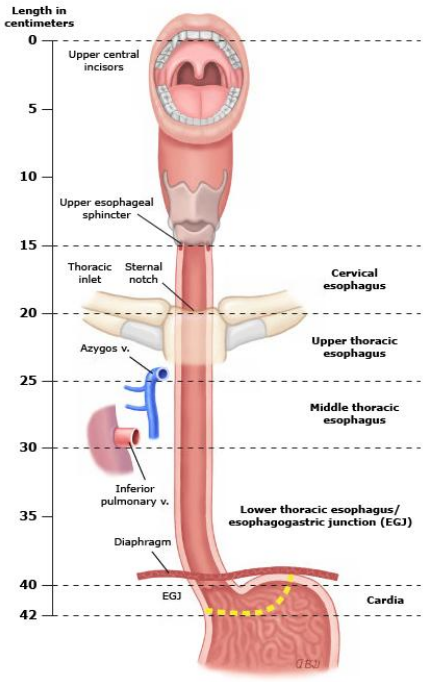
ESOPHAGEAL CANCER

GENERAL OVERVIEW AND DIAGNOSTIC WORK-UP

- **Histology.** Two major types: squamous-cell carcinoma (SCC) and adenocarcinoma (AC). SCC predominates worldwide; AC is the dominant histology in many Western populations.
- **Typical location.** SCC is more often cervical/mid-thoracic; AC is usually distal/at the gastro-oesophageal junction (GEJ).
- **Risk factors.** SCC: tobacco, alcohol and other environmental exposures. AC: Barrett oesophagus, obesity and smoking. HPV is not considered a major established driver of oesophageal SCC in Western practice.
- **Presentation.** Progressive dysphagia, weight loss, odynophagia, anaemia/bleeding or aspiration symptoms.
- **Nutrition.** Assess nutritional status at diagnosis; early dietetic involvement is essential. Enteral access should be individualised and coordinated with the surgical/RT plan.



Anatomical localisation of the oesophagus and GEJ.

STAGING WORK-UP

- **Endoscopy.** Upper GI endoscopy with multiple biopsies; endoscopic ultrasound when it can refine T/N staging in potentially curable disease.
- **Imaging.** FDG PET-CT is preferred for staging potentially curable oesophageal/GEJ cancer because it improves detection of occult distant disease; diagnostic CT remains complementary.
- **Airway assessment.** Bronchoscopy for upper/mid-thoracic tumours at or above the carina, or when airway invasion is suspected.
- **Cervical SCC.** ENT assessment/laryngoscopy when clinically appropriate.
- **GEJ rule (AJCC 8).** Tumours involving the GEJ with an epicentre ≤2 cm into the proximal stomach are staged as oesophageal cancer; tumours >2 cm distal are staged as gastric cancer.

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AJCC 8 STAGING

TNM definitions

Primary tumour (T)	Regional lymph nodes (N)	Metastasis (M)
TX: cannot be assessed T0: no primary tumour Tis: high-grade dysplasia T1a: lamina propria / muscularis mucosae T1b: submucosa T2: muscularis propria T3: adventitia T4a: pleura, pericardium, azygos vein, diaphragm or peritoneum T4b: aorta, vertebral body, airway or other unresectable adjacent structures	NX: cannot be assessed N0: no regional LN N1: 1–2 positive regional LN N2: 3–6 positive regional LN N3: ≥7 positive regional LN	M0: no distant metastasis M1: distant metastasis

ANATOMICAL LOCATION

- **Upper.** Cervical oesophagus 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 the GEJ.

PRACTICAL STAGING POINTS

- **Early disease.** For cT1 lesions, accurate distinction between T1a and T1b is crucial because it determines whether endoscopic therapy can be curative.
- **Potentially curable locally advanced disease.** Discuss all cases in a specialised oesophagogastric MDT with surgical, oncology, radiation oncology, gastroenterology, radiology, pathology and nutrition expertise.
- **Biomarkers in advanced disease.** For AC: HER2, PD-L1 CPS and MMR/MSI; for SCC: PD-L1 (TPS/CPS/TAP depending drug) and MMR/MSI when clinically relevant.

