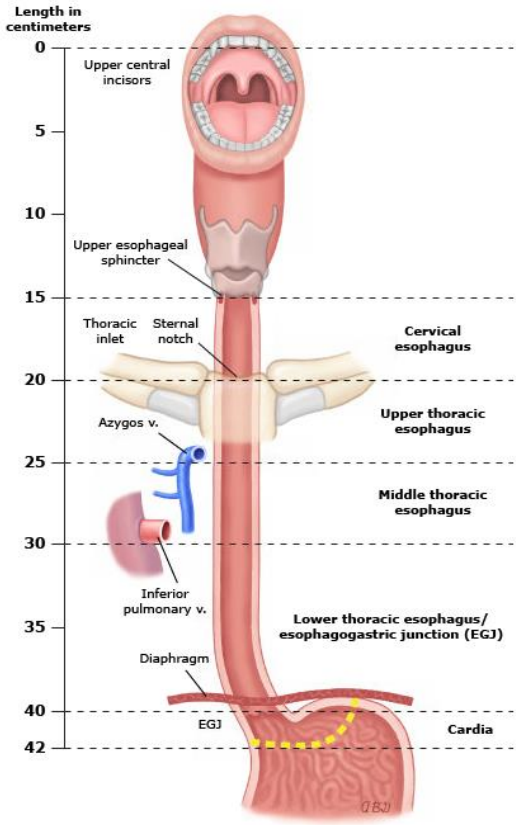
# ESOPHAGEAL CANCER

## General Overview




- 6th most common cause of death worldwide.
- Two histological types: squamous cell carcinoma (SCC) and adenocarcinoma (AC)
- SCC mostly located in the mid-esophagus while AC mostly located near the junction (GEJ)
- Worldwide SCC predominates, but in Western countries >60% AC.
- Risk factors: smoking, HPV and alcohol (SCC); Barrett, o besity and smoking (AC)
- Clinical symptoms: dysphagia and weight loss

## Staging (AJCC Version 8) and Prognosis

- PET-CT, endoscopy, (endoscopic ultrasound)
- Bronchoscopy indicated for tumors located at or > carina.
- Laryngoscopy is recommended of cervical SCC
- All patients should be checked for nutritional status (if needed jejunostomia)

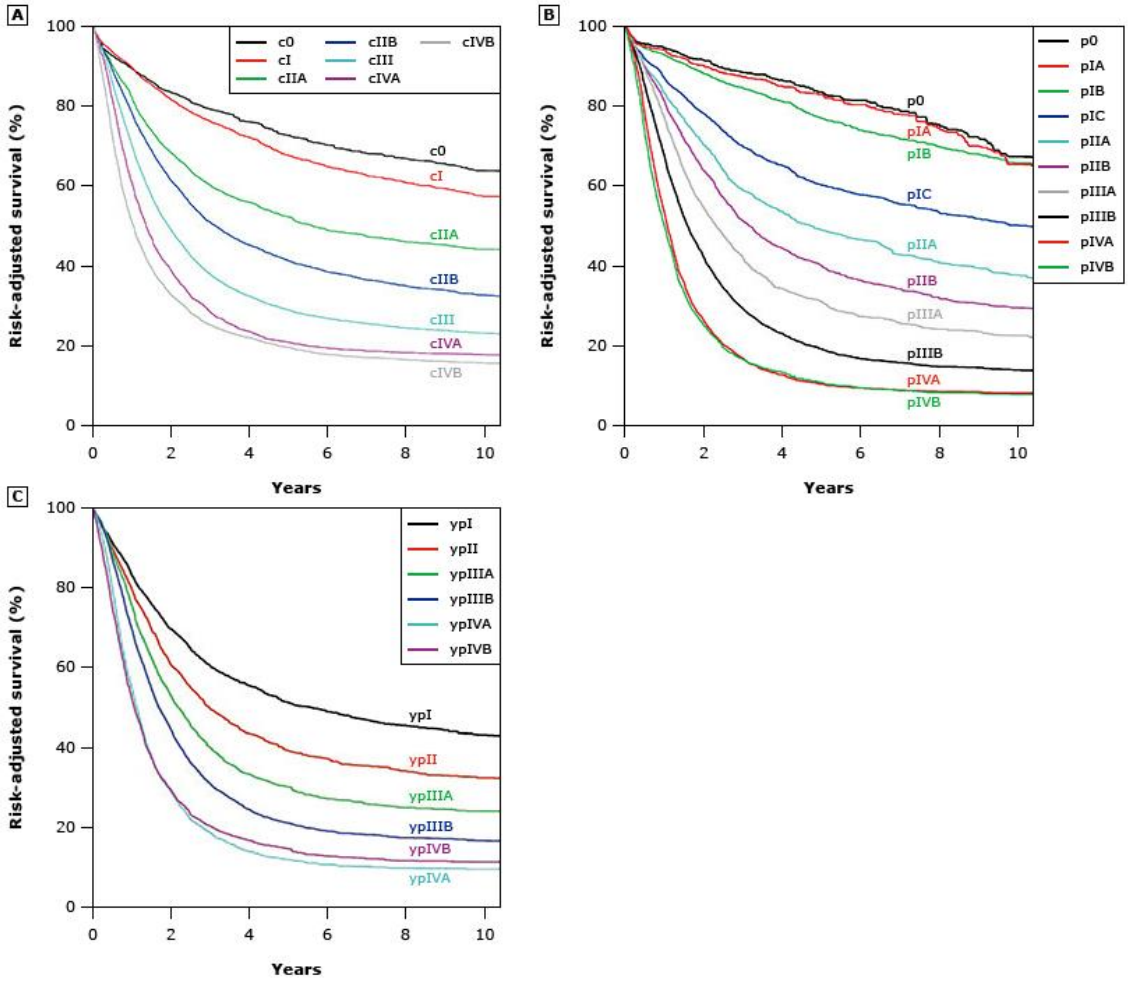
- Tumors involving the GEJ with the tumor epicenter no more than 2cm into the proximal stomach are staged as esophageal cancer while GEJ tumors with their epicenter >2cm into the proximal stomach as gastric cancer, as are all cardi cancers not involving the GEJ (even if <2cm of the GEJ)

