding RNA, have been implicated in the development of radiation resistance in lung cancer (78).

In a previous study, certain circRNAs were positively associated with the occurrence of radioresistance in NSCLC. Based on the response of patients to radiotherapy, NSCLC tissues were divided into radioresistance and radiation-sensitive groups (44). circ_0007580 and circ_0086720 were highly expressed in radioresistant NSCLC tissues.

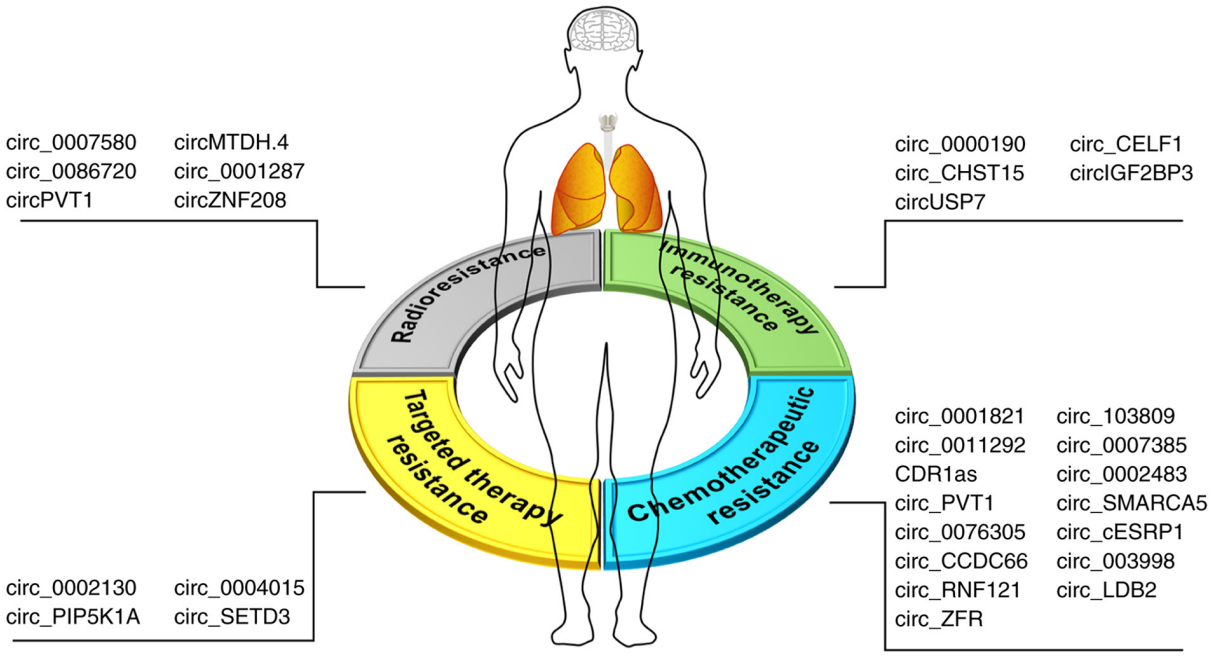



Figure 3. CircRNAs and adjuvant therapy resistance in lung cancer. The circRNAs are mainly divided into four aspects: CircRNAs related to drug resistance in chemotherapy of lung cancer, circRNAs related to drug resistance in targeted therapy of lung cancer, circRNAs related to drug resistance in immunotherapy of lung cancer and circRNAs related to drug resistance in radiotherapy of lung cancer. Circ, circular.

Additionally, knockdown of the target circRNAs enhanced the radiotherapy sensitivity of NSCLC cells (44). Huang *et al* (79) induced radioresistance in NSCLC cell lines and found a positive correlation between circPVT1 expression level and the occurrence of radioresistance in NSCLC cell lines. In addition, circPVT1 knockdown enhanced the radiosensitivity of NSCLC cell lines.

Other circRNAs have been reported to be negatively associated with the occurrence of radioresistance in NSCLC. For example, Zhang *et al* (80) discovered that the expression level of circ_0001287 was significantly lower in cancerous tissues from 87 patients with NSCLC than in paracancerous tissues. Circ_0001287 overexpression inhibited the proliferation, migration and invasion of radioresistant H1299 cells. Clinicopathological analysis revealed that patients with low circ_0001287 expression were more likely to have positive lymph node metastasis and poorly differentiated cancer, implying that circRNAs may enhance the sensitivity to radiotherapy in lung cancer cells.

