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Setting the scene in gastric (oesophageal) and pancreatic cancer

EU parliament & DICE Nov 2022

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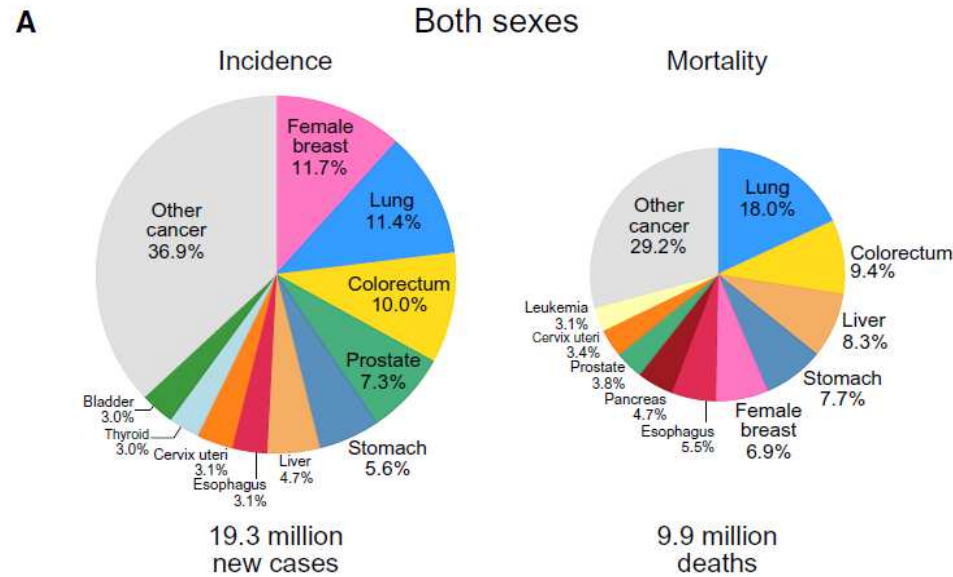


TABLE 1. New Cases and Deaths for 36 Cancers and All Cancers Combined in 2020

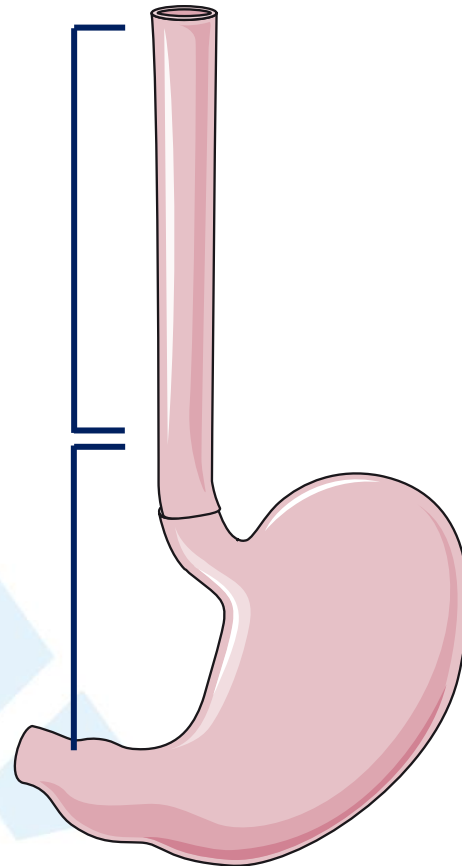
CANCER SITE	NO. OF NEW CASES (% OF ALL SITES)	NO. OF NEW DEATHS (% OF ALL SITES)
Female breast	2,261,419 (11.7)	684,996 (6.9)
Lung	2,206,771 (11.4)	1,796,144 (18.0)
Prostate	1,414,259 (7.3)	375,304 (3.8)
Nonmelanoma of skin ^a	1,198,073 (6.2)	63,731 (0.6)
Colon	1,148,515 (6.0)	576,858 (5.8)
Stomach	1,089,103 (5.6)	768,793 (7.7)
Liver	905,677 (4.7)	830,180 (8.3)
Rectum	732,210 (3.8)	339,022 (3.4)
Cervix uteri	604,127 (3.1)	341,831 (3.4)
Esophagus	604,100 (3.1)	544,076 (5.5)

FIGURE 4. Distribution of Cases and Deaths for the Top 10 Most Common Cancers in 2020 for (A) Both Sexes, (B) Men, and (C) Women. For each sex, the area of the pie chart reflects the proportion of the total number of cases or deaths; nonmelanoma skin cancers (excluding basal cell carcinoma for incidence) are included in the “other” category. Source: GLOBOCAN 2020.

Oesophageal & gastric cancer

SCC*

ADC*



❖ Difference in :

- Pathogenesis
- Epidemiology
- Tumor biology
- Pattern of recurrence
- Prognosis

*SCC: squamous cell cancer

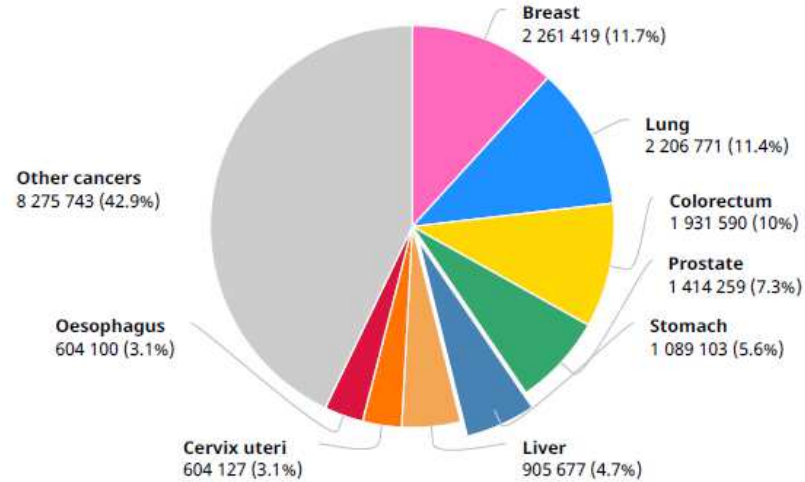
*ADC: adenocarcinoma

Stomach

Source: Globocan 2020

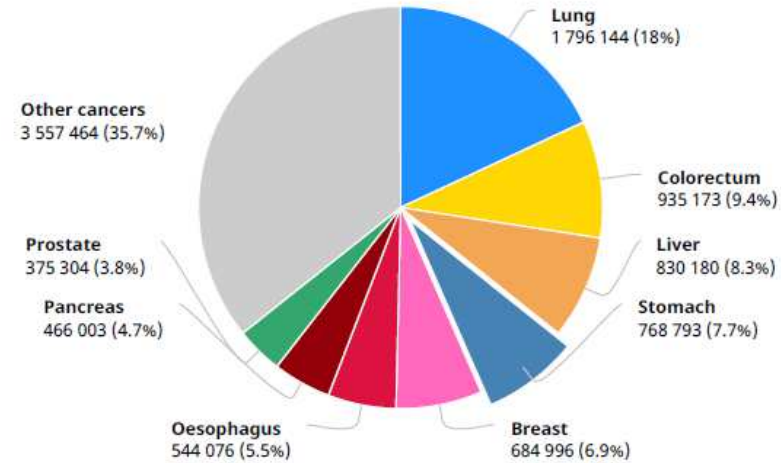


Number of new cases in 2020, both sexes, all ages



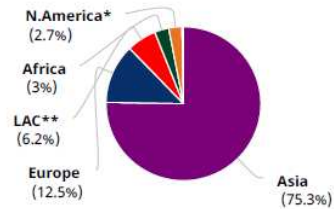
Total: 19 292 789 cases

Number of deaths in 2020, both sexes, all ages



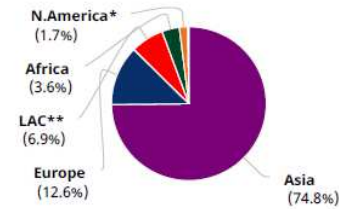
Total: 9 958 133 deaths

Incidence, both sexes



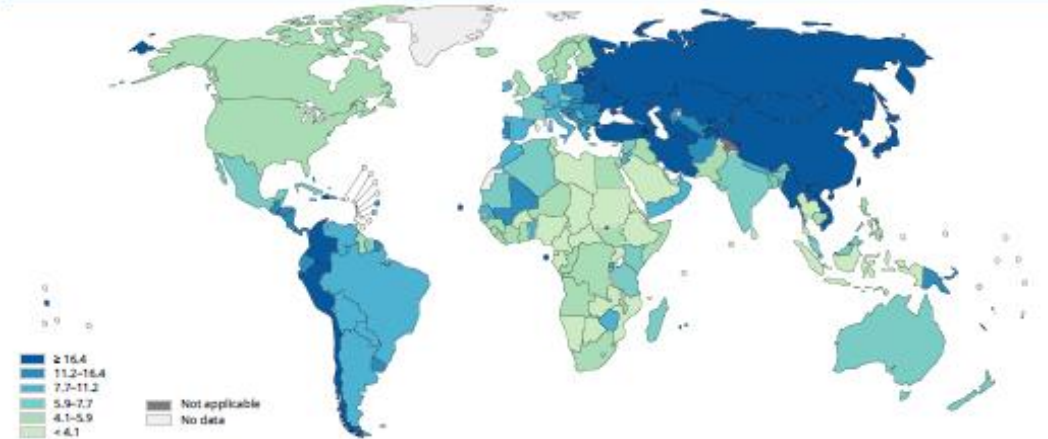
Region	Population	Number
Asia	819 944	
Europe	136 038	
**Latin America and the Caribbean	67 617	
Africa	32 402	
*Northern America	29 772	
Oceania	3 330	
Total	1 089 103	

