Καρκίνος γαστρεντερικού

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Επιμελήτρια Α’, Παθολόγος Ογκολόγος

Α’ΠΚ, ΓΝΑ Λαικό

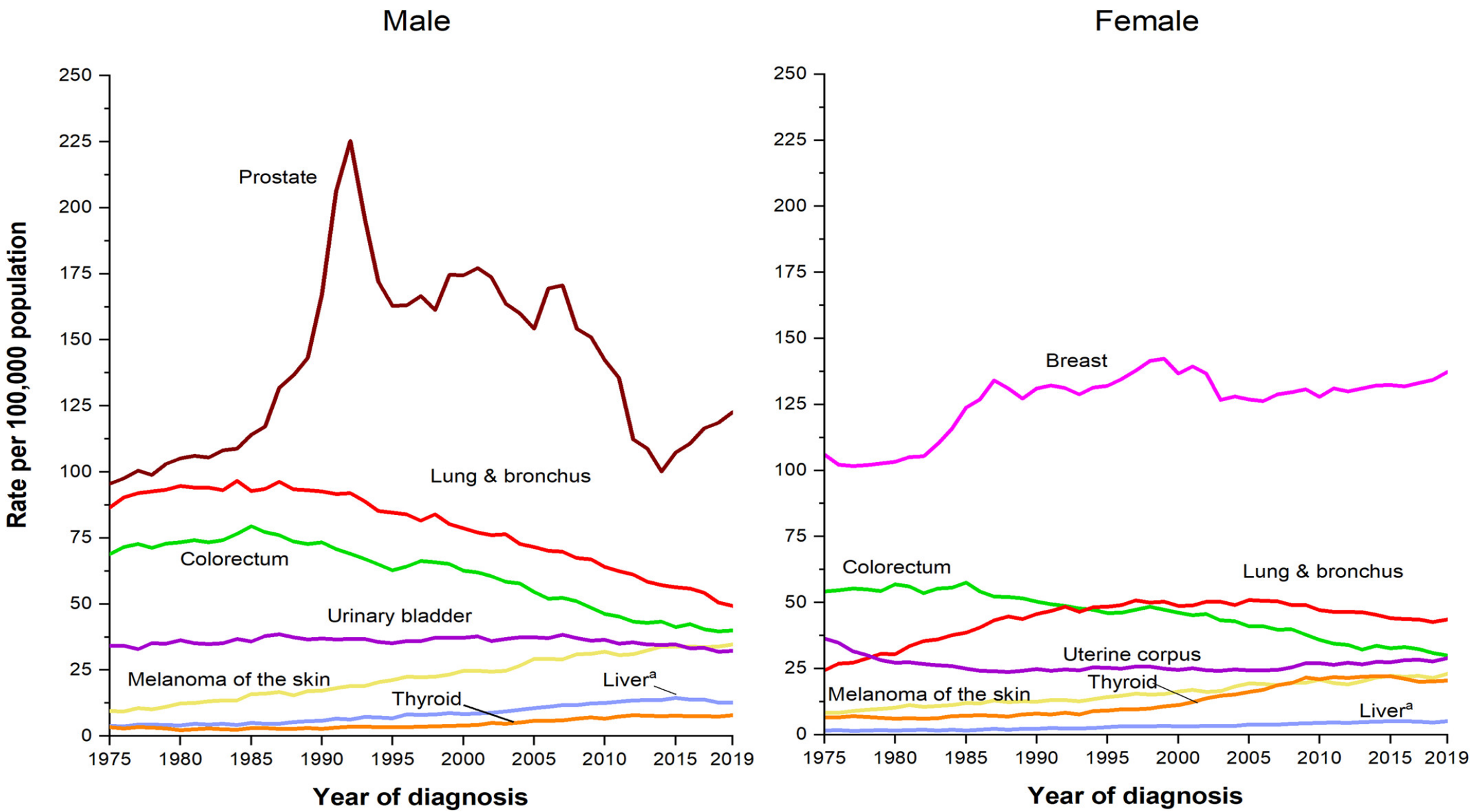
Estimated New Cases

Males				Females		
Prostate	288,300	29%		Breast	297,790	31%
Lung & bronchus	117,550	12%		Lung & bronchus	120,790	13%
Colon & rectum	81,860	8%		Colon & rectum	71,160	8%
Urinary bladder	62,420	6%		Uterine corpus	66,200	7%
Melanoma of the skin	58,120	6%		Melanoma of the skin	39,490	4%
Kidney & renal pelvis	52,360	5%		Non-Hodgkin lymphoma	35,670	4%
Non-Hodgkin lymphoma	44,880	4%		Thyroid	31,180	3%
Oral cavity & pharynx	39,290	4%		Pancreas	30,920	3%
Leukemia	35,670	4%		Kidney & renal pelvis	29,440	3%
Pancreas	33,130	3%		Leukemia	23,940	3%
All Sites	**1,010,310**	**100%**		**All Sites**	**948,000**	**100%**

Estimated Deaths

Males				Females		
Lung & bronchus	67,160	21%		Lung & bronchus	59,910	21%
Prostate	34,700	11%		Breast	43,170	15%
Colon & rectum	28,470	9%		Colon & rectum	24,080	8%
Pancreas	26,620	8%		Pancreas	23,930	8%
Liver & intrahepatic bile duct	19,000	6%		Ovary	13,270	5%
Leukemia	13,900	4%		Uterine corpus	13,030	5%
Esophagus	12,920	4%		Liver & intrahepatic bile duct	10,380	4%
Urinary bladder	12,160	4%		Leukemia	9,810	3%
Non-Hodgkin lymphoma	11,780	4%		Non-Hodgkin lymphoma	8,400	3%
Brain & other nervous system	11,020	3%		Brain & other nervous system	7,970	3%
All Sites	**322,080**	**100%**		**All Sites**	**287,740**	**100%**

CA A Cancer J Clinicians, Volume: 73, Issue: 1, Pages: 17-48, First published: 12 January 2023, DOI: (10.3322/caac.21763)

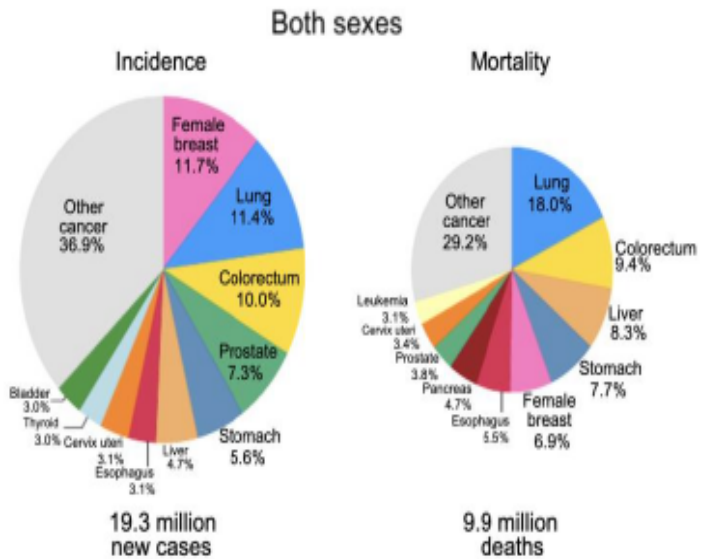

Male
Female
Rate per 100,000 population
250
225
200
175
150
125
100
75
50
25
0
1975
1980
1985
1990
1995
2000
2005
2010
2015
2019
Year of diagnosis
Prostate
Lung & bronchus
Colorectum
Urinary bladder
Melanoma of the skin
Liver[a]
Thyroid
Breast
Colorectum
Lung & bronchus
Uterine corpus
Thyroid
Melanoma of the skin
Liver[a]
Year of diagnosis

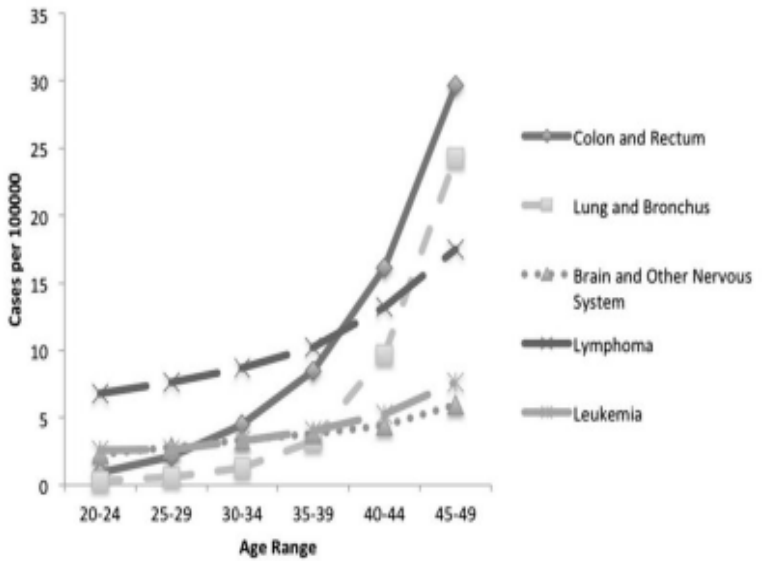
ΚΑΡΚΙΝΟΣ ΠΑΧΕΟΣ ΕΝΤΕΡΟΥ

COLON CANCER IS A PROBLEM OF HEALTH

Estimates incidence and Mortality of CRC

- Colorectal cancer (CRC) ranks third in terms of incidence and second in terms of mortality.
- Mortality declines in developed countries: Improved cancer management, screening and early detection programs





1. Sung et al. CA Cancer J Clin 2021 May;71(3):209-249, 2. Bhandari A et al. J Investig Med. 2017;65(2):311-315, 3. Akimoto N et al Nat Rev Clin Oncol 2021 Apr;18(4):230-243

