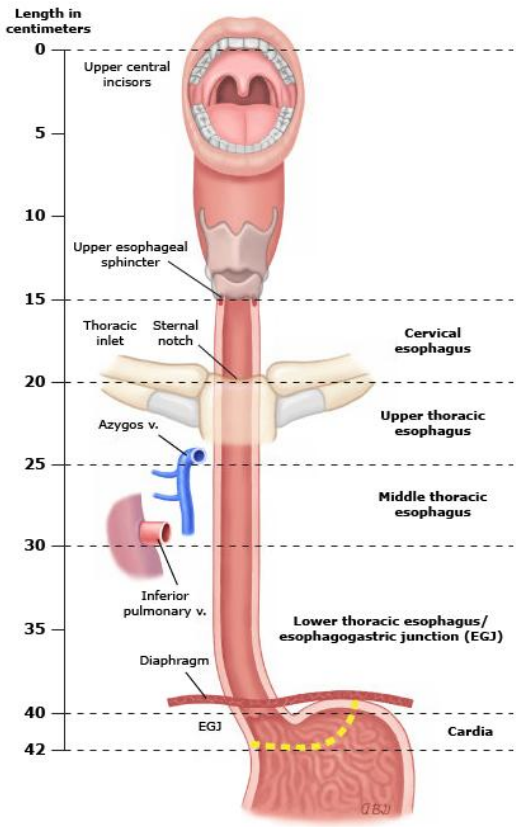
ESOPHAGEAL CANCER

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)

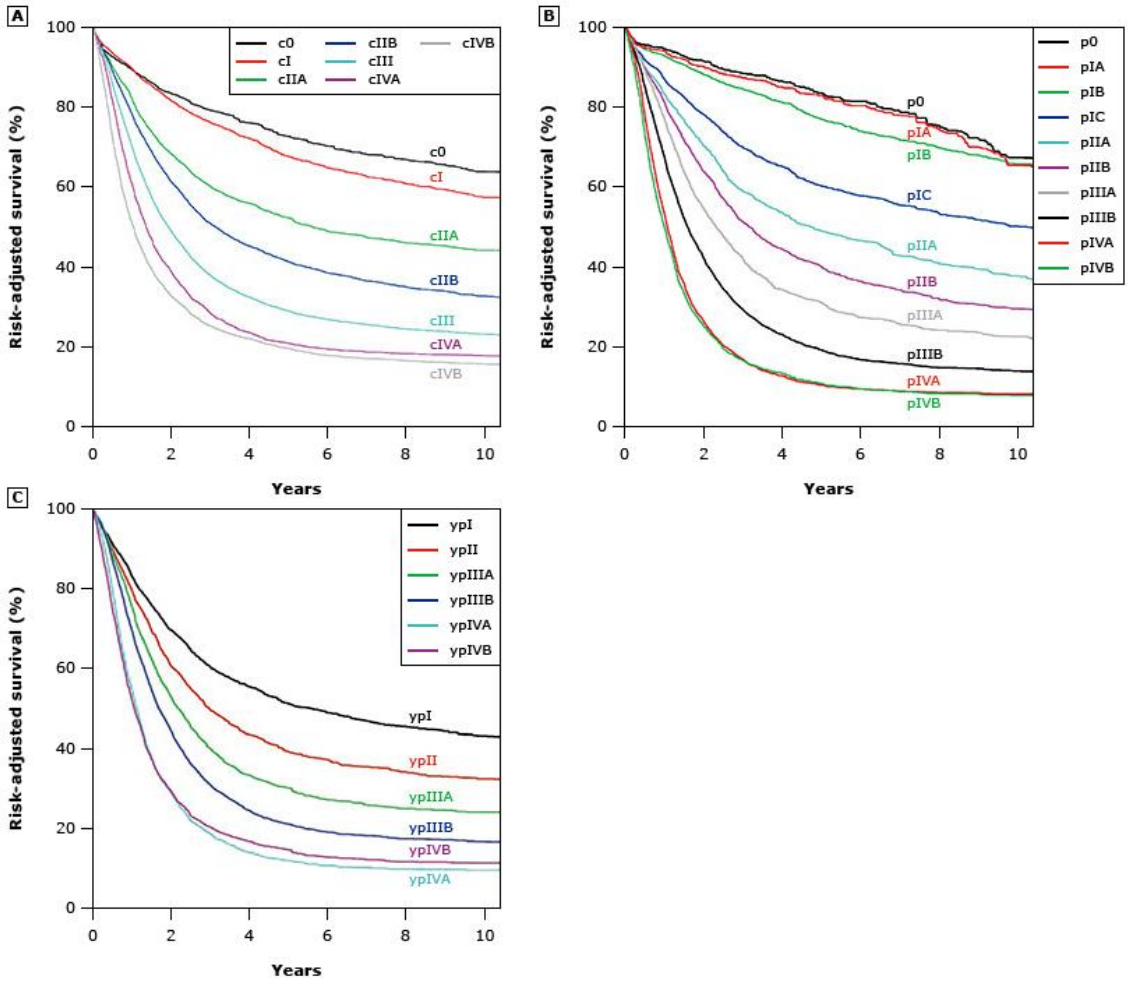
- Tumors involving the GEJ with the tumor epicenter no more than 2cm into the proximal stomach are staged as esophageal cancer while GEJ tumors with their epicenter >2cm into the proximal stomach as gastric cancer, as are all cardi cancers not involving the GEJ (even if <2cm of the GEJ)