Mortality, both sexes

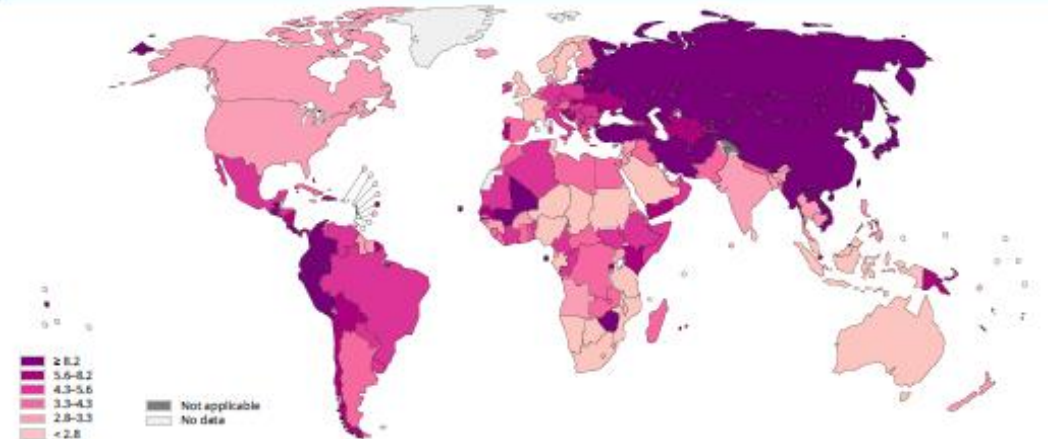


Region	Population	Number
Asia	575 206	
Europe	96 997	
**Latin America and the Caribbean	53 392	
Africa	27 945	
*Northern America	13 391	
Oceania	1 862	
Total	768 793	

Age standardized (World) incidence rates, stomach, males, all ages



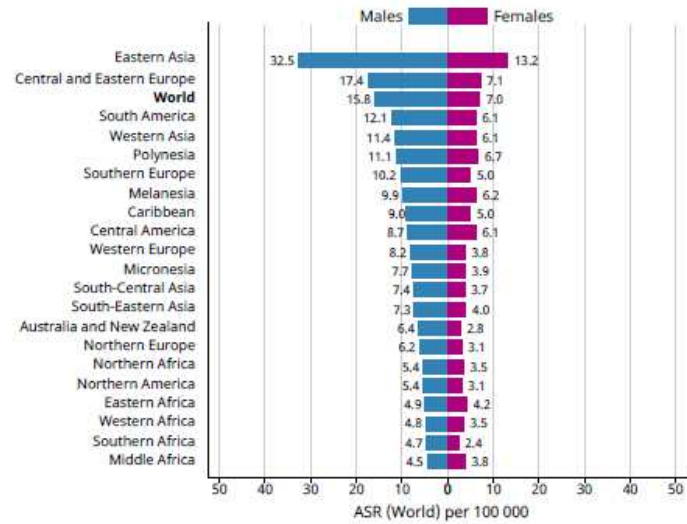
Age standardized (World) incidence rates, stomach, females, all ages



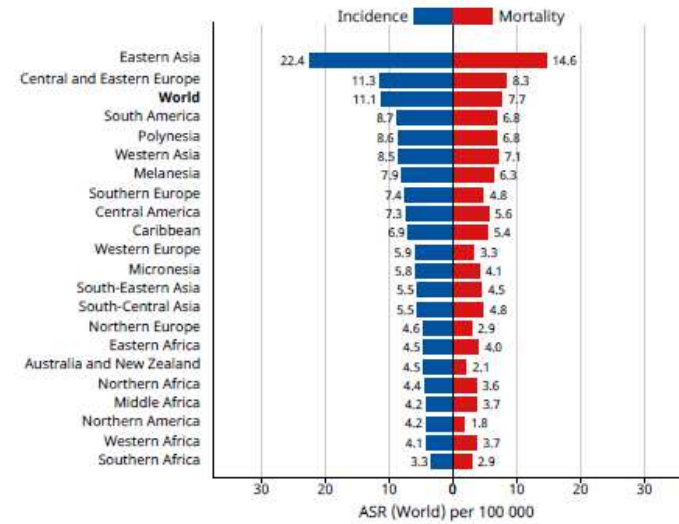
Data source: GLOBOCAN 2020
Graph production: IARC <https://gco.iarc.fr/about/>
World Health Organization

World Health Organization
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Age standardized (World) incidence rates, stomach, by sex

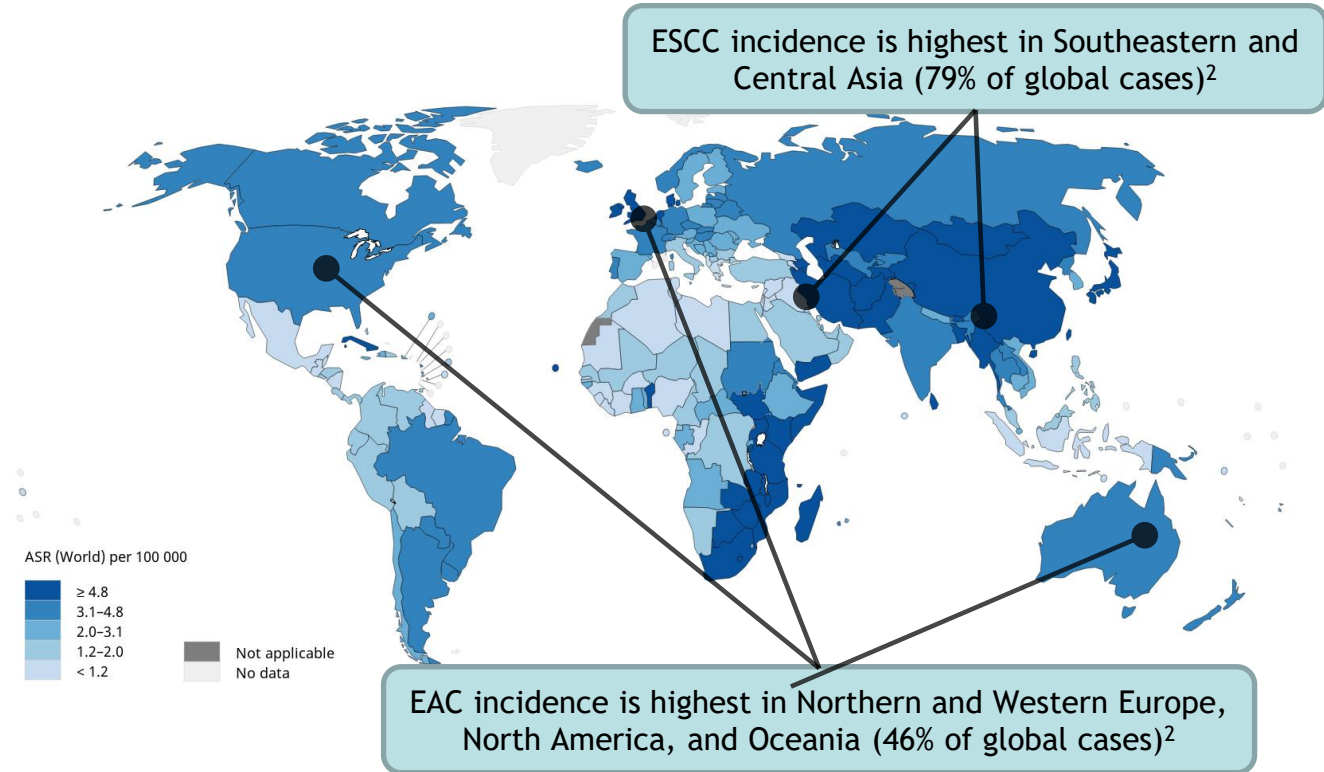


Age standardized (World) incidence and mortality rates, stomach



- EC is the 7th most common cancer worldwide^{1,a}
 - However, EC is considered rare in North America and Europe¹
- Incidence rates for ESCC and EAC are ~5.2 and ~0.7 per 100,000 people, respectively^{2,b}
- The incidence of ESCC is stable, but the incidence of EAC is rising in high-income countries²

Estimated age-standardized incidence rates of EC^{1,a}

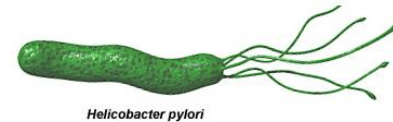


^aBased on estimates for 2018. ^bBased on estimates for 2012.