- Location (position of the epicenter of the tumor):
  - Upper: cervical esophagus to lower border of azygous vein
  - Middle: lower border of azygos vein to lower border of inferior pulmonary vein
  - Lower: Lower border of inferior pulmonary vein to stomach, including GEJ

| Primary Tumor (T) | Regional Lymph Nodes (N) | Distant Metastasis (M) |
|---|---|---|
| **Tx: Primary tumor cannot be assessed**<br>**T0**: No evidence of primary tumor<br>**Tis**: high-grade dysplasia<br>**T1**: invasion lamina propria, muscularis mucosae(T1a) or submucosa (T1b)<br>**T2**: invasion muscularis propria<br>**T3**: invasion adventitia<br>**T4**: Tumor invades adjacent structures:<br>T4a: pleura, pericard, diaphgragm, perit.<br>T4b : aorta, vertebral body, airway | **Nx**: LN cannot be assessed<br>**N0**: no regional LN<br>**N1**: M+ in 1 or 2 regional LN<br>**N2**: M+ in 3 to 6 regional LN<br>**N3:** M+ in 7 or more regional LN | **M0**: no distant M+<br>**M1**: distant M+ |

Update: December 2024

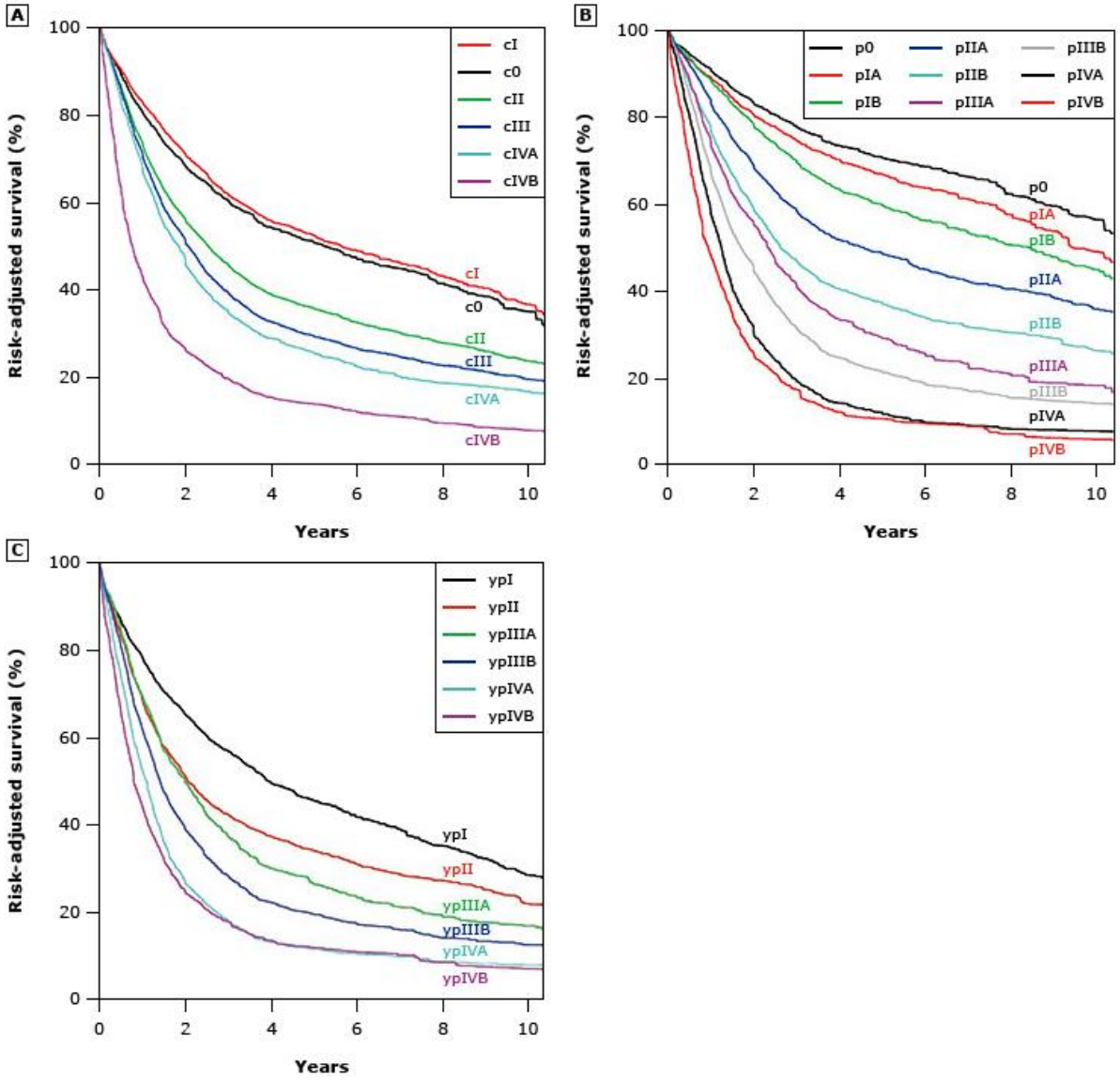