CircRNAs can also be used as reference targets for differential radiotherapy in lung cancer. In a series of experiments conducted by Jin *et al* (81), it was found that radioresistant A549-R11 cells were significantly more resistant to conventional X-ray radiotherapy than their paternal A549 cells, although both cell types demonstrated comparable sensitivity to carbon-ion radiotherapy (CIRT). CircZNF208 is highly expressed in radioresistant cells, and inhibiting its expression can improve the sensitivity of A549 and A549-R11 cells to X-ray irradiation. Since CIRT is costly, few hospitals have X-ray irradiation therapy equipment, and therefore the treatment is mainly covered by commercial insurance companies (78). CircZNF208 is expected to be a new marker for identifying patients who are most likely to benefit from CIRT therapy (Fig. 3).

## 8. CircRNAs and the prognosis of patients with lung cancer

The prognosis of patients with lung cancer is a critical follow-up process for effective tumor treatment, as it serves as a reference point for adjusting medication, changing treatment regimens and evaluating patient survival time (82).

*CircRNAs play an oncogenic role in the development and progression of lung cancer.* CircRNA expression levels have been indicated to vary significantly between cancerous and paracancerous tissues. The majority of circRNAs were overexpressed in cancerous tissues and were associated with poor survival, late TNM Classification of Malignant Tumors staging and positive lymph node metastasis. These findings suggest that most circRNAs play an oncogenic role in lung cancer, promoting tumor invasion and metastasis, which is associated with patient survival. Dou *et al* (83) found that the expression of circ_0001944 was significantly higher in NSCLC than in adjacent healthy tissues in 47 paired NSCLC tissues. The Kaplan-Meier survival curve revealed that patients with NSCLC who expressed high circ_0001944 levels had a poor prognosis. In the 40th month, the survival rate of the high expression group was only 50%, while the low expression group had a higher rate of ~90%. Shi *et al* (84) reported that patients with lung squamous cell carcinoma (LUSC) who expressed high levels of circ_PVT1 had a lower overall survival (OS) than patients with LUSC who expressed low levels of circ_PVT1. Multivariate analysis confirmed that circ_PVT1 expression is a potential independent predictor of OS. Circ_PVT1 may therefore be used to predict the prognosis of lung cancer. Wang *et al* (85) showed that circ_PRMT5 was highly expressed in cancer tissues compared with para-cancer tissues ($P<0.001$), and that this level of expression was negatively associated with OS ($P=0.019$) and progression-free

survival (P=0.004). Kaplan-Meier survival curves revealed that other circRNAs highly expressed in cancer tissues, including circ_0067934 (86), circ_0016760 (87), circ_001569 (88), circ_AASDH (89) and circ_MTHFD2 (32), indicated that patients with high expression had a poor OS (P<0.05). Cox regression analysis revealed that circRNA may be a significant independent prognostic factor for patients with NSCLC.

*CircRNAs have a role as tumor suppressor genes in the development and progression of lung cancer.* The expression of a few circRNAs has been demonstrated to be lower in cancerous tissues than in adjacent tissues, and patients expressing high circRNA levels in cancerous tissues had a longer survival duration than those expressing low circRNA levels. Liu *et al* (90) used RT-qPCR on 53 cancerous and adjacent tissues and found that circ_0001649 expression in NSCLC tissues was significantly lower than in adjacent tissues. Additionally, patients with low circ_0001649 expression had an advanced clinical stage and lymph node metastasis. Kaplan-Meier curve analysis revealed that patients with a high level of circ_0001649 expression had a significantly longer OS than those with low circ_0001649 expression (P=0.004). These findings suggested that circ_0001649 may inhibit proliferation, migration and invasion of NSCLC cells by acting as a tumor suppressor gene in NSCLC. A tumor model of nude mice was then established to confirm the tumor-suppressive effect. Tumors overexpressing circ_0001649 were smaller in volume and weight than those in the negative control group. A lung metastatic tumor model was developed, and circ_0001649 overexpression in mice resulted in a reduction in pulmonary metastatic nodules (87). Therefore, circ_0001649 may be a therapeutic target for lung cancer. Chen *et al* (91) found that circ_0000079 (CiR79) expression level was significantly downregulated in the cancerous tissues of patients with NSCLC compared with normal control lung tissue, particularly those with cisplatin resistance (P<0.005). In their study, the reduction of circ_0000079 level was related to the decline of OS in patients with NSCLC. Cell experiments revealed that high circ_0000079 expression inhibited cisplatin resistance in A549/DDP and H460/DDP cells, implying that circ_0000079 could be used as a prognostic indicator and therapeutic target for NSCLC. Chi *et al* (92) showed that overexpression of hsa_circ_103820 significantly inhibited the proliferation, migration and invasion of lung cancer cells, while knockdown of hsa_circ_103820 played a tumorigenic role. These results suggested that hsa_circ_103820 has a potential novel function as a tumor suppressor in lung cancer.

