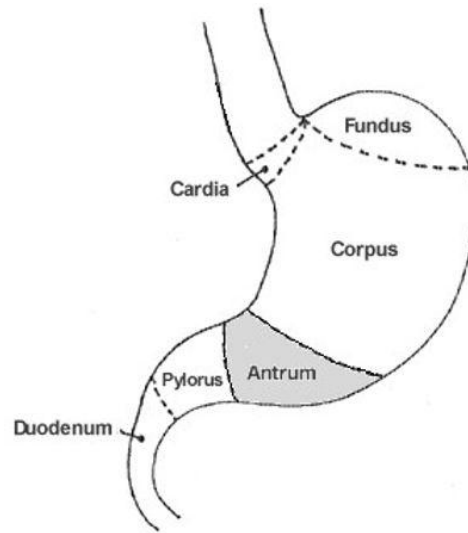


GASTRIC CANCER

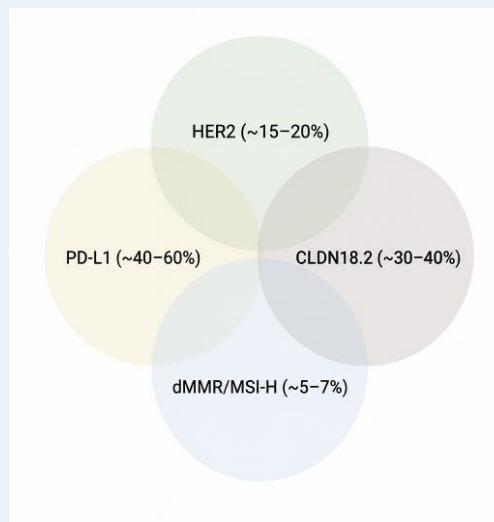
GENERAL OVERVIEW

- **Epidemiology.** Major global cancer burden, with highest incidence in East Asia; incidence has declined in many Western countries.
- **Risk factors.** *Helicobacter pylori*, smoking, high-salt diet, low fruit/vegetable intake, alcohol, autoimmune gastritis and family history.
- **Histology.** Lauren intestinal and diffuse types remain clinically useful; diffuse/signet-ring tumours are enriched in younger patients and may be associated with CDH1 alterations.
- **Hereditary disease.** Hereditary diffuse gastric cancer is uncommon (germline CDH1/CTNNA1); consider genetics in appropriate age/family-history patterns. Gastric cancer can also occur in Lynch, FAP, Peutz-Jeghers, Li-Fraumeni and other syndromes.
- **Symptoms.** Weight loss, epigastric pain, early satiety, anaemia/bleeding, dysphagia for proximal/GEJ tumours



MOLECULAR SUBTYPES AND CLINICALLY ACTIONABLE BIOMARKERS

- **TCGA subtypes.** Chromosomal instability (CIN), microsatellite instability (MSI), Epstein-Barr virus (EBV)-positive and genomically stable (GS) disease.
- **At advanced-stage diagnosis, test at minimum.** HER2, PD-L1 (CPS; TAP if tislelizumab is considered), MMR/MSI and CLDN18.2. Consider broad NGS for rare actionable alterations/trial eligibility.
- **Important overlap.** HER2, PD-L1, CLDN18.2 and MSI are not mutually exclusive; treatment choice should integrate the complete biomarker profile.



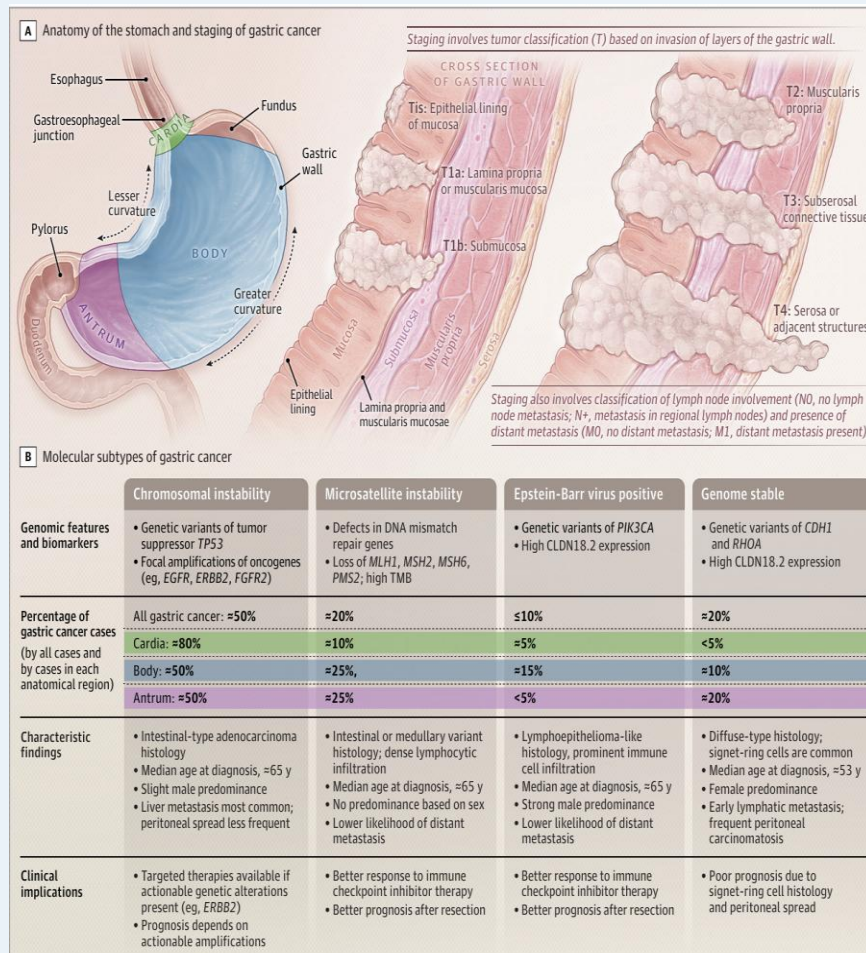
Approximate biomarker overlap in advanced gastric cancer.