- Prognosis: risk adjusted survival after treatment decision for clinical (A), pathological (B) and posttreatment pathological staged AC of the esophagus and GEJ (C)




- Pathological stages posttreatment AC (ypTNM)

| ypT | ypN | M | Stage |
|---|---|---|---|
| T0-2 | N0 | 0 | I |
| T3 | N0 | 0 | II |
| T0-2 | N1 | 0 | IIIA |
| T3 | N1 | 0 | IIIB |
| T0-3 | N2 | 0 | IIIB |
| T4a | N0 | 0 | IIIB |
| T4a | N1-2 | 0 | IVA |
| T4a | NX | 0 | IVA |
| T4b | N0-2 | 0 | IVA |
| Any T | N3 | 0 | IVA |
| Any T | Any N | 1 | IVB |

- Prognosis: risk adjusted survival after treatment decision for clinical (A), pathological (B) and posttreatment pathological staged SCC (C)




- Pathological stages posttreatment SCC (ypTNM)

| ypT | ypN | M | Stage |
|---|---|---|---|
| T0-2 | N0 | 0 | I |
| T3 | N0 | 0 | II |
| T0-2 | N1 | 0 | IIIA |
| T3 | N1 | 0 | IIIB |
| T0-3 | N2 | 0 | IIIB |
| T4a | N0 | 0 | IIIB |
| T4a | N1-2 | 0 | IVA |
| T4a | NX | 0 | IVA |
| T4b | N0-2 | 0 | IVA |
| Any T | N3 | 0 | IVA |
| Any T | Any N | 1 | IVB |

