The lung is the major organ of the respiratory system and used to inhale oxygen and remove the metabolic waste in the form of CO₂ from the body. Malfunctioning of the lungs can lead to serious complications and disturbs normal living conditions. Lung cancer is one of the severe conditions which have a relatively high mortality risk. Previously, it was the leading cause of death among men in more than 25 developed countries. Now it has become a worldwide cause of death among men. The most common cause of lung cancer is smoking, especially in men. Prognosis of this condition is still poor for malignant tumors. Read everything important about it here.
Bronchial carcinoma is defined as a malignant tumor of the lung, originating from the respiratory epithelium of the bronchi, bronchioles, and alveoli. In 90% of men and 80% of women, bronchial carcinoma appears associated with the inhalation of tobacco smoke. The terms bronchial carcinoma and lung carcinoma are non-uniform; this is because the English term lung carcinoma is increasingly preferred. The disease is also known as lung cancer.

Epidemiology, Risk Factors, and Etiology of Lung Cancer

Lung cancer proliferation

The incidence of lung cancer is over 200,000 new cases per year in the USA. It affects approximately 52% of men and 48% of women because of different smoking habits. However, the proportion of affected women is rising steadily. In Great Britain and Poland, lung cancer is already the most common terminal cancer in women. In both sexes, it is the second most common cancer disease.

The peak age of new cases is between 55 and 65 years. Studies prove that there is a greater incidence among individuals with low incomes and poor education.

Spread and causes of lung cancer

Lung cancer is rare in patients under 40, and its risk increases up to age 80. Major and minor risk factors related to lung cancer include:

- Cigarette smoking
- Passive smoking
- Occupational lung diseases
  - Exposure to asbestos
  - Exposure to radon gas
  - Exposure to uranium
  - Chromium and nickel refining
  - Welders, coal miners, tar refiners, roofers
- Secondary lung metastasis can occur from any primary tumor elsewhere in the
body (such as the liver)
Lung Cancer

SURVIVAL OF LUNG CANCER IS AMONGST THE LOWEST OF ALL CANCERS

Five year survival estimates among adults (aged 15-99 years) diagnosed with lung cancer between 2007 and 2011 and followed up to 2012

LUNG CANCER INCIDENCE AND MORTALITY RATES

Rate per 100,000 population


Men 48% Decrease in incidence rates
Women 105% Increase in incidence rates

Men 55% Decrease in mortality rates
Women 76% Increase in mortality rates

SMOKING IS STRONGLY ASSOCIATED WITH AN INCREASED RISK OF DEVELOPING LUNG CANCER

Percentage of males smoking cigarettes

2011 21%
1974 51%

26% of men smoked heavily (20 cigarettes per day) in 1974 compared to 6% in 2011

Percentage of females smoking cigarettes

2011 19%
1974 41%

13% of women smoked heavily (20 cigarettes per day) in 1974 compared to 4% in 2011

The narrowing gap in lung cancer incidence rates between males and females may be due to increasingly similar smoking habits between the two sexes.

www.ons.gov.uk

Image: “Lung cancer is the second most common cancer for both men and women in England, accounting for 14% of..."
Genetics is not associated with lung cancer etiology; it is rarely caused by inherited mutations. In the US, roughly 3400 non-smokers die from lung cancer every year. Most of them develop occupational lung diseases, such as coal or heavy metal miners or those who are exposed to substances like halogenated hydrocarbons or asbestos. Passive smokers unintentionally inhale smoke from their surroundings, which increases the risk.

Some benign etiologies for lung nodules and cancer include:

- Hamartomas
- Slow resolving local pneumonia
- Granulomas after previous chronic infections like TB, histoplasmosis, and coccidiomycosis

Image: “Correlation between smoking and lung cancer in US males, showing a 20-year time lag between increased smoking rates and increased incidence of lung cancer.” by Sakurambo. License: Public Domain

Etiology of Bronchial Carcinoma
Causes of bronchial carcinoma

The major risk factor for bronchial carcinoma is smoking; 95% of cancer patients are smokers or former smokers. The inhalation of carcinogens such as benzopyrene and tar, which are contained in cigarettes, results in DNA mutations.