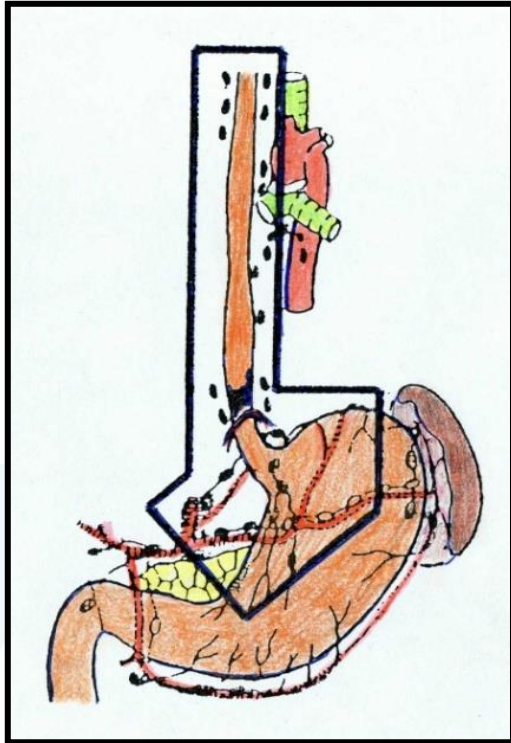
ASR, age-standardized incidence rate; EAC, esophageal adenocarcinoma; EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma.

1. Ferlay J, et al. 2018. Global Cancer (GLOBOCAN) Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available at: <http://gco.iarc.fr/today/home>. Accessed May 15, 2020. 2. Arnold M, et al. *Gut*. 2015;64:381-387.

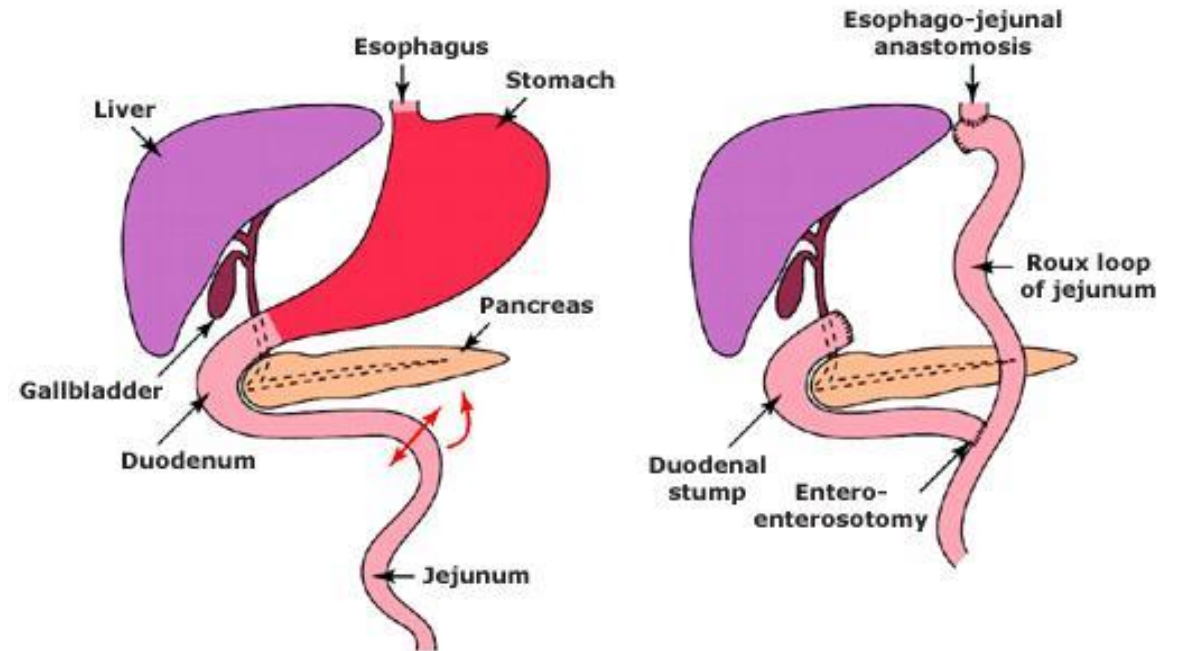
- Male > Female (2:1)
- Smoking
- Nutrition
- GE reflux disease - obesity
- H. pylori infection
 - Atrophic gastritis
 - Partial gastrectomy
- Genetic predisposition: < 3% of all gastric cancers
(e.g. HNPCC, FAP, hereditary diffuse gastric cancer, Peutz Jeghers)
- Alcohol for Squamous Cell Cancer of the oesophagus



Helicobacter pylori



Subtotal oesophagectomy



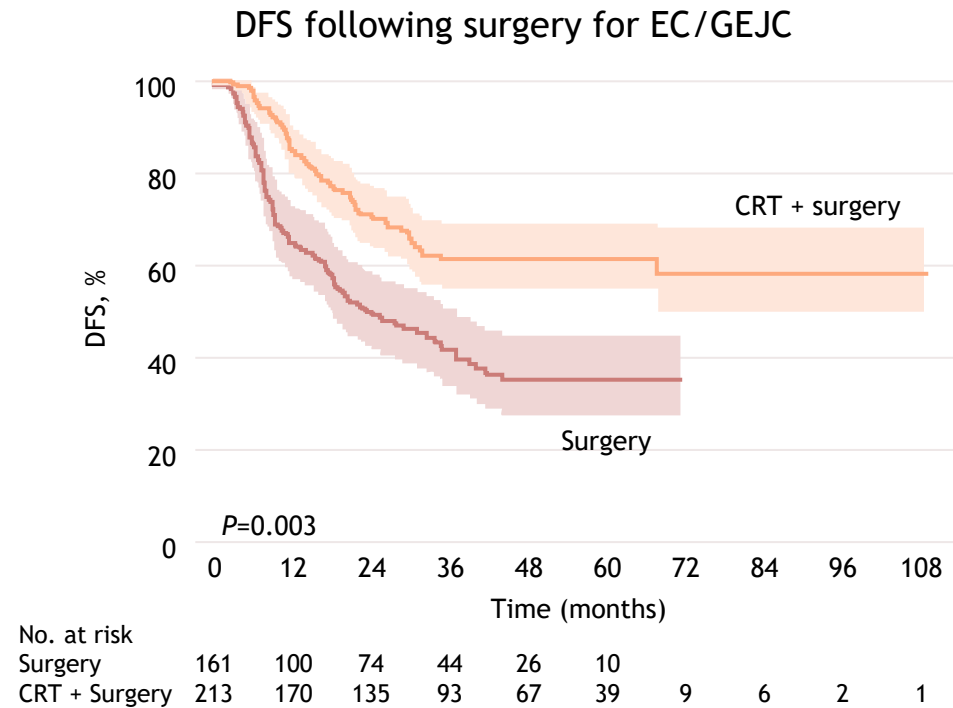
Total gastrectomy

KEY:

**experience, expertise & multidisciplinary collaboration in
spirit of innovation**

- The risk of recurrence within the first 2 yrs after surgery for EC/GEJC is >50%
 - Additionally, 5-year survival is poor

Further improvement in outcomes has been achieved with a move toward multimodality treatment



Histologic classification

Esophageal Cancer (EC)

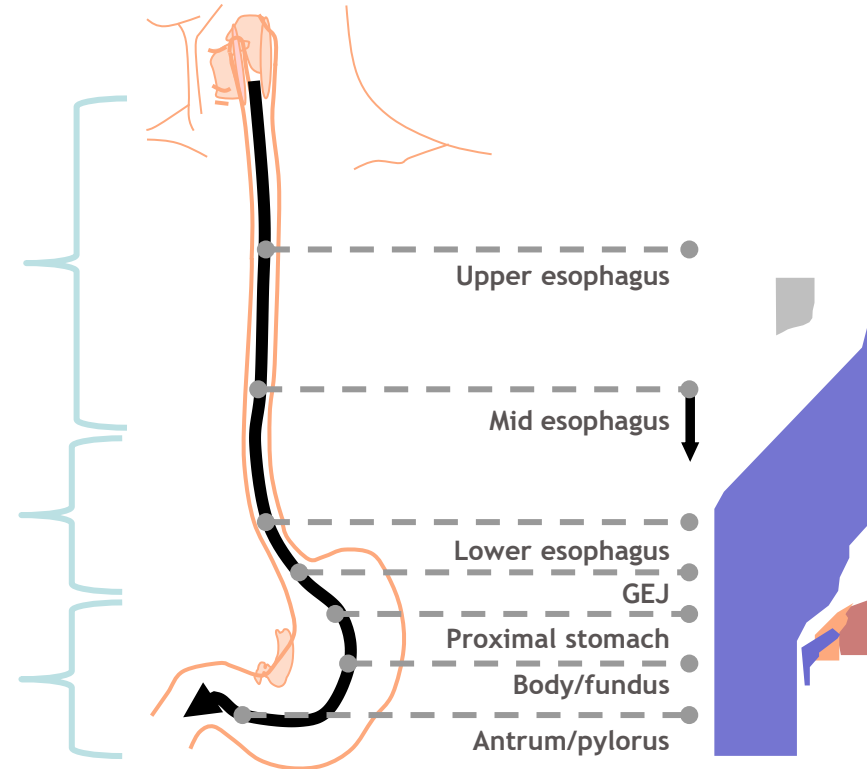
- 15% of EC is classified as adenocarcinoma (ADC)¹

Gastroesophageal Cancer (GEJC)

- ~90% of GEJ cases are ADC^{2,3}

Gastric Cancer (GC)

- ~90% of GC cases are ADC⁴



Molecular classification^{5,6}

ESCC

- Beyond the scope of this training

Gastroesophageal ADCs with CIN

- *ERBB2* amplification
- *VEGFA* amplification
- *TP53* mutation

Gastric ADCs with EBV Infection

- EBV-CIMP
- *PIK3CA* mutation
- *PD-L1/2* overexpression

Gastric ADCs with MSI

- Hypermethylation
- Gastric-CIMP
- *MLH1* silencing

Gastric ADCs with GS

- Diffuse histology
- *CDH1*, *RHOA* mutations
- *CLDN18-ARHGAP* fusions

ADC, adenocarcinoma; ARHGAP, Rho GTPase activating proteins; CDH1, cadherin-1; CLDN18, claudin 18; CIMP, CpG island methylator phenotype; CIN, chromosomal instability; EAC, esophageal adenocarcinoma; EBV, Epstein-Barr virus;

EC, esophageal cancer; *ERBB2*, erb-b2 receptor tyrosine kinase 2; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; GEJ, gastroesophageal junction; GEJC, gastroesophageal junction cancer; GS, genomic stability; GTP, guanosine triphosphate; *MLH1*, mutL homolog; *PD-L1/2*, programmed death ligand 1/2; *PIK3CA*, phosphatidylinositol-4,5-bisphosphonate 3-kinase catalytic subunit alpha; *RHOA*, ras homolog family member A; *TP53*, tumor protein 53; *VEGF-A*, vascular endothelial growth factor A.