Update: December 2024

## Treatment

- Management of carcinoma in the cervical esophagus is more closely related to SCC of the H&N and therefore definitive chemoradiotherapy (cisplatin 75 mg/m² w1 and w5, 2 cycles of infusional 5-FU 1000 mg/m² d1-4 weeks 1 and 5) (1) is preferred over surgery
- For patients with T3/4N0 and node-positive disease we recommend neoadjuvant therapy
    - Concurrent chemoradiotherapy for esophageal tumors (both SCC and AC)
    - Perioperative chemotherapy FLOT) for GEJ tumors (cfr gastric cancer) is an alternative
- Chemoradiotherapy schedule:
    - CROSS schedule: carboplatin + paclitaxel weekly (2)
    - Alternative: cisplatin + 5FU (cfr above)
- Postoperative therapy:
    - In case of no neo-adj therapy and pT3/4, N+ or bad prognostic factors (LV invasion, young patients, …): adjuvant chemotherapy (no validated schedule, eg. FOLFOX)
    - In case of residual disease after preoperative chemoRT: nivolumab for 1 year based on the checkmate 577 trial (3)
- Follow-up after surgery:
    - Every 3-4 months for the first 2y with imaging (preferably CT), followed by 6 monthly until 5 years.

- Metastatic disease
    - Many trials included both esophageal and gastric cancer regardless of histology and therefore general treatment such as chemotherapy regimens converged.
    - With molecular targeted and immunotherapy, therapies for SCC and AD have diverged
    - All AC should be tested for HER2 (IHC + ISH)
    - Al SCC + AC should be tested for MSI and PD-L1
    - **Squamous cell cancer**:
        - 1st line (4,5):
            - If CPS ≥10 or TPS ≥1 : chemo (platinum/5FU) + pembro or nivolumab
            - Preference for FOLFOX as chemotherapy
        - 2nd or later lines: Nivolumab, Taxanes or FOLFIRI

    - **Adenocarcinoma** :
        - 1st line (6-9):
            - HER2+: pembrolizumab + trastuzumab + 5FU + platinum
            - HER2- / CPS ≥10: chemo + pembrolizumab or nivolumab
            - HER2-/ CPS≥5: chemo + nivolumab
            - HER2-/CPS≥1: chemo + pembrolizumab
            - Preference for FOLFOX as platinum based chemotherapy
        - 2nd line (10-12):
            - MSI-H: pembrolizumab monotherapy
            - HER2+ (confirmed on repeated biopsy): trastuzumab deruxtecan, based on DESTINY Gastric01
            - HER2-: Paclitaxel + ramucirumab or ramucirumab monotherapy
        - Later lines: FOLFIRI, TAS102

- Pembrolizumab reimbursement Belgium:
  - 1st line HER2+ AC gastric or GEJ, CPS ≥ 1 in combination with trastuzumab, 5FU and platinum (in theory no reimbursement in combination with capecitabine or oxaliplatin)
  - 1st line HER2 neg. AC gastric or GEJ, CPS ≥ 1 in combination with platinum and 5-FU
  - 1st line HER2 neg. esoph / gastric / GEJ, CPS ≥10 in combination with platinum and 5FU
  - 2nd or later lines: MSI-H gastric

- Nivolumab reimbursement Belgium:
  - Adjuvant esophageal / GEJ after neo-adj chemoRT and residual disease (no pCR)
  - 2nd line monotherapy in SCC after platinum+5FU
  - 1st line SCC in combination with platinum/5FU if TPS≥1
  - 1st line HER2 negative esoph, gastric or GEJ, CPS≥5 in combination with platinum /5FU

- Trastuzumab deruxtecan reimbursement Belgium
  - HER2+ AC gastric or GEJ
  - Previously treated with trastuzumab
  - HER2+ ISH positive

## References


1) RTOG 85-01 (Herskovic trial): NEJM 1992;326(24):1593
2) CROSS trial: NEJM 2012 (van Hagen et al), Lancet onc 2014 (Shapiro), JCO 2021 (Eyck BM)
3) Checkmate 577 : NEJM 2021 (Kelly RJ et al)
4) CheckMate 648 : NEJM 2022 (Doki Y et al)
5) Keynote 590 : Lancet 2021 (Sun JM et al)
6) TOGA trial : Lancet 2010 (Bang YJ et al)
7) Janjigian YY et al Lancet Oncol 2020
8) Checkmate 649 : Lancet 2021 (Janjigian et al) Nature 2022 (Shitara K et al)
9) Keynote 859 : Lancet oncol 2023 (Rha SY et al)
10) DESTINY-Gastric01 : NEJM 2020 (Shitara K et al)
11) REGARD trial: Lancet 2014 (Fuchs CS et al)
12) RAINBOW trial: Lancet Oncol 2014 (Wilke H et al)


## What's new ?

- RATIONALE 302: tislelizumab versus chemo in ESCC 2nd line (JCO 2022 and ESMO open 2024)
- RATIONALE 306: chemo + /- tislelizumab as 1st line (Lancet oncol 2023, Xu et al)