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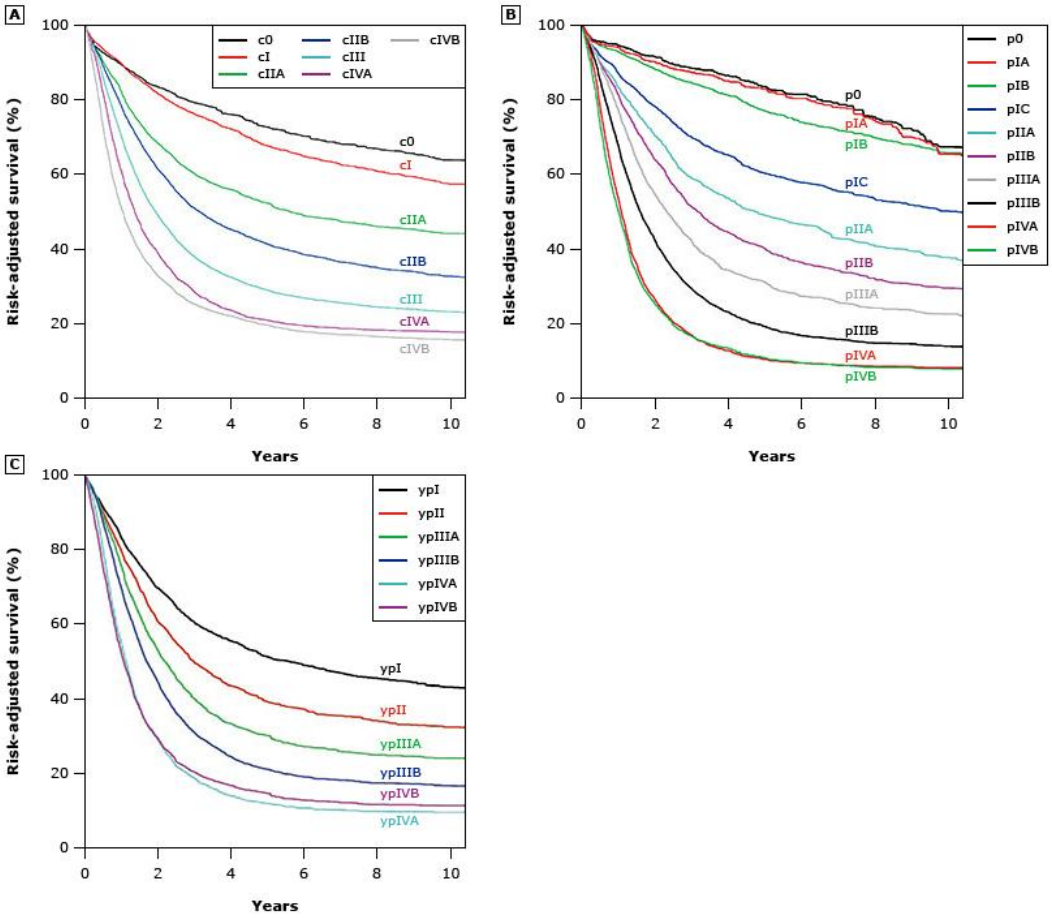
PROGNOSIS AFTER TREATMENT — ADENOCARCINOMA