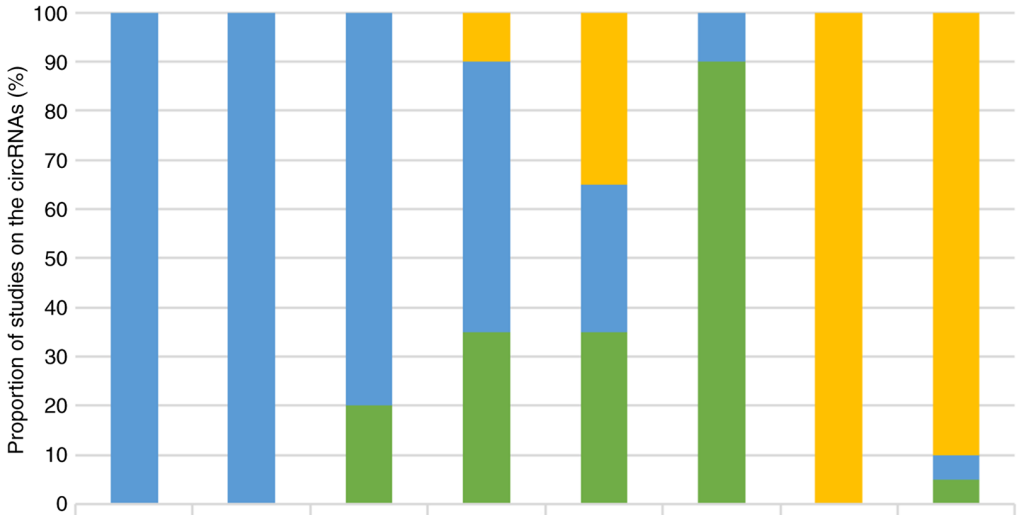
*Prognostic value of circRNAs and TNM staging of lung cancer.* Notably, the associated prognosis for certain circRNAs is related to their level of expression and is inversely proportional to the TNM stage of patients. Through RT-qPCR analysis of cancerous and paracancerous tissues of 284 patients, Zhang *et al* (93) found that the expression level of circ_0001946 in paracancerous tissues of patients with NSCLC was more than three times higher than that in cancerous tissues. High expression of circ_0001946 is related to a reduction in lymph node metastasis, decreased TNM stage and an improved prognosis in patients with NSCLC. Patients were divided into quartile 1-25%, quartile 25-50%, quartile 50-75% and quartile 75-100% groups based on their expression level of circ_0001946, which ranged from low to high. The survival analysis using the Kaplan-Meier curve revealed that disease-free survival (DFS) and OS were positively associated with circ_0001946 expression levels (both P<0.001). High expression of circ_0001946 was associated with improved DFS in stage I, II and III patients (all P<0.05), however, only stage III patients had a prolonged OS (P=0.037). These findings indicate that circ_0001946 may have a high prognostic value in stage III patients. Tong *et al* (62) revealed lower circ_SMARCA5 expression in cancer tissues of patients with NSCLC than in adjacent tissues, and circ_SMARCA5 expression was negatively correlated with tumor size, lymph node metastasis and TNM stage, but positively correlated with DFS and OS. The study also grouped circRNA expression levels from low to high, defining the circ_SMARCA5 high expression group as being within 50-100% of the relative expression quantile and the circ_SMARCA5 low expression group as being within 0-50% of the relative expression quantile. Kaplan-Meier curve survival analysis revealed significantly longer DFS and OS in the circ_SMARCA5 high expression group than in the circ_SMARCA5 low expression group (P<0.001). High expression of circ_SMARCA5 exacerbated the decline in NSCLC cell survival after chemotherapy, implying that high expression of circ_SMARCA5 increased NSCLC cell sensitivity to chemotherapy. Previous studies on the association of circRNA expression levels and survival in patients with cancer have also divided patients into high and low expression groups and found differences in the survival time of patients. For example, Tong *et al* (62) and Zhang *et al* (93) further classified expression levels and elucidated the relationship between expression levels and prognosis. Additionally, Zhang *et al* further investigated TNM staging and prognosis. The majority of previous studies did not subdivide staging at the TNM level, which may have been attributed to the small sample size (mostly 50-100 cases). This may have resulted in poor statistical power, particularly for the subgroup analysis of the association of circRNAs with the prognosis of stage I, II and III patients.

