Definition and Clinical Pathology of Esophageal Carcinoma

Squamous cell- and adenocarcinoma

Esophageal carcinoma describes a malignant tumor of the esophagus and is manifested most frequently as squamous cell- or adenocarcinoma.

A squamous cell carcinoma primarily grows endophytic-ulcerative. It thereby penetrates the esophageal wall to the outside and quickly infiltrates neighboring organs. A growth into the lumen of the esophagus is more likely to occur secondarily and at an advanced stage. A squamous cell carcinoma is found mostly in the area of one of three
physiological **bottlenecks**: esophagus entry (about 20 %), aortic arch/left main bronchus (approx. 35 %) and diaphragm constriction (about 45 %).

It is also common for an **adenocarcinoma** to grow into the esophageal lumen. Almost always it is located in the **lower third of the esophagus**.

![Image: “Comparison of dose distribution calculated using AAA and AXB dose calculation algorithms for mid-esophageal cancer,” by Openi. License: CC BY 4.0]

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**Epidemiology of Esophageal Carcinoma**

**Esophageal cancer is significantly more common in men**

In Europe, esophageal cancer is relatively rare with an **incidence** of 6/100,000 inhabitants. Compared to squamous cell carcinoma, adenocarcinoma is increasing in its frequency (about 60 %) in Western industrialized countries. Squamous cell carcinoma, however, is more represented in other countries such as China, Turkmenistan, South Africa and Japan. This underlines the assumption that dietary and environmental factors play an etiological role.

More men than women are affected (M : F = 5 : 1), and furthermore, a peak age around the 6th and 7th decade of life can be established.

**Etiology of Esophageal Carcinoma**

**Environmental influences and Barrett’s esophagus as etiological factors**

Triggering factors of squamous cell carcinoma are long-term consumption of highly concentrated alcohol and very hot foods and beverages, smoking, as well as **nitrosamines** and **aflatoxins**. Furthermore, scarring after burns or radiation, **achalasia**, **papillomaviruses** (HPV 16) and the **Plummer-Vinson syndrome** (in cases of chronic iron deficiency) can favor the formation of esophageal cancer. Vitamin deficiency and poor oral hygiene are also risk factors.

Adenocarcinoma, however, arises at the base of **Barrett’s esophagus** in over 50 % of the cases. Here, the esophageal squamous epithelium turns into **columnar epithelium**, in the course of chronic reflux esophagitis. Alcohol consumption and smoking are not considered abetting factors here!
Note: Esophageal adenocarcinoma usually arises in the course of a Barrett's esophagus!

Symptoms of Esophageal Carcinoma

Dysphagia and B-symptoms

Esophageal tumors are often noticed late, as they display rather nonspecific symptoms:

- **Dysphagia**: In patients > 45 years, esophageal carcinoma is the most likely cause of progressive dysphagia!
- Retrosternal pain, possibly radiating to the back.
- **Regurgitation**.
- **Hiccoughs** in case of infiltration of the vagus nerve.
- Hoarseness in case of infiltration of the recurrent laryngeal nerve.
- **Hematemesis** (vomiting blood).
- **Cough and aspiration pneumonia** in case of esophageal bronchial fistula.

Accompanying **B-symptoms** (weight loss, night sweats and fever) may occur.

Note: Dysphagia only occurs at luminal narrowing of more than 60 %, which often occurs at very late stage!

Metastasis

Due to the lack of esophageal serosa coating, esophagus carcinoma metastasizes into adjacent organs and structures early on **per continuitatem**. For the same reason, the carcinoma also quickly spreads **lymphogenously** into regional, nuchal, cervical and celiac lymph nodes. **Hematogenic metastasis** into the liver, lungs and bones, however, occurs later and most patients don’t experience it anymore.

Differential Diagnosis of Esophageal Carcinoma

In terms of differential diagnosis, **esophageal diverticula**, stenoses after burns or inflammation, a cardia of the stomach or **benign esophagus tumors** have to be taken into consideration. Benign tumors of the esophagus are rare and often asymptomatic. They can grow in an **intramural** or **intraluminal** manner. They are diagnosed via esophageal bolus swallow test, endoscopy and endoscopic ultrasonography. Small intraluminal tumors can usually be removed endoscopically with a **cautery snare** – larger ones are removed surgically.

Classification and Staging of Esophageal Carcinoma
Classification of the tumor stages is carried out according to general **TNM-classification**: 

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>TIS</td>
<td>Carcinoma in situ (basement membrane is not crossed)</td>
</tr>
<tr>
<td>T1a</td>
<td>Infiltration of the lamina propria</td>
</tr>
<tr>
<td>T1b</td>
<td>Infiltration of the submucosa</td>
</tr>
<tr>
<td>T2</td>
<td>Infiltration of the muscularis propria</td>
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<tr>
<td>T3</td>
<td>Infiltration of the adventitia</td>
</tr>
<tr>
<td>T4a</td>
<td>Infiltration of neighboring structures (T4a: pleura, pericardium or diaphragm; T4b: other structures such as the aorta or vertebral bodies, etc.)</td>
</tr>
<tr>
<td>N0</td>
<td>Without regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>1 - 2 regional lymph node metastases</td>
</tr>
<tr>
<td>N2</td>
<td>3 - 6 regional lymph node metastases</td>
</tr>
<tr>
<td>N3</td>
<td>≥ 7 regional lymph node metastases</td>
</tr>
<tr>
<td>M0</td>
<td>No remote metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Remote metastasis (hematogenous or non-regional lymph node metastases)</td>
</tr>
</tbody>
</table>

Resulting from this, is the UICC (Union for International Cancer Control) specified staging:

<table>
<thead>
<tr>
<th>Stadium</th>
<th>TNM</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1, N0, M0</td>
</tr>
<tr>
<td>IB</td>
<td>T2, N0, M0</td>
</tr>
<tr>
<td>II</td>
<td>T3, N0, M0</td>
</tr>
<tr>
<td>IIA</td>
<td>Until T2, N1, M0</td>
</tr>
<tr>
<td>IIB</td>
<td>From T3, N1, M0</td>
</tr>
<tr>
<td>III</td>
<td>From N2, M0</td>
</tr>
<tr>
<td>IV</td>
<td>M1</td>
</tr>
</tbody>
</table>

**Diagnostics of Esophageal Carcinoma**

**Anamnesis as an indication of esophageal carcinoma**

Whenever a patient complains about **dysphagia**, esophageal cancer always has to be ruled out, especially in elderly patients. One should specifically ask about the above-described symptoms. Unfortunately, however, patients often only have little discomfort, even in advanced tumor stages.
Esophageal bolus swallow test

By using an esophageal bolus swallow test, asymmetries, contour changes, stenoses or dilatations can be identified. The location, extent and degree of functional limitation of the esophagus can also be judged.

Esophagoscopy with biopsies

A definitive diagnosis can only be made through histological results. For this purpose, an esophagoscopy is carried out and biopsies from at least ten suspect areas are removed. In case of a squamous cell carcinoma, the histological picture shows nests of atypical keratinocytes with lymphocytic infiltrates. Adenocarcinoma is typically presented by metaplastic glandular tissue, goblet cells and columnar epithelium (etiology: Barrett’s esophagus).

Staging of Esophageal Carcinoma

In order to assess the extent of the tumor, following investigations about the relevant issues are usually carried out:

- **Endosonography:** Depth of infiltration? Regional lymph node involvement?
- **CT and MRI:** Assessment of anatomical relationships, remote metastases?
- **PET/PET-CT:** Remote metastases (most sensitive detection method)?

- **Bone scintigraphy:** Bone metastases?

  In case of relevant suspicion also:

  - **Laryngo-/Bronchoscopy:** Infiltration of the airways?
Therapy of Esophageal Carcinoma

The stage of the esophageal carcinoma determines the treatment

**Early adenocarcinomas (T1a):** These are treated with endoscopic mucosal resection. The cure rate is very high. In the course of the intervention, a frozen section diagnosis is always carried out: If this shows that the tumor has already infiltrated the submucosa, a subtotal esophagectomy will be carried out.

**From TNM stage T1b to UICC stage IIA:** A subtotal esophagectomy with radical lymphadenectomy with curative intent (R0 resection) is carried out. The resected esophagus is replaced with a gastric pull-up (“gastric tube”) or colon interponate. It is a 2-cave-procedure (thoraco-abdominal access path) with high surgery mortality (about 5%). Among the postoperative complications are: anastomotic leakage, interponate necrosis, stenosis, bleeding, chylothorax (injury of the thoracic duct) and hoarseness (injury of the recurrent laryngeal nerve). Especially in case of adenocarcinoma, perioperative chemotherapy with 5-FU and cis-platinum increases the chance of survival.

**Stage IIB and III:** Downstaging using neoadjuvant chemoradiation (cisplatin, 5-FU) can be attempted in order to subsequently perform curative surgery.

In inoperable patients, or for squamous cell carcinoma in the area of the upper esophagus, sole curative radiation chemotherapy may be considered. However, adenocarcinomas do not respond to radiotherapy!

**Palliative: From T4 or M1** curative treatment is no longer possible. The aim of palliative care is to maintain the passage of food. This can be achieved through irradiation or laser therapy. In most cases, however, a metal stent has to be placed endoscopically. The timely use of a PEG tube (percutaneous endoscopic gastrostomy) usually prolongs survival time significantly, as many patients otherwise mostly succumb to complications of cancer cachexia.

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Image: “Rabbit esophageal tumor featured by barium meal and stent implant. (A) Normal rabbit esophagus. (B) Rabbit esophageal cancer. (C) Implantation of the stent. Arrow, tumor location,” by Openi. License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/)
Prognosis of Esophageal Carcinoma

Esophageal cancer carries a high mortality rate

The overall prognosis is poor. The 5-year survival rate of all patients is less than 10 %. Palliative patients usually survive less than a year, while the 5-year survival rate of R0-resected patients is approximately 40 %.

The problem is the late diagnosis: In 90 % of patients a locally advanced stage (at least T3, N1) is found.

Prevention of Esophageal Carcinoma

Esophageal cancer can be avoided

The above-mentioned risk factors (in particular alcohol consumption and smoking) should be avoided. Patients at increased risk (e.g., known Barrett’s esophagus) should regularly receive esophagoscopical check-ups.

Review Questions

The answers are below the references.

1. Which type of malignant tumor most likely arises based on a Barrett’s esophagus?
   A. Squamous cell carcinoma
   B. Non-small cell carcinoma
   C. GIST (gastrointestinal stromal tumor)
   D. Mesenchymal tumor
   E. Adenocarcinoma

2. Which of the following symptoms do not quite fit the symptoms and consequences of advanced esophageal cancer?
   A. Coughing and pneumonia
   B. Vomiting and weight loss
   C. Fever
   D. Elevated tumor marker chromogranin A
   E. Hoarseness

3. Until which UICC stage is esophageal cancer primarily surgically treatable with curative intent?
   A. Up to stage IA.
   B. Up to stage IIA.
   C. Up to stage III.
   D. Perioperative chemo radiotherapy is always performed, regardless of the stage.
   E. Neoadjuvant chemotherapy is always performed, regardless of the stage.
References


Correct answers: 1E, 2D, 3B

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