# Ovine Pulmonary Adenocarcinoma – "Jaagsiekte"

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## Introduction

Ovine pulmonary adenocarcinoma (OPA) / Jaagsiekte (Afrikaans = driving sickness) is an infectious pulmonary neoplasia of small ruminants, principally of sheep and less commonly goats. Infection with the betaretrovirus, jaagsiekte sheep retrovirus (JSRV) leads to the formation of lung tumours manifesting as progressive respiratory failure, chronic weight loss and death or culling of the affected animals.

Jaagsiekte sheep retrovirus (JSRV) associated pulmonary adenocarcinoma is the most common pulmonary tumour of sheep and occurs in many countries across the globe, being endemic in South Africa. OPA is absent from Australia and New Zealand and has been eradicated from Iceland. This condition has devastating economic effects on the sheep industry not only due to the high mortality / culling rates but also due to the lack of a vaccine or reliable diagnostic tests for the early detection of the disease.

## The Virus

Jaagsiekte sheep retrovirus (JSRV) the causative agent of OPA is a betaretrovirus that has not yet been cultured in vitro, but the virus has been cloned and sequenced and classification of this virus is based on its genetic organisation and its structural proteins. Betaretroviruses occur as either exogenous or endogenous viruses with JSRV being exogenous and exclusively associated with OPA. There are a group of endogenous betaretroviruses that are closely genetically related to JSRV but do not cause OPA.

## Pathogenesis

The primary route of infection is via inhalation of infectious viral particles, with infection of young lambs via colostrum or milk being considered uncommon. Once within the lower respiratory tract, the virus infects type II alveolar epithelial cells and club cells where the oncogenic activity of the envelope glycoprotein (Env) of exogenous jaagsiekte sheep retrovirus (JSRV) promotes the neoplastic proliferation of these cells. In infected flocks, many lambs become infected at a very early age, but only a minority go on to develop OPA.

The incubation period is variable depending on the infection status of the flock. In previously unaffected flocks, shorter incubation periods of 6–8 months are documented, while in endemically affected flocks, there are longer incubation periods with clinical disease detected most in sheep over 2 years of age, with a peak occurrence at the age of 3–4 years. In exceptional cases, the disease occurs in animals as young as 2–3 months of age and experimentally infected newborn lambs can develop OPA in 3–4 weeks. The duration of the disease depends on the age of clinical onset. In lambs younger than six months developing clinical signs, progression is usually acute. In adult sheep, the disease progresses more slowly, with clinical signs extending over several weeks or months, until the animal dies. Animals coinfected with bacteria, other viruses or verminous pneumonia, usually show more severe disease.

Mortality rates to OPA are highest in the first years following the introduction of the virus into a flock reaching up to 50%. However, as the disease becomes endemic the mortality rate falls to around 1–5%. Longitudinal studies in flocks with endemic OPA have shown that approximately 30% of the sheep had histologically confirmed lesions and that 40% of these animals with OPA pathology were not clinically affected.

In JSRV infected flocks a high proportion of sheep may be infected but very few of them develop clinical signs. These seemingly healthy animals are important sources of infection and responsible for the spread of the disease because is difficult to identify infected sheep or the preclinical stages of the disease.

## Clinical Signs

Clinically, OPA is most frequently diagnosed in sheep (and rarely in goats) of 1–4 years of age with peak occurrence at 3-4 years, characterised by progressive respiratory embarrassment (dypnea), particularly after exercise (the severity of the signs reflects the extent of tumour development in the lungs), anorexia, weight loss, emaciation and typically one or more variably sized, generally well-circumscribed pulmonary adenocarcinomas visible on diagnostic imaging. Distinction from infection with small ruminant lentivirus (SRLV), which includes maedi/visna virus and caprine arthritis encephalitis virus, is challenging, due to the extensive clinical and pathological overlap of these conditions. Concurrent secondary bacterial pneumonia, particularly due to *Mannheimia haemolytica*, frequently masks the underlying neoplastic change. Cases with co-infections (SRLV, *Mannheimia haemolytica*) usually show more severe disease.

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As the pulmonary neoplasia progresses, the production of surfactant-containing fluid by the transformed type II alveolar epithelial cells and Clara cells increases, resulting in a prominent accumulation of fluid within the respiratory tract, giving rise to moist rales that are readily detected by auscultation. Raising the hindquarters and lowering the head of these affected sheep results in copious amounts of respiratory tract fluid being discharged from nostrils "wheelbarrow test".

Animals may remain afebrile and have a good appetite but still lose condition. Coughing and inappetence are uncommon in the initial stages of infection, but once apparent, weight loss is progressive, and the disease is terminal within weeks or months. Death is often the result of secondary bacterial pneumonia and the disease course is shortened in febrile animals with complicating bacterial infections. Pulmonary adenocarcinoma may be detected in animals from 2 months to 11 years of age.