*Prognostic value and clinical features of circRNAs.* The association between patients with lung cancer and various circRNAs is shown in Table II, which also lists the number of cases, as well as clinical features, namely age, sex, smoking history, degree of tumor differentiation, tumor diameter, tumor pathological type, tumor stage, lymph node metastasis and survival duration of the high expression group. Most available literature regarding research on circRNAs and lung cancer seems to be from studies published in Asia. To avoid differences between races, the present review uniformly selected studies with Asian patients (23,39,62,83,85,87,93-106). Almost all circRNAs and tumor prognoses were associated with TNM stage and lymph node metastasis in the 20 groups of circRNAs listed in the table. Additionally, high circRNA expression in cancerous tissues was associated with a shortened OS, whereas low expression of circRNAs in cancerous tissues exerted the opposite effect. Only one case was shown to be associated with TNM stage and degree of differentiation, but not with the other factors that were investigated. All 20 study groups included age and sex as clinical features; however, there was no statistically

Table II. Association of circRNAs with clinicopathological features of patients with lung cancer.

| CircRNA | Age | Sex | Smoking history | Degree of differentiation | Tumor diameter | Tumor pathological type | TNM staging | Lymph node metastasis | Survival duration of patients with high circRNA expression | Number of cases included in the study | (Refs.) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| hsa_circ_0016760 | P=0.504 | P=0.420 | P=0.412 | P=0.513 | P=0.039[a] | - | P=0.023[a] | P=0.037[a] | Short OS | 80 | (87) |
| hsa_circ_0001421 | P=0.107 | P=0.116 | - | - | P=0.015[a] | - | P=0.018[a] | P=0.153 | Short OS | 48 | (94) |
| circ_0003645 | P=0.435 | P=0.784 | P=0.293 | P=0.607 | - | - | P=0.019[a] | P=0.010[a] | Short OS | 59 | (95) |
| circ_000984 | P>0.05 | P>0.05 | - | - | P>0.05 | - | P=0.004[a] | P=0.005[a] | Short DFS/OS | 155 | (96) |
| circ_0001649 | P=0.572 | P=0.544 | P=0.406 | P=0.557 | - | - | P=0.010[a] | P=0.029[a] | Long OS | 53 | (97) |
| circ_0020123 | P=0.270 | P=0.788 | P=0.781 | P=0.391 | - | - | P=0.037[a] | P=0.029[a] | Short OS | 55 | (98) |
| circ_0074027 | P=0.579 | P=0.393 | P=0.404 | P=0.025[a] | - | - | P=0.011[a] | P=0.095 | Short OS | 52 | (99) |
| circ_CRIM1 | P=0.209 | P=0.676 | P=0.400 | - | P=0.204 | - | P=0.021[a] | P=0.022[a] | Short OS | 92 | (100) |
| circ_PRMT5 | P=0.205 | P=0.822 | P=0.607 | P=0.274 | P=0.002[a] | - | P=0.028[a] | P=0.018[a] | Short DFS/OS | 90 | (85) |
| hsa_circ_0007534 | P=0.837 | P=0.828 | P=0.529 | P=0.298 | - | - | P=0.039[a] | P=0.024[a] | Short OS | 98 | (101) |
| circ_0016760 | P=0.825 | P=0.820 | P=0.503 | P=0.128 | - | - | P=0.044[a] | P=0.003[a] | Short OS | 83 | (102) |
| circ_MEMO1 | P>0.05 | P>0.05 | - | - | P>0.05 | - | P<0.05[a] | P<0.05[a] | Short OS | 52 | (39) |
| circ_SMARCA5 | P=0.209 | P=0.178 | P=0.190 | P=0.260 | P=0.001[a] | - | P=0.001[a] | P=0.004[a] | Long DFS/OS | 460 | (62) |
| circ_0001944 | P=0.191 | P=0.181 | P=0.058 | - | P=0.110 | - | P=0.011[a] | P=0.002[a] | Short DFS | 47 | (83) |
| circ_PVT1 | P=0.3216 | P=0.1936 | P=0.1733 | P=0.1151 | P=0.0468[a] | - | P=0.0001[a] | P=0.0014[a] | Short OS | 104 | (103) |
| circ_0001946 | P=0.446 | P=0.187 | P=0.670 | P=0.185 | P=0.097 | - | P=0.001[a] | P<0.001[a] | Long DFS/OS | 284 | (93) |
| circ_TADA2A | P=0.791 | P=0.284 | P=0.787 | - | P=0.020[a] | P=0.301 | P=0.038[a] | P=0.001[a] | Short OS | 60 | (104) |
| circ_0000517 | P=0.592 | P=0.793 | P=0.438 | P=0.071 | - | - | P=0.024[a] | P=0.020[a] | Short OS | 60 | (23) |
| circ_0005909 | P=0.988 | P=0.241 | - | - | P=0.217 | - | P=0.023[a] | - | Short OS | 102 | (105) |
| hsa_circ_0003222 | P>0.05 | P>0.05 | P>0.05 | P<0.05[a] | P<0.05[a] | P>0.05 | P<0.05[a] | P<0.05[a] | Short OS | 30 | (106) |