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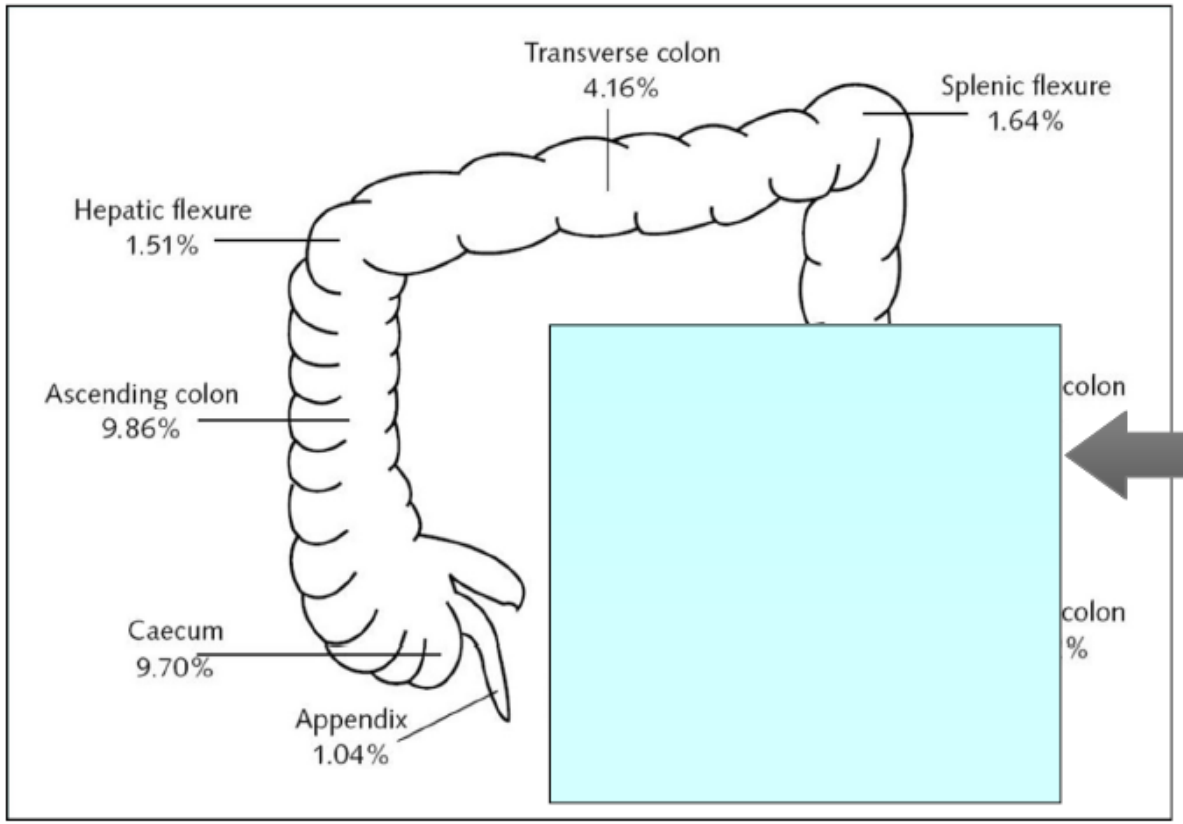
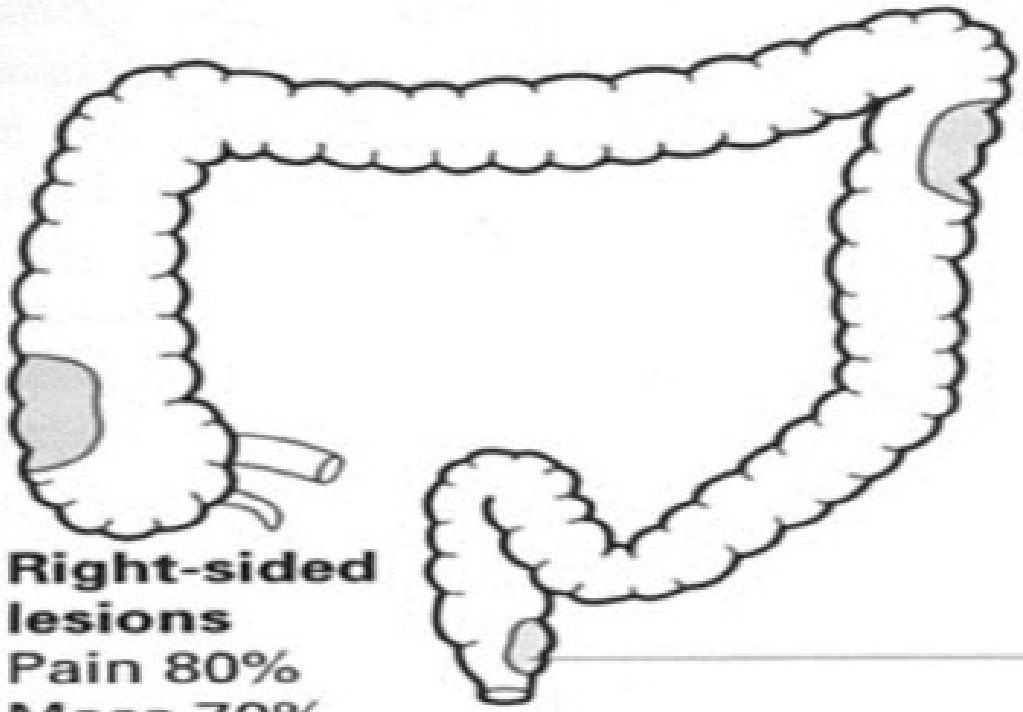
What is CRC?

Where does CRC occur?



60% in this part of the large bowel

Symptoms associated with CRC



Left colon
Pain 60%
Mass 40%
Bleeding 20%
Change in bowel habit 60%
Weight loss 15%
Vomiting 10%
Obstruction 20%

Right-sided lesions
Pain 80%
Mass 70%
Rectal bleeding 20%
Diarrhoea + change in bowel habit 40%
Weight loss 50%
Vomiting 30%
Obstruction 5%

Rectum
Pain 5%
Mass 0%
Bleeding 60%
Change in bowel habit 80%
Weight loss 25%
Vomiting 0%
Obstruction 5%

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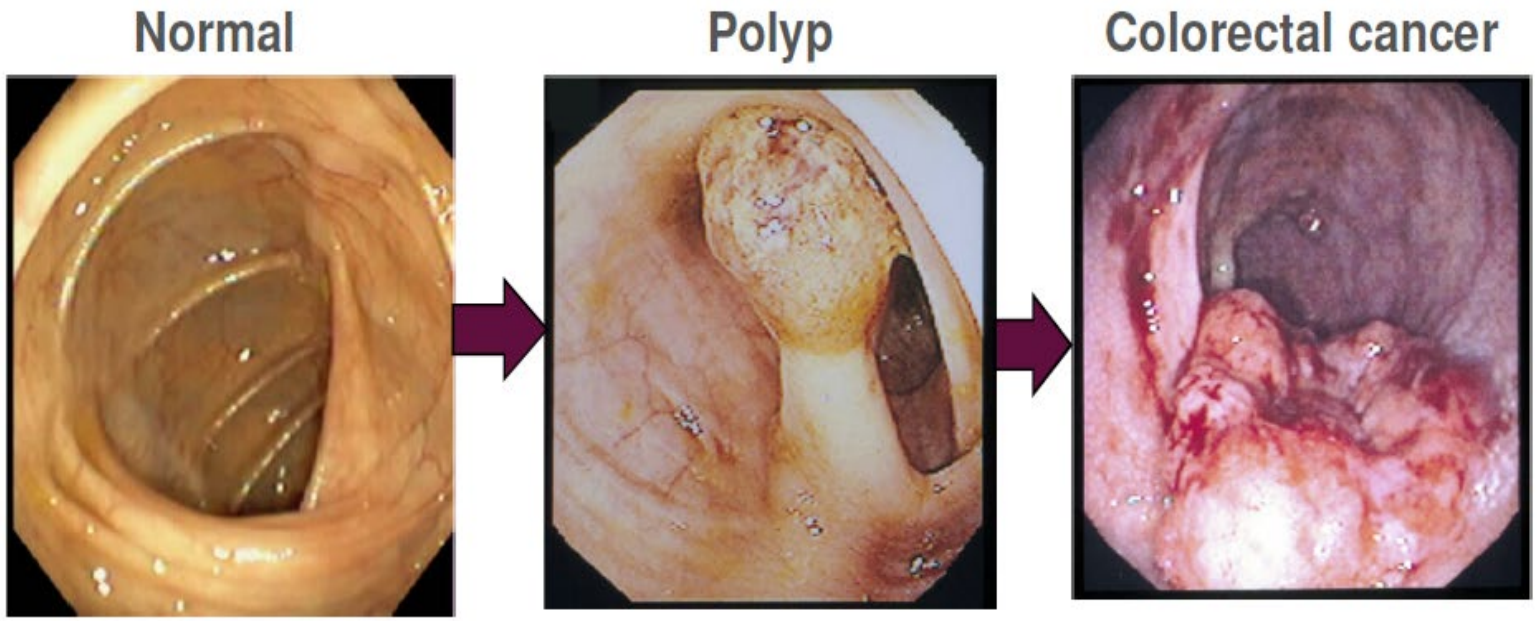
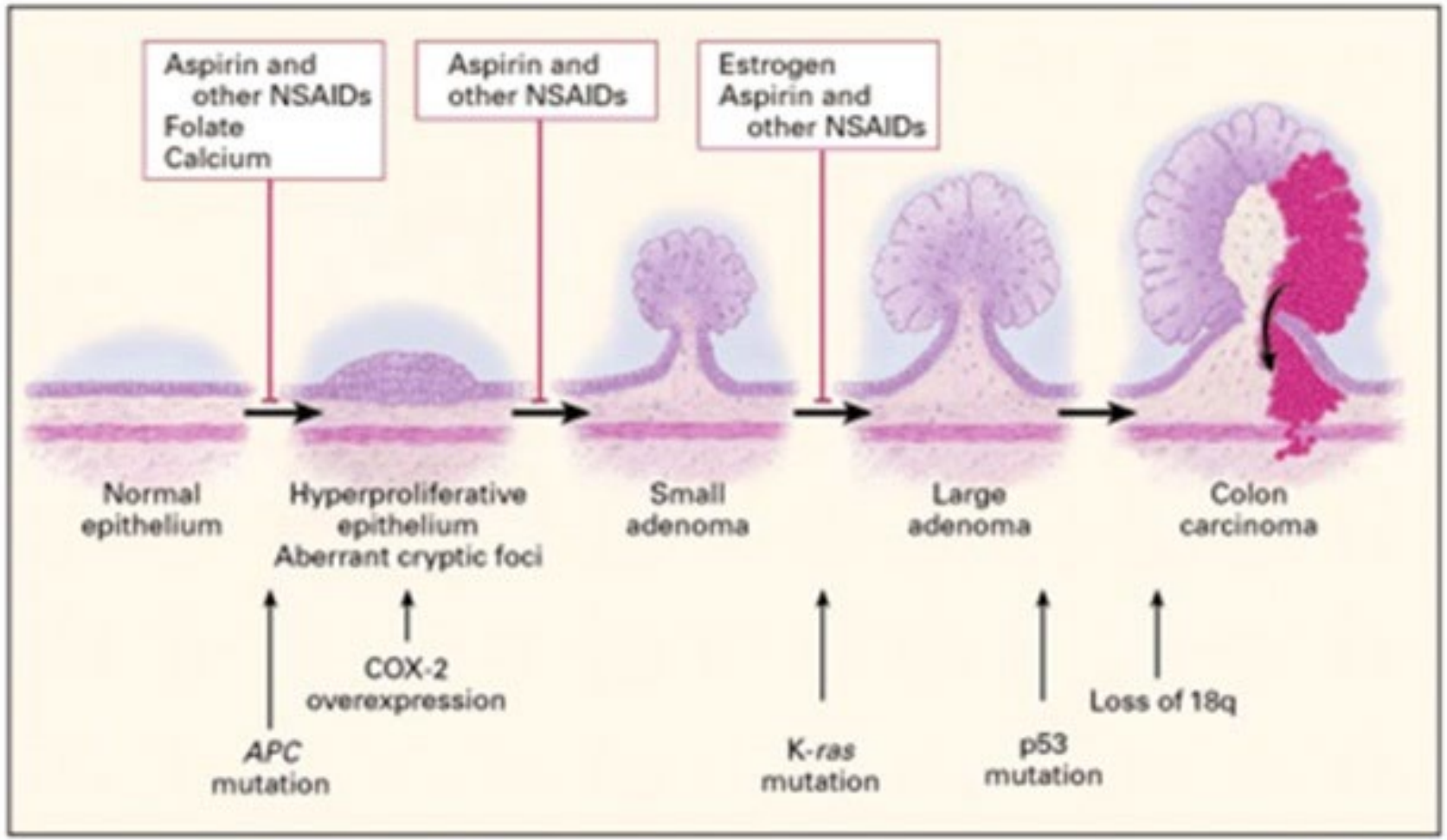
Wilson & Jungner: Pre-clinical phase: Slow progression from adenoma (polyp) to cancer

- Colorectal cancer often starts with polyps





Colon cancers result from a series of pathologic changes that transform normal epithelium into invasive carcinoma. Specific genetic events, shown by vertical arrows, accompany this multistep process.