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

Update: December 2025

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

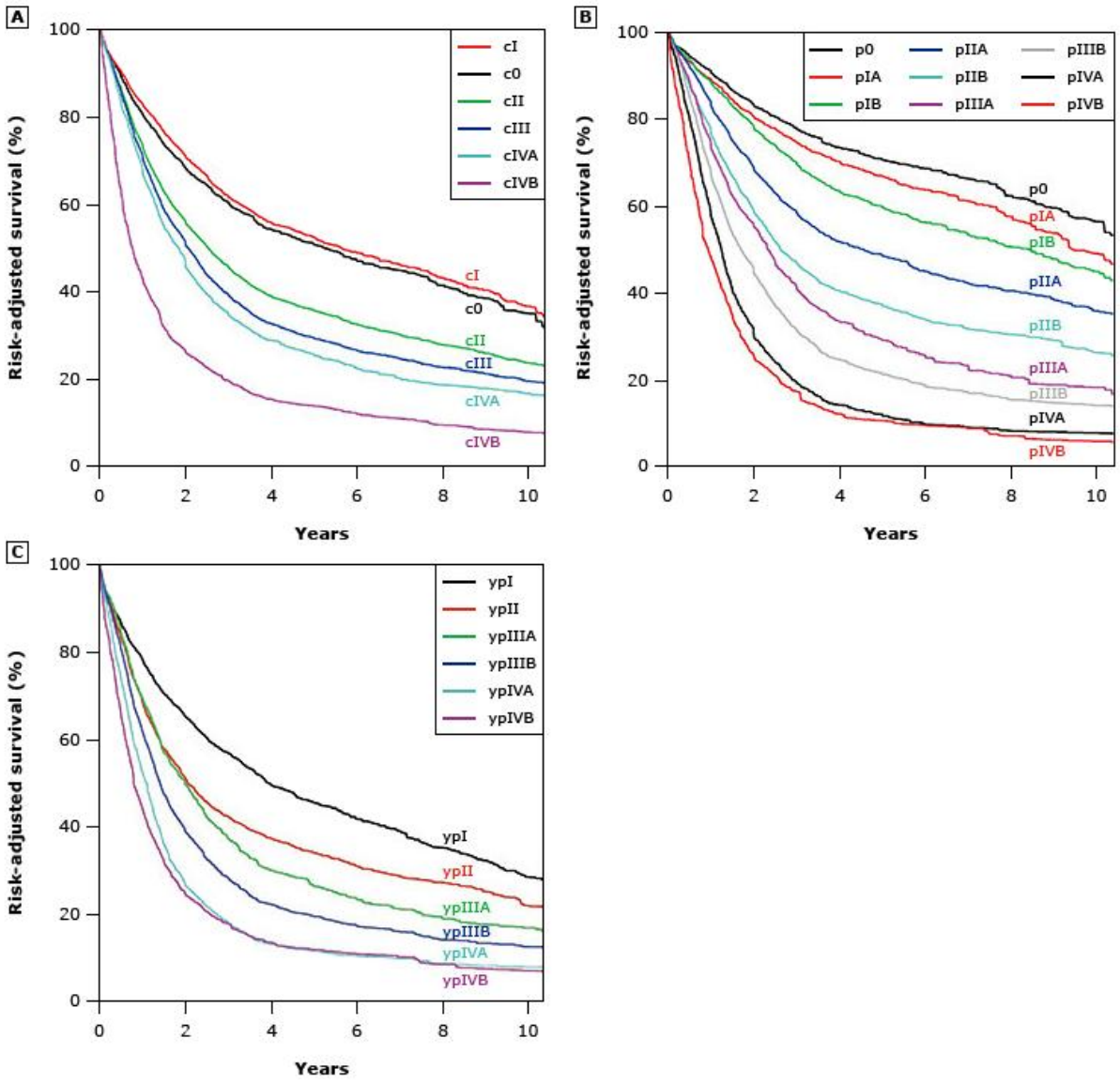


- Pathological stages posttreatment AC (ypTNM)

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

Update: December 2025

- 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 2025

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 (SCC)
    - Perioperative chemotherapy (FLOT + durvalumab) for GEJ tumors and distal esophageal tumors (cfr gastric cancer) is the best option based on the ESOPEC trial (2) and Matterhorn (NEJM 2025)
- Chemoradiotherapy schedule:
    - CROSS schedule: carboplatin + paclitaxel weekly (3)
    - 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 (4)
- 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 (5-8):
            - If CPS ≥10 or TPS ≥1 : chemo (platinum/5FU) + pembro or nivolumab
            - If TAP ≥5: chemo + tislelizumab
            - Preference for FOLFOX as chemotherapy
        - 2nd or later lines: Nivolumab, Tislelizumab, Taxanes or FOLFIRI

    - **Adenocarcinoma** :
        - 1st line (9-12):
            - HER2+: pembrolizumab + trastuzumab + 5FU + platinum
            - HER2- / CPS ≥10: chemo + pembrolizumab or nivolumab
            - HER2-/ CPS≥5: chemo + nivolumab
            - HER2-/CPS≥1: chemo + pembrolizumab
            - HER2-/TAP≥5: chemo + tislelizumab
            - Preference for FOLFOX as platinum based chemotherapy