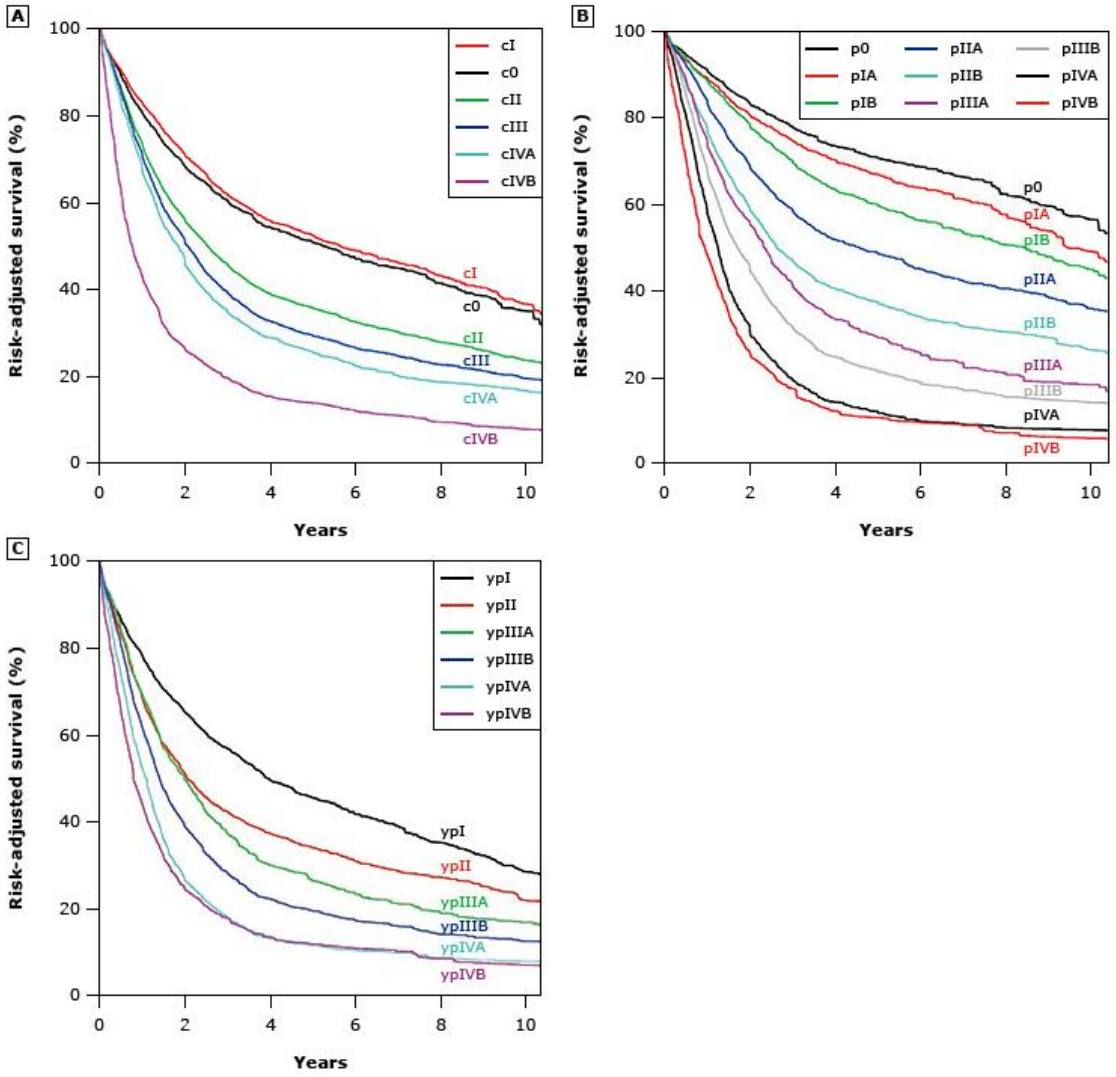
Risk-adjusted survival by clinical, pathological and post-treatment pathological stage for oesophageal/GEJ adenocarcinoma

Post-treatment pathological stage grouping (adenocarcinoma)

Stage	ypTNM
I	ypT0–2 N0 M0
II	ypT3 N0 M0
IIIA	ypT0–2 N1 M0
IIIB	ypT3 N1 M0 OR ypT0–3 N2 M0 OR ypT4a N0 M0
IVA	ypT4a N1–2 M0 OR ypT4a NX M0 OR ypT4b N0–2 M0 OR Any T N3 M0
IVB	Any T Any N M1

ESOPHAGEAL CANCER

PROGNOSIS AFTER TREATMENT — SQUAMOUS-CELL CARCINOMA



Risk-adjusted survival by clinical, pathological and post-treatment pathological stage for oesophageal SCC

Post-treatment pathological stage grouping (SCC)

Stage	ypTNM
I	ypT0–2 N0 M0
II	ypT3 N0 M0
IIIA	ypT0–2 N1 M0
IIIB	ypT3 N1 M0 OR ypT0–3 N2 M0 OR ypT4a N0 M0
IVA	ypT4a N1–2 M0 OR ypT4a NX M0 OR ypT4b N0–2 M0 OR Any T N3 M0
IVB	Any T Any N M1

ESOPHAGEAL CANCER

LOCALISED / RESECTABLE DISEASE

CERVICAL OESOPHAGEAL SCC

- **Preferred approach.** Definitive chemoradiotherapy is generally preferred over surgery because organ-preserving local control is achievable and surgery is highly morbid.
- **Chemotherapy.** Cisplatin/5-FU remains a validated regimen; carboplatin/paclitaxel-based chemoradiotherapy is also commonly used depending on local protocol and patient fitness.

THORACIC SCC

- **Locally advanced resectable SCC.** Neoadjuvant chemoradiotherapy followed by oesophagectomy remains a standard strategy; the CROSS regimen (weekly carboplatin/paclitaxel with 41.4 Gy) is the most established schedule.
- **Definitive CRT.** A curative alternative for patients in whom surgery is not appropriate or not desired; particularly relevant for proximal/cervical disease.
- **Clinical complete response after nCRT.** SANO supports active surveillance as a potential alternative to immediate surgery in expert centres, but long-term follow-up remains important and this should be offered with strict response assessment and shared decision making.