**Gross Pathology**

On the gross pathology level, there are three lung lesion patterns which have been described with OPA in sheep namely:

- Classical
- Atypical
- Mixed

Classical OPA
Lungs fail to collapse on opening of the thorax, with affected lungs being enlarged and heavier than normal, due to extensive nodular and coalescing firm grey neoplastic nodules predominantly in **cranioventral lung lobes** of both lungs, although the extent of neoplasia on either side does vary. Neoplastic nodules are frequently large > 3 cm in diameter and associated with regions of pulmonary atelectasis.

On cut surface lungs exude voluminous quantities of clear fluid and the presence of frothy white fluid in the respiratory passages (bronchi, trachea) is a prominent feature. Concurrent pneumonia is often present and frequently abscesses are present in the adenomatous tissue.

Atypical OPA
Characterised by well-demarcated, solitary, or multiple aggregated neoplastic nodules, distributed primarily through the **caudal pulmonary lobes** on both sides of the lungs. These neoplastic foci in the atypical form of OPA are more solid than in the classical form, being hard white nodules that have a dry-cut surface and show clear demarcation from surrounding tissues. The presence of excess fluid is not a prominent feature and in general, lungs tend to exude less fluid than classical OPA.

Mixed OPA
Lesions of the mixed form of OPA are located mainly in the cranial pulmonary lobes, are multifocal to coalescing, flat to slightly raised, firm, white to grey, and variable in size (up to 3 cm in diameter), and have a dry cut surface. Fluid exudation is variable but not a prominent feature. Some of the **gross lesions are very small** (1–2 mm diameter), subtle, and poorly delineated.

OPA in most cases is restricted to the lungs, with intra- and extrathoracic metastasis to thoracic lymph nodes, liver, kidney, heart, skeletal muscle, digestive tract, spleen, skin, or adrenal glands is infrequent. The frequency of metastasis is considered lower in the atypical form compared to the classical and mixed forms. In experimental infection of lambs, regression of pulmonary neoplasms has been observed and thought to be the result of T lymphocyte cell-mediated immune responses.

Adult sheep, which on post-mortem examination appear to have died from acute pasteurellosis, should have their lungs examined carefully, as lesions of OPA may be masked by coexisting bronchopneumonia, verminous pneumonia, chronic progressive pneumonia (maedi-visna) or combinations of these.

**Histopathology**

Pulmonary histopathology is characterised by the proliferation of mainly type II pneumocytes with non-ciliated (Clara) and epithelial cells of the terminal bronchioli less frequently involved. Cuboidal and/or columnar tumour cells replace the normal squamous alveolar epithelial cells forming papillary fronds which project into the alveolar spaces. In chronic cases, extensive fibrosis may be observed and occasionally, nodules of loose connective tissue in a mucopolysaccharide substance (fibro-myxoid nodules) are noted. A striking feature is the accumulation of large numbers of alveolar macrophages in the alveoli adjacent to the neoplastic lesions. There is little correlation between pulmonary histopathology and the gross lesion pattern.

Additional pulmonary lesions which may be observed include varying degrees of broncho-, interstitial, bronchointerstitial, or granulomatous pneumonia; pulmonary abscessation, prominent perivascular, peribronchiolar and interstitial lymphoid infiltrates (in cases with concurrent maedi-visna) and verminous pneumonia.

Immunohistochemistry (IHC) enables the identification of infected cells expressing JSRV-related antigens and is detectable in the cytoplasm of alveolar and bronchiolar neoplastic cells where JSRV actively replicates. Positive labelling may also be observed in fibromyxoid nodules and, in early lesions, lymphoreticular cells. JSRV IHC remains a test of great diagnostic value in this disease.

**Diagnostic techniques**

As JSRV cannot currently be propagated in vitro, there are no reliable routine diagnostic laboratory methods for the antemortem diagnosis of OPA in individual animals, therefore flock history, clinical signs, postmortem lesions, histopathology and immunohistochemistry are the primary methods for the diagnosis of the disease. Although viral DNA and RNA can be detected by molecular methods, lambs become persistently infected by JSRV at an early age, and therefore, in an OPA-affected flock, most sheep are infected and will test positive. Serum antibodies to JSRV have not yet been detected in infected sheep and therefore, serological tests are not available as diagnostic tests.

JSRV-specific PCR consistently detects the virus in pulmonary fluids, tumour cells in nasal excretions, peripheral blood mononuclear cells, lymphoid tissues and in bronchoalveolar lavage samples. In pre-clinical OPA, measurable JSRV proteins are absent outside of the tumour and circulation of specific JSRV antibodies remains undetectable. Although JRSV is present in peri-bronchial lymphocytes, lung tissue, lymphoid organs, milk and colostrum in naturally infected sheep, in pre-clinical disease there are only low numbers of infected blood mononuclear cells (monocytes, B and T lymphocytes) and so insufficient JSRV nucleic acid in circulation to be detected by JSRV-specific PCR's on EDTA blood samples.