GASTRIC CANCER

STAGING AND DIAGNOSTIC WORK-UP

INITIAL WORK-UP

- **Local staging.** Upper GI endoscopy with multiple biopsies; endoscopic ultrasound can refine T/N staging
- **Imaging.** Contrast-enhanced CT thorax/abdomen/pelvis. PET-CT is not routinely required.
- **Staging laparoscopy.** Strongly consider for cT3/cT4 and/or node-positive potentially resectable disease.
- **GEJ rule (AJCC 8).** Tumours involving the GEJ with epicentre ≤ 2 cm into the proximal stomach are staged as oesophageal cancer; tumours with epicentre >2 cm distal to the GEJ are staged as gastric cancer.
- **Baseline fitness.** ECOG PS, nutritional assessment, renal/hepatic function, iron/B12 status.



Anatomy, depth of invasion and molecular subtypes (Patel et al., JAMA, 2026)

AJCC 8 — TNM definitions

Primary tumour (T)	Regional lymph nodes (N)	Metastasis (M)
T1: lamina propria/muscularis mucosae (T1a) or submucosa (T1b) T2: muscularis propria T3: subserosal connective tissue T4a: serosa T4b: adjacent structures/organs	N0: 0 nodes N1: 1–2 N2: 3–6 N3a: 7–15 N3b: ≥ 16	M0: no distant metastasis M1: distant metastasis

GASTRIC CANCER

LOCALIZED / RESECTABLE DISEASE

UZA Guidelines:

- **Early mucosal disease.** Endoscopic resection can be curative for carefully selected T1a lesions meeting endoscopic criteria; discuss in upper-GI MDT.
- **cT2–T4 and/or node-positive disease.** Perioperative FLOT remains the chemotherapy backbone. MATTERHORN showed improved event-free survival and higher pCR with the addition of durvalumab.
- **Belgian access note.** As of 18 August 2026, the current Belgian Imfinzi reimbursement text does not list perioperative gastric/GEJ cancer. Durvalumab is available by compassionate use.
- **MSI-H/dMMR.** The benefit of conventional perioperative cytotoxic chemotherapy may be smaller in this subgroup. Discuss individually in MDT and prioritize clinical-trial/immunotherapy strategies when available; do not omit curative-intent therapy without multidisciplinary discussion.
- **Primary surgery.** If adequate oncologic surgery was performed without perioperative treatment, offer adjuvant fluoropyrimidine/oxaliplatin-based chemotherapy according to pathological stage and fitness. Consider postoperative chemoradiotherapy mainly for selected R1 or inadequate lymphadenectomy situations.

SURGERY AND FOLLOW-UP

- **Surgery.** Gastrectomy tailored to tumour location with adequate margins and D2 lymphadenectomy as standard in fit patients treated in an experienced centre.
- **Peritoneal disease.** Cytoreductive surgery + HIPEC is not standard for limited gastric peritoneal metastases after the negative PERISCOPE-II phase III result; use only in trials/exceptional MDT-selected contexts.
- **Follow-up.** Clinical review and CT-based surveillance can be performed every 3–6 months during the first 2 years and every 6–12 months to 5 years, adapted to recurrence risk, symptoms and local practice. Monitor nutritional consequences after gastrectomy (weight, iron, B12, vitamin D/calcium as appropriate).