There is a direct correlation between the number of consumed cigarettes and mortality from lung cancer. The risk is estimated in pack years. A pack-year is the year in which a patient smoked a pack of cigarettes daily (about 20 pieces). If a patient smokes two packs of cigarettes daily for 40 years, he has accumulated 80 pack years. At 40 pack-years, the risk of dying from bronchial carcinoma is 60 to 70 times higher than that of a non-smoker. The risk decreases continuously when the patient stops smoking.

Significant, but rare, causes of lung carcinoma are exposure to asbestos, radon, polycyclic hydrocarbons, nickel, chromates, and inorganic arsenic compounds. Also, lung scarring (for example after tuberculosis or silicosis) may lead to carcinoma.

Lung Cancer Pathogenesis

Bronchial carcinomas are of monoclonal origin. This means that a single cell mutates to a tumor cell and multiplies. The mutations are activated by dominant oncogenes or inactivated by tumor suppressor genes.
The dominant oncogenes need a mutation of only one allele. For example, point mutations of the K-ras gene or oncogenes of the myc family are present by the bronchial carcinoma. Both alleles have to be inactivated at tumor suppressor genes so that the mutation becomes effective. The most frequent mutations are mutations of the gene p53 and RB. If a tumor suppressor allele already mutated in the germline, bronchial carcinoma may have a familial disposition.

A significant feature of malignant cells of bronchial carcinomas is the expression of nicotine receptors. If nicotine binds onto a cancer cell, it inhibits apoptosis and promotes growth. Therefore, nicotine abstinence is an essential part of the therapy. Nevertheless, about 50% of patients with newly diagnosed lung carcinoma keep smoking.

Metastasis occurs in the regional lymph nodes, in the liver, adrenal glands, bones, and the brain.

**Signs and symptoms of lung cancer**

![Image: “Lung CA seen on CXR” by James Heilman, MD. License: CC BY-SA 3.0](image)

Usually, lung neoplasm is an *incidental finding on routine imaging studies*. Patients usually do not have severe symptoms. Tumor or cancerous cells can be anywhere in the lungs; they may be benign or malignant. Usually, symptoms develop when the tumor has reached an advanced stage (invasive/malignant stage).

Common symptoms include a *persistent cough, hemoptysis, shortness of breath, chest pain, decreased appetite, unexplained weight loss, and wheeze*. If the carcinoma has already spread, it can present with jaundice, bone pain, constipation, or bloody stools. *Breast*, colon, prostate, and bladder cancer can metastasize to the lungs. Lung cancer can metastasize to the bones, brain, liver, and adrenal glands.

**Types of Lung Cancer**

The classification of bronchial carcinoma is made in small-cell and non-small cell lung carcinomas. The distinction is made in terms of biological behavior, prognosis, and treatment options.
Lung cancer is a broad term used to describe tumors that arise in the respiratory system from the respiratory epithelium (bronchi, bronchioles, and alveoli). Broadly based on histology, we classify lung tumors into two types:

1. **Small cell lung cancer**
2. **Non-small cell lung cancer**
   - Adenocarcinoma
   - Squamous cell carcinoma
   - Large cell carcinoma
   - Bronchial carcinoid
   - Mesothelioma

**Adenocarcinoma** is the most common lung cancer, followed by squamous and small cell carcinoma and then large cell carcinoma.

Small cell (oat) cell carcinoma of the lung

![Image: “Histopathologic image of small cell carcinoma of the lung. CT-guided core needle biopsy. H & E stain.” by KGH. License: CC BY-SA 3.0](image)

Small cell carcinoma, also called oat cell cancer, is a **poorly differentiated neuroendocrine tumor** of the lungs. It is highly prevalent in smokers. Cancers that are more invasive and aggressive are more difficult to distinguish from the tissue in which they formed. This condition is **more common in males than in females**.

The tumor appears as a central nodule or mass with endo-bronchial growth on a chest X-ray. In some patients, the tumor cells start producing peptide hormones, such as adrenocorticotropic hormone (ACTH), arginine vasopressin (AVP), atrial natriuretic factor (ANF), and gastrin-releasing peptide (GRP), which can be a part of paraneoplastic syndromes. Tumor cells can spread to other sites and cause cervical or axillary lymphadenopathy. A histological examination will show islands of small, deeply basophilic cells with areas of necrosis. Kulchitsky cells appear as small dark blue cells.