In flocks in which the disease is suspected, its presence must be confirmed, at least once, by histopathological examination of affected lung tissue. Collection of lung tissue into 10% buffered formalin from several affected sites and, where possible, from multiple affected animals. The rationale behind this sampling technique is that secondary bacterial pneumonia, which is frequently the cause of death, often masks the lesions (both macroscopic and microscopic) of the neoplastic changes.

Diagnostic imaging is sometimes applied as a screening technique to detect affected animals. Ultrasound can be used as a diagnostic flock test while, radiography and computed topography are currently more research-based.

**Control**

Disease control relies on strict biosecurity including quarantining, cleaning and disinfection of contaminated areas and equipment and removal of affected animals and their offspring as soon as the disease is detected. Reliable diagnostic tests to identify pre-clinically infected animals currently remain elusive.

Nevertheless, the development of detection techniques for improving the identification of early infected animals remains critical to the implementation of effective strategies for OPA eradication. The latest approach in the preclinical detection of OPA is the RT-PCR test on nasal swabs as a flock test, not for testing individual animals. However, the nasal swab RT-PCR has not yet been validated on pooled samples, and so large numbers of single animal RT-PCR's are required.

**FURTHER READING**


1. OIE (WOAH). Ovine Pulmonary Adenocarcinoma. *OIE Terrestrial Manual*. **2018**. Chapter 3.7.8.
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3. Ortin A. et al. Ovine pulmonary adenocarcinoma: a transmissible lung cancer of sheep, difficult to control. *Small Ruminant Research* 2019. https://doi.org/10.1016/j.smallrumres.2019.05.014.
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# MULTIPLE-CHOICE QUESTIONS

**QUESTION 1**

**Which of the following infectious agents is the course of ovine pulmonary adenocarcinoma?**
a. Endogenous Beta retrovirus
b. Maedi-Visna virus
c. Jaagsiekte sheep retrovirus
d. Small ruminant lentivirus
e. Caprine arthritis encephalitis virus

**QUESTION 2**

**What is the primary route of infection for ovine pulmonary adenocarcinoma?**
a. Ingestion
b. Inhalation
c. Vector-borne
d. Contaminated vaccines
e. Percutaneous

**QUESTION 3**

**Which of the following pulmonary cells undergo neoplastic transformation in cases of ovine pulmonary adenocarcinoma?**
a. Alveolar macrophages
b. Bronchial epithelial cells
c. Pleural mesothelial cells
d. Alveolar type II epithelial cells
e. Tracheal epithelial cells

**QUESTION 4**

**In flocks endemically infected with OPA, at what age does the peak occurrence of clinical disease occur?**
a. 3 to 4 years
b. One to 2 years
c. 6 months to one year
d. One to 2 months
e. 3 to 4 weeks

**QUESTION 5**

**Which of the following clinical signs are uncommon in the early stages of jaagsiekte?**
a. Exercise intolerance
b. Dyspnea
c. Body condition loss
d. Maintain appetite
e. Coughing

**QUESTION 6**

**On gross pathology which of the following is the standout and consistent feature of the classical form of OPA?**
a. Neoplasia predominantly affects the caudal lung lobe
b. On cut surfaces the lungs exude voluminous quantities of fluid
c. Gross neoplastic lesions are small being 1 to 2 mm in diameter
d. Concurrent pneumonia is uncommon
e. Tumor tissue is solid with no abscessation

**QUESTION 7**

**Which of the following cells do not express JRSV-related antigens on immunohistochemical staining of lung tissue sections?**
a. Alveolar epithelial cells
b. Terminal bronchial epithelial cells
c. Cells within the fibro-myxoid nodules
d. Lymphoreticular cells
e. Endothelial cells

**QUESTION 8**

**Which of the following diagnostic techniques is not currently employed in the diagnosis of jaagsiekte?**
a. Clinical examination
b. Antibody serology
c. Post-mortem lesions
d. Histopathology
e. Immunohistochemistry

**QUESTION 9**

**In flocks where OPA is suspected, which of the following diagnostic techniques are used to confirm the presence of the disease?**
a. Serology
b. Virus isolation
c. RT – PCR
d. Histopathology
e. Bacterial culture

**QUESTION 10**

**Which of the following would not be considered a sound biosecurity measure for the control of OPA?**
a. Quarantining new introductions
b. Cleaning and disinfection of contaminated areas
c. Cleaning and disinfection of equipment
d. Removal of clinically affected animals from the flock
e. Retaining the offspring of infected animals in the flock

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