Comprehensive review of fetal adenocarcinoma of the lung

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Abstract: Fetal adenocarcinoma of the lung (FLAC) is a rare tumor. It accounts for ~0.1%–0.5% of all pulmonary neoplasms. Due to its rarity, much of the world literature regarding FLAC comes from case reports and case series. FLAC is an adenocarcinoma resembling developing fetal lung in its pseudoglandular stage (8–16 weeks of gestation). It is distinguishable from pulmonary blastoma (PB) because it lacks the mesenchymal component which is a hallmark finding in PB. Due to differences in histopathology and clinical course, FLAC has been further categorized into low-grade (L-FLAC) and high-grade (H-FLAC) forms. L-FLAC displays low nuclear atypia and prominent morule formation and has a pure pattern. H-FLAC typically presents with at least 50% fetal morphology, and is often associated with other conventional types of lung adenocarcinoma. FLAC expresses neuroendocrine markers and thyroid transcription factor 1 in most cases. L-FLAC has an aberrant nuclear/cytoplasmic expression of β-catenin and presents mutations in this gene. H-FLAC overexpresses p53. These tumors have a very low frequency of mutations in KRAS and EGFR; it is thought that they are different from a molecular point of view to conventional lung adenocarcinomas. Approximately 25%–40% of patients are asymptomatic at presentation; most of them are incidental findings on chest radiographs. H-FLAC is more common in elderly male patients, with a heavy smoking history. L-FLAC tends to occur in young females. Patients with L-FLAC are usually diagnosed with stage I–II disease, while patients with H-FLAC usually present with a more advanced-stage disease. Poor prognostic factors for FLAC are thoracic lymphadenopathy, metastases at diagnosis, and tumor recurrence; however, the 10-year survival for FLAC is estimated at 75%.

Keywords: lung cancer, fetal adenocarcinoma, outcomes, chemotherapy, radiotherapy, L-FLAC, H-FLAC, p53

Introduction

Fetal adenocarcinoma is a rare type of lung neoplasia. It accounts for ~0.1%–0.5% of all pulmonary neoplasms.¹ This tumor was first described by WG Barnard in 1945 and 1952, as a biphasic tumor of the lung comprising an epithelial component surrounded by mesenchymal stroma that resembled the fetal lung, hence naming it “embryoma of the lung.”⁴,⁵ In 1961, Spencer introduced the term pulmonary blastoma (PB) after studying additional cases.⁶ Later on, several authors reported other epithelial lung tumors that shared histological characteristics of the epithelial component present in PB, but lacked the mesenchymal component.⁷ In 1984, Kodama et al introduced the phrase “well differentiated fetal adenocarcinoma of the lung” (FLAC) to categorize these tumors.⁸ Finally, in 1999 the World Health Organization (WHO) classified this tumor as a variant of lung adenocarcinoma and it is now known as FLAC. The

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DOI: http://dx.doi.org/10.2147/LCTT.S137410
Running head recto: Fetal adenocarcinoma of the lung
Running head verso: Ricaurte et al
Volume: 9
Year: 2018
Article Designation: REVIEW
Journal name: Lung Cancer: Targets and Therapy

This article was published in the following Dove Press journal:
Lung Cancer: Targets and Therapy

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biphasic tumor is now part of the sarcomatoid carcinomas category and termed PB. Today, FLAC is recognized as a very uncommon lung adenocarcinoma with different pathogenesis, clinical manifestations, histopathology, and prognosis than PB.9–11 Much of the world literature regarding FLAC comes from case reports and case series. This review will describe the histopathological findings of this tumor, the genomics, diagnosis, and clinical characteristics, treatment, and outcomes. Surgical resection is the standard treatment, although adjuvant therapy with radiotherapy and chemotherapy has been reported.