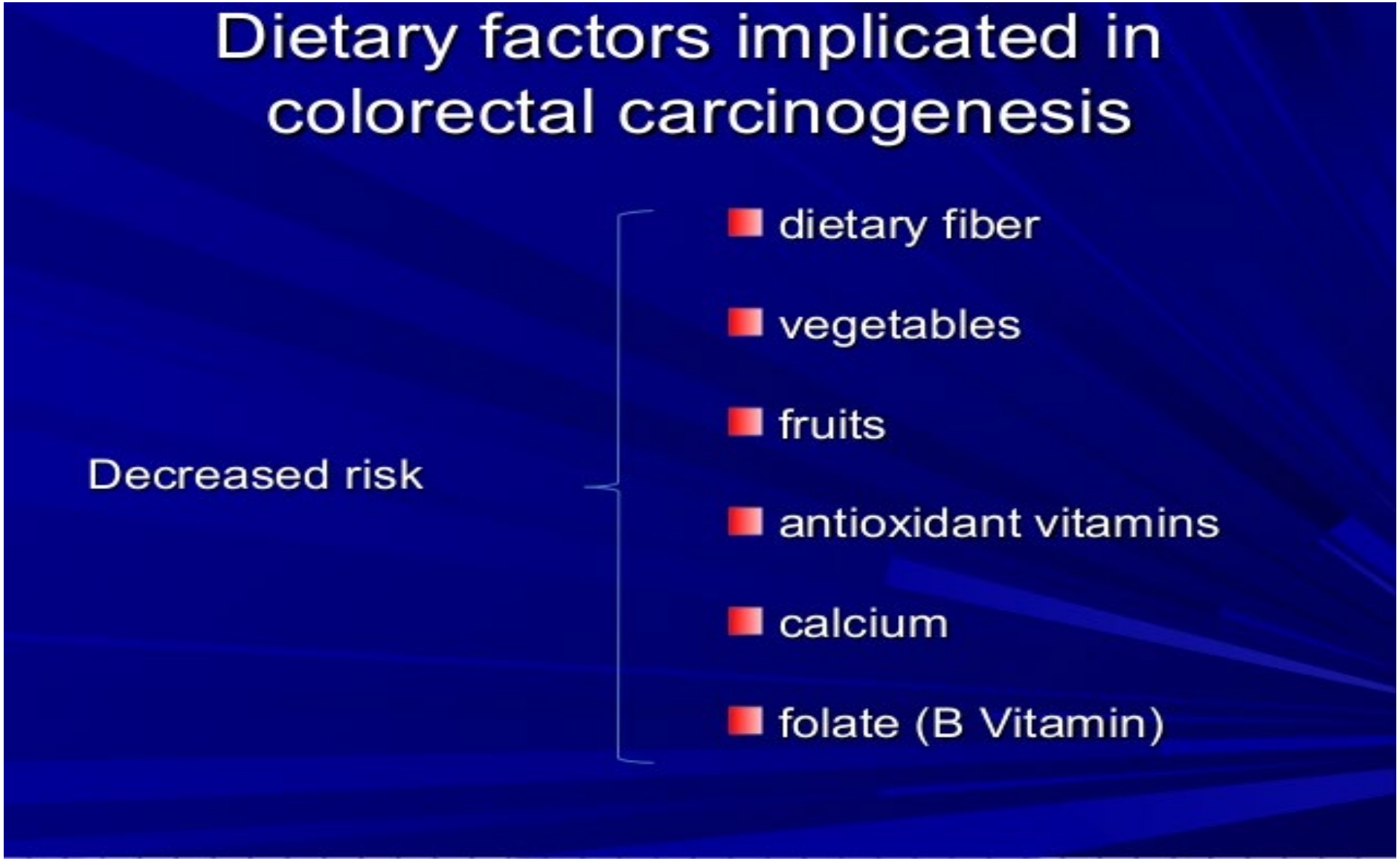
Risk factors for CRC

- Age
- Adenomas, Polyps
- Sedentary lifestyle, Diet, Obesity
- Family History of CRC
- Inflammatory Bowel Disease (IBD)
- Hereditary Syndromes (familial adenomatous polyposis (FAP))

Dietary factors implicated in colorectal carcinogenesis

Increased risk

- consumption of red meat
- animal and saturated fat
- refined carbohydrates
- alcohol


Dietary factors implicated in colorectal carcinogenesis
Decreased risk
dietary fiber
vegetables
fruits
antioxidant vitamins
calcium
folate (B Vitamin)

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CRC: primary prevention

- Healthy life style:
  - Eating healthy and balanced and exercise

  - Don't smoke

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CRC – ideal candidate for screening

- High incidence and mortality in the Western world
- Slow progression from adenoma to carcinoma (large 'window of opportunity' (10-15 years) in which removing of the polyp or early CRC is resulting into recovery)
- High patient survival in case of early detection and removing of the polyps or the cancer by colonoscopy or surgery
- CRC-screening (FOBT) can reduce mortality by about 15%*

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FOBT

- FOBT means Faecal Occult Blood Test
- Since adenomas and CRC are bleeding regularly, the blood, which can not be seen with the naked eye, can be found in the stool when analysed properly
- There is a guajac based FOBT (gFOBT - Hemoccult) and an immunochemical FOBT (iFOBT)
- Until now, only for the gFOBT, there are Randomised Controlled Trials (RCTs) indicating a cause-specific mortality reduction
- However, since the iFOBT is based on the same mechanism, it is very plausible that it is also leading to a cause-specific mortality reduction

Screening

⦿Στα 50 ένα απ΄τα παρακάτω:
Πολύποδες + Ca
-Σιγμοειδοσκόπηση κάθε 5 χρόνια
-Κολονοσκόπηση κάθε 10 χρόνια
-Βαριούχος υποκλυσμός κάθε 5 χρόνια
-CT colonography κάθε 5 χρόνια
Ca
-FOBT κάθε χρόνο
-FIT κάθε χρόνο
-Stool DNA κάθε χρόνο
⦿Πιο συχνά screening
-personal history of CRC/history
-personal history of inflammatory bowel disease
-Family history of CRC/polyps
-FAP/HNSCC

GENETICS

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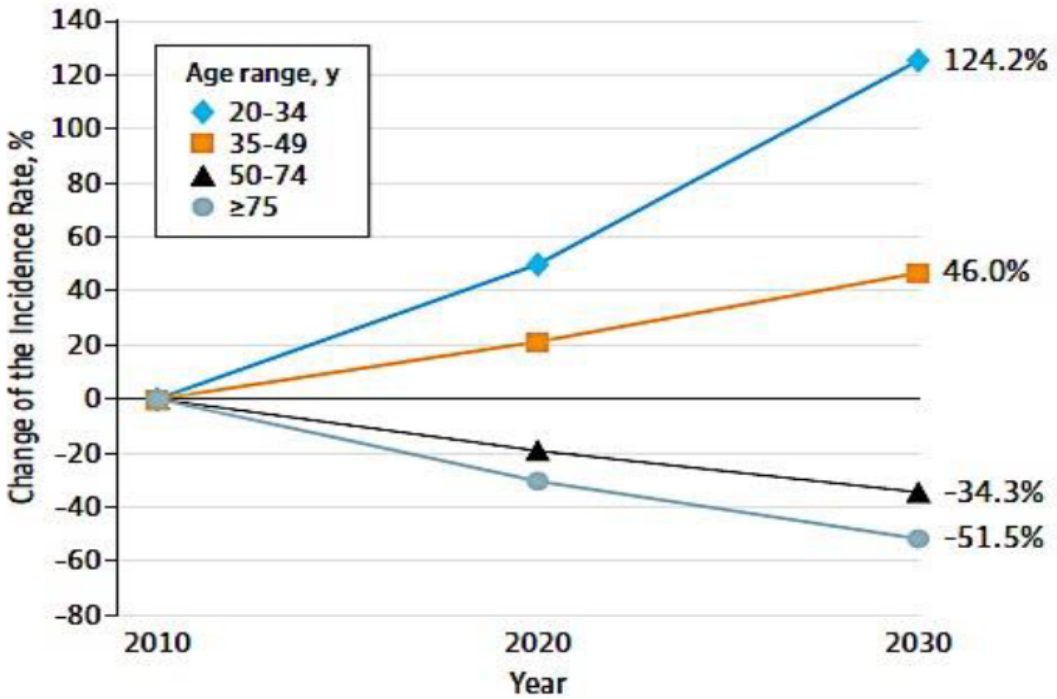
Prediction is more worrisome



Annual percentage change-based predicted incidence rates of rectosigmoid and rectal cancers by age compared with incidence rate in 2010

Bailey CE, *et al*. JAMA Surgery. 2015;150:17-22.

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Hereditary CRC syndromes

Table 1. Genes and Syndromes Linked to Hereditary Risks of CRC

Syndrome	Acronym	Alternate Name	Associated Gene(s)	Key Phenotypic Characteristics
Lynch syndrome		Hereditary nonpolyposis colorectal cancer, Muir-Torre syndrome	*MLH1, MSH2, MSH6, PMS2, EPCAM*	Risk of other cancers (endometrial, ovarian, gastric, small bowel, urothelial, hepatobiliary, pancreatic, brain), sebaceous adenomas/carcinomas
Familial adenomatous polyposis	FAP	Gardner syndrome	*APC*	Duodenal/ampullary neoplasia, thyroid neoplasia, desmoid tumors, brain tumors, fundic gland polyps, osteomas
MUTYH-associated polyposis	MAP		*MUTYH*	Autosomal recessive inheritance; variable degree of polyposis; colorectal cancers/polyps may be more likely to harbor *KRAS* G12C mutations
Peutz-Jeghers syndrome			*STK11*	Mucocutaneous pigmentation, Peutz-Jegher hamartomas in small and/or large bowel, risk of other cancers (breast, pancreatic)
Juvenile polyposis coli			*SMAD4, BMPR1A*	Large and/or small bowel juvenile polyps, gastric cancer risk, some patients with congenital heart defects and/or hereditary hemorrhagic telangiectasia
PTEN hamartoma tumor syndrome		Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome	*PTEN*	Macrocephaly, colorectal hamartomas, trichilemmomas, risk of other cancers (breast, thyroid, uterine, kidney)
Li-Fraumeni syndrome			*TP53*	Risk of multiple early-onset cancers (leukemia, sarcoma, premenopausal breast cancer, adrenal cancer, brain tumors)
Polymerase proofreading-associated polyposis	PPAP		*POLD1, POLE*	Not fully defined; low-level colorectal polyposis; may increase risk of endometrial cancer; cancers may be preferentially microsatellite stable
Familial colorectal cancer type X	FCCX		Likely numerous genes; mostly unknown	Microsatellite-stable CRC involving multiple generations; absence of gastrointestinal polyposis

Abbreviation: CRC, colorectal cancer.

Yurgelum M, *et al.* J Clin Oncol. 2015;33:388-93.

Screening for high-risk people

- A first-degree relative (sibling, parent, child) who has had colorectal cancer or an adenomatous polyp:

  Screening should begin at age 40 years

- Family history of familial adenomatous polyposis (FAP):

  Screening should begin at puberty

  Sigmoidoscopy - annually, beginning at age 10 to 12 years

  Colonoscopy - every five years

- Family history of hereditary nonpolyposis colorectal cancer (HNPCC):

  Screening should begin at age 21 years

  Sigmoidoscopy - annually, beginning at age 10 to 12 years

  Colonoscopy - every one to two years, beginning at age 20 to 25 years or 10 years younger than the earliest case in the family, whichever comes first

- Personal history of adenomatous polyps

  Screening should be based on pathological findings

  Advanced or multiple adenomas (3 or greater): First follow-up colonoscopy should occur in 3 yrs

  1 or 2 small (< 1 cm) tubular adenomas: First follow-up colonoscopy should occur at 5 years

- Personal history of colorectal cancer:

  After colon resection

  Approximately six months after the surgery

  If the colonoscopy performed at six months is normal, subsequent colonoscopy should be repeated at 3 years and then if normal, every 5 years

- Personal history of inflammatory bowel disease

  Every one to two years after an eight year history of the disease with pancolitis or

  Every one to two years after 15 years history of left-sided colitis or

  For all patients beginning with eight to ten years of disease to document the extent of the disease

