

## Molecular Biology of Lung Carcinosarcoma: A Review of the Literature

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**ABSTRACT**

*Lung Carcinosarcoma (LCS) is a rare, malignant aggressive biphasic tumor with an unfavorable prognosis, high mortality rate, and is composed of a mixture of epithelial and mesenchymal elements. The epithelial or carcinomatous element is most commonly squamous followed by adenocarcinoma, whereas the mesenchymal or sarcomatous element commonly contains the main component of the tumor and shows poorly differentiated spindle cell characteristics. Moreover, other foci of differentiated sarcomatous elements such as chondrosarcoma and osteosarcoma may be observed.*

*LCS accounts for less than 0.1% of all lung cancers, has a poor prognosis due to late diagnosis and early metastases. It has been estimated that the median survival time is 9 (3-25) months, a prognosis poorer than other non-small cell lung carcinomas (NSCLC).*

*According to the most recent 2015 World Health Organization (WHO) classification, pleomorphic carcinoma, giant cell carcinoma, lung blastoma, spindle cell carcinoma, and carcinosarcoma consist a heterogeneous category of primary lung cancer accounting from 0.3% to 3% of all primary lung malignancies, known as lung sarcomatoid carcinoma, depending on the observed morphology.*

*Although genetic mutations of some common lung cancer subtypes have been extensively investigated, the molecular characteristics of LCS and the existence of abnormal target genes still remain unknown.*

**Keywords**

Lung carcinosarcoma, NSCLC, Histopathology.

**Introduction**

Primary lung carcinosarcoma (LCS) is a rare malignancy histological subtype of non-small lung cancer (NSCLC) with a poor prognosis [1-15].

It accounts for 0.1-1.0 % of all malignant lung neoplasms [13,16-20]. LCS is reported to arise in elderly men between 50–80 years who are heavy smokers [1,4,10,16-28], has a male-to-female ratio of 7.25:1 and a median age at onset of 65 years.

It was initially suggested that LCS divides into two distinct clinicopathological types [29], a central endobronchial (squamous

type), that is slow-growing and has squamous epithelial differentiation in more than 90% of cases, and a peripheral invasive (glandular type), characterized by early metastatic spread, poor clinical outcome and glandular epithelial differentiation in approximately 50% of cases [13]. Koss et al. reported central localization in 62% of cases [1].

In another study found that one-third of these tumors were located peripherally [29], whereas Yazici et al. reported a peripheral location in 85.7% of cases [30]. However, in the last decades this classification, has been considered less stringent.

The clinical presentation of the centrally localized type involves a cough, dyspnoea, and haemoptysis, like other endobronchial tumours. The second type of LCS, the peripheral solid parenchymal

type, often presents as a large mass. These tumors are asymptomatic in the early stage, during which time they may involve the adjacent organs or structures such as the mediastinum, pleura, and thoracic wall [31].

Metastasis is frequent and is most common to the lymph nodes, followed by the kidneys, bones, liver, and brain [1]. Regional and distant metastases are infrequent [3].

These tumours are histologically heterogeneous and possibly represent a continuum of epithelial and mesenchymal differentiation [13]. LCS is defined by the presence of epithelial elements (squamous or adenocarcinoma) combined with sarcomatous elements such as rhabdomyosarcoma, osteosarcoma, or chondrosarcoma [1]. Few reports have shown the presence of common chromosomal abnormalities in the epithelial and sarcomatous components of LCS [32,33], suggesting a monoclonal origin of LCS tumors.

For immunohistochemistry, EMA, CK5/6, CK7, TIF1, P63, chromogranin A, CD56, and synaptophysin can be used as markers for carcinomatous components, and desmin, vimentin, and smooth muscle/sarcomeric actin can be used as markers for sarcomatous elements [1,34].

Its clinical characteristics, preoperative diagnostic methods, and prognostic factors are still not completely understood [35]. The diagnosis is often made at a late stage when there is multiple metastasis [36]. Final diagnosis is accomplished through histological examination combined with the use of different methods, such as the method of monoclonal antibody reactions. Expression of cytokeratin and vimentin confirm the diagnosis of the tumor [36].

