

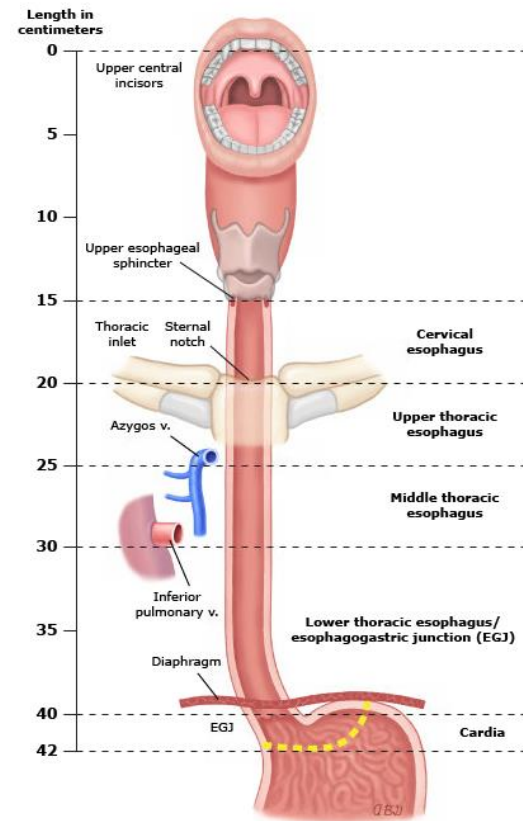
# ESOPHAGEAL CANCER

## General Overview

- 6<sup>th</sup> 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, obesity and smoking (AC)
- Clinical symptoms: dysphagia and weight loss

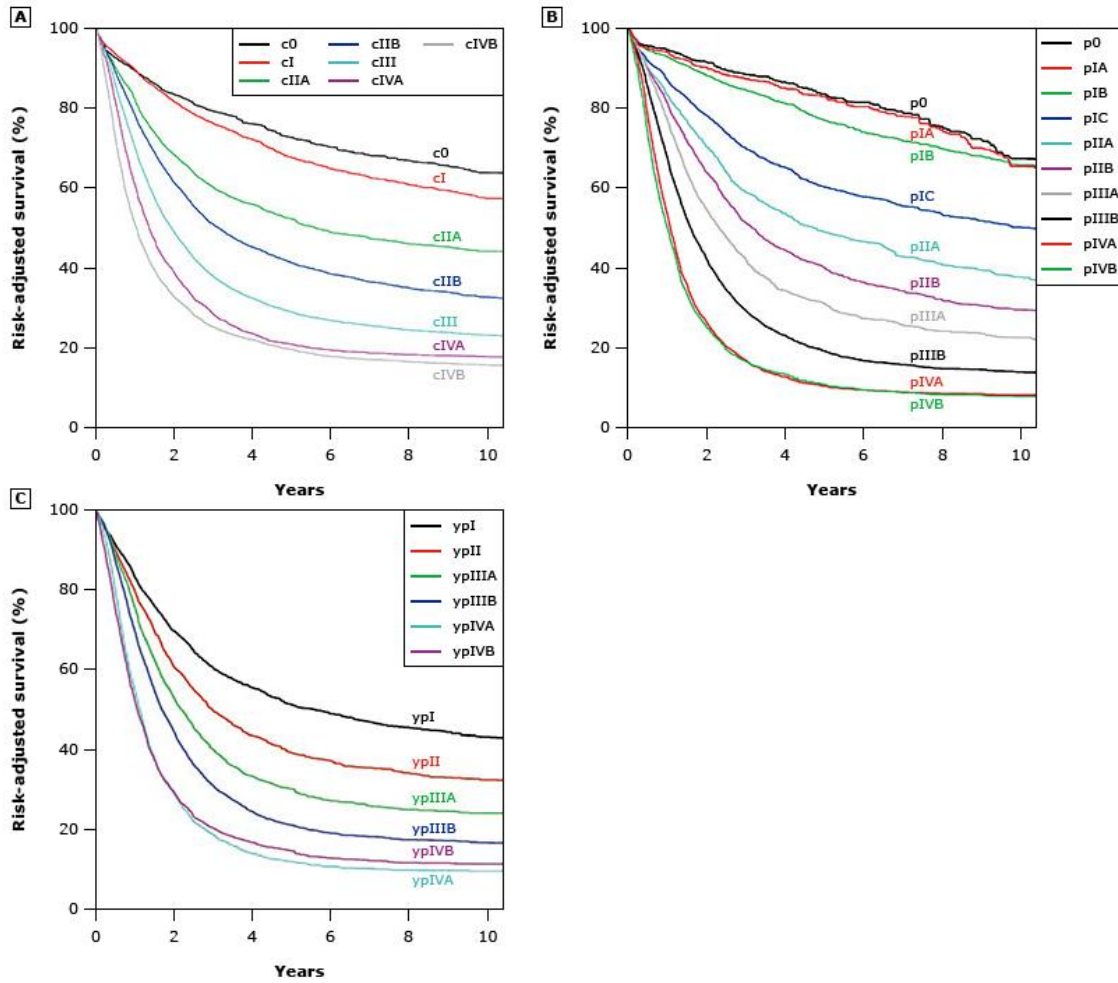
## Staging (AJCC Version 8) and Prognosis