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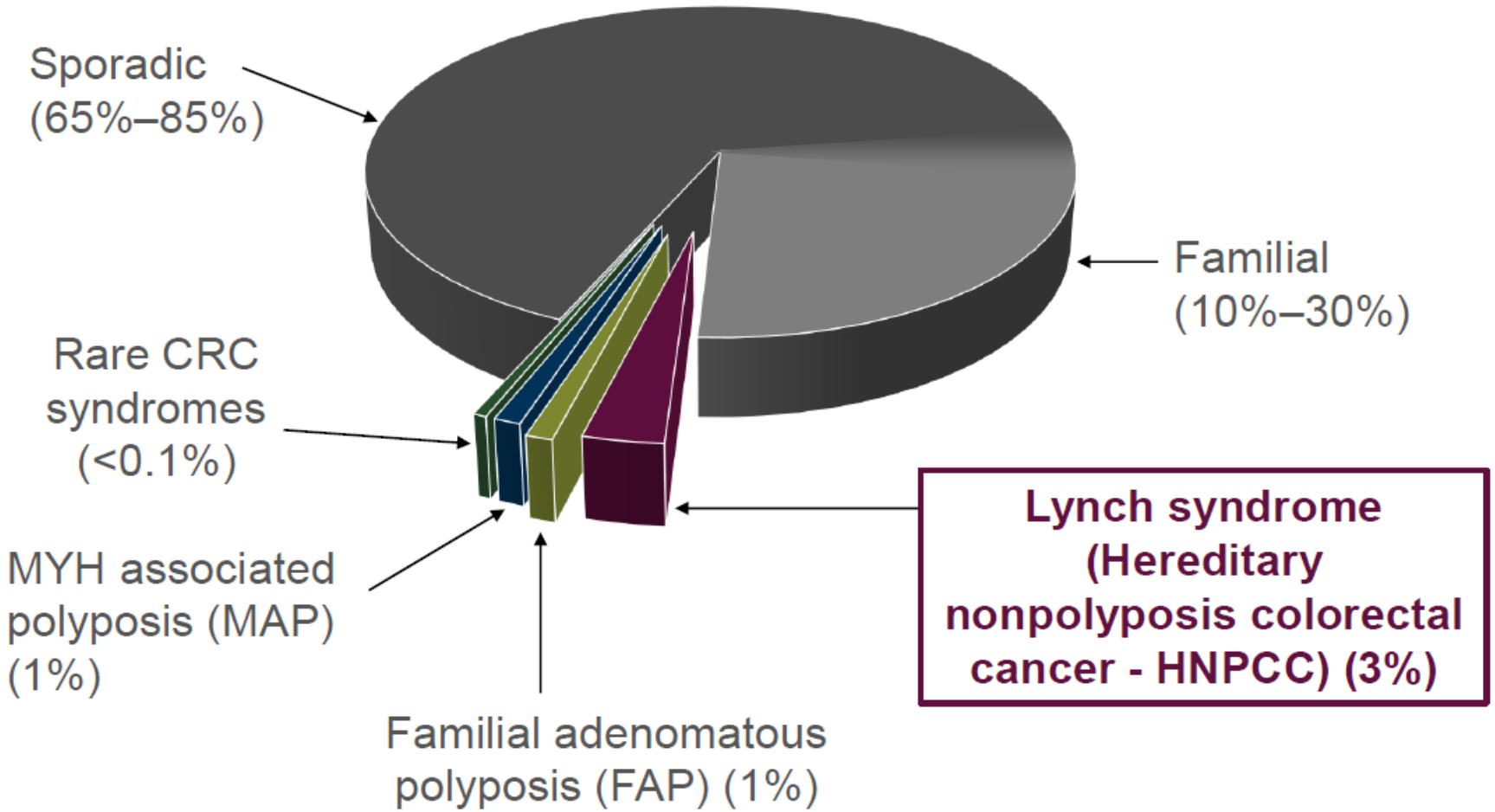
Genetics of CRC



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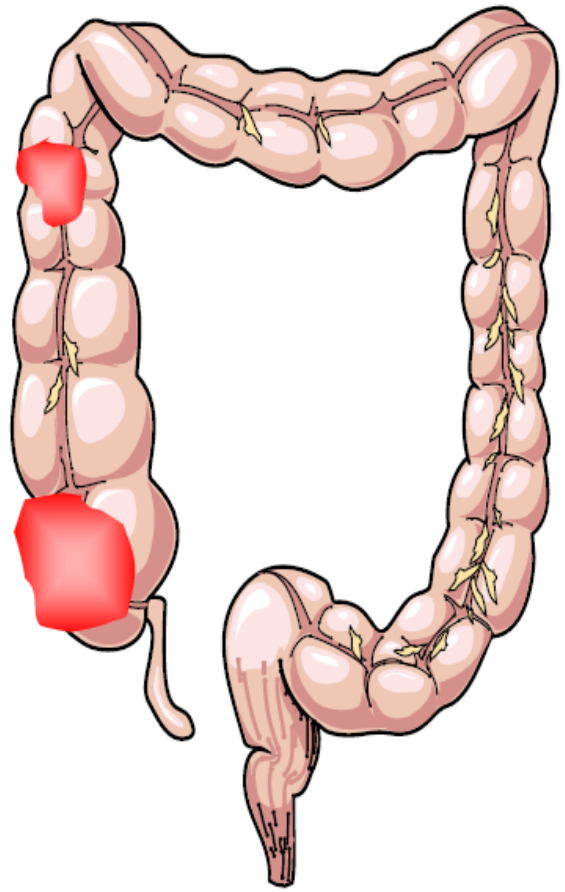
Clinical features of Lynch Syndrome

- Early onset of CRC (~45 years)
- Proximal colon predominantly
- Lymphocytic infiltration
- Endometrial and other cancers:
  any abdominal organ but RCC,
  PLUS sebaceous skin and brain tumours
- Second CRC primaries (~50%)



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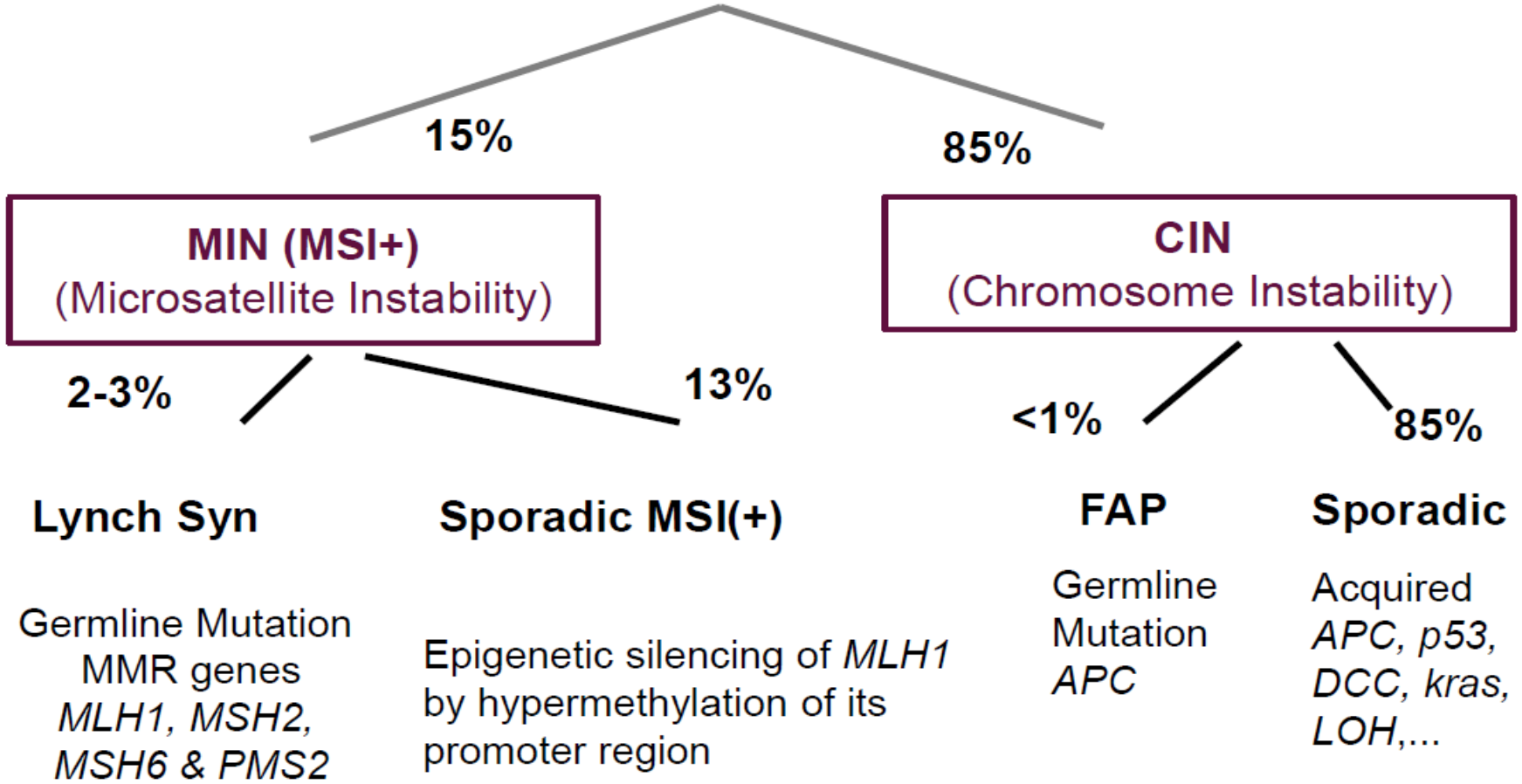
Colorectal cancer



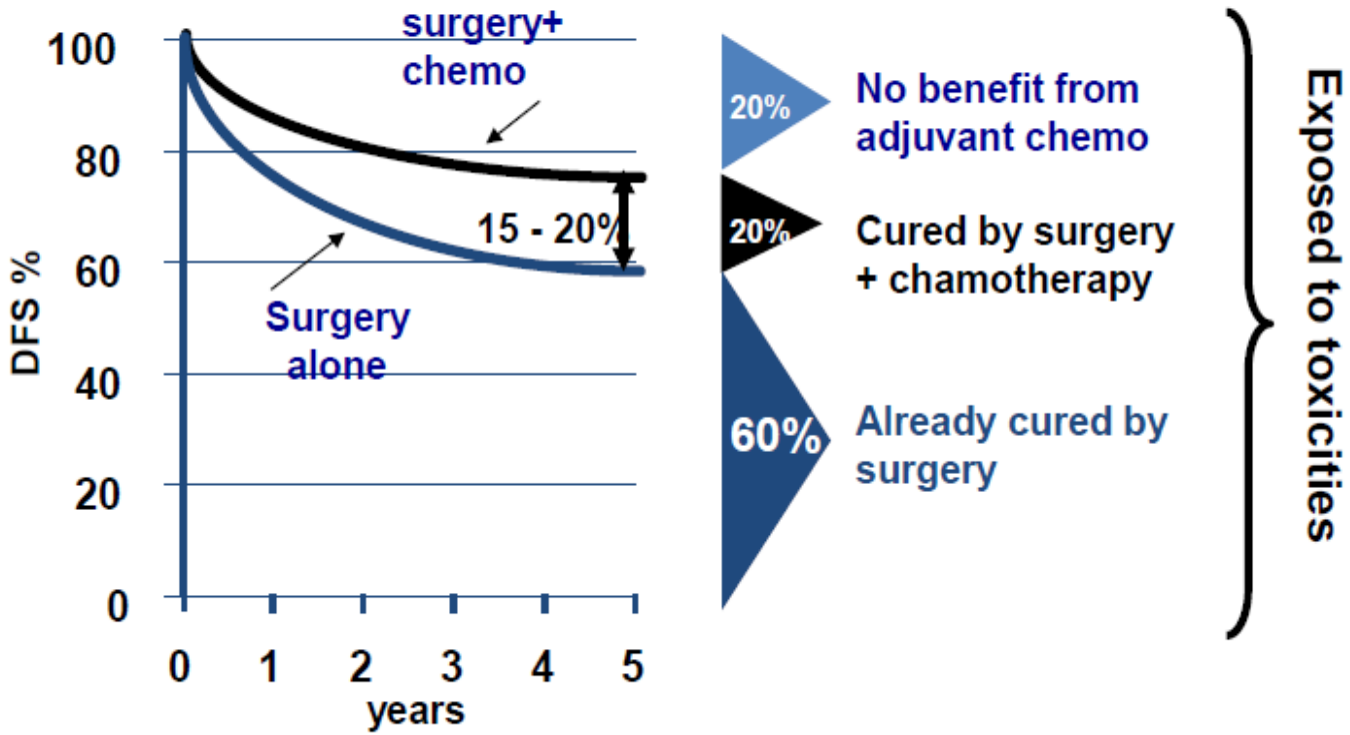
Work-up

- Once diagnosis is established, local and distant extent of disease determined
- Review of biopsy specimen important assessing need for clinical staging studies and surgical resection
- Polyps with an area of invasive malignancy that have been completely removed and lack associated adverse histologic features (positive margin, poor differentiation, lymphovascular invasion) have low risk of spread; polypectomy alone may be adequate. This is more easily determined if the polyp is pedunculated.