Preoperative tissue diagnosis is consequently difficult due to the heterogeneity of the tumor, with biopsy often just reflecting one element of the tumor. Similarly there are no clear findings on imaging which indicate a likely diagnosis. Given the associated or perceived worse prognosis when compared with other types of NSCLC, it is necessary to focus on the optimal management of patients with LCS.

Standard therapy for LCS has not yet been established because of the low incidence of this type of tumor. The treatment of choice is complete surgical resection with negative tumor margins, whereas adjuvant or neoadjuvant therapy can be considered in selected cases, however chemotherapy and radiotherapy are not active in this type of tumor [37]. It is often refractory to chemotherapy and radiation therapy [1]. The rate of reversibility ranged from 87-93 % [38].

Complete surgical resection is still the only effective treatment for LCS as mentioned, but the prognosis is poor. The clinical and prognostic properties of carcinosarcomas are still unknown, and more studies and larger multicentric series are needed.

Pazopanib, a multi-targeted tyrosine kinase inhibitor against the

proto-oncogene c-Kit (c-KIT), platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), and vascular endothelial growth factor receptor (VEGFR), has been reported to show beneficial outcomes in patients with metastatic non-adipocytic soft-tissue sarcoma and renal cell carcinoma, and superior safety and quality-of-life profiles compared with sunitinib, which is a similar targeted drug [39,40]. This inhibitor has the potential to become one of the new treatment options for inoperable LCS. However, there is limited information on systemic treatment options such as chemotherapy and radiotherapy [9,41].

Although few reports showed that doxorubicin-based regimens had some effect on metastatic LCS [6,9], standard chemotherapy for metastatic LCS has not yet been developed [42]. Nevertheless, the aggressive nature and poor differentiation of this tumor render the treatment difficult and results in a poor prognosis [43]. Although relatively satisfying survival rates have been reported in some series, 49.3% by Petrov et al. [37] and 57% by Yazici et al. [30], the survival was poor in others, 21.3% in Koss et al. [1]. A median survival time of 9 (8) to 12 months (6) after potentially curative surgical resection has been recorded. Several papers have reported a median survival of approximately 1 year (21), and a six months survival rate 27% [36].

A recent case series has only identified increased tumor size (>6 cm) as a prognostic indicator for reduced survival [1].

### Histopathology and Histogenesis of LCS

According to the 2004 WHO classification of lung tumors, carcinosarcomas are defined as tumors consisting of an admixture of malignant epithelial and mesenchymal components. Those malignant tumors are poorly differentiated non-small cell lung carcinomas (NSCLC) that contain a component of sarcomatoid differentiation, so called sarcomatoid carcinoma [3,4,10,12].

Immunohistochemical techniques are used to differentiate the epithelial and mesenchymal tumor elements of carcinosarcomas. Previous analyses in LCS cases [3,4,9,10-12,14,15,18,32,44,45], showed that the epithelial and mesenchymal component of this biphasic tumour harbor a different morphology, but is monoclonal in origin.

The carcinomatous component is more often squamous cell carcinoma (69%), adenocarcinoma (20%) and large cell carcinoma (11%), whereas a small cell carcinoma component has been only described in one case by Huwer et al. [4]. In a study by Koss et al. the frequency of epithelial components was squamous cell carcinoma (46%), adenocarcinoma (31%), and adenosquamous carcinoma (19%) [1]. Similarly, in another study 67%, the epithelial component was squamous cell carcinoma, and adenocarcinoma in 33% [58]. Braham et al. [17] confirmed such findings. Takeda et al. reported a rate of 69% for squamous cell carcinoma, 24% for adenocarcinoma, and 6% for a combination

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of carcinomas [27].

The most common mesenchymal component is poorly differentiated spindle cell sarcoma, whereas foci of rhabdomyosarcoma, osteosarcoma, chondrosarcoma [1,26,27,46-50], and combinations of these components [51] have also been observed [1,10,21,52]. Additional histological ingredients of the sarcomatous tumor component comprise fibrosarcoma, leiomyosarcoma, and undifferentiated sarcoma, all of which may occur separately or in combination with each other [17,27,46].

When heterologous sarcoma elements such as cartilage or skeletal muscle are present, it is easier to confirm the biphasic nature of the tumor, although immunostains can be of further help such as Myogenin and Myo D1 for rhabdomyosarcoma, smooth muscle actin and desmin for leiomyosarcoma, and S100 for chondrosarcoma [10]. Because of this heterogeneity, carcinosarcomas are difficult to diagnose preoperatively.