Small cell lung cancer can complicate into the **paraneoplastic syndrome**, **Lambert-Eaton myasthenic syndrome**, **myelitis**, **encephalitis**, and **sub-acute cerebral degeneration**.

Non-small cell lung carcinoma

There are three subgroups of non-small cell lung carcinoma (NSCLC):
Adenocarcinoma accounts for about 30% and is particularly common in non-smokers. It often develops based on scar tissue, as given in the case of old tuberculosis. The carcinoma is usually peripheral and metastasizes early. The adenocarcinoma is often counted to the bronchiole-alveolar carcinoma.

Carcinoma of the glandular epithelium of the lungs is the most common type of lung cancer among non-smokers. Smoking is the major risk factor for this type of cancer as well. These tumors are located in the lung tissue peripheries. Histologically, cancer tissues have a papillary structure and broncho-alveolar pattern with glandular cells and cellular mucin (differentiated cells).

If the tumor contains poorly differentiated cells, they are arranged in a micropapillary pattern; this type of cancer has a worse prognosis. Bronchioloalveolar carcinoma is a subtype of adenocarcinoma that grows along the alveoli without invasion and appears as hazy infiltrates, similar to consolidation on the X-ray. It has a relatively better prognosis.

Squamous cell carcinoma accounts for approximately 40% of NSCLC tumors and is often centrally located. It is believed that chronic irritation of the mucous membrane leads to squamous epithelial dysplasia. It grows rather slowly and metastasizes late. Histologically, it is divided into the keratinizing and non-keratinizing types.

Squamous cell carcinoma of the lungs occurs after squamous dysplasia at the bronchus. They are identified as a hilar mass associated with the cavitation and located in the center of the chest X-ray. This type of tumor is associated with serum hypercalcemia due to PTH secretion, causing a paraneoplastic syndrome. Histological analysis shows keratin pearls and intercellular bridges. An infiltrating nest of tumor cells shows central necrosis, resulting in cavitation. This type of cancer is associated with
Large cell carcinoma is rare, accounting for 10% of cases. These carcinomas are likely dedifferentiated adeno- or squamous carcinoma.

This type of cancer also occurs in the peripheral lung tissue. Large cell cancer accounts for fewer than 10% of lung cancers. It is a poorly differentiated tumor, with sheets of large malignant cells, and is often associated with necrosis. Usually, the tumor cells are arranged in syncytial groups. Large cell carcinoma variants include basaloid carcinoma and lymphoepithelioma-like carcinoma related to EBV. The basaloid variant resembles a high-grade neuroendocrine tumor.

The rest are undifferentiated carcinomas, carcinoid tumors, and rare types of tumors.

Note: If there are no risk factors such as smoking, radon or asbestos exposure, metastases of squamous-cell carcinomas other localizations need to be considered in the differential diagnosis. Therefore, ear, nose, and throat carcinomas, as well as skin- and cervix-carcinomas, are possible.

Classification of Lung Cancer

Benign vs. malignant tumor

Lung cancer can be a benign, localized nodule or invasive, metastatic carcinoma. Various types of cancers involving the lungs are discussed below. Before that, we will discuss various clues indicating the benign or malignant nature of the tumor.

<table>
<thead>
<tr>
<th>Features</th>
<th>Mostly benign</th>
<th>Mostly malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth</td>
<td>Not growing</td>
<td>Rapid growth in serial chest scans</td>
</tr>
<tr>
<td>Size</td>
<td>Less than 1 cm</td>
<td>More than 1 cm</td>
</tr>
<tr>
<td>Calcification</td>
<td>Calcified</td>
<td>Non-calcified or speculated calcification</td>
</tr>
<tr>
<td>Smoking</td>
<td>Non-smoker</td>
<td>Smoker</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>PET scan</td>
<td>No glucose avid in PET scan</td>
<td>Glucose avid on PET scan</td>
</tr>
</tbody>
</table>
Localization of Bronchial Carcinoma

For treatment planning, the localization and spread of lung cancer are very important because these factors determine whether the tumor can be resected.