Pathology
FLAC is an adenocarcinoma resembling developing fetal lung in its pseudoglandular stage (8–16 weeks of gestation).12–14 The tumor is usually solitary, well demarcated, and peripherally located although endobronchial involvement has been described.12,15–17 FLAC comprises complex, branch forming tubular glands lined by glycogen-rich, non-ciliated columnar or cuboidal cells. The cells have clear cytoplasm; large vesicular nuclei are seen in addition to supranuclear or subnuclear vacuoles. The malignant glands are densely packed and situated within loose to moderate cellular fibroblastic stroma. There is a morphologic resemblance to early secretory endometrium.12,14,16–20 Due to differences in histopathology and clinical course, FLAC has been further categorized into low-grade (L-FLAC) and high-grade (H-FLAC) forms.11,14

A study that screened 920 adenocarcinomas calculated the prevalence of FLAC to be 0.87%; among these 0.32% were L-FLAC and 0.54% were H-FLAC.18

L-FLAC displays low nuclear atypia and prominent morule formation (Figure 1A). The stroma is typically loose fibromyxoid tissue with spindle cells.12,14,18,21 L-FLAC is pure in pattern.12 In contrast, H-FLAC presents typically with at least 50% fetal morphology, and is often associated with other conventional types of lung adenocarcinoma (lepidic, papillary, acinar, micropapillary, and solid patterns). Although not recognized in the last WHO classification, a hepatoid pattern defined as a solid to trabecular growth of tumor cells with eosinophilic cytoplasm and clear cell component has also been described.14,18,22,23 According to WHO, H-FLAC diagnosis is rendered when the fetal histology is predominant. Additionally, these high-grade tumors have prominent nuclear atypia, prominent nucleoli, and frequent mitosis, in addition to lacking morule formation (Figure 1B).12,14,18,21,23 Currently, L-FLAC and H-FLAC are recognized by the WHO classification under the name of FLAC; nevertheless, some authors question whether H-FLAC is a distinct variant of lung cancer, which can present as a biphasic tumor or as pure fetal H-FLAC.18,23

The histopathological and immunohistochemical characteristics of L-FLAC and H-FLAC are summarized in Table 1. These two categories of FLAC also show differences in their immunohistochemical profile. Both L-FLAC and H-FLAC show positivity for neuroendocrine markers

![Figure 1](https://www.dovepress.com/)

**Figure 1** Morphological characteristics of fetal lung adenocarcinomas.

**Notes:** (A) Histology and immunophenotype of L-FLAC, which consists of complex glandular structures lined with glycogen-rich columnar cells, with low nuclear atypia, and morule formation. (B) H-FLAC exhibits the absence of morules, broad areas of necrosis, and complex acinar glands that consist of columnar tumor cells with supranuclear or subnuclear cytoplasmic clearing, large vesicular nuclei, prominent nucleoli.

**Abbreviations:** L-FLAC, low-grade fetal adenocarcinoma of the lung; H-FLAC, high-grade fetal adenocarcinoma of the lung; APC, adenomatous polyposis coli; ERβ, estrogen receptor β.
(chromogranin A and synaptophysin). Initially, positivity was thought to be more prominent in L-FLAC compared to H-FLAC; however, recent studies have shown that the grade of positivity of neuroendocrine markers in H-FLAC is dependent on the percentage of the fetal lung-like component present in the tumor.21,23 A similar behavior has been described with thyroid transcription factor 1 expression in H-FLAC.14 Additionally, L-FLAC has shown an aberrant nuclear/cyttoplasmic expression of β-catenin, a characteristic which is more prominent in the morular component of the tumor with no p53 overexpression. In contrast, β-catenin expression in H-FLAC is usually membranous and these tumors commonly overexpress p53, resembling traditional lung adenocarcinoma.18,24–29 Interestingly, PB shares part of the immunohistochemical profile of both categories of FLAC, since it has aberrant nuclear/cyttoplasmic β-catenin staining, more prominently in the epithelial compartment and also overexpresses p53.26,28–30 Alfafetoprotein (AFP), glypican 3, and SALL-4 are also expressed in H-FLAC, with a more prominent expression profile in the non-fetal lung-like component compared to the fetal lung-like component.23