The histogenesis of carcinosarcomas remains unclear. Several theories have been proposed regarding the histogenesis of carcinosarcoma. Recent reports suggest the combination theory, as molecular genetic research has shown carcinomatous and sarcomatous components to share the same characteristics [53]. That theory suggests that carcinomatous and sarcomatous components originate from a common multipotent stem cell that undergoes divergent differentiation into both epithelial and mesenchymal lineages, or occurs metaplasia of carcinoma into sarcoma cells [3,7,10,11].

However, two recent studies have provided molecular evidence that the divergent epithelial and mesenchymal cell lineages indeed share the same histological origin [7,32], favouring the classification of LCS as a biphasic monoclonal malignancy. By using immunohistochemical and ultrastructural studies in a case of LCS, Haraguchi et al. [54], suggested that the malignant mesenchymal component was derived from the epithelial component, supporting earlier concepts according to which the carcinoma is the main tumor element, whereas the sarcomatous changes are secondary, e.g., through mesenchymal metaplasia [28].

Due to the heterogeneity of the tumor, obtaining a tissue diagnosis of carcinosarcomas is difficult as a needle biopsy would often just reflect one element of the tumor, as the sarcomatous component may predominate and overcast the carcinomatous component. Therefore, extensive sampling is recommended, and it is suggested to submit one section per centimeter of maximum tumor diameter along with areas of hemorrhage and necrosis. The immunohistochemical stains used for epithelial components are cytokeratin (CK5/6, CK7), EMA, TTF1, Napsin, chromogranin A, CD56, synaptophysin P40, and p63, which is variable based on the morphology of the epithelial component. The sarcomatous component is negative for keratin, whereas other markers are positive according to the differentiation, such as rhabdomyosarcoma: desmin, myogenin, and MyoD1,

chondrosarcoma: S100, and osteosarcoma: osteocalcin that stains the osteoid matrix [10] and smooth muscle/sarcomeric actin [1,34].

### **Role of Epithelial–Mesenchymal Transition (EMT) in LCS pathogenesis**

Rudolf Virchow suggested that the biphasic appearance of carcinosarcoma is attributed to a single progenitor undergoing aberrant epithelial and mesenchymal differentiation at the early stages of neoplastic transformation [43,55]. A contrary opinion suggests that sarcomatoid metaplasia of carcinoma cells occurs at later stages of cancer progression [32,43]. It has also been suggested that the evolution of sarcoma from pure carcinoma, based on evidence of identical allelic losses, shared by epithelial and mesenchymal components [32].

Ultrastructural analyses in LCS cases have also demonstrated the presence of tonofibrils and desmosomes, that are characteristic structures of epithelial cells, not only in the epithelial component but also in the sarcomatous one, suggesting generation of the sarcomatous component from the carcinomatous one [54]. For these reasons, the current perceptions of EMT are based on this final alteration model.

EMT is a process by which epithelial cells lose their cell polarity and cell-to-cell adhesion, gain migratory/motility and invasive properties, reorganize cytoskeletal components and become mesenchymal stem cells. All those alterations result in decreased expression of epithelial cytokeratins, decreased expression of cell-to-cell adhesion proteins (E-cadherin and plakoglobin), and increased expression of vimentin, smooth-muscle actin, and fibronectin [56-58].

Epithelial cells are formed of cells with apical-basolateral polarity, connected to each other by lateral adherens junctions constituted of a complex of E-cadherin, several types of catenins, and actin structures, and anchored to the basement membrane across integrins [56,57]. These adhesive structures and continued expression of adhesion molecules prevent the epithelial cells from undergoing shape, polarity, and motility alterations [57]. On the other hand, mesenchymal cells are more loosely organized and are not typically in contact with the basal membrane as they form weak, disorganized adhesions to neighboring cells and exhibit spindle-like morphology with front-to-back polarity. In contrast to cytokeratin-rich filaments observed in epithelial tissues, mesenchymal cells are characterized by vimentin and are able to show independent motility and invasion through the basement membrane into surrounding tissue due to extra cellular matrix-degrading enzymes secretion [57].