Hilar tumors are defined by endobronchial growth, which can even lead to bronchial stenosis. Beyond the stenosis arises emphysema and, with complete closure atelectasis, a tendency to develop retention-pneumonia.

Abscesses often arise from retention-pneumonia, which are difficult to treat with antibiotics. This lung carcinoma is the most common localization.

Peripheral nodules can disintegrate into tumor caverns, resulting in typical hemoptysis. If this cavern collapses, it becomes a malignant effusion or empyema.

A special form is Pancoast-syndrome. It is defined by a tumorous outbreak at the lung apex, which grows into the brachial plexus and the vessels.

The Stokes-collar is a tumorous outbreak into the upper mediastinum with the relocation of the superior vena cava. This results in upper inflow congestion.

The diffuse bronchial-carcinoma arises in alveolar carcinomas, often impressed radiographically as pneumonia.

Symptoms of lung cancer
Cough is one of the primary symptoms of lung cancer. In smokers, this cough is often trivialized because it is typical of COPD or the so-called smoker’s cough. Other possible symptoms are hemoptysis, dyspnea, bronchospasm, and circumscribed pneumonic processes with fever and a productive cough. When the tumor spreads to the pleura and ribs, the patients are suffering from chest pain.

Many patients also report B-symptoms with fever, night sweats, and weight loss of more than 10% of body weight in the last six months.

In the Pancoast syndrome, neuritic pain and vasomotor crises in hands and arms are of importance. If the tumor process is advanced, it can cause hoarseness by recurrent paresis and Horner syndrome, caused by paresis of the sympathetic nervous system.

If cancer has metastasized, metastases can cause discomfort. Brain metastases can cause neurological deficits and personality changes. Bone metastases can cause pain and pathological fractures. If the bone marrow is infiltrated, the patient will suffer from leukopenia and that results in infections.

Para-neoplastic syndromes are typical for lung cancer. They can occur initially and are clinically important. Small cell lung cancer can produce ACTH, leading to hypokalemia and Cushing’s syndrome. In addition, inadequate ADH formation with hyponatremia is possible and is called Schwartz-Bartter-syndrome. Lambert-Eaton-syndrome, which is also typical for small cell lung cancer, is characterized by myasthenia in the pelvic girdle.

Squamous cell carcinomas can cause the secretion of ectopic parathyroid hormone, which leads to hypercalcemia and hypophosphatemia. In contrast, clubbed fingers and periostitis occur in adenocarcinoma.

Regardless of the cancer sub-type, polymyositis, dermatomyositis, thrombophlebitis migrans, and nephrotic syndrome are possible.

A rare variant is Pierre-Marie-Bamberger-syndrome with pulmonary hypertrophic osteoarthropathy.

Investigations of Lung Cancer

Diagnosis of lung cancer

After a detailed history regarding chronic disease systems, a proper clinical examination of the whole body should be conducted to look for signs related to malignancy, especially swollen lymph nodes. Afterward, laboratory and radiology investigations are done.

Usually, lung cancer is diagnosed incidentally while treating some other disease or condition or during routine medical checkups. Cancer cells can be detected with sputum analysis. A lung tissue biopsy can be done using a needle biopsy or a bronchoscopy. Non-invasive investigations include CT scan, chest x-ray, MRI, and PET scan. Various antigens, called carcinogenic antigens, can be detected in the serum-like cytokeratin 19 fragments. Fluctuating parathyroid hormone levels are also checked in some types of lung cancers.

Usually, lung cancer is diagnosed at a later stage, which makes it difficult to treat when cancer has already metastasized to other organ systems. The advanced stage of lung carcinoma has a poor prognosis and a low five-year survival rate.
Early Detection and screening

Two screening studies are on-going in major parts of the world:

1. The National Lung Cancer Screening Trial (NLST), a prospective comparison of spiral CT and standard chest x-ray used in 50,000 current or former smokers
2. Study in Europe comparing CT scanning with the standard of care in subjects with a history of heavy smoking

Profile of a patient who should be referred for a chest X-ray to rule out cancer

Unexplained hemoptysis or any of the following persistent signs and symptoms lasting more than three weeks or fewer than three weeks in patients with risk factors for lung disease:

- Chest and/or shoulder pain
- Shortness of breath
- Weight loss
- Loss of appetite
- Abnormal chest signs
- Hoarseness
- Finger clubbing
- Cervical and/or supra-clavicle lymphadenopathy
- Persistent cough
- Features suggestive of metastatic lung disease (secondary cancer from the brain, bone, skin or liver)

Profile of a patient who should be referred urgently to a specialist

- Finger clubbing
- Severe weight loss
- SVC obstruction
- Persistent hemoptysis and are smoker or ex-smoker for many years; now of more than 40 years old age
- Smoker with cervical lymphadenopathy

Staging According to TNM-Classification

The staging is based on the TNM-classification after UICC (Union Internationale Contre le Cancer).

<table>
<thead>
<tr>
<th>TNM</th>
<th>Carcinoma in situ</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumor 3 cm or smaller in diameter, surrounded by lung or visceral pleura, distal to the main bronchus.</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt; 3 cm in diameter or involvement of the main bronchus 2 cm or more distal of the carina or associated with atelectasis to the hilus, but not the entire lung.</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invasion of the chest wall, diaphragm, mediastinal pleura or pericardium, or tumor in the main bronchus &lt; 2 cm distal to the carina or atelectasis of the entire lung.</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invasion into the mediastinum, heart, great vessels, esophagus, spinal or carina, or intralobular tumor nodules or malignant pleural effusion.</td>
</tr>
<tr>
<td>NO</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N2</td>
<td>Ipsilateral peribronchial or hilar lymph node involvement</td>
</tr>
<tr>
<td>N2</td>
<td>Ipsilateral mediastinal lymph nodes or subcarinal lymph node involvement</td>
</tr>
</tbody>
</table>
Non-small cell lung cancer is classified based on the TNM-classification in four staging groups, which decide the therapy.

In small cell lung carcinoma, there is a distinction in two stages. In the limited stage, the tumor is confined to one hemithorax, and the lymph node metastases are located in the radiation field. In the extensive stage, the tumor extension exceeds the limited stage. About 70% of small cell carcinomas are diagnosed in the extensive stage.

Note: The FEV1-value is crucial for determining resectability. The FEV1-setpoint is set for a planned pneumonectomy > 2.5 l, in lobectomy > 1.75 l and segmental resection > 1.5 l. If this setpoint is undershot, perfusion scintigraphy is mounted in order to assess the foreseeable postoperative FEV1-value.

Complications of Lung Cancer

Smoking leads to a neoplasm of the lungs, which is diagnosed in an advanced stage and is difficult to treat. The following major complications can occur in various types of lung cancers due to their advanced stage:

- Paraneoplastic syndrome
- Superior sulcus syndrome, leading to Horner’s syndrome
- Superior vena cava syndrome
- Compression of the recurrent laryngeal nerve can lead to hoarseness of voice
- Pleural effusion bloody
- Pericardial effusion often bloody
- Secondary metastasis, such as to the liver, bones, stomach, adrenal glands, and brain.

Lung cancer metastasis

- **Adrenals:** Roughly 50% of lung cancers metastasize to the adrenal glands
- **Liver:** 30–50% of lung cancers metastasize to the liver
- **Brain and bones:** 20% of lung cancers metastasize to the brain and bones

Symptoms secondary to regional metastases

- Esophageal compression, leading to dysphagia
- Laryngeal nerve paralysis, leading to hoarseness
- Symptomatic nerve paralysis, leading to Horner’s syndrome (enophthalmos, ptosis, miosis, and anhidrosis)
- Cervical/thoracic nerve invasion, leading to Pancoast syndrome
- Lymphatic obstruction, leading to pleural effusion
- Vascular obstruction, leading to SVC syndrome
- Pericardial/cardiac extension, leading to effusion, tamponade

Therapy of Lung Cancer
As with most cancers, treatments for lung cancer include **surgery, chemotherapy, and radiation**. The choice of treatment depends on the patient’s general health, the stage or extent of the disease, and the type of cancer. The type of treatment an individual patient receives may also be based on the results of genetic screening, which can identify mutations that render some lung cancers susceptible to specific drugs. Surgery involves:

- Segmentectomy
- Lobectomy
- Pneumonectomy

Radiation may be used alone or in conjunction with surgery—either before surgery to shrink tumors or following surgery to destroy small amounts of cancerous tissue.