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

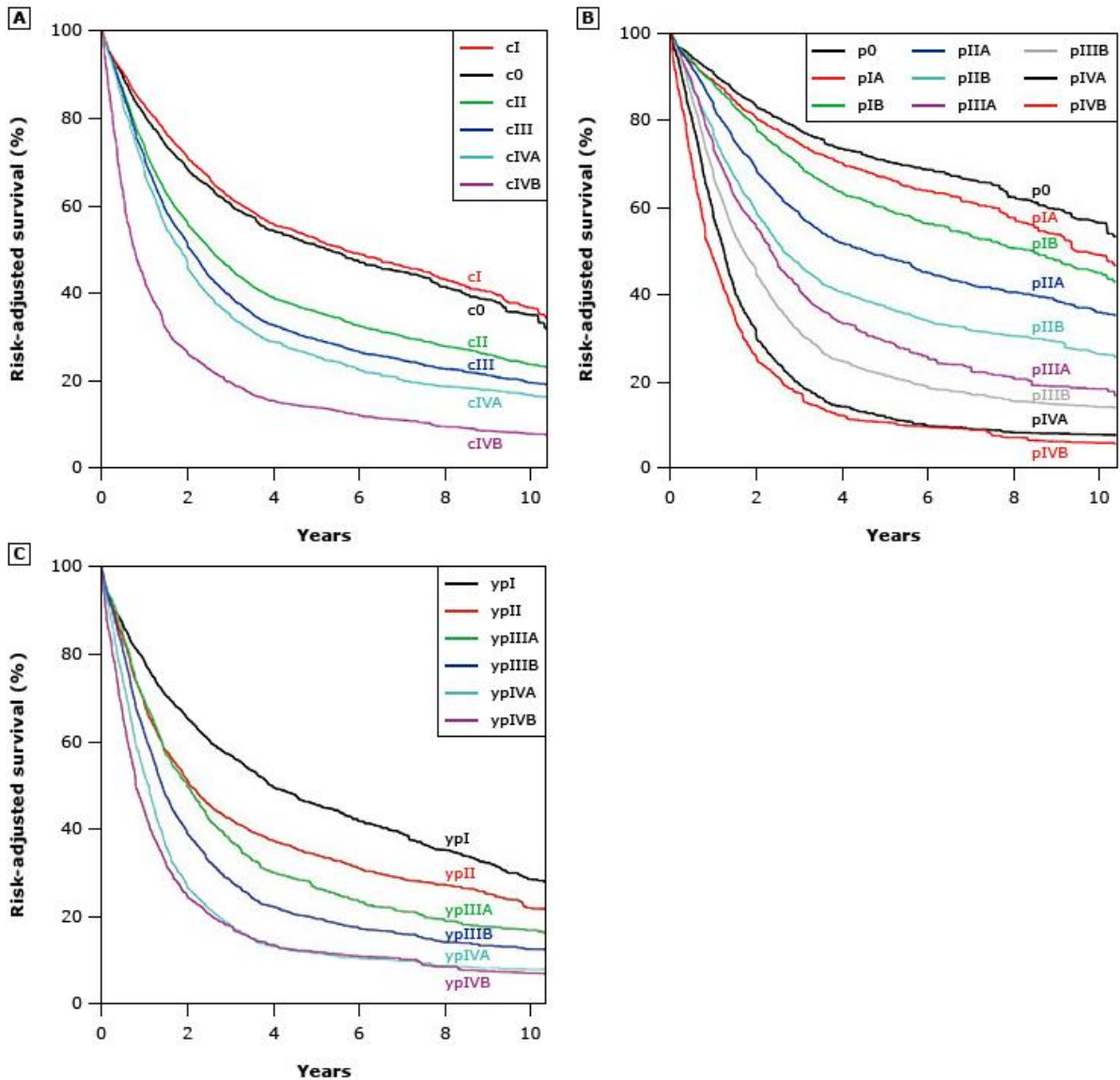
- Prognosis: risk adjusted survival after treatment decision for clinical (A), pathological (B) and posttreatment pathological staged AC of the esophagus and GEJ (C)



- 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

## 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/m<sup>2</sup> w1 and w5, 2 cycles of infusional 5-FU 1000 mg/m<sup>2</sup> 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)
  - All SCC + AC should be tested for MSI and PD-L1
  - **Squamous cell cancer:**
    - 1<sup>st</sup> line (4,5):
      - If CPS ≥10 or TPS ≥1 : chemo (platinum/5FU) + pembro or nivolumab
      - Preference for FOLFOX as chemotherapy
    - 2<sup>nd</sup> or later lines: Nivolumab, Taxanes or FOLFIRI
  - **Adenocarcinoma :**
    - 1<sup>st</sup> 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
    - 2<sup>nd</sup> 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:
  - 1<sup>st</sup> line HER2+ AC gastric or GEJ, CPS  $\geq 1$  in combination with trastuzumab, 5FU and platinum (in theory no reimbursement in combination with capecitabine or oxaliplatin)
  - 1<sup>st</sup> line HER2 neg. AC gastric or GEJ, CPS  $\geq 1$  in combination with platinum and 5-FU
  - 1<sup>st</sup> line HER2 neg. esoph / gastric / GEJ, CPS  $\geq 10$  in combination with platinum and 5FU
  - 2<sup>nd</sup> or later lines: MSI-H gastric
  
- Nivolumab reimbursement Belgium:
  - Adjuvant esophageal / GEJ after neo-adj chemoRT and residual disease (no pCR)
  - 2<sup>nd</sup> line monotherapy in SCC after platinum+5FU
  - 1<sup>st</sup> line SCC in combination with platinum/5FU if TPS $\geq 1$
  - 1<sup>st</sup> line HER2 negative esoph, gastric or GEJ, CPS $\geq 5$  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 : 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 ?