[a]Statistically significant. '-' refers to clinical features that have not been used as indicators of circRNAs. As shown in the table, most circRNAs were strongly associated with lymph node metastasis and TNM staging. All study population were ethnically Asian. CircRNA, circular RNA; OS, overall survival; DFS, disease-free survival.




| | Age | Gender | Smoking history | Degree of differentiation | Tumor diameter | Pathologic types | Tumor staging | Lymph node metastasis |
|---|---|---|---|---|---|---|---|---|
| Statistically significant | 0 | 0 | 0 | 2 | 7 | 0 | 20 | 18 |
| No statistical significance | 20 | 20 | 16 | 11 | 6 | 2 | 0 | 1 |
| Not included in the study | 0 | 0 | 4 | 7 | 7 | 18 | 0 | 1 |

Figure 4. Association of circRNAs with clinicopathological features of patients with lung cancer. The percentage values shown on the Y-axis refer to the proportion of studies on circRNAs in the 20 lung cancer cases presented in the table. 'Statistically significant' and 'No statistical significance' refers to the associations between circRNA levels and the clinical features, while 'Not included in the study' refers to clinical features that have not been used as indicators of circRNAs.

significant association between age, sex and circRNA expression level. When smoking history was included as a clinical characteristic, no statistical significance between smoking history and circRNA expression was observed in any of the 16 groups. The degree of tumor differentiation was included as a clinical characteristic in 13 groups; however, only two groups showed a statistically significant association between the degree of tumor differentiation and the level of circRNA expression. Tumor diameter was included as a clinical characteristic in 13 groups, and there was a statistically significant difference between tumor diameter and circRNA expression level in seven groups. Only two of the 20 groups included pathological type as a clinical characteristic, and no statistically significant association between pathological type and circRNA expression level was found. According to the findings of the 20 studies, the level of circRNA expression level correlated with TNM stage and lymph node metastasis, and the majority of the highly expressed circRNAs in cancerous tissues were positively correlated with late TNM stage and positive lymph node metastasis, implying a poor prognosis for patients. Nearly all studies reported that circRNA expression was unrelated to age, sex, smoking history and pathological type (Fig. 4). The relationship between circRNA expression levels, tumor diameter and degree of tumor differentiation is still debatable. The tumor diameter limit in these studies may differ compared with that established in previous studies (3 vs. 5 cm as the dividing point). However, only 20 circRNAs are listed in the table, which may relate to a low statistical significance. Therefore, these findings suggest that circRNAs may be useful as prognostic markers for lung cancer, but additional research is needed to establish their validity as independent prognostic factors.