        - 2nd line (13-15):

- 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

- Tislelizumab reimbursement Belgium (since 1 dec 2025)
  - Monotherapy SCC esophagus after platinum chemotherapy
  - 1st line SCC esophagus with PD-L1 TAP score ≥ 5
  - 1st line AC GEJ / gastric with PD-L1 TAP score ≥ 5

References

1) RTOG 85-01 (Herskovic trial): NEJM 1992;326(24):1593
2) ESOPEC (Hoeppner et al): NEJM 2025;392(4)
3) CROSS trial: NEJM 2012 (van Hagen et al), Lancet onc 2014 (Shapiro), JCO 2021 (Eyck BM)
4) Checkmate 577 : NEJM 2021 (Kelly RJ et al)
5) CheckMate 648 : NEJM 2022 (Doki Y et al)
6) Keynote 590 : Lancet 2021 (Sun JM et al)
7) RATIONALE 302: tislelizumab versus chemo in ESCC 2nd line (JCO 2022 and ESMO open 2024)
8) RATIONALE 306: chemo + /- tislelizumab as 1st line (Lancet oncol 2023, Xu et al)
9) TOGA trial : Lancet 2010 (Bang YJ et al)
10) Janjigian YY et al Lancet Oncol 2020
11) Checkmate 649 : Lancet 2021 (Janjigian et al) Nature 2022 (Shitara K et al)
12) Keynote 859 : Lancet oncol 2023 (Rha SY et al)
13) DESTINY-Gastric01 : NEJM 2020 (Shitara K et al)
14) REGARD trial: Lancet 2014 (Fuchs CS et al)

Update: December 2025

15) RAINBOW trial: Lancet Oncol 2014 (Wilke H et al)

What's new ?

- SANO trial: neoadjuvant chemoRT followed by surveillance vs standard surgery for esophageal cancer. (Lancet Oncol April 2025)
- NOTCH1 mutation predictive biomarker for OS with tislelizumab vs chemo 2nd line (JCO 2025)