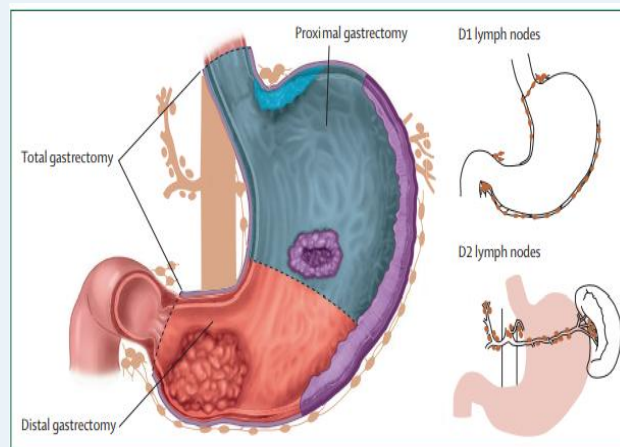


Figure 2: Surgery for gastric cancer

Illustration of the most common types of surgery for gastric cancer, according to tumour location: distal gastrectomy (red) for pyloric tumours, proximal gastrectomy (blue) for cardia and lower gastro-oesophageal junction tumours, and total gastrectomy (purple) for body or more extensive tumours. Insets show the lymph node distribution of D1 and D2 lymph nodes.

Typical gastric resections and D1/D2 nodal fields (Lancet 2025)

GASTRIC CANCER

ADVANCED / METASTATIC DISEASE — FIRST LINE

BIOMARKER TESTING BEFORE FIRST-LINE TREATMENT

- **Required for practical treatment selection.** HER2 (IHC ± ISH), PD-L1 CPS, MMR/MSI and CLDN18.2 IHC. If tislelizumab is considered, ensure validated PD-L1 TAP scoring.
- **Re-biopsy / repeat testing.** Consider when tissue is old or limited and at progression after HER2-directed therapy because HER2 expression can be heterogeneous or lost.

FIRST-LINE SYSTEMIC THERAPY

- **HER2-positive, PD-L1 CPS ≥1.** Pembrolizumab + trastuzumab + fluoropyrimidine/platinum is reimbursed in Belgium for metastatic gastric/GEJ adenocarcinoma,
- **HER2-positive, CPS <1.** Trastuzumab + fluoropyrimidine/platinum remains a standard reimbursed option. HERIZON-GEA-01 has shown superior PFS with zanidatamab-based first-line therapy, but this is not yet the Belgian reimbursed standard.
- **HER2-negative, PD-L1 CPS ≥5.** Nivolumab + fluoropyrimidine/platinum is reimbursed in Belgium.
- **HER2-negative, PD-L1 CPS ≥1.** Pembrolizumab + fluoropyrimidine/platinum is reimbursed in Belgium.
- **HER2-negative, PD-L1 TAP ≥5%.** Tislelizumab + fluoropyrimidine/platinum is reimbursed in Belgium.
- **HER2-negative, CLDN18.2-positive.** Zolbetuximab + mFOLFOX6 or CAPOX is EU-authorized on the basis of SPOTLIGHT/GLOW. No Belgian reimbursement listing was identified in the current BCFI/RIZIV sources on 18 August 2026; reimbursement planned from sept 2026.
- **Chemotherapy backbone.** FOLFOX/CAPOX are convenient oxaliplatin-based backbones

MSI-H / dMMR

- **Principle.** Strongly favour an immune-checkpoint-inhibitor-containing strategy in advanced disease. Belgian reimbursement must still follow the applicable PD-L1/line-specific conditions; pembrolizumab monotherapy is reimbursed after ≥1 prior treatment for MSI-H/dMMR gastric cancer.

GASTRIC CANCER

SECOND LINE AND LATER LINES

SECOND LINE

- **HER2-positive after trastuzumab.** Reconfirm HER2 when feasible. Trastuzumab deruxtecan (T-DXd) is preferred: DESTINY-Gastric04 showed superior OS versus ramucirumab + paclitaxel (median 14.7 vs 11.4 months; HR 0.70). Belgian reimbursement is available for advanced HER2-positive gastric/GEJ adenocarcinoma after a prior trastuzumab-containing regimen, with ISH-confirmed HER2 amplification.
- **HER2-negative / no target.** Paclitaxel + ramucirumab (RAINBOW) remains the preferred evidence-based standard for fit patients; ramucirumab monotherapy (REGARD) is an option when combination chemotherapy is unsuitable.
- **MSI-H/dMMR without prior ICI.** Pembrolizumab monotherapy is a reimbursed later-line option in Belgium, subject to the current reimbursement criteria.
- **Other options.** FOLFIRI or irinotecan can be used depending on prior exposure, neuropathy and performance status.