Biomarker	Prevalence	Prognostic value	Predictive value
HER2	12-23% ⁸	HER2+ has been associated with aggressive disease and shortened survival, although data are conflicting ^{9,10}	Correlation between HER2+ and trastuzumab response ⁹
MSI ^a	Metastatic GC: 4-5% ^{5,11} Early disease: 9-22% ^{15,16}	MSI-H has been associated with reduced risk of mortality, lymph node metastasis, and tumor invasion; however, association with improved prognosis remains ambiguous in light of conflicting data ¹⁷	Correlation between MSI-H and I-O clinical benefit has been observed in a small patient population ^{5,6,18}
PD-L1 ^a	PD-L1 TC \geq 1%: 12-16% ¹ PD-L1 CPS \geq 1 58% ²	PD-L1 expressors may be associated with poorer prognoses, ³ although some studies contradict these findings ⁴	Correlation between PD-L1 CPS and clinical benefit has been indicated in GC/GEJC ⁵⁻⁷
TMB	17% ^{19,b}	Exploratory marker	Correlation between TMB-H (\geq 175 mut/exome, \geq 10 mut/Mb) and I-O clinical benefit has been observed ^{19,20}
EBV ^a	5-16% ¹¹⁻¹³	No prognostic difference between EBV+ and EBV- GC ¹³	Correlation between EBV+ and I-O clinical benefit has been observed in a small patient population ¹⁴

HER2 status currently guides frontline treatment, while PD-L1 and MSI status inform treatment at later lines of therapy in some countries

^aPrevalence may vary depending on stage of disease. ^bThe KEYNOTE-061 study protocol was amended to enrol only PD-L1 CPS \geq 1, and so these data may not show the true prevalence of TMB-H. CPS combined positive score; EBV, Epstein-Barr virus; GC, gastric cancer; GEJC, gastroesophageal junction cancer; HER2, human epidermal growth factor 2; I-O, immuno-oncology; MSI, microsatellite instability; MSI-H, microsatellite instability-high; PD-L1, programmed death ligand 1; TC, tumor cell; TMB, tumor mutational burden; TMB-H, tumor mutational burden-high.

1. Kang Y-K, Van Cutsem E et al. *Lancet*. 2017;390:2461-2471.
2. Kulangara K, et al. *J Clin Oncol*. 2018;36(suppl):4065.
3. Zhang L, et al. *Int J Clin Exp Pathol*. 2015;8:11084–11091.
4. Kim JW, et al. *Gastric Cancer*. 2016;19:42–52.
5. Fuchs CS, et al. Oral presentation at ASCO 2017. June 2-6, 2017. Chicago, IL, USA. Abstract 4003.
6. Shitara K, et al. *Lancet*. 2018;392:123–133.
7. Tabernero J, et al. Oral presentation at ASCO 2019. May 31–June 4, 2019; Chicago, IL. Abstract LBA4007.
8. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) Gastric Cancer V.2.2020. © 2020 National Comprehensive Cancer Network, Inc. 2020.
9. Bang Y-J, et al. *Lancet* 2010;376:687–697.
10. Boku N. *Gastric Cancer*. 2014;17:1-12.
11. Kawazoe A, et al. *Gastric Cancer*. 2017;20:407–415.
12. Shibata D, Weiss LM. *Am J Pathol*. 1992;140:769–774.
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14. Kim ST, et al. *Nature Med*. 2018;24:1449-1458.
15. The Cancer Genome Atlas Research Network. *Nature*. 2014;513:202–209.
16. Schlößer HA, et al. *Oncoimmunology*. 2016;5:e1100789.
17. Zhu L, et al. *Mol Clin Oncol*. 2015;3:699–705.
18. Shitara K, et al. *Ann Oncol*. 2019;30(suppl 5):v851-v934.
19. Shitara J *Clin Oncol*. 2020;38:15(suppl):4537.
20. Fuchs CS, et al. Oral presentation at ASCO 2020. May 29-31, 2020. Abstract 4503.

CIN

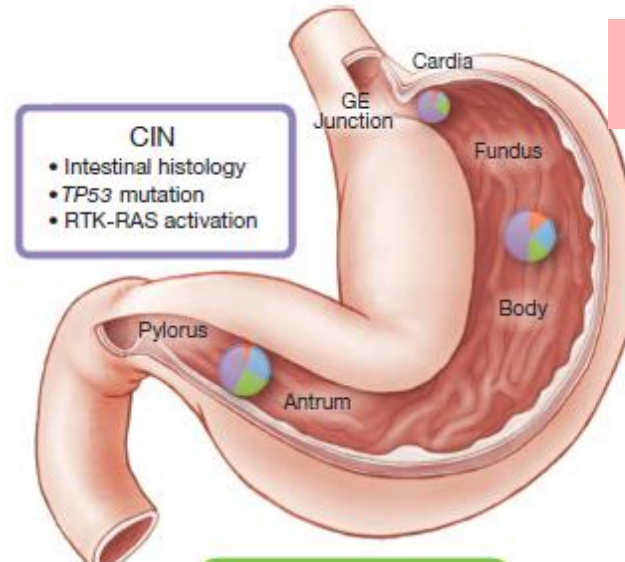
Chromosomal instability

- Intestinal histology
- Aneuploidy
- RTK amplification
- *TP53* mutations
- *HER2*, *EGFR*, *MET*

GS

Genomically stable

- Diffuse histology, young age
- *CDH1*, *RHOA* mutations (mobility, adhesion)
- Sensitivity to m-TOR inhibitors in vitro



CIN

- Intestinal histology
- *TP53* mutation
- RTK-RAS activation

EBV

- High EBV burden
- Extensive DNA hypermethylation

EBV

- *PIK3CA* mutation
- *PD-L1/2* overexpression
- EBV-CIMP
- *CDKN2A* silencing
- Immune cell signalling

- Amplification of *PD-L1/2*
- *PIK3CA* mutations

MSI

- Hypermutation
- Gastric-CIMP
- *MLH1* silencing
- Mitotic pathways

MSI

Microsatellite unstable

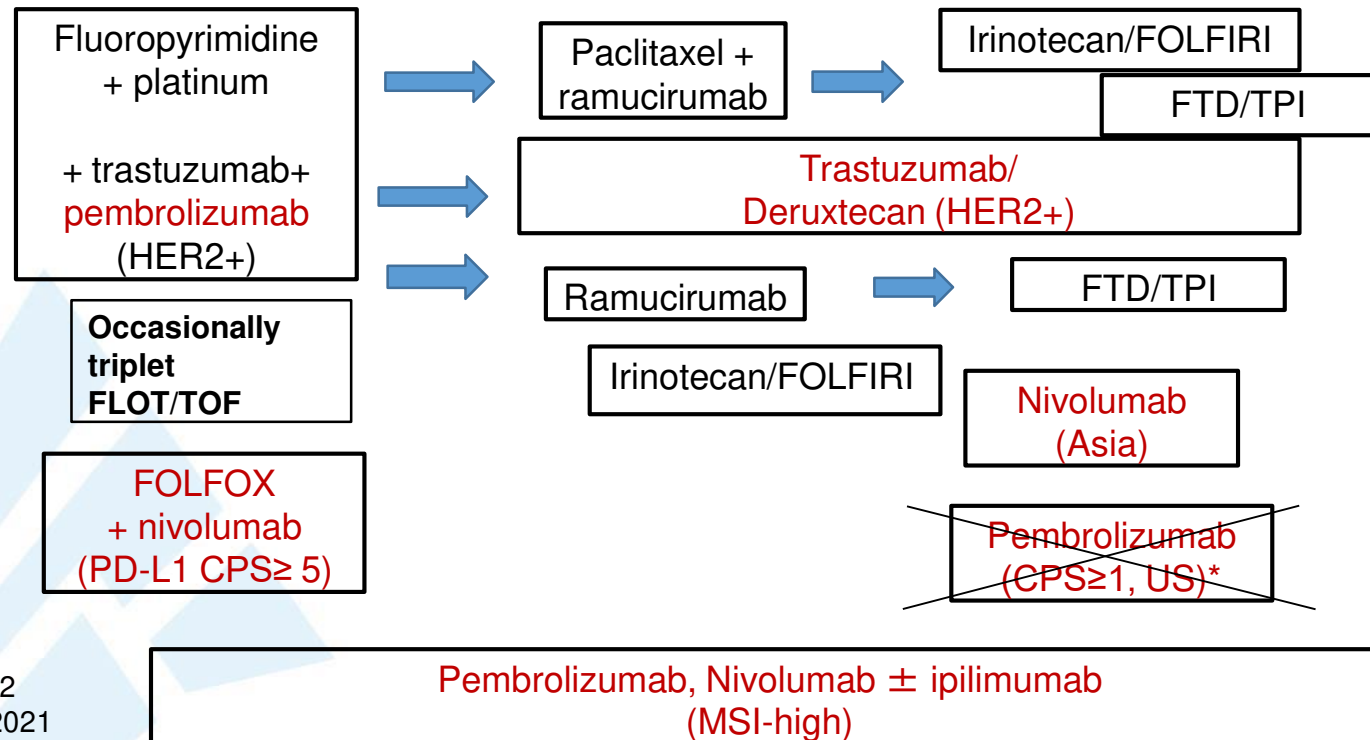
- Older age, High MSI
- Elevated mutation rate
- Hypermethylation (*MLH1*)