Work-up

- CEA >5 ng/mL worse prognosis, stage for stage
- CEA that does not normalize following surgery implies persistent disease
- CT abdomen/pelvis for stage II, III and IV
- Chest CT high rate of indeterminate nodules, may be reserved for patients with rectal cancer or other distant metastatic sites
- Liver MR if potentially resectable hepatic metastases
- PET may be helpful with persistent/rising CEA, or prior to resection of metastases

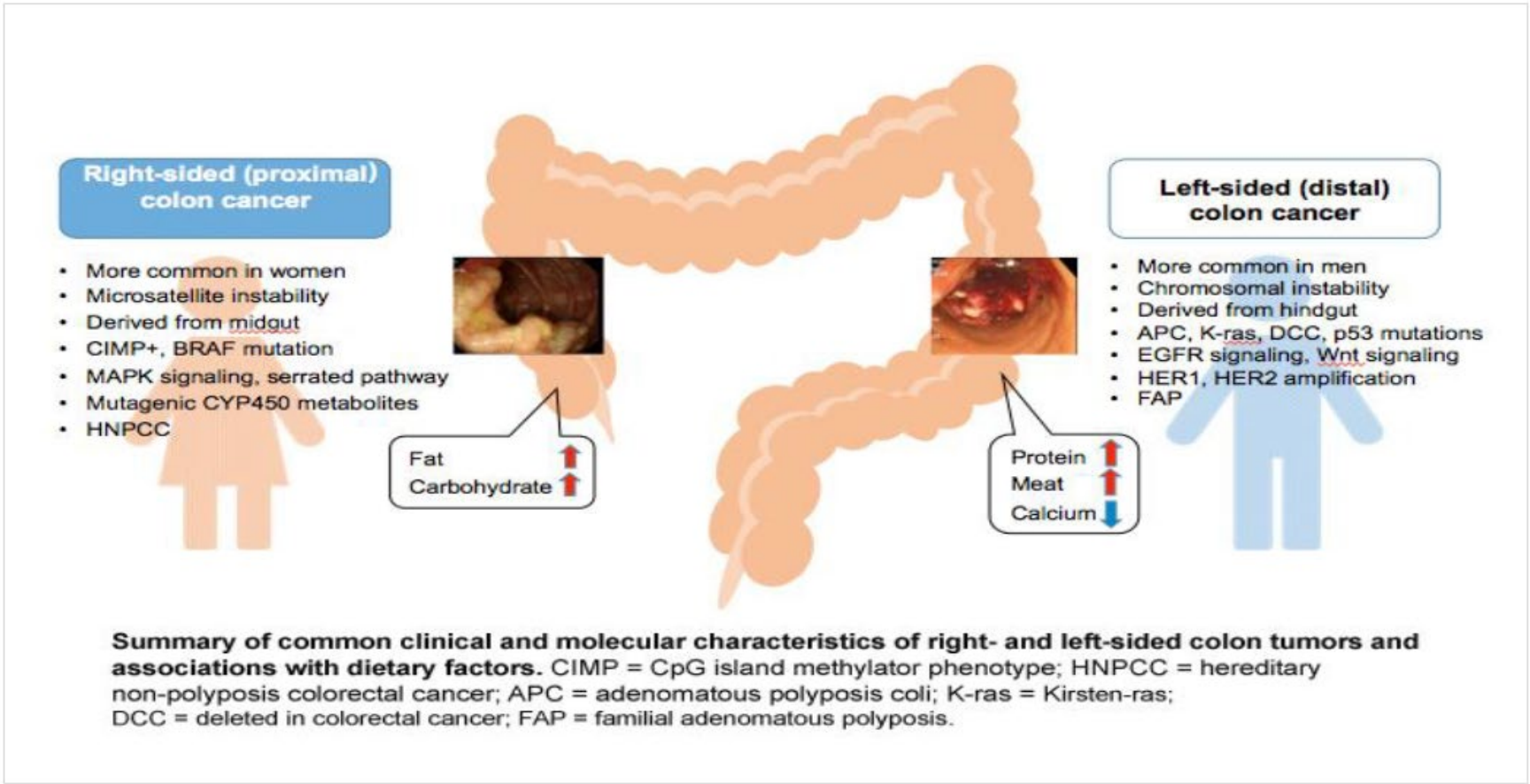
Adjuvant chemo for stage III: What benefit?



Certainties

- ✓ Oxaliplatin-based chemotherapy is the standard treatment for stage III
- ✓ FPs adjuvant chemotherapy maintains its efficacy in adequately selected elderly patients
- ✓ No improvement with antiVEGF and EGFR's inhibitors combinations
- ✓ The sooner adjuvant treatment is given, the higher is the benefit

A „re-discovered“ decision maker: Localisation of primary tumour

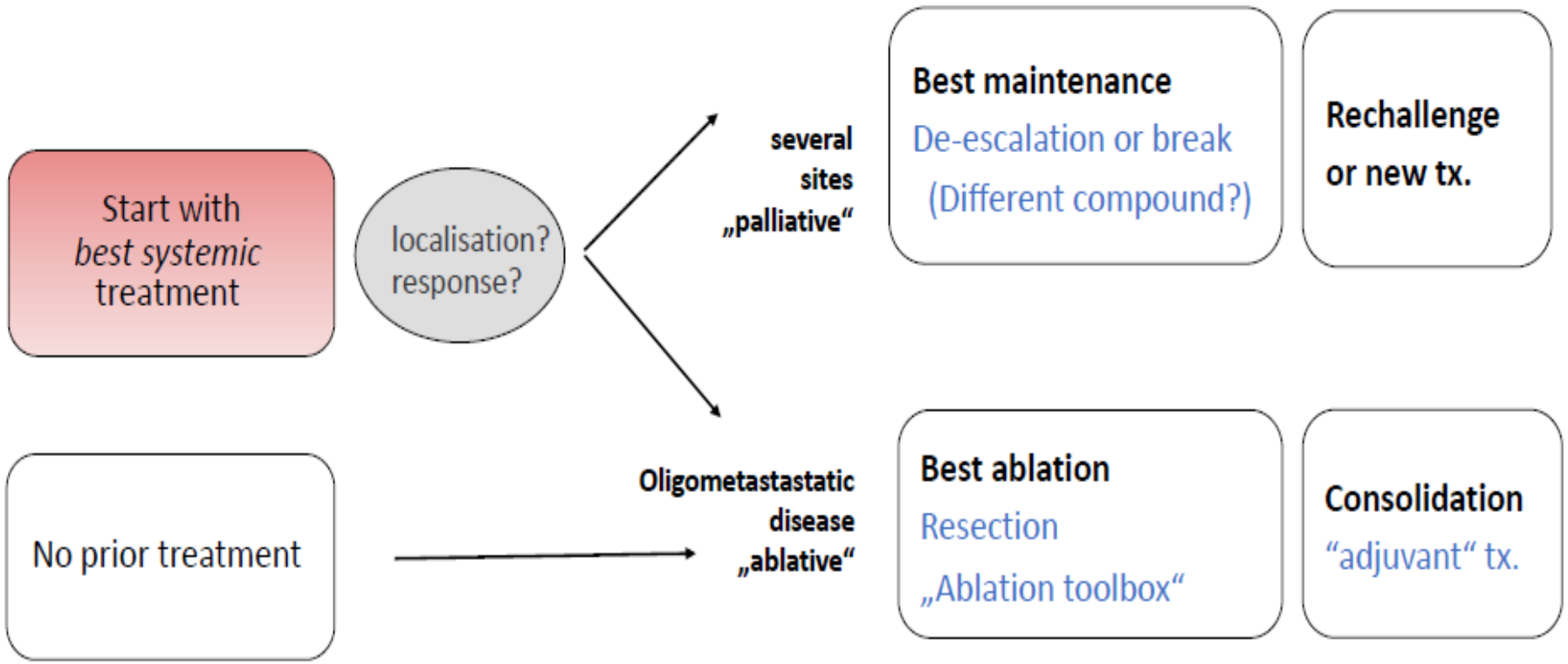


Summary of common clinical and molecular characteristics of right- and left-sided colon tumors and associations with dietary factors. CIMP = CpG island methylator phenotype; HNPCC = hereditary non-polyposis colorectal cancer; APC = adenomatous polyposis coli; K-ras = Kirsten-ras; DCC = deleted in colorectal cancer; FAP = familial adenomatous polyposis.

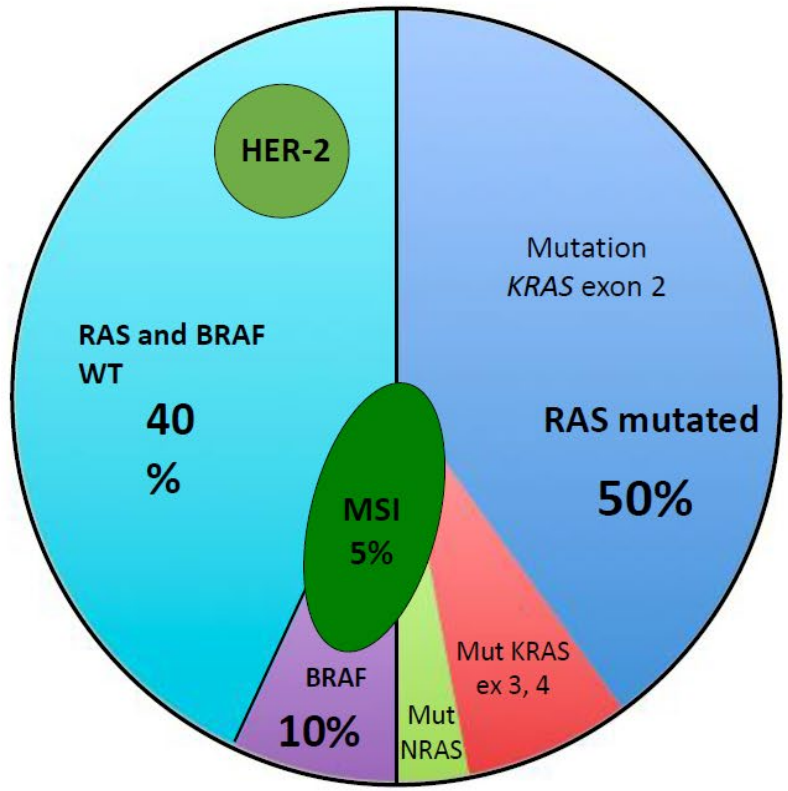
Ng et al., World J Gastroenterol 2015

Principles in 1st line mCRC treatment

FIT PATIENTS



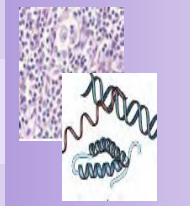
Genomic markers in mCRC with (potential) existing tx options



SPECTAcolor: Folprecht et al., ESMO 2016

Proposed ESMO consensus: Therapy should be individualized

Tumour	• Clinical presentation; symptoms; speed of progression
	• TNM stage; tumor burden; tumor localization
	• Tumor biology: RAS/BRAF status
Patient	• Age
	• Performance status
	• Organ function
	• Comorbidities
Treatment	• Toxicity profile
	• Flexibility
	• Therapy intent
	• QoL, patient expectations and preferences



1. Van Cutsem E, et al. 'The ESMO consensus on metastatic CRC – 2015' (presented at WCGC 2015); available at http://web.oncoletter.ch/files/cto_layout/Kongressdateien/WCGIC2015/ESMO%20Guidelines%20

Μεταστατικός καρκίνος παχέος εντέρου

- Βάση της θεραπείας η ΧΜΘ (5-FU based)
- Τοπικές θεραπείες (RF, chemoembolization, μεταστασεκτομές)
- Στοχεύουσες θεραπείες (ani-VEGF, anti-EGFR) αναλόγως μοραικού προφίλ
- Ανοσοθεραπεία σε MSI high

ΚΑΡΚΙΝΟΣ ΟΡΘΟΥ

DEFINITIONS

Rectal cancer:

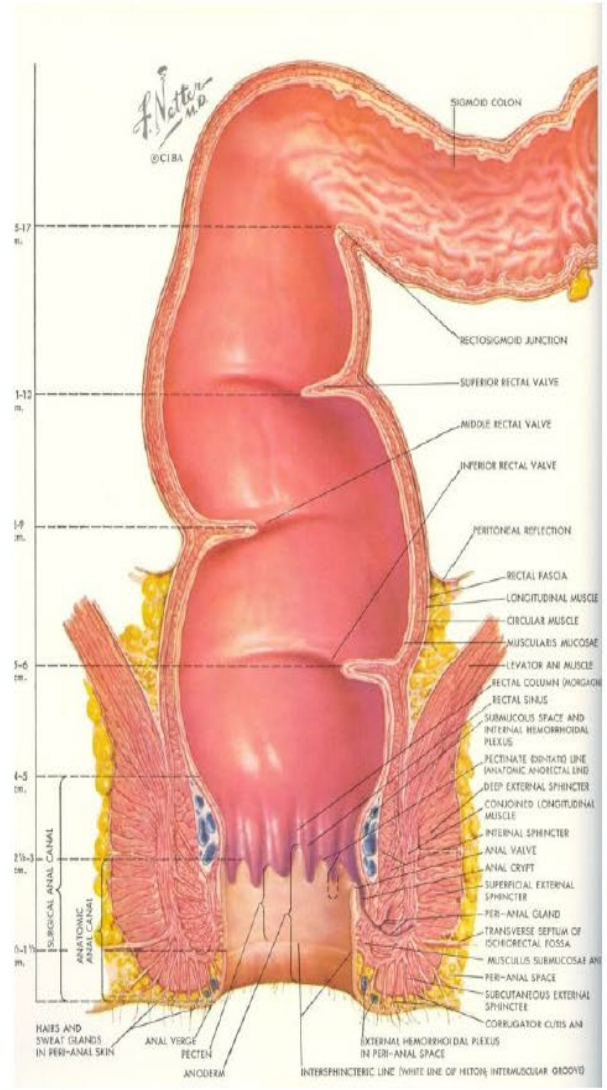
Adenocarcinoma with tumour < 15 cm from anal verge measured by a rigid rectoscope.