LATER LINES / SELECTED OPTIONS

- **Trifluridine/tipiracil (TAS-102).** Evidence-based option in refractory metastatic gastric/GEJ cancer where available/reimbursable.
- **Regorafenib.** INTEGRATE IIa demonstrated benefit versus placebo/best supportive care, but regorafenib is not reimbursed for gastric cancer in Belgium.
- **Clinical trial.** Strongly consider for CLDN18.2, HER2, FGFR2, MET, NRG1 and cellular-therapy approaches or after standard options are exhausted.

SAFETY PEARLS

- **T-DXd.** Be alert for interstitial lung disease/pneumonitis; interrupt promptly and investigate new respiratory symptoms.
- **Ramucirumab.** Monitor hypertension, proteinuria, bleeding/thrombotic risk and wound-healing issues.
- **Checkpoint inhibitors.** Immune-related toxicity can occur in any organ system and may present late.

GASTRIC CANCER

BELGIAN REIMBURSEMENT — QUICK REFERENCE

Drug	Gastric/GEJ situation	Belgian practical note
Pembrolizumab	1L metastatic HER2+ gastric/GEJ, CPS ≥1	With trastuzumab + fluoropyrimidine + platinum;
Pembrolizumab	1L HER2- locally advanced unresectable/metastatic gastric/GEJ, CPS ≥1	With fluoropyrimidine + platinum
Pembrolizumab	Later-line MSI-H/dMMR gastric	Monotherapy after ≥1 prior treatment
Nivolumab	1L HER2- advanced/metastatic gastric/GEJ/oesophageal AC, CPS ≥5	With fluoropyrimidine + platinum
Tislelizumab	1L HER2- unresectable/metastatic gastric/GEJ, TAP ≥5%	With fluoropyrimidine + platinum; reimbursed since 2025
Trastuzumab	1L metastatic HER2-amplified gastric/GEJ	With capecitabine or 5-FU + cisplatin
T-DXd	Advanced HER2+ gastric/GEJ after trastuzumab	ISH-positive; 6.4 mg/kg q3w
Durvalumab	Perioperative gastric/GEJ (MATTERHORN)	Compassionate use
Zolbetuximab	HER2- / CLDN18.2+ advanced gastric/GEJ	Reimbursement planned for sept 2026

WHAT'S NEW? — 2024–2026

LOCALIZED DISEASE

- **MATTERHORN (NEJM 2025)**. Perioperative durvalumab + FLOT improved 2-year EFS (67.4% vs 58.5%; HR 0.71) and pCR (19.2% vs 7.2%). OS was not yet formally significant at the stringent prespecified interim threshold. Belgian reimbursement remains a separate issue.
- **KEYNOTE-585 (JCO 2025)**. Adding pembrolizumab to perioperative chemotherapy increased pathological response and showed an EFS signal, but no clear OS advantage; it is not the preferred perioperative immunotherapy evidence base versus MATTERHORN.
- **TOPGEAR (NEJM 2024)**. Adding preoperative chemoradiotherapy to perioperative chemotherapy did not improve overall survival; routine preoperative CRT is not supported for gastric cancer.
- **PERISCOPE II (Lancet Oncology 2026)**. No survival benefit for gastrectomy/cytoreductive surgery + HIPEC in limited peritoneal metastatic disease; not standard outside trials.

ADVANCED DISEASE

- **DESTINY-Gastric04 (NEJM 2025)**. T-DXd is superior to ramucirumab + paclitaxel in HER2-positive disease after trastuzumab, establishing T-DXd as the preferred second-line HER2-directed therapy when HER2 remains positive.
- **HERIZON-GEA-01 (NEJM 2026)**. Zanidatamab + chemotherapy, with or without tislelizumab, improved PFS versus trastuzumab + chemotherapy; the zanidatamab + tislelizumab arm also improved interim OS (26.4 vs 19.2 months). Not yet Belgian standard reimbursement.
- **ILLUSTRO (Nature Medicine 2026)**. Zolbetuximab + FOLFOX + nivolumab showed encouraging phase II activity in CLDN18.2-positive disease; randomized LUCERNA will define the role of dual CLDN18.2/PD-1 targeting.
- **Claudin18.2 CAR-T (Lancet 2025)**. Phase II data support clinically meaningful activity of CLDN18.2-directed CAR-T in heavily pretreated gastric/GEJ cancer; investigational.
- **Domvanalimab + zimberelimab + chemotherapy**. Phase II TIGIT/PD-1 combination results were encouraging; phase III development is ongoing.
- **INTEGRATE IIa / FRUTIGA**. Regorafenib and fruquintinib-based strategies provide additional later-line evidence, but availability and Belgian reimbursement remain limiting.

GASTRIC CANCER

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