### Genomics

Multiple molecular studies have reported very low rates of mutations in KRAS, EGFR, and PIK3CA in FLAC. A mutational analysis performed in a Chinese population identified an L858R point mutation in EGFR in a H-FLAC case and a T790M EGFR mutation in a L-FLAC case. The remaining cases had wild-type EGFR and harbored no other mutations in KRAS, PIK3CA, or BRAF.15 Another study identified an exon 19 deletion and the L858R point mutation of EGFR in one and two cases, respectively, of H-FLAC. E545A point mutation of PIK3CA was also detected in another H-FLAC case. No mutations on KRAS or BRAF were identified in this study.14 Morita et al23 reported one case of H-FLAC with an L858R mutation of EGFR and another showed a KRAS mutation in either codon 12 or 13. The remaining cases tested presented wild-type EGFR and KRAS. Conventional lung adenocarcinoma has a mutation frequency of 32%–64% for EGFR and 13% for KRAS.31–36

Given the high mutation frequency for these genes in lung adenocarcinoma in comparison to the low frequency seen in FLAC, several authors have suggested that these tumors may have distinctive molecular features and, because of this, the

| FLAC | L-FLAC | H-FLAC |
|------|--------|--------|
| Morphologic resemblance to the fetal lung in its pseudoglandular stage (8–16 weeks of gestation) and to early secretory endometrium | Low nuclear atypia and prominent morule formation | Prominent nuclear atypia, prominent nucleoli, and frequent mitosis |
| Complex, branch forming tubular glands lined by glycogen-rich, non-ciliated columnar or cuboidal cells. Cells have clear cytoplasm, large vesicular nuclei and supranuclear or subnuclear vacuoles | Pure pattern | Absent morule formation |
| Positivity for neuroendocrine markers (chromogranin A and synaptophysin) and TTF-1 | Aberrant nuclear/cyttoplasmic expression of β-catenin, more prominent in the morular component of the tumor | β-catenin expression is membranous |
| ERβ expression in these tumors mimics that of β-catenin | No p53 overexpression | AFP, GPC-3, and SALL-4 positivity more prominent in the non-fetal lung-like compartment |
| Low rates of mutations in KRAS, EGFR, and PIK3CA | Mutations in exon 3 of β-catenin. Mutations in these phosphorylation sites interfere with β-catenin degradation and cause it to accumulate in the nucleus and cytoplasm | No mutations in the β-catenin gene |
| Theoretical mutational inactivation of the APC or PTEN genes | Commonly nuclear p53 overexpression | p53 mutations |

**Notes:** Diagnosis is rendered when the fetal histology is predominant. Lepidic, papillary, acinar, micropapillary, solid patterns, and hepatoid. *Grade of positivity for neuroendocrine markers (chromogranin A and synaptophysin) for H-FLAC is dependent on the percentage of the fetal lung-like component present in the tumor. *No mutation present in β-catenin gene analyses but aberrant nuclear/cyttoplasmic expression of β-catenin seen in immunohistochemistry.

**Abbreviations:** FLAC, fetal adenocarcinoma of the lung; L-FLAC, low-grade FLAC; H-FLAC, high-grade FLAC; APC, adenomatous polyposis coli; ERβ, estrogen receptor β; AFP, alfafetoprotein; GPC-3, glypican 3; TTF-1, thyroid transcription factor 1.
recognition of FLAC as a separate histopathological entity has been debated.\textsuperscript{14,18,23}