DISTAL OESOPHAGEAL / GEJ ADENOCARCINOMA

- **Preferred perioperative strategy.** For resectable locally advanced oesophageal adenocarcinoma, perioperative FLOT is preferred over CROSS based on ESOPEC (3-year OS 57.4% vs 50.7%; HR 0.70).
- **Important distinction.** MATTERHORN evaluated gastric/GEJ adenocarcinoma, not pure oesophageal adenocarcinoma. FLOT + durvalumab should therefore not automatically be extrapolated to all distal oesophageal AC.
- **Early cT1a disease.** Endoscopic resection can be curative when oncological criteria are fulfilled; deeper T1b disease usually requires oesophagectomy or multimodality treatment depending on risk.

ESOPHAGEAL CANCER

POSTOPERATIVE TREATMENT, SURVEILLANCE AND SANO

POSTOPERATIVE SYSTEMIC THERAPY

- **After neoadjuvant chemoradiotherapy + R0 surgery.** If residual pathological disease is present (ypT+ and/or ypN+), adjuvant nivolumab for up to 1 year is standard based on CheckMate 577 and is reimbursed in Belgium.
- **After perioperative FLOT.** Complete the planned postoperative FLOT when recovery and fitness permit. CheckMate 577 does not apply after perioperative chemotherapy without prior chemoradiotherapy.
- **No preoperative therapy.** Adjuvant treatment should be individualised according to pathology, histology and tumour location; for distal AC/GEJ, follow gastric/GEJ principles.

SANO ACTIVE-SURVEILLANCE STRATEGY

- **Phase III result.** In patients with a clinical complete response after neoadjuvant chemoradiotherapy, 2-year overall survival with active surveillance was non-inferior to standard surgery (74% vs 71% in the modified intention-to-treat analysis).
- **Caveat.** Median follow-up in the primary report was 38 months; long-term oncological safety remains important.
- **UZA interpretation.** Potential option for carefully selected cCR patients in an experienced multidisciplinary programme with rigorous endoscopic, EUS/PET-CT and imaging surveillance; not a casual “watch-and-wait” approach.

FOLLOW-UP

- **After curative treatment.** Clinical review and CT-based surveillance every 3–6 months for the first 2 years, then every 6–12 months to 5 years, adapted to recurrence risk and symptoms.
- **Supportive care.** Monitor weight, swallowing, anastomotic strictures, reflux, micronutrient deficiency and functional recovery.

ESOPHAGEAL CANCER

ADVANCED / METASTATIC SCC

BIOMARKER TESTING

- **PD-L1.** Report the assay/score relevant to the intended agent: nivolumab uses tumour-cell TPS, pembrolizumab uses CPS, and tislelizumab uses TAP in the Belgian reimbursement context.
- **MMR/MSI.** Consider testing, particularly when histology or family history is atypical or if tumour-agnostic immunotherapy options may become relevant.

FIRST-LINE SYSTEMIC THERAPY — BELGIUM

- **Nivolumab + fluoropyrimidine/platinum.** Reimbursed for unresectable/advanced/recurrent/metastatic oesophageal SCC with PD-L1 TPS ≥1%.
- **Pembrolizumab + fluoropyrimidine/platinum.** Reimbursed for locally advanced unresectable or metastatic oesophageal carcinoma with PD-L1 CPS ≥10.
- **Tislelizumab + platinum-based chemotherapy.** Reimbursed for unresectable locally advanced/metastatic oesophageal SCC with PD-L1 TAP ≥5%.
- **Chemotherapy backbone.** Fluoropyrimidine/platinum remains standard; FOLFOX is often a practical alternative to cisplatin/5-FU where allowed by the reimbursement text.

SECOND LINE AND LATER

- **Nivolumab.** Reimbursed monotherapy after prior fluoropyrimidine/platinum in oesophageal SCC.
- **Tislelizumab.** Reimbursed monotherapy after prior platinum-containing chemotherapy.
- **Chemotherapy.** Taxane or irinotecan/FOLFIRI according to prior exposure, performance status and toxicity profile.
- **Clinical trial.** Strongly consider after progression on chemo-immunotherapy.

