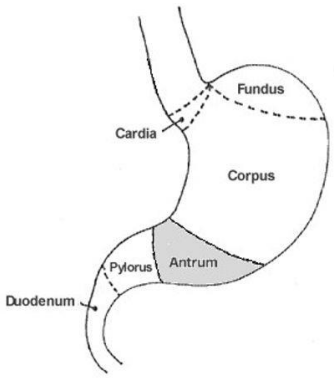
GASTRIC CANCER

General Overview



- 5th leading cause of cancer worldwide (4th leading cause of cancer deaths). Highest rates in Eastern Asia. Global incidence has declined (thanks to refrigerators (less salt-based preservation))
- Risk factors: H. Pylori infection, family history, salt and low vegetables intake, smoking, alcohol
- 2 main histologic variants: "**intestinal type**" and "**diffuse type**"
- Diffuse type more frequent in young patients and female, some with CDH1 mutations
- True hereditary (diffuse type) only in 1-3% but familial aggregation in about 10% of cases.
- Association with Lynch, FAP, Peutz-Jeghers, Li Fraumeni and Cowden syndrome.
- Clinical symptoms: weight loss, abdominal pain,…

Staging (AJCC Version 8) and Prognosis

- CT thorax/abdomen, endoscopy, (endoscopic ultrasound)
- 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 cardia cancers not involving the GEJ (even if <2cm of the GEJ)

Primary Tumor (T)	Regional Lymph Nodes (N)	Distant Metastasis (M)
Tx: Primary tumor cannot be assessed **T0**: No evidence of primary tumor **Tis**: Ca in situ, high grade dysplasia **T1**: invasion lamina propria, muscularis mucosae(T1a) or submucosa (T1b) **T2**: invasion muscularis propria **T3**: penetrates the subserosal connective tissue without invasion off the visceral peritoneum or adjacent structures **T4**: Tumor invades : T4a: serosa (visceral peritoneum) T4b: adjacent structures/organs	**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 reg LN N3a: 7-15 regional LN N3b: ≥16 regional LN	**M0**: no distant M+ **M1**: distant M+

- Prognosis: 5y survival
  - I: 86%
  - II: 69%
  - III: 21%
  - IV: 4%

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- Pathological stages posttreatment (ypTNM)

ypT	ypN	M	Stage
T1-2	N0	0	I
T1	N1	0	I
T3,4	N0	0	II
T2,3	N1	0	II
T1,2	N2	0	II
T1	N3	0	II
T4a	N1	0	III
T3,4	N2	0	III
T2-4	N3	0	III
T4b	N0,1	0	III
Any T	Any N	1	IV

Treatment

- Among persons with *H. pylori* infection who had a family history of gastric cancer in first-degree relatives, *H. pylori* eradication treatment reduced the risk of gastric cancer (NEJM 2020)
- For patients with T2-4N0 and node-positive disease we recommend peri-operative chemotherapy with FLOT
- For patients with primary surgery adjuvant chemo(RT) is recommended (ex. FOLFOX 6m)
- 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.
    - All gastric cancers should be tested for HER2 (IHC + ISH), MSI and PD-L1
    - 1st line (1-4):
        - 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 (5-7):
        - 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, regorafenib (not reimbursed)

- 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- AC gastric or GEJ, CPS ≥ 1 in combination with platinum and 5-FU

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  - 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) TOGA trial : Lancet 2010 (Bang YJ et al)
2) Janjigian YY et al Lancet Oncol 2020 ; Janjigian YY Et al Nature 2021 (Keynote-811) and lancet '23
3) Checkmate 649 : Nature 2022 (Shitara K et al)
4) Keynote 859 : Lancet oncol 2023 (Rha SY et al)
5) DESTINY-Gastric01 : NEJM 2020 (Shitara K et al) and Nat med 2024 (Shitara K et al)
6) REGARD trial: Lancet 2014 (Fuchs CS et al)
7) RAINBOW trial: Lancet Oncol 2014 (Wilke H et al)

What's new ?

- FOLFOX + Zolbetuximab in CLDN18.2 positive HER2neg metastatic gastric (SPOTLIGHT study)
  - Shitara et al Lancet 2023
  - Phase 3 study; PFS 10.6 vs 8.6m
- CAPOX + Zolbetuximab in CLDN18.2 positive gastric cancer (GLOW study)
  - Shah et al. Nat med 2023
  - Phase 3 study; PFS 8.2 vs 6.8m
- BRCA2 germline mutations identify gastric cancers responsive to PARP-I (Cancer res may 2023)
- Destiny Gastric 02 (Lancet oncol 2023): single arm phase 2 trastuzumab deruxtecan
- FRUTIGA trial: (Wang et al, Nat med 2024) phase 3 paclitaxel +/- fruquintinib 2nd line
- TOPGEAR: addition of preop chemoRT to periop chemo did not improve OS (NEJM 2024)
- INTEGRATE IIa: phase III study with regorafenib vs BSC for refractory gastric (JCO Oct 2024)