Other molecular markers have also been implicated in the tumorigenesis of FLAC. The Wnt signaling pathway is important during embryogenesis, but when altered can lead to tumor formation. The Wnt signal causes $\beta$-catenin to translocate to the nucleus, which activates target genes that form complexes with lymphoid enhancer factor/T-cell factor. In normal circumstances, a multi-protein complex (that includes the adenomatous polyposis coli [APC] tumor suppressor protein) degrades excess $\beta$-catenin, hence keeping its levels regulated. Mutational inactivation of APC or direct mutations on $\beta$-catenin that inhibit its degradation will cause nuclear accumulation of the protein. This will lead to the activation of oncogenic target genes such as $c$-myc and cyclin D1.\textsuperscript{17} Since the final step in the altered Wnt pathway is the nuclear accumulation of $\beta$-catenin, alterations in this pathway may be detected with direct gene analysis and with immunohistochemistry.\textsuperscript{18} Studies have indicated that various morule forming tumors (L-FLAC, cribriform papillary thyroid carcinoma, adenoma of the gall bladder, adenoma of the colon, pancreatoblastoma) express $\beta$-catenin in an aberrant nuclear/cytoplasmic fashion in the morular formations of the tumor. Estrogen receptor $\beta$ (ER$\beta$) expression in these tumors mimics that of $\beta$-catenin. These findings suggest that the morular formation of these tumors is induced by the nuclear/cytoplasmic translocation of $\beta$-catenin and ER$\beta$; whether these two events are related warrants further investigation.\textsuperscript{24,30,39}

Initially, Nakatani et al followed by other authors described that L-FLAC consistently showed an aberrant nuclear/cytoplasmic $\beta$-catenin expression. H-FLAC displays a membranous expression of the protein.\textsuperscript{18,23,27} Afterwards, the L-FLAC with aberrant $\beta$-catenin expression was further characterized through gene sequencing. One study identified that all the L-FLAC had somatic missense mutations in exon 3 of $\beta$-catenin that resulted in the substitution of serine/threonine residues at GSK-3$\beta$ phosphorylation sites or at an amino acid flanking one of these residues.\textsuperscript{30} Other studies showed that most, but not all, L-FLAC had mutations in exon 3 of $\beta$-catenin. Mutations in these phosphorylation sites interfere with $\beta$-catenin degradation and cause it to accumulate in the nucleus and cytoplasm. The author in these studies suggested that the sporadic L-FLAC cases that lacked $\beta$-catenin mutations could have mutational inactivation of the APC or PTEN tumor suppressor genes; these genetic alterations also lead to an aberrant nuclear/cytoplasmic expression of $\beta$-catenin.\textsuperscript{25,26} All three studies demonstrated that H-FLAC harbored no mutations in the $\beta$-catenin gene. Interestingly, PB with morular formation in the epithelial component has aberrant nuclear/cytoplasmic expression of $\beta$-catenin and mutations in the $\beta$-catenin gene. PB without morules shows no alterations in the Wnt signaling pathway.\textsuperscript{25,26,30} $\beta$-catenin mutations have been reported to be rare in lung cancers; therefore, the high prevalence of these mutations in L-FLAC and PB with morules is a molecular hallmark and can become a diagnostic tool for these tumors.\textsuperscript{30,40–43}

Another molecular distinction between L-FLAC and H-FLAC is p53 mutations. Various studies have confirmed that H-FLAC demonstrates nuclear p53 overexpression; this pattern is not present in L-FLAC.\textsuperscript{18,23} Besides, Bodner and Koss identified that none of the L-FLAC cases contained p53 gene mutations, while all the PB they studied contained missense mutations in exons 5, 7, and 8. According to this study, p53 mutations are statistically more frequent in PB than in L-FLAC. The frequency of p53 gene mutations in PB and H-FLAC displays a similar frequency to conventional lung cancer; however, the lack of p53 mutations in L-FLAC cases suggests that favorable prognosis of this tumor may be related to a lesser number of molecular alterations.\textsuperscript{29} H-FLAC appears to be closer to conventional lung cancer; this supports the concept of discriminating between L-FLAC and H-FLAC.\textsuperscript{25}