ESOPHAGEAL CANCER

ADVANCED ADENOCARCINOMA / GEJ AND BELGIAN REIMBURSEMENT

ADENOCARCINOMA — PRACTICAL FIRST-LINE APPROACH

- **HER2-negative oesophageal/GEJ AC, CPS ≥5.** Nivolumab + fluoropyrimidine/platinum is reimbursed in Belgium.
- **Oesophageal carcinoma or HER2-negative GEJ AC, CPS ≥10.** Pembrolizumab + fluoropyrimidine/platinum is reimbursed in Belgium.
- **HER2-positive GEJ / gastric-type disease.** Pembrolizumab + trastuzumab + fluoropyrimidine/platinum is reimbursed for metastatic HER2-positive gastric/GEJ adenocarcinoma with CPS ≥1; this is a GEJ/gastric indication rather than a general oesophageal-AC indication.
- **Tislelizumab.** Belgian reimbursement for adenocarcinoma applies to HER2-negative gastric/GEJ disease with TAP ≥5%, not to pure oesophageal adenocarcinoma.

SECOND LINE / LATER

- **HER2-positive gastric/GEJ-type disease after trastuzumab.** Trastuzumab deruxtecan is reimbursed in Belgium for advanced HER2-positive gastric/GEJ adenocarcinoma after prior trastuzumab, with ISH-confirmed HER2 amplification.
- **HER2-negative / no target.** Paclitaxel + ramucirumab or ramucirumab monotherapy are evidence-based options for gastric/GEJ adenocarcinoma; for pure oesophageal AC, select treatment according to tumour location, prior regimen and MDT consensus.
- **Later lines.** FOLFIRI/irinotecan and trifluridine-tipiracil can be considered in appropriate gastro-oesophageal adenocarcinoma settings.

Belgian reimbursement — quick reference

Drug	Situation	Belgian practical note
Nivolumab	Adjuvant oesophagus/GEJ after nCRT + R0 surgery with residual disease	Reimbursed; monotherapy up to 1 year
Nivolumab	1L unresectable/metastatic ESCC, TPS ≥1%	With fluoropyrimidine + platinum
Nivolumab	1L HER2-negative advanced gastric/GEJ/oesophageal AC, CPS ≥5	With fluoropyrimidine + platinum
Pembrolizumab	1L locally advanced unresectable/metastatic oesophageal carcinoma or HER2-neg GEJ AC, CPS ≥10	With fluoropyrimidine + platinum
Tislelizumab	1L unresectable locally advanced/metastatic ESCC, TAP ≥5%	With platinum-based chemotherapy
Tislelizumab	Post-platinum ESCC	Monotherapy
T-DXd	Advanced HER2+ gastric/GEJ AC after trastuzumab	ISH-positive; reimbursed

ESOPHAGEAL CANCER

WHAT'S NEW? — 2025–2026

PRACTICE-CHANGING / PRACTICE-INFORMING UPDATES

- **ESOPEC (NEJM 2025).** Perioperative FLOT improved survival versus CROSS in resectable oesophageal adenocarcinoma; this firmly shifts fit patients with distal oesophageal AC toward perioperative FLOT.
- **SANO (Lancet Oncology 2025).** Active surveillance after a clinical complete response to neoadjuvant chemoradiotherapy was non-inferior to standard surgery for 2-year OS (74% vs 71%). This supports a selective organ-preservation strategy in expert programmes while longer follow-up matures.
- **NOTCH1 biomarker analysis — RATIONALE-302 (JCO 2025).** NOTCH1 mutation was associated with greater OS benefit from tislelizumab versus chemotherapy (18.4 vs 5.3 months; HR 0.35). This is hypothesis-generating and not a clinically validated selection biomarker.
- **JUPITER-06 final OS (Ann Oncol 2026).** Toripalimab + paclitaxel/cisplatin produced sustained OS benefit in advanced ESCC (median 17.7 vs 12.9 months; HR 0.72). Toripalimab is not part of current Belgian standard reimbursement for ESCC.
- **Perioperative immunotherapy.** Do not extrapolate MATTERHORN indiscriminately from gastric/GEJ cancer to pure oesophageal adenocarcinoma; treatment choice should follow tumour epicentre and evidence base.

UZA TAKE-HOME

- **SCC.** CROSS/definitive CRT remain central in curative disease; adjuvant nivolumab for residual disease after nCRT+surgery; chemo-immunotherapy in metastatic disease.
- **Adenocarcinoma.** Perioperative FLOT is preferred for resectable oesophageal AC after ESOPEC; advanced therapy is biomarker-driven and overlaps with gastric/GEJ treatment depending on epicentre.
- **Always distinguish.** Pure oesophageal AC versus GEJ/gastric AC, because evidence and Belgian reimbursement are not identical.

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