Or based on MRI criteria ("sigmoid take-off") or surgical criteria (subperitoneal/fixed part).

LARC: no universal consensus

cT3-4 or any N+

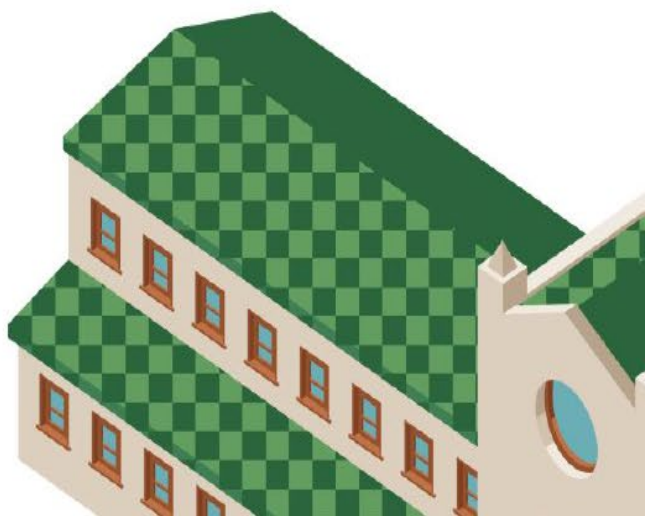
No R0 resection is expected or higher risk of LR



CLINICAL WORK-UP
THE "MANDATORY" BASICS

- ✓ Colonoscopy incl. biopsy
- ✓ Digital rectal examination/Rigid rectoscopy
- ✓ CT scan of thorax/abdomen
- ✓ **MRI of pelvis**
- ✓ Performance status, organ function, CEA

- ✓ Multidisciplinary Tumour Board (MDT)

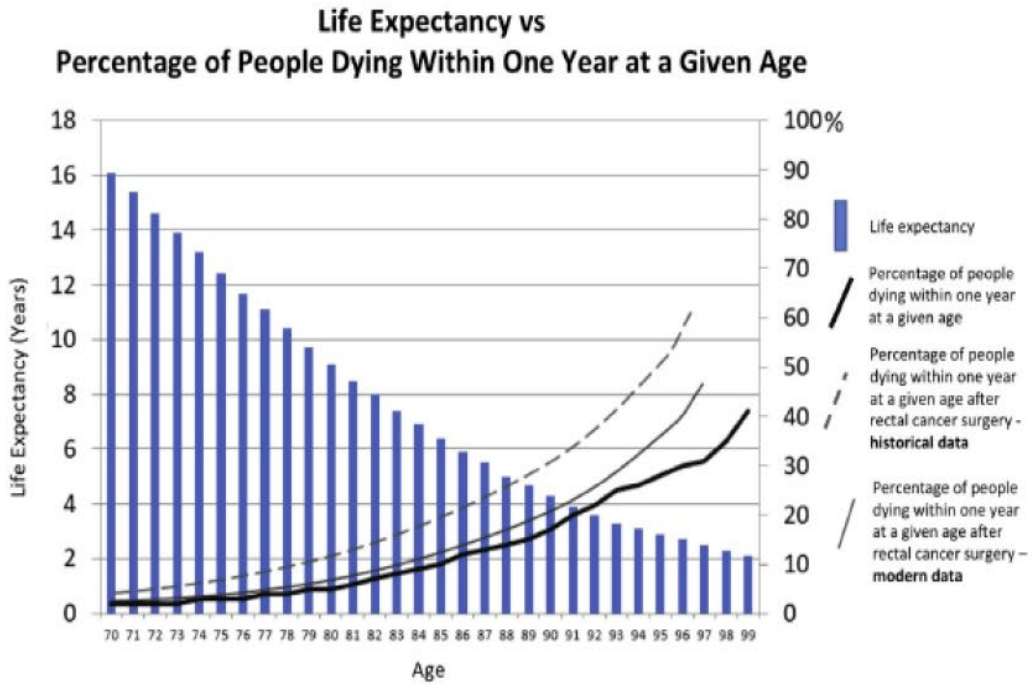


ESMO Clinical Practice Guidelines. Glynne-Jones et al, Ann Oncol 2017

CLINICAL WORK-UP

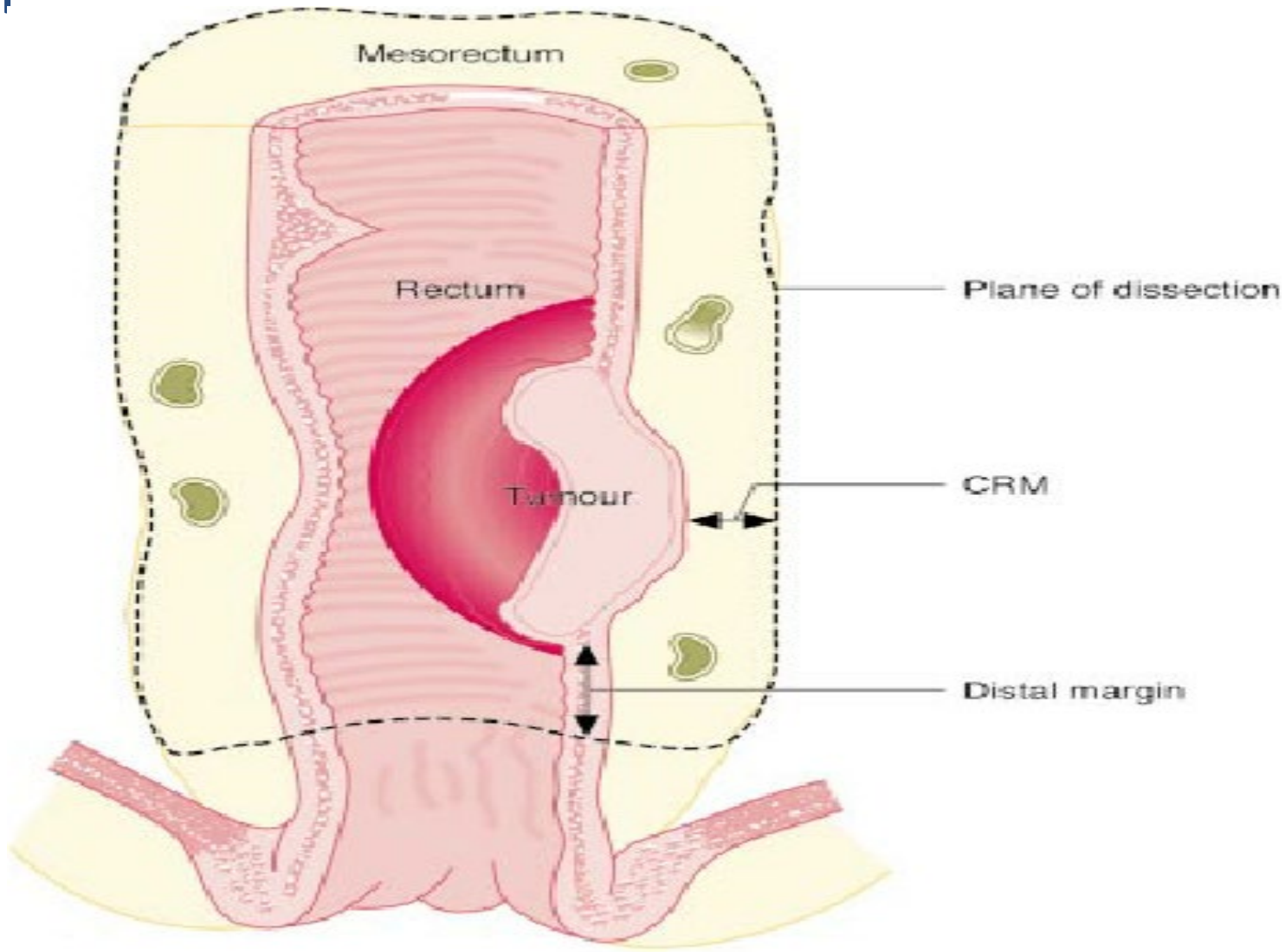
Potential ”extras”

- Analyses of tumour mutational status
- PET/CT (PET/MRI)
- Trans-anal ultrasound (TRUS)
- MRI of liver
- In-depth patient frailty analysis
- Pre-habilitation

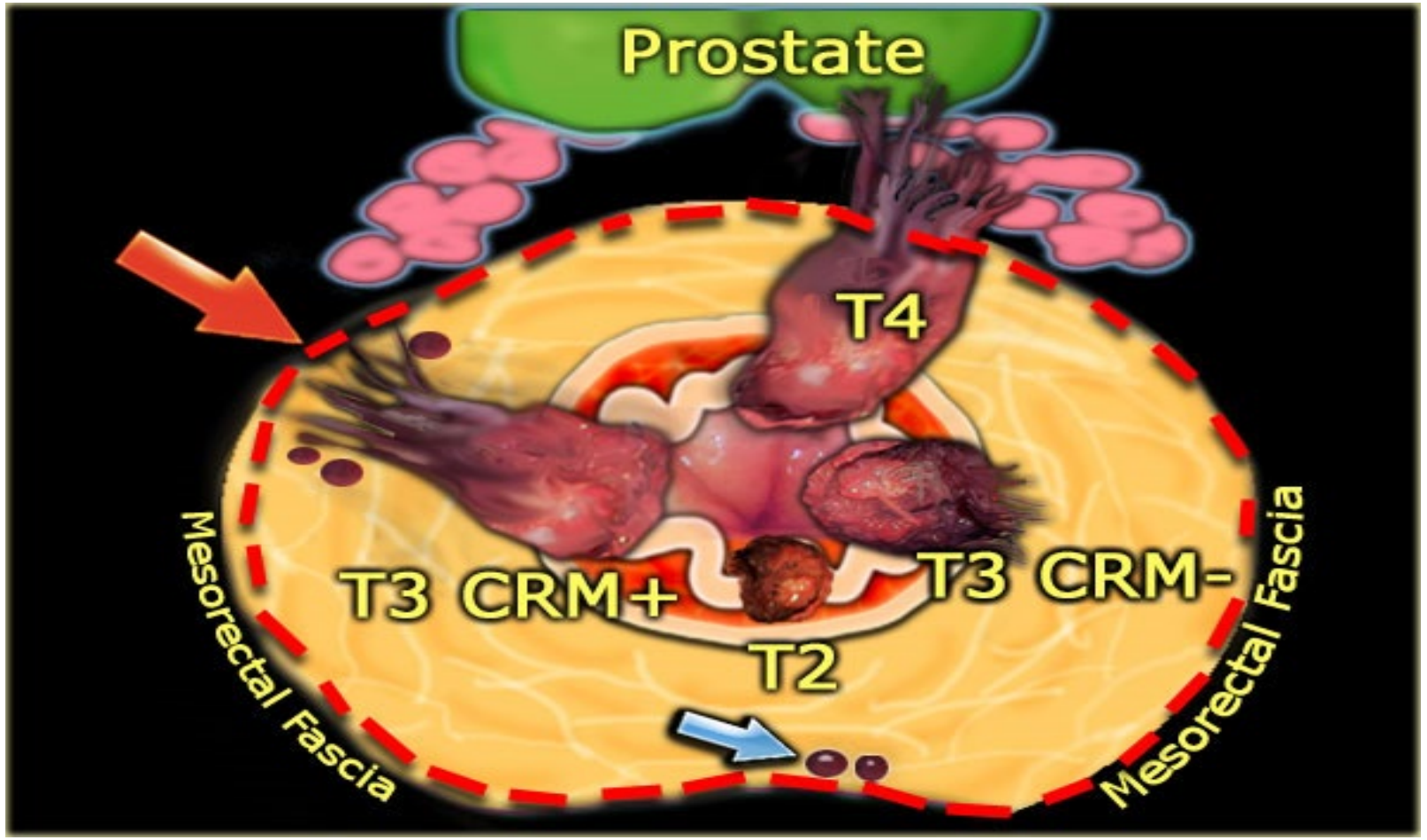


Montroni et al, EJSO 2018

CRM


Mesorectum
Rectum
Tumour
Plane of dissection
CRM
Distal margin

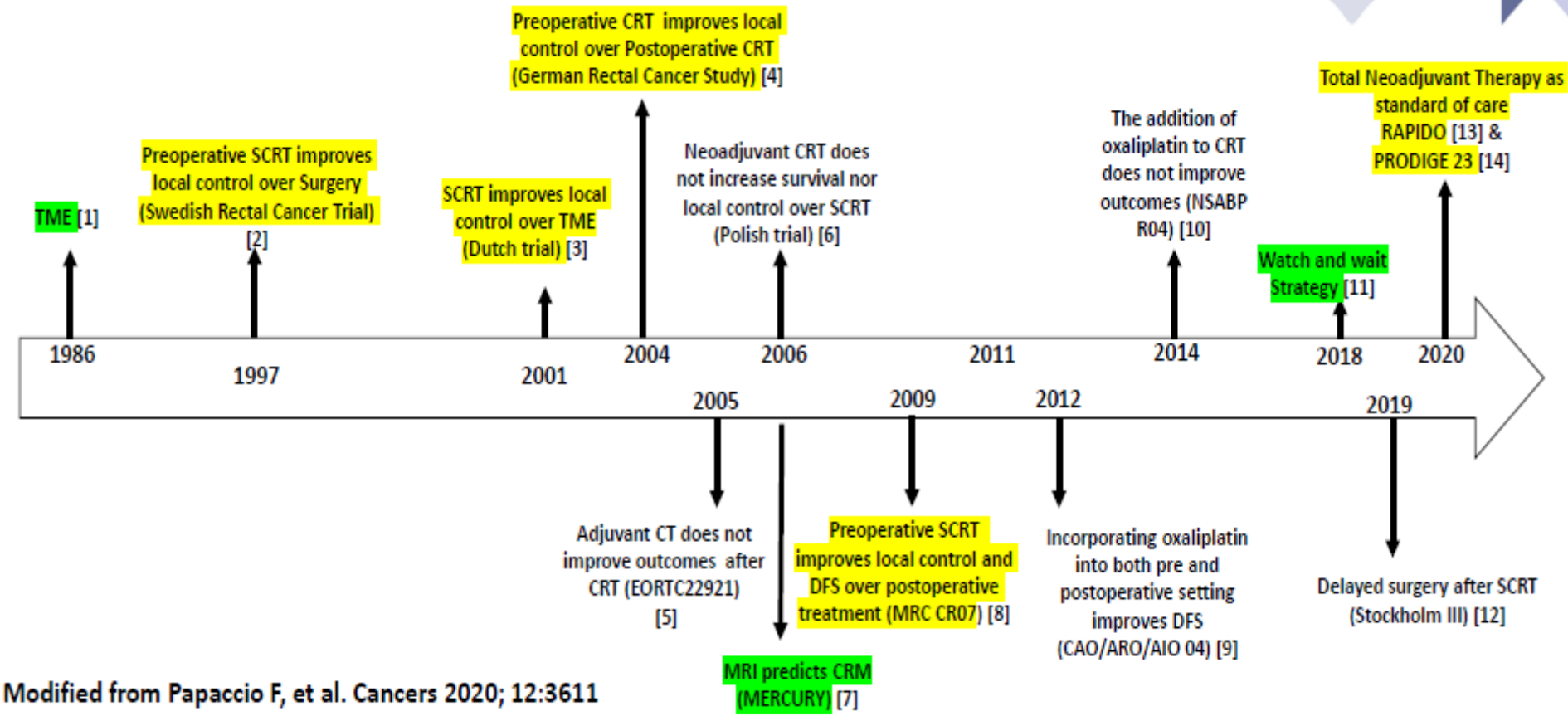
CRM


Prostate
T4
T3 CRM+
T3 CRM-
T2
Mesorectal Fascia
Mesorectal Fascia

TME (Total mesorectal excision)

- Standard of care
- Εχει μειώσει τα % υποτροπής σε <10% σε στάδια I και T2,T3a N0
- 6 w post CRT

IMPORTANT STEPS IN THE TREATMENT OF LOCALIZED RECTAL CANCER (1986-2021)



Modified from Papaccio F, et al. Cancers 2020; 12:3611

1. Heald, R.J, et al. *Lancet* 1986, *327*, 1479. 2. *N. Engl. J. Med.* 1997, *336*, 980. 3.Kapiteijn, E. et al. *N. Engl. J. Med.* 2001, *345*, 638. 4.Sauer, R. et al. *N. Engl. J. Med.* 2004, *351*, 1731. 5. Bosset, J.-F. et al, *J. Clin. Oncol.* 2005, *23*, 5620. 6. Bujko, K.et al. *Br. J. Surg.* 2006, *93*, 1215. 7. *BMJ* 2006, *333*, 779. 8. Sebag-Montefiore, D, et al. *Lancet* 2009, *373*, 811. 9. Rödel, C. et al. *Lancet Oncol* 2015, *16*, 979. 10. O'Connell, M.J. et al. *J Clin Oncol* 2014; *32*, 1927. 11. van der Valk, et al. *Lancet* 2018, *391*, 2537.
12. Erlandsson, J. et al. *Lancet Oncol* 2017, *18*, 336. 13. Bahadoer RR, et al. *Lancet Oncol* 2021; 22:29-42. 14.Conroy T, et al. *J Clin Oncol* 2020 38.15_suppl.4007.

MSI RECTAL CANCER: UPFRONT TESTING IMPERATIVE

About 5% of rectal cancers are MSI[1,2]

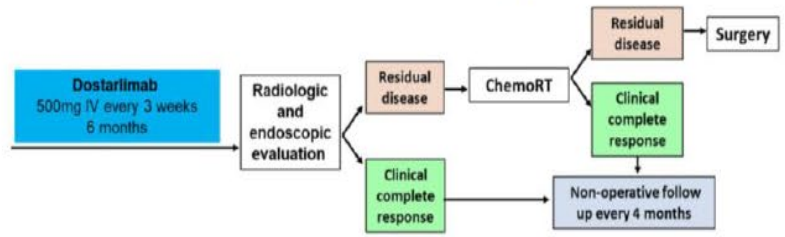
About 80% of MSI rectal cancers are related to Lynch Syndrome (young age!)

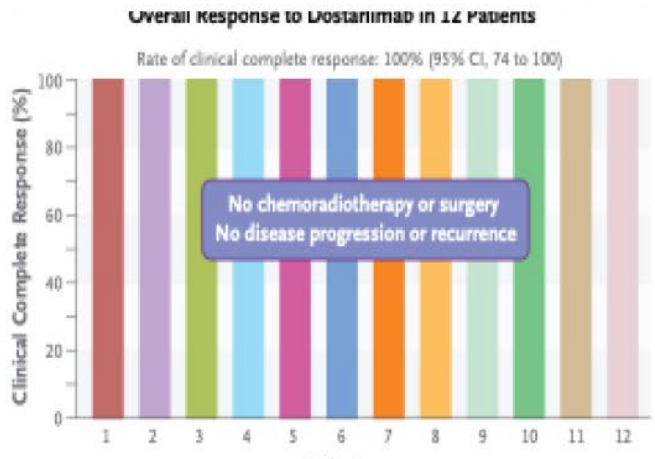
FP-based chemoradiation is modestly active with similar pCR rates vs MSS

Systemic chemotherapy may be less active vs MSS (low level of evidence but consistent with other settings: caution).

[1] *Alex et al, Clin Cancer Research 2017;* [2] *Cercek A et al, Clin Cancer Research 2020*

Dostarlimab trial @MSK





- Expanded cohort and longer fu needed
- RCT rather unfeasible

Cercek A et al, ASCO22 and NEJM 2022

CONCLUSIONS 1

- MULTIDISCIPLINARY DISCUSSION ESSENTIAL
- DEFINE AIMS OF THERAPY AND OPTIMAL TREATMENT
- SELECTIVE APPROACH ACCORDING TO MRI IF R0 RESECTION IS THE AIM
  - T1-T3a-b. SURGERY ALONE
  - LOW LOCAL RISK: 5X5 RT VS SURGERY ALONE
  - IF MODERATE LOCAL RISK: RT 5x5 VS LONG COURSE CRT
- TREAT ACCORDING TO AIM :

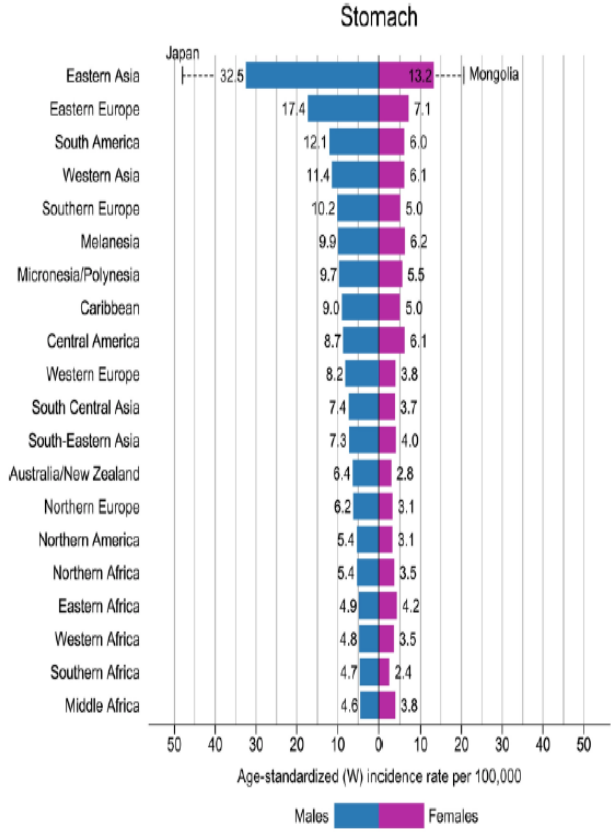
  R0 RESECTION vs cCR
- IF AIMING AT cCR A MORE INTENSIVE TREATMENT COULD BE JUSTIFIED LoE 1 GoR A

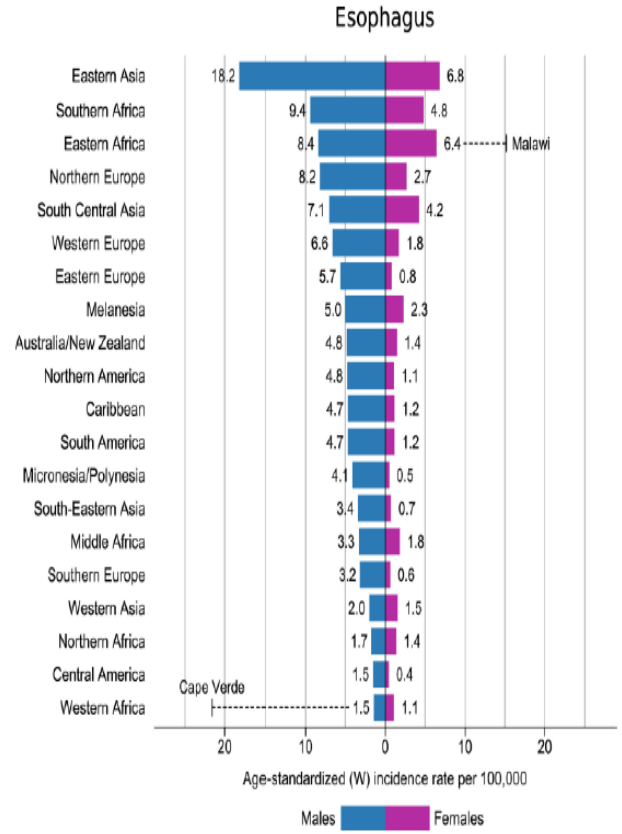
CONCLUSIONS 2

- **IN HIGH RISK MRI DEFINED PATIENTS:**
  - MESORECTAL FASCIA INVOLVED OR CLOSED, EMVI+, N2, o LATERAL NODES.
  - **A MORE INTENSIVE MULTIMODAL APPROACH IS JUSTIFIED**
  - **LoE1 GoRA**
  - **TOTAL NEOADJUVANT TREATMENT SHOULD BE CONSIDERED**
    - CRT followed by CT should be favored
    - Higher pCR rates expected
    - Better tolerance and compliance vs postoperative Treatment
    - Better Disease related treatment failure and better Disease free survival

ΚΑΡΚΙΝΟΣ ΣΤΟΜΑΧΟΥ-ΟΙΣΟΦΑΓΟΥ

EPIDEMIOLOGY





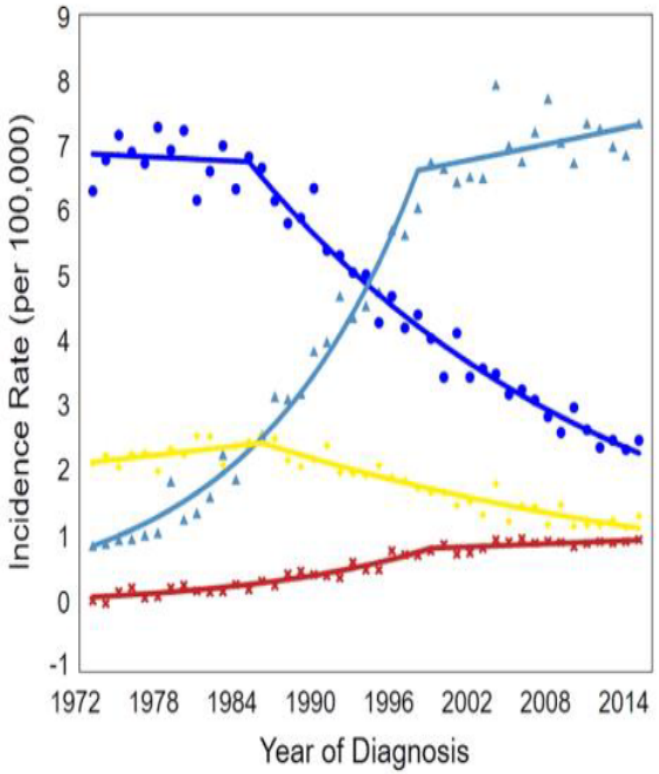
- 5th most common cancer
- 4th leading cause of cancer death (after lung, colorectal, liver,)

- 8th most common cancer
- 6th leading cause of cancer death

Sung et al CA Cancer J Clin . 2021 May;71(3):209-249.

EPIDEMIOLOGY- TRENDS

Incidence: according to SEER database: 1993-2015



Adenocarcinoma- male

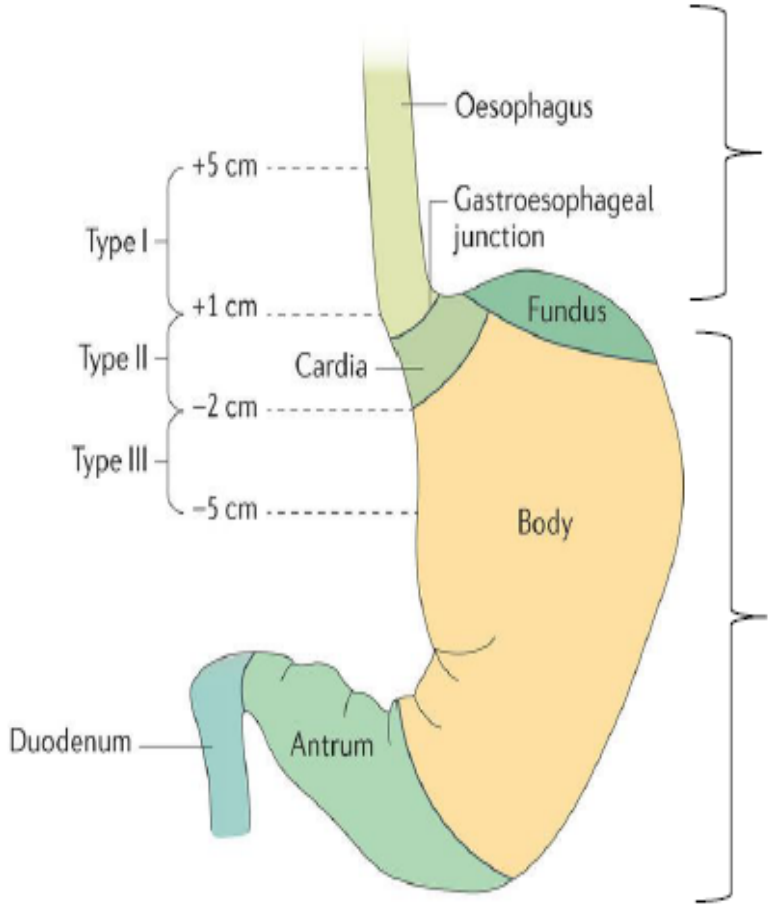
Squamous Cell Carcinoma- male

Squamous Cell Carcinoma- female

Adenocarcinoma- female

He H. et al. A SEER database analysis. Thorac Cancer. 2020

GASTRIC AND GASTROESOPHAGEAL CANCER NOMENCLATURE



Nature Reviews | Disease Primers

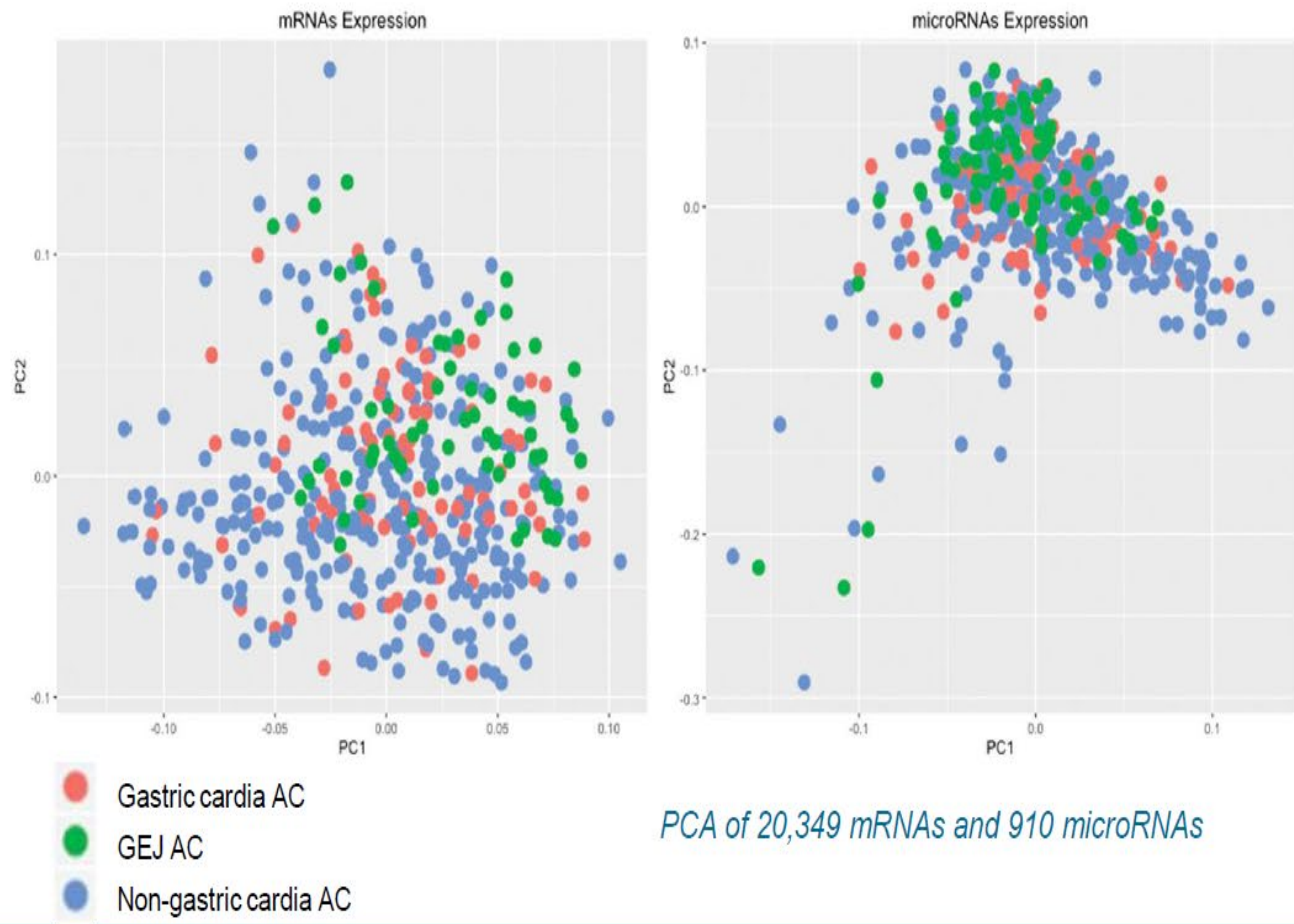
Lower esophageal, gastresophageal junction adenocarcinoma
→ ESMO Esophageal Cancer Guidelines

Gastric cancer
→ ESMO Gastric Cancer Guidelines

ESMO

Ajani et al, Nat Rev Dis Primers. 2017 Jun 1;3:17036. doi: 10.1038/nrdp.2017.36

According to molecular fingerprints, GEJ are more similar to gastric than to esophageal cancers



PCA of 20,349 mRNAs and 910 microRNAs

Fernandes Barra et al., Oncotarget 2017

Radboudumc

RISK FACTORS- OESOPHAGEAL AND GASTRIC CANCER

SCC

Smoking

Alcohol

Low fruit and vegetable diet

Chewing betel

Dusty environment

Low socioeconomic level

Consumption of food and beverages at very hot temperatures

Oesophageal AC

Obesity

Reflux

Barrett's oesophagus

Smoking

Alcohol

Diet

Chewing betel

Gastric Cancer

Cardia

Obesity

Gastroesophageal reflux

Western countries

Nocardia

Helicobacter pylori

Pickled vegetable

Salt

Low fruit diet

Smoking

Alcohol

EBV

Eastern Europe, East Asia

Van Cutsem E, et al. Lancet. 2016; Rawla P, Barsouk A. Prz Gastroenterol. 2019;
Crew KD, Neugut AI. World J Gastroenterol. 2006;; Lv L, et al. J Cancer. 2021; Arnold M, et al. Gut. 2020.

EARLY/LOCALLY ADVANCED GASTRIC & ESOPHAGEAL CANCER

Pre-operative workup

Multidisciplinary work is essential

Staging is used determine extent of spread, length of tumour and depth of invasion:

- Endoscopy and biopsy
- Endoscopic ultrasound – most useful in early or late tumours, and to biopsy lymph nodes
- CT scan of chest and abdomen
- PET scan if available to detect CT occult metastasis. Less useful in gastric/diffuse cancers.
- Adenocarcinoma patients with gastric or tumours below the gastresophageal junction should have laparoscopy

In patients who are candidates for surgery, assessment of **medical fitness** is recommended (cardiac, PFTs)

Nutrition assessment and early **intervention** (ESPEN guidelines) improves outcomes.

ESOPHAGEAL SQUAMOUS CELL CARCINOMA

Management of early/locally advanced disease: recommendations

Very early tumours (T1N0) can be considered for **endoscopic** resection

For all other SCC oesophagus tumours either **surgery** or **definitive chemoradiotherapy** (CRT) should be offered

Adding **neoadjuvant chemoradiotherapy** to surgery in SCC oesophagus improves survival and is recommended

The exception to this is cT2N0 tumours where the evidence is conflicting for benefit of CRT before surgery, these patients should be discussed on an individual basis

ESOPHAGEAL ADENOCARCINOMA

Management of early/locally advanced disease: recommendations

Very early tumours (T1N0) can be considered for **endoscopic** resection

For all T2 adenocarcinoma of the esophagus **surgery** should be offered to fit patients.