**Non-small cell lung cancer**
Patients in the early stages and good general health are candidates for surgery. The tumor is resected by lobectomy or pneumonectomy, including resection of regional lymph nodes. In smokers, even solitary nodules without calcification should be resected due to the suspicion of carcinoma.

If the patient is not a candidate for surgery, radiation therapy with curative intent is indicated. The median survival time of irradiated non-operable patients is, however, less than a year. Subsequent chemotherapy prolongs life expectancy.

The chemotherapy is performed with cisplatin or carboplatin in combination with vinorelbine, gemcitabine, paclitaxel, docetaxel, or topotecan. Under chemotherapy, the average survival time of inoperable patients is 9 - 10 months.

Palliative treatment options for advanced tumors in bronchostenosis can be palliative radiation therapy and endoscopic laser therapy with stent placement. These treatments may reduce symptoms of dyspnea.

**Small cell lung cancer**

Small cell lung cancer is usually disseminated and inoperable at the time of diagnosis. Most patients (80%) respond well to chemotherapy, usually etoposide plus cisplatin or carboplatin. The median survival during chemotherapy is 40 - 70 weeks.

In cases with brain metastases, whole-brain radiotherapy is indicated. It is also prophylactically indicated after chemotherapy with complete remission. Only 1 - 5 % of patients are healed, mostly in the extensive stage of small cell lung cancer.

**Follow-up and aftercare**

The follow-up involves the physical examination, a chest X-ray in two planes, and abdominal ultrasonography. As a tumor marker, the neuron-specific enolase is used in small cell lung cancer. For non-small cell lung cancer, CEA and CYFRa21-1 are used.

**Prevention of Lung Cancer**

The probability of developing lung cancer can be greatly reduced by avoiding smoking. Smokers who quit also reduce their risk significantly. Testing for radon gas and avoiding exposure to coal products, asbestos, and other airborne carcinogens will also lower the risk.

**Special Types of Bronchial Carcinoma**

**Bronchioalveolar carcinoma**
Bronchioalveolar carcinoma accounts for about 3% of pulmonary malignancies and probably comes from type II pneumocytes of the alveoli. It is characterized by a slow growth along the alveolar and bronchial wall. Lymph nodes and the interstitial area are rarely affected. Women and men are diagnosed with equal frequency.

**Note:** There is no association between bronchioalveolar carcinoma and cigarette smoking. Bronchioalveolar carcinoma symptoms are diffusion disorder with hypoxia and restrictive ventilatory disorder by tumor growth. Some patients have large quantities of mucous sputum. The material extraction for cytological examination is carried out via bronchoscopy. Solitary lesions can be resected. The tumor is resistant to radio- and chemotherapy.

### Semimalignant and benign bronchial tumors

#### Bronchial adenomas

Bronchial adenomas are a collective term for histologically differentiated, emanating from the epithelium intrabronchial tumors that spread invasively and can metastasize. Approximately 80 – 90 % of all cases are carcinoids. They proceed from endocrine cells of the APUD-system of the bronchial mucosa. Occasionally, they produce the carcinoids ACTH or ADH, which lead to paraneoplastic syndromes. In the case of metastases to the liver, a typical carcinoid-syndrome can occur.

About 15 % are adenoid cystic tumors, also called cylindromas. These tumors are vascular; therefore, they bleed profusely if punctured.

The rarest form of bronchial adenoma is the mucoepidermoid tumor, accounting for 2 - 3% of cases. They develop from the salivary glands. These tumors grow slowly and rarely metastasize.

#### Benign bronchial tumors

The benign bronchial tumors include chondromas, hematomas, osteomas, fibromas, and hemangiomas. They emerge from mesenchymal tissue and grow mainly in the central bronchi, thereby leading to stridor and dyspnea with coughing. Semi-malignant and benign bronchial tumors can be cured by resection.

**Note:** Benign bronchial tumors are significant mainly in the demarcation of bronchial carcinoma.
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