EMT starts with the disconnection of epithelial cells from connecting junctions due to suppression of transcription genes that encode adherens and tight junctions. This alteration results in cell polarity loss and internalization of E-cadherin, targeting it for degradation, and finally leads to cytoskeletal remodeling that in turn results in cell detachment, and metalloprotease activation

promotes migration of those now mesenchymal-type cells [56].

Even though EMT is a necessary procedure during development and morphogenesis, is usually maintained in a silent condition in adults. However, EMT inducers can be abnormally activated during tumor progression and invasion [56,59]. EMT molecular explanation in carcinogenesis has revealed dysregulation in cell-signaling pathways with significant 'cross talk' among these complex pathways [57,60].

Several EMT induction signaling pathways were examined in 22 cases of LCS cases. High nuclear activity in the transcription factor c-Jun was observed along with continuous overexpression of vimentin and fascin, suggesting that EMT spread in carcinosarcomas may be through the c-Jun/ vimentin signaling pathway [61].

### Role of mutations in LCS pathogenesis

The mutational characteristics of LCS are difficult to determine because it is relatively rare compared to other more common histological types. However, molecular analysis of LCS is an important step for better understanding the molecular basis and potential treatment options for this tumor. Immunohistochemical and molecular analyses in LCS cases identified mutations of TP53, but not of KRAS or beta-catenin [20,21]. In addition, some gene mutations, such as TP53 mutation, commonly presented in carcinosarcoma, may assist in diagnosis [7,12].

Mutations of EGFR, MDM2 or CDK4 have not yet been investigated in this malignancy. Cytogenetic aberrations include allelic gains at 1q,3q,5p, 8q,12p, and losses at 3q, 5q, 17p [21]. In-frame deletions at exon 19 in the EGFR gene in both the carcinomatous component and the sarcomatous component have been detected in resected LCS specimens, indicating the potential to identify oncogenic driver mutations for targeting in LCS tumors [62].

Previous research demonstrated that VEGF, but not c-KIT, epidermal growth factor receptor (EGFR), or human epidermal growth factor receptor 2 (HER-2), was strongly expressed in both the carcinomatous component and the sarcomatous component in 30 cases of uterine carcinosarcoma, but not in LCS [63].

Blastomatoid LCS, however, displayed several more imbalances that have not yet been described for LCS. The high number of chromosomal imbalances indicates a high degree of chromosomal instability and tumor progression in the blastomatoid variant of carcinosarcoma. Furthermore, the observed imbalances may be of help in the differential diagnosis, in particular if +1q, +8q, and -5q are detected [64].

The developmental origin of both tumor components is unclear and an origin from two or more stem cells (multiclonal hypothesis) or an origin from a single multipotent stem cell that differentiates into separate epithelial and mesenchymal directions (monoclonal hypothesis) seems possible [55]. Previous analyses in LCS

cases [32], biphasic lung blastoma [65], and carcinosarcomas of other localizations [55] provide evidence that the epithelial and mesenchymal component of these biphasic tumors harbor a different morphology, but are monoclonal in origin.

Over-expression of MDM2 has previously been observed in 83% of biphasic lung blastomas, but it has so far not been studied in LCSs [66]. It has also been found that similar to lung blastoma, LCS may harbor MDM2 and lack EGFR mutations, however further research is required [64]. Therefore, presence of TP53, MDM2, and lack of KRAS and EGFR mutations may not be helpful in the differential diagnosis of both tumors. Only the presence or absence of beta-catenin mutations will serve as a useful diagnostic tool in certain cases [64]. The mutational characteristics of LCS are difficult to determine because it is relatively rare compared to other more common histological types.

### Conclusions

Lung carcinosarcoma is a rare biphasic lung tumor that presents either as a polypoid lesion involving the endobronchial tree or a solid mass involving the peripheral lung parenchyma. It is important to identify the epithelial and mesenchymal components to make the diagnosis. Histopathologic examination and immunohistochemical staining can help to distinguish it from other carcinomatous and sarcomatous neoplasms. Carcinosarcomas of the lung are aggressive cancers with a poor prognosis. The histological and immunohistochemical characteristics are very different from those of non-small cell lung carcinoma. Due to its rare occurrence and histological heterogeneity, the management of lung carcinosarcoma is a therapeutic challenge and remains highly individualized.

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