Immunohistochemical and molecular analyses of p53 and $\beta$-catenin have demonstrated that the epithelial and mesenchymal components of PB with morules are monoclonal.\textsuperscript{29,30} This finding has led to two different theories about the histogenesis of L-FLAC, H-FLAC, and PB. One theory states that when PB develops, if a $\beta$-catenin mutation occurs early in the process it will lead to L-FLAC, as a one-sided epithelial outgrowth with morule formation. If this mutation does not occur, PB with no morule formation with an abundant mesenchymal component will develop. This would suggest that these entities can be organized into a spectrum where PB with morules is placed between L-FLAC and PB without morules.\textsuperscript{30} In contrast, Nakatani et al suggest that L-FLAC and H-FLAC are histogenetically different tumors. They speculate that the formation of a biphasic pattern present in PB is a later event that arises from either L-FLAC or H-FLAC through the process of epithelial and mesenchymal transition. According to the extent of epithelial–mesenchymal transition, the proportion of the epithelial and mesenchymal components may vary.\textsuperscript{26} Further studies are warranted to solve this debate. Genomic characteristics of L-FLAC and H-FLAC are summarized in Table 1.
Diagnosis and clinical characteristics
Approximately 25%–40% of patients present with asymptomatic disease; therefore, most of the cases are diagnosed through incidental findings on chest radiographs. Symptoms are related to bronchial irritation: chest pain is usually the main complaint, cough, hemoptysis, and dyspnea have also been reported. Pleural effusion is uncommon. On chest radiographs, FLAC is seen as a peripherally located well-demarcated lesion ranging from 2 to 12 cm with peripherally placed radiopacities. On computed tomography, these tumors show a heterogeneous appearance with enhancing whorls of soft tissue and non-enhancing areas of necrosis. Metastases to the same or opposite lung, or to the mediastinal compartment may also be apparent. Patients with H-FLAC may present with elevated serum levels of AFP. From a pathologic point of view, FLAC is difficult to diagnose preoperatively. Usually the diagnosis is made on postoperative specimens or at autopsy.

L-FLAC and H-FLAC also show different clinical characteristics. H-FLAC is more common in elderly male patients, around the sixth to seventh decade of life, with a heavy smoking history (93% smoking rate). The L-FLAC tends to occur in young females at the third to fourth decade of life. Patients with L-FLAC usually present with stage I–II disease, while patients with H-FLAC usually present with a more advanced-stage disease (stage III–IV) (Table 2).

Treatment
Due to the fact that PB and FLAC were categorized as two separate entities, studies that evaluate the treatment of this entity in an independent manner are limited. Surgical resection is the standard treatment for PB and FLAC. Radiotherapy and chemotherapy have been used as adjuvant therapy, although in some reports they have shown limited effect.

Table 2 Clinical characteristics in L-FLAC and H-FLAC

| L-FLAC                        | H-FLAC                        |
|-------------------------------|-------------------------------|
| Young females at the third to fourth decade of life | Elderly male patients, sixth to seventh decade of life |
| Present with stage I–II disease | Present with an advanced-stage disease (III–IV) |

| Treatment | Outcomes |
|-----------|----------|
| Standard: surgical resection | Poor prognostic factors for FLAC include thoracic lymphadenopathy, metastasis at diagnosis, and tumor recurrence. Size of the tumor has been debated. Koss et al showed that the median survival for patients with FLAC was not reached at 10 years while that of PB was of ~1 year. Larsen and Sorensen showed a median survival for FLAC of 34 months and for PB of 11 months. Several studies have shown 10-year survival for FLAC of 75% and for PB of 15%. The prognostic studies performed by Kodama et al and Koss et al showed differences in outcomes and survival within all of the FLAC cases. Nakatani et al suggested that the grade of malignancy and the tumor stage explained the differences in prognosis seen in these two studies, and further stated that even though it is not known whether the prognosis of H-FLAC is worse than the stage-matched conventional adenocarcinoma, L-FLAC probably has a better prognosis than the stage-matched conventional pulmonary adenocarcinoma. |

Table 3 Therapeutic approach for patients with FLAC

| Treatment                  | Poor prognostic factors |
|----------------------------|-------------------------|
| • Standard: surgical resection | • Thoracic lymphadenopathy |
| • Radiotherapy and chemotherapy used as adjuvant therapy have shown limited effect | • Metastases at diagnosis |
| • Tumor recurrence          |                         |

Abbreviations: L-FLAC, low-grade fetal adenocarcinoma of the lung; H-FLAC, high-grade fetal adenocarcinoma of the lung.
Disclosure
The authors report no conflicts of interest in this work.

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