## 9. Limitations of circRNAs as diagnostic markers for lung cancer

CircRNAs are non-coding RNAs. Several studies have confirmed that circRNAs regulate the expression of cancer-related genes through circRNA-miRNA-mRNA pathways, thus affecting the proliferation, invasion and migration of cells in lung cancer. Their unique biological characteristics cause circRNAs to be regarded as potential biomarkers in the diagnosis of lung cancer. However, the exact mechanism of circRNAs in the development of lung cancer has not been fully elucidated. There are several studies on the carcinogenesis and tumor suppression of circRNAs in the development of lung cancer, but most of the studies first verified the differential expression of circRNAs in cancerous tissues and adjacent tissues, and then verified their expression in cells and animal models. On the other hand, differentially expressed circRNAs were reported in different studies. Specific circRNAs with higher diagnostic values in lung cancer have not been established, and no expert consensus has been formed on the diagnostic value of certain circRNAs in lung cancer (107). Certain circRNAs, such as CDR1as, are differentially expressed in NSCLC, liver cancer (C22.001), stomach cancer (C16.902), esophageal cancer (C15.901), bile duct cancer (C22.101) and other types of cancer (108), which could be used as biomarkers for lung cancer screening. However, the diagnostic specificity of these circRNAs is not high.

The diagnostic value of circRNAs in lung cancer is currently limited to the laboratory stage. The subsequent clinical application also faces problems, such as diagnostic accuracy and economic burden. Currently, biomarkers

developed for lung cancer screening in clinical practice include the carcinoembryonic antigen, squamous cell carcinoma antigen, neuron-specific enolase, pro-gastrin-releasing peptide, carcinoma antigen 125, cytokeratin fragment 19, human epididymis protein 4 and others (109). The diagnostic value of circRNAs in lung cancer has not been compared with such traditional biomarkers. In conclusion, further studies are needed to confirm the clinical application of circRNAs, but circRNAs are promising as pot0ential biomarkers for lung cancer.

## 10. Conclusion

Lung cancer is one of the most common malignant tumors in China, with the highest mortality rates among patients with cancer (110,111). Patients with advanced lung cancer have a very poor prognosis, necessitating the development of early diagnostics and therapies for effective management of the disease (112). CircRNAs are found in abundance in cells, urine, saliva, plasma and other tissues, and are characterized by their stability, universality, conservatism and specificity. Because of their abundance in human tissues, sampling is associated with minimal trauma, speed, minimal risk, low cost, wide usage, and has high operability, implying their potential use as a marker for the early diagnosis of patients with lung cancer. Although circRNAs are abnormally expressed in a variety of tumors, their biological function remains largely unknown. Currently, the majority of studies on circRNAs have mainly focused on their abnormal expression in lung cancer and their regulatory role in gene expression via the miRNA 'sponge' mechanism. However, findings from related studies indicate that circRNAs have a variety of functions in other diseases, including protein binding and regulating transcription and translation. It would be useful to further investigate these findings in relation to other diseases, such as lung cancer. While the majority of studies have demonstrated the diagnostic value of circRNAs in lung cancer, their clinical application is still constrained by their low abundance in blood and high detection cost. More in-depth and comprehensive clinical trials are required to verify the value of circRNAs as diagnostic markers. At present, the use of circRNAs for lung cancer detection is primarily based on their differential expression between cancerous and adjacent normal tissues, with few studies incorporating tumor staging and pathological typing as grouping criteria. Therefore, additional research is required to identify highly specific and sensitive circRNAs during the early developmental stages of lung cancer. Additionally, elucidating the underlying biological mechanism and identifying molecular targets would pave the way for effective lung cancer diagnosis, treatment and prognosis.

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## Availability of data and materials

Not applicable.

## Authors' contributions

CS was responsible for the conception and design of the study, the collection and assembly of data, as well as the data analysis and interpretation. ZT and DR were responsible for the provision of study materials. ZT was also responsible for administrative support. CS, ZT, DR, CW, YX and MS contributed to writing the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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