GS

- Diffuse histology
- *CDH1*, *RHOA* mutations
- *CLDN18-ARHGAP* fusion
- Cell adhesion

Updated algorithm for metastatic gastric adenocarcinoma in 2022

(personal opinion EVC based on evidence)



FTD/TPI = TAS-102
* Withdrawn May 2021

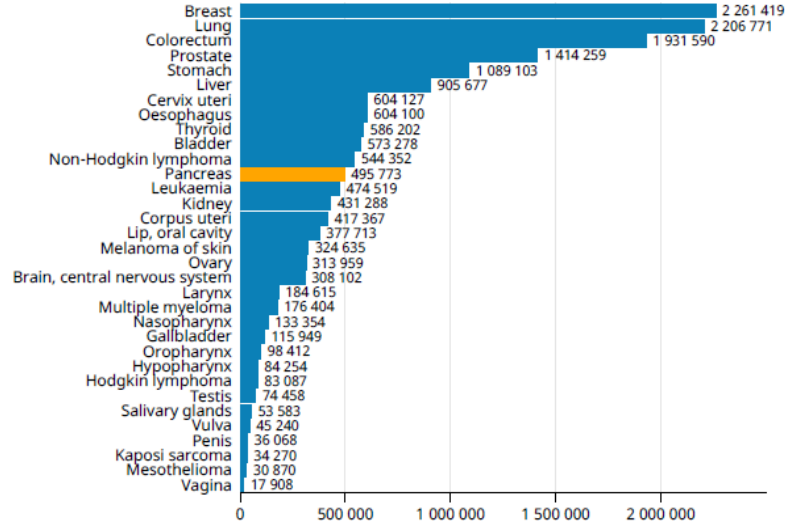


Pancreas

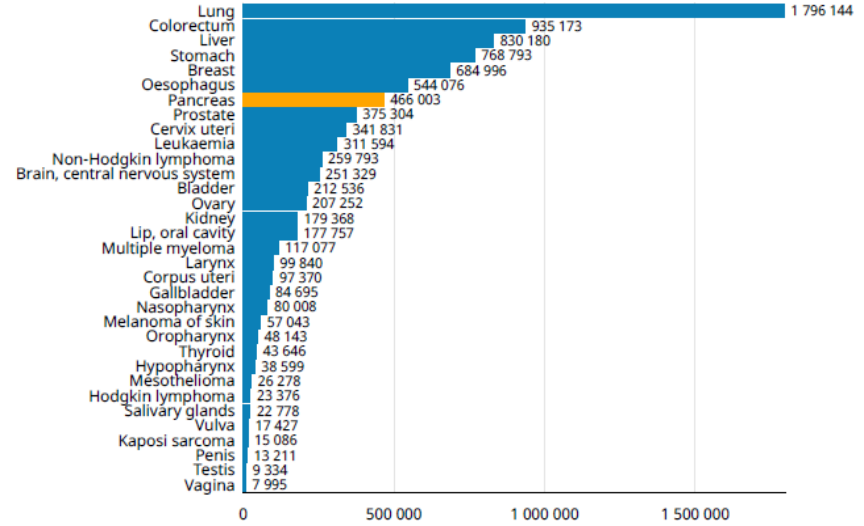
Source: Globocan 2020



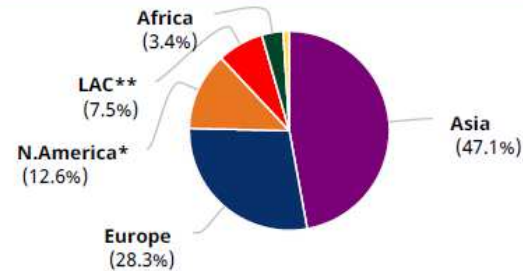
Number of new cases in 2020, both sexes, all ages



Number of deaths in 2020, both sexes, all ages

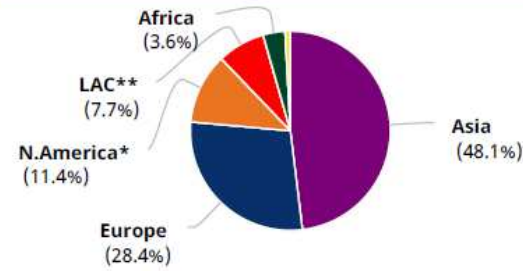


Incidence, both sexes



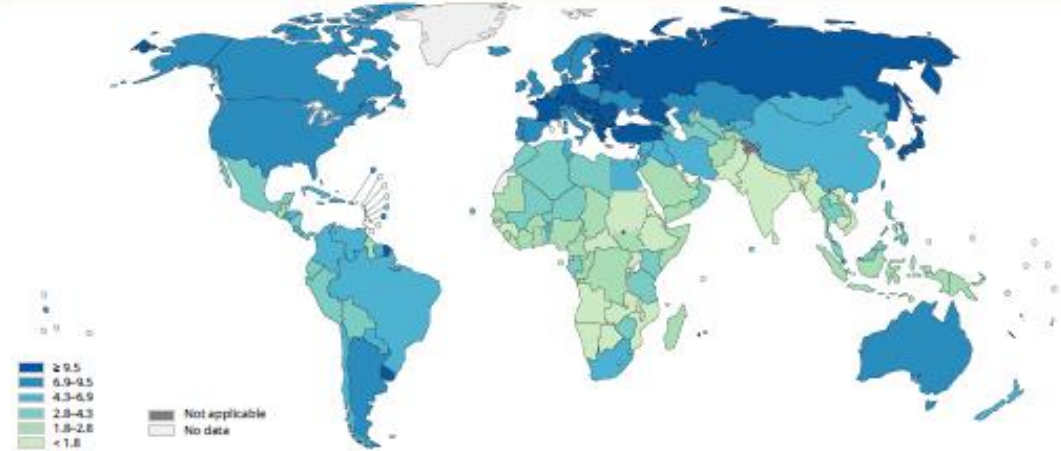
Region	Population	Number
Asia	233 701	
Europe	140 116	
*Northern America	62 643	
**Latin America and the Caribbean	37 352	
Africa	17 070	
Oceania	4 891	
Total	495 773	

Mortality, both sexes

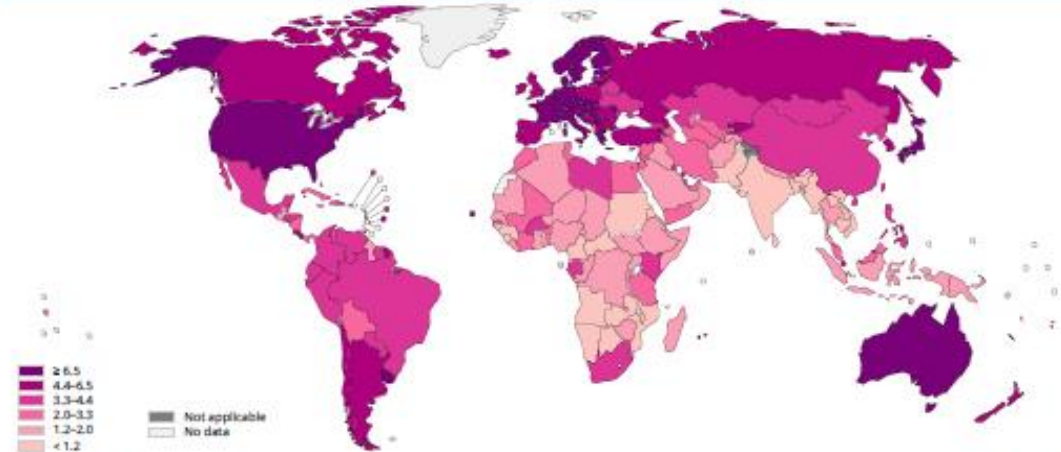


Region	Population	Number
Asia	224 034	
Europe	132 134	
*Northern America	53 277	
**Latin America and the Caribbean	36 030	
Africa	16 549	
Oceania	3 979	
Total	466 003	

Age standardized (World) incidence rates, pancreas, males, all ages



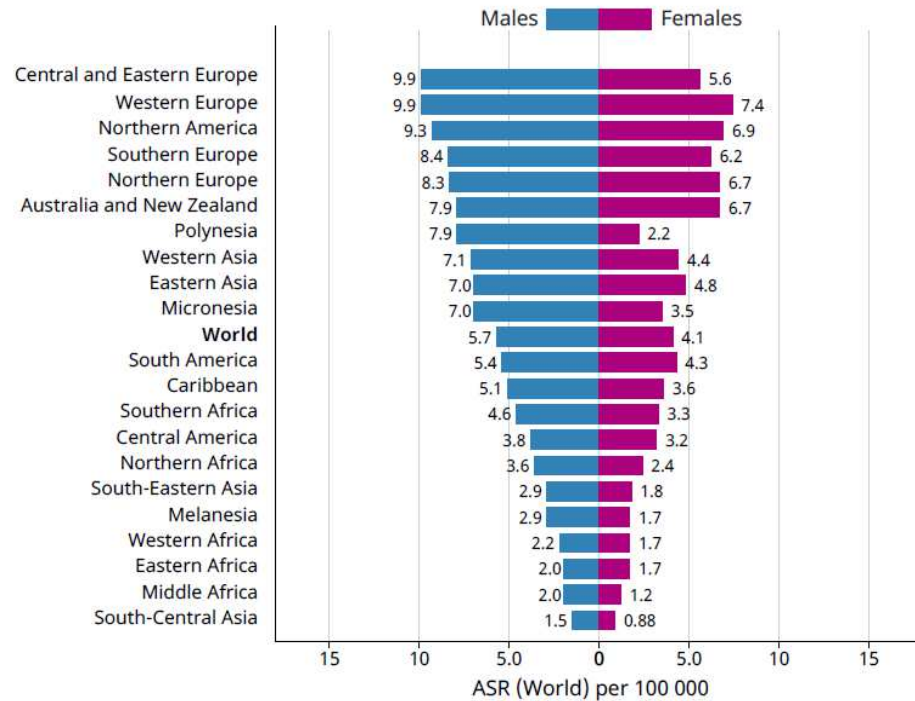
Age standardized (World) incidence rates, pancreas, females, all ages



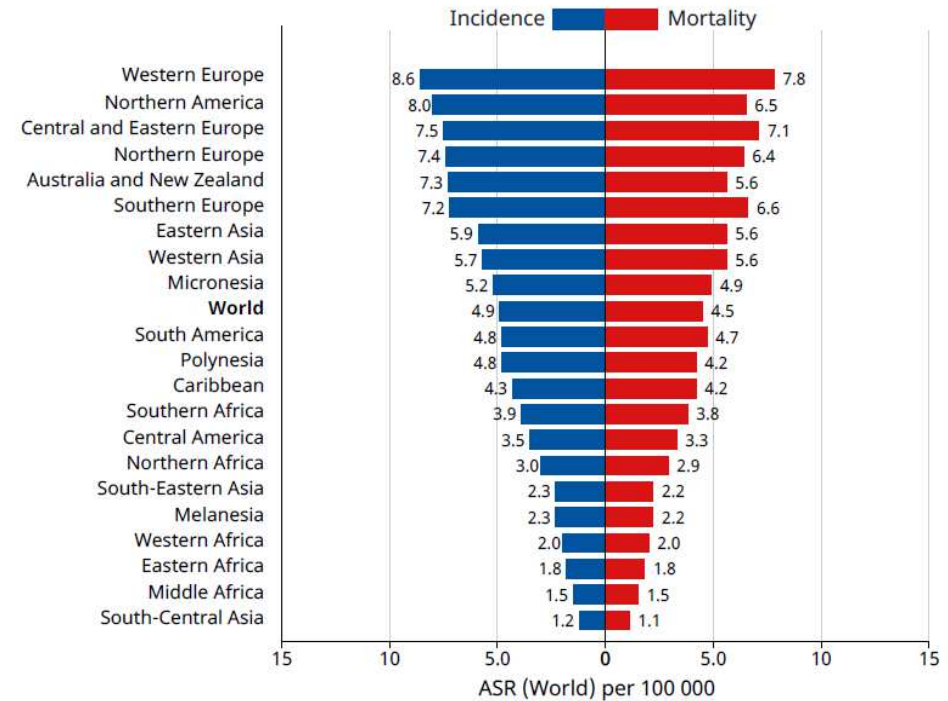
Data source: GLOBOCAN 2020
Graph production: IARC <https://oncotem/boards/>
World Health Organization

World Health Organization
© International Agency for Research on Cancer 2020

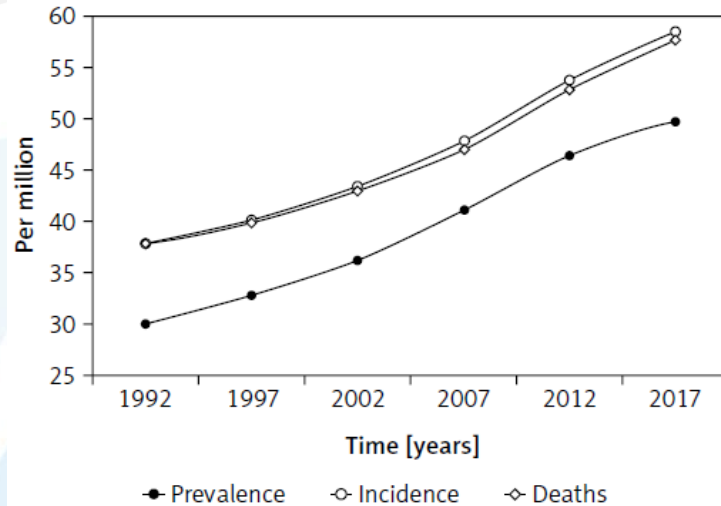
Age standardized (World) incidence rates, pancreas, by sex



Age standardized (World) incidence and mortality rates, pancreas

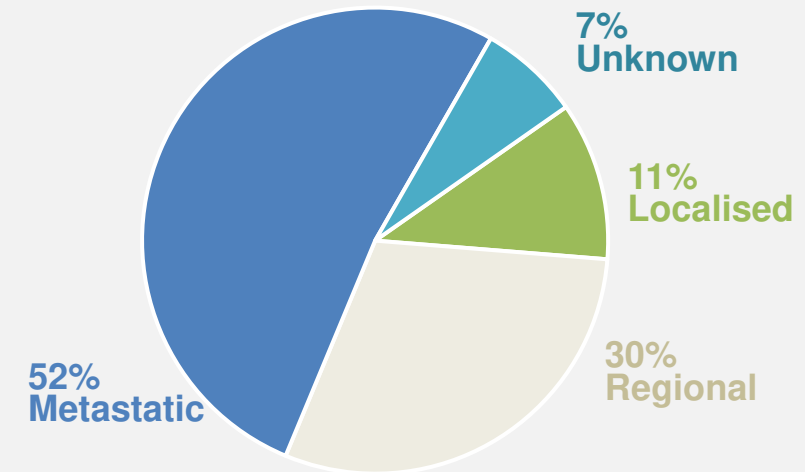


Worldwide incidence, prevalence, and mortality of pancreatic cancer during the last 25 years



Overall, incidence, prevalence and mortality have increased by 55%, 63% and 53% during the last 25 years

Cases by Stage at Diagnosis (based on SEER 2012-2018 data)³



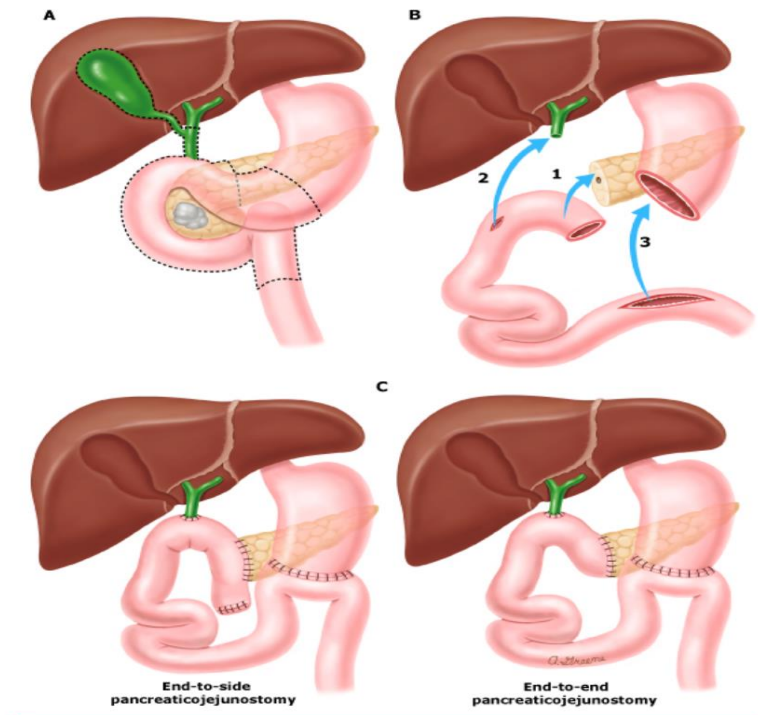
Only 3% of patients with metastatic disease survive for 5 years

1. Sung H, et al. *CA Cancer J Clin.* 2021;71(3):209-249. 2. Lippi G, Marriuzzi C. *Arch Med Sci.* 2020;16(4):820-824.
 3. Surveillance, Epidemiology, and End Results (SEER) Program. Cancer stat facts: pancreatic cancer. Accessed 5 May 2022. <https://seer.cancer.gov/statfacts/html/pancreas.html>.

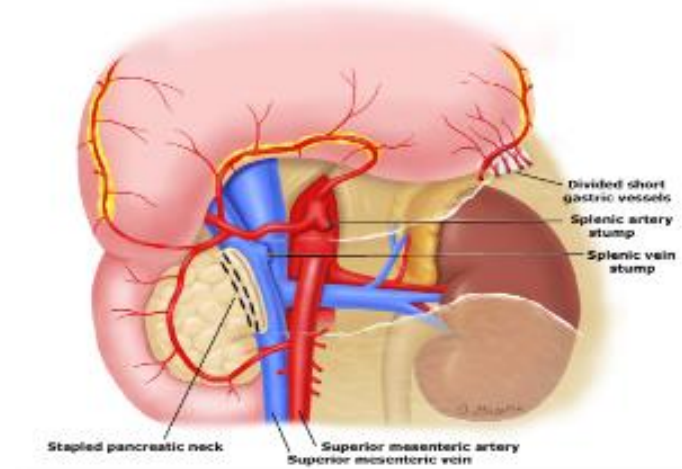
- ❑ ~ 85% of patients are diagnosed with advanced unresectable disease & often rapid progression / very symptomatic
 - ✓ Expertise for diagnosis (BIOPSIES) & endoscopic palliation/drainage!!
 - ✓ Symptom control!
 - ✓ Expertise in all aspects is required
- ❑ ~ 80% of patients who have resection and adjuvant therapy relapse
- ❑ “Cure” rate is only ~5%

- ❑ Median survival of patients with metastases without treatment is only around 3 months
- ❑ Incidence numbers and numbers of deaths are almost identical

Conventional pancreaticoduodenectomy (Whipple procedure)



Distal pancreatectomy with splenectomy



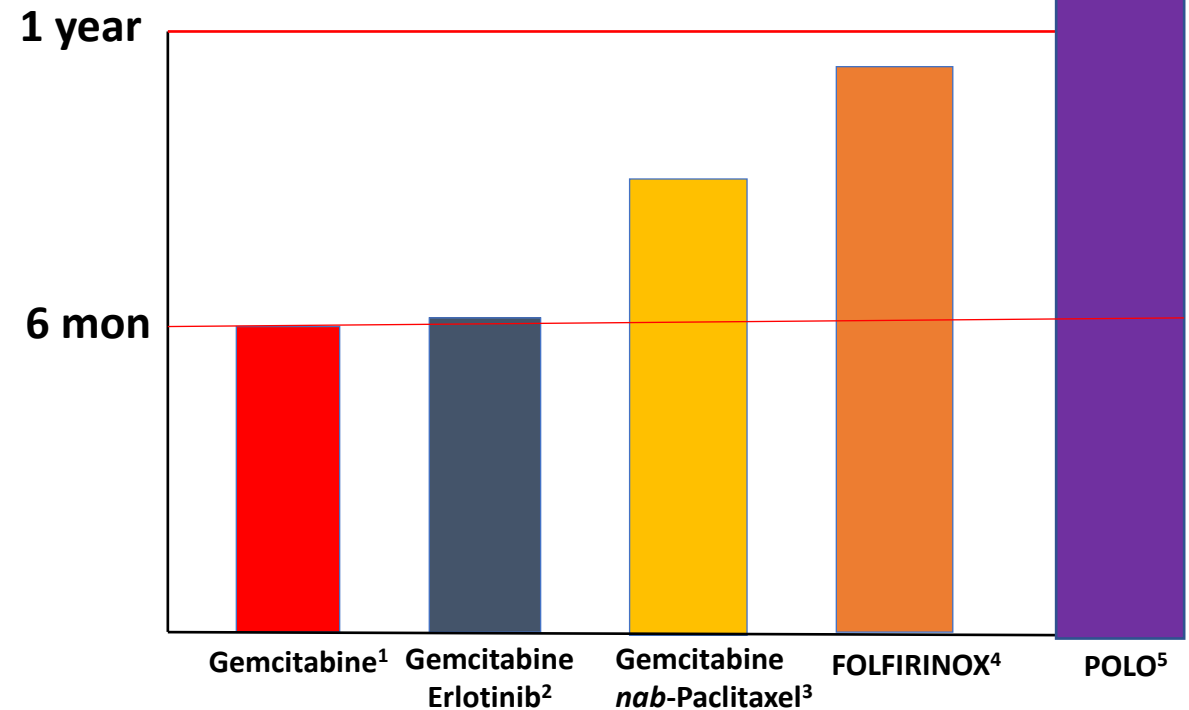
Operative bed following distal pancreatectomy and splenectomy.

Benefits

Toxicity



- Prolong survival
- Improve clinical symptoms
- Improve quality of life



1. Burris HA 3rd, et al. *J Clin Oncol*. 1997;15(6):2403-2413.

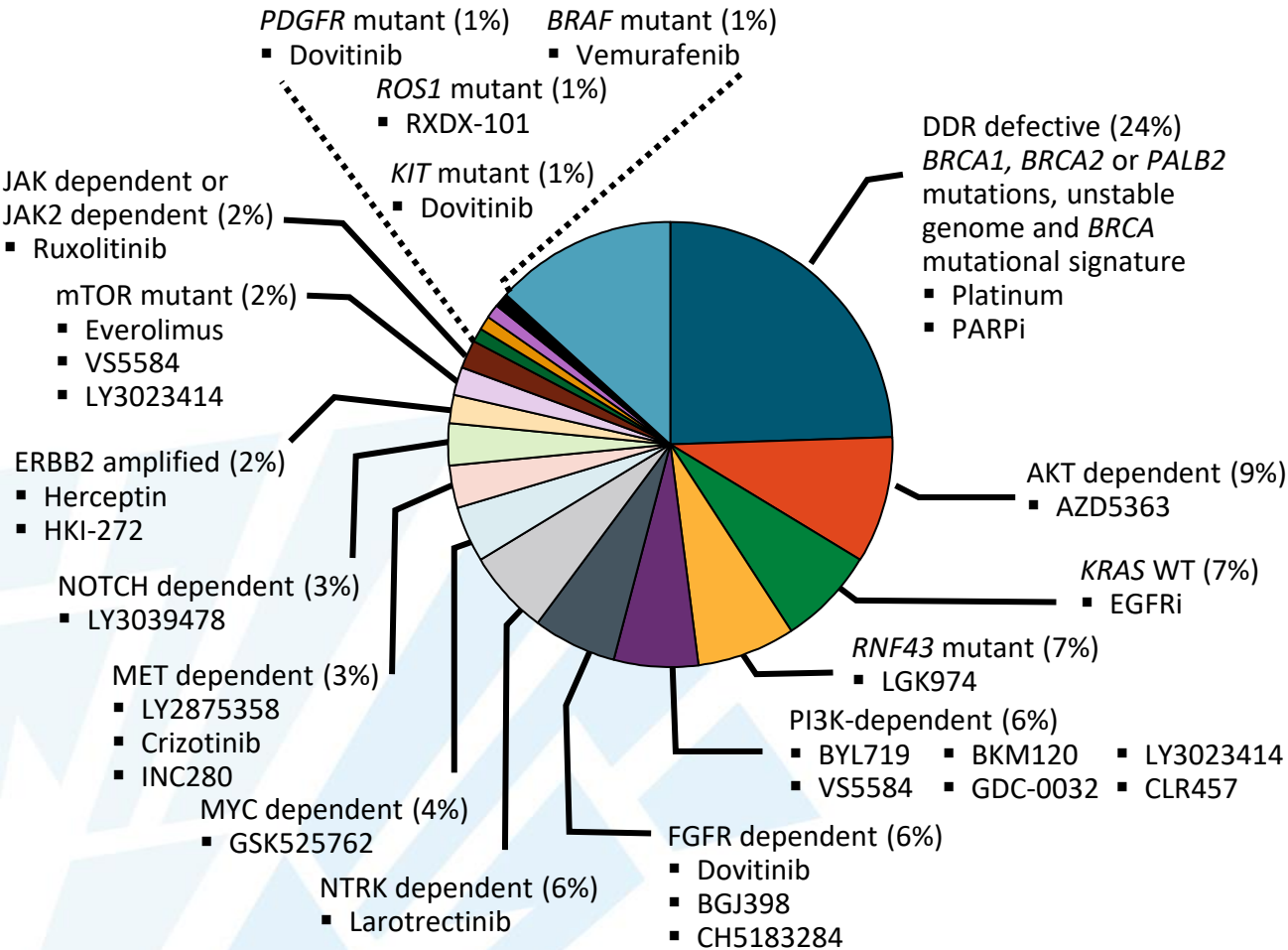
2. Moore MJ, et al. *J Clin Oncol*. 2007;25(15):1960-1966.

3. Von Hoff DD, ...Van Cutsem E et al. *N Engl J Med*. 2013;369(18):1691-1703.

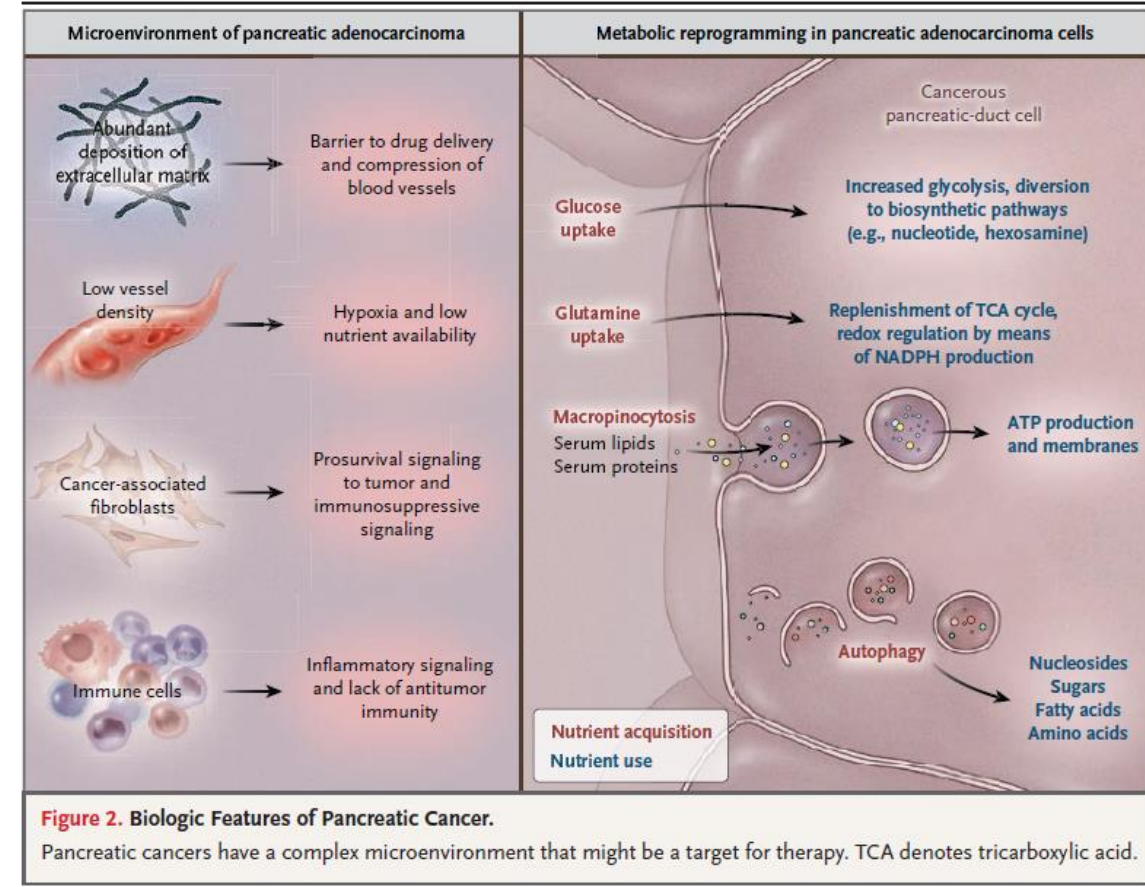
4. Conroy T, et al. *N Engl J Med*. 2011;364(19):1817-1825;

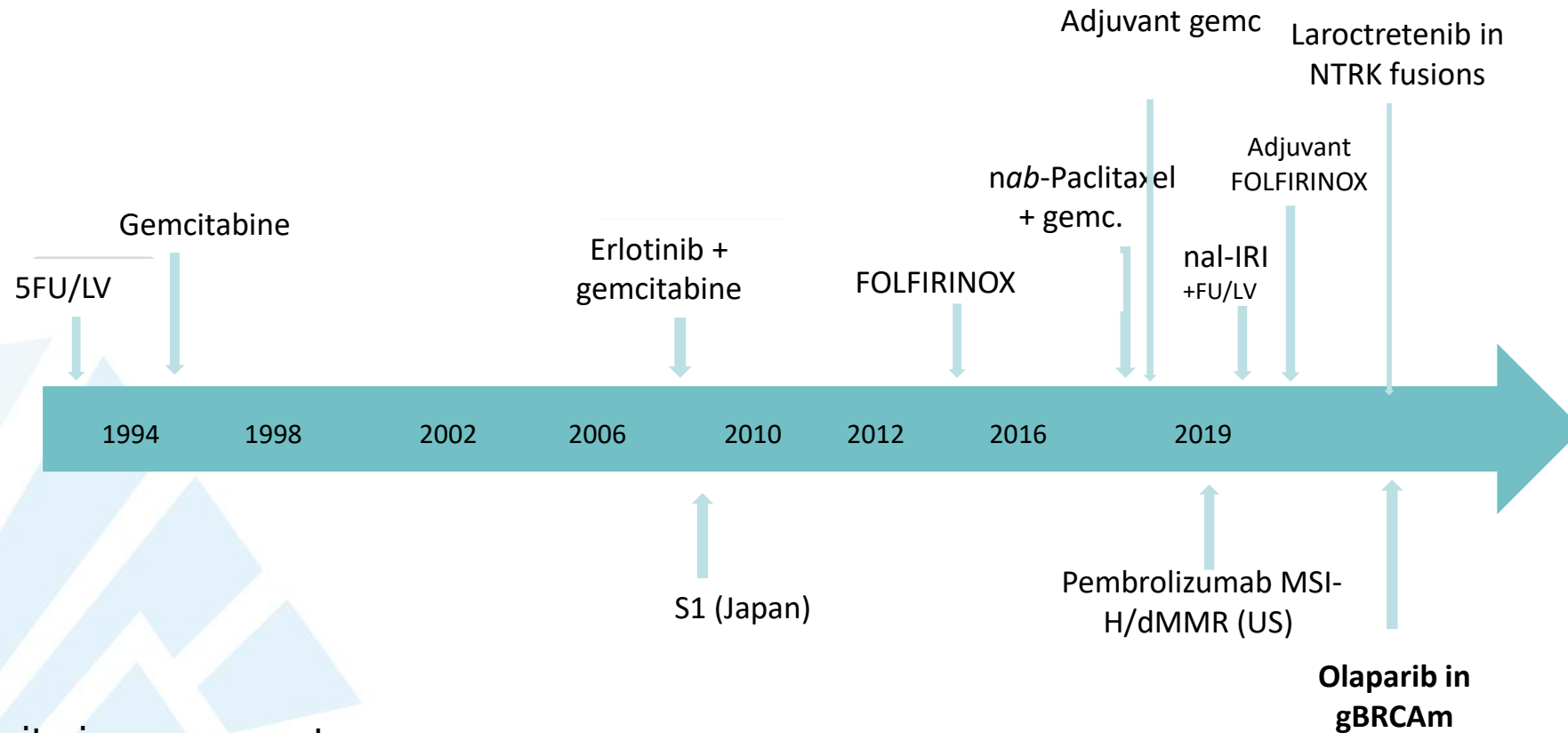
5. Golan T...Van Cutsem E et al, *NEJM*, 2019.

Many Druggable Alterations



But only very few with proven clinical activity

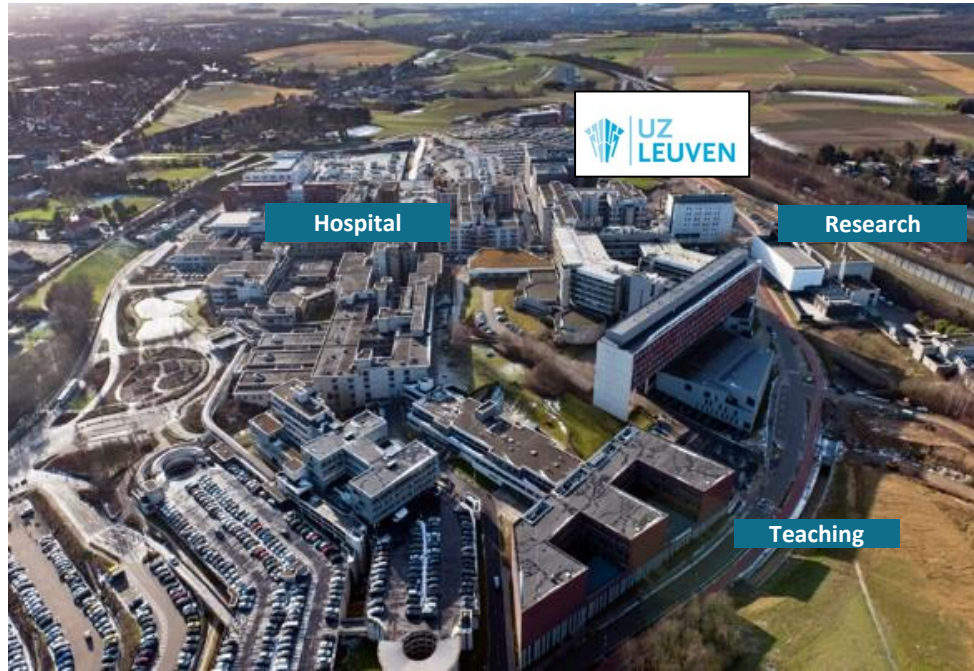




But despite improvements:

- ✓ Median survival remains under 1 year in advanced stages
- ✓ In early stage, 5-year survival rate is only about 20-25%: expertise, high volume, diagnostic excellence, laparoscopic surgery, interventional endoscopy, GI oncology expertise

Leuven, Belgium



- 25 km east of Brussel: ~ 100,000 inhabitants
- KUL: University founded in 1425: > 60,000 students:
 - ✓ Reuters World Ranking of Most Innovative Universities: Nr 7 in world; Nr 1 in Europe
- Largest Beer Brewery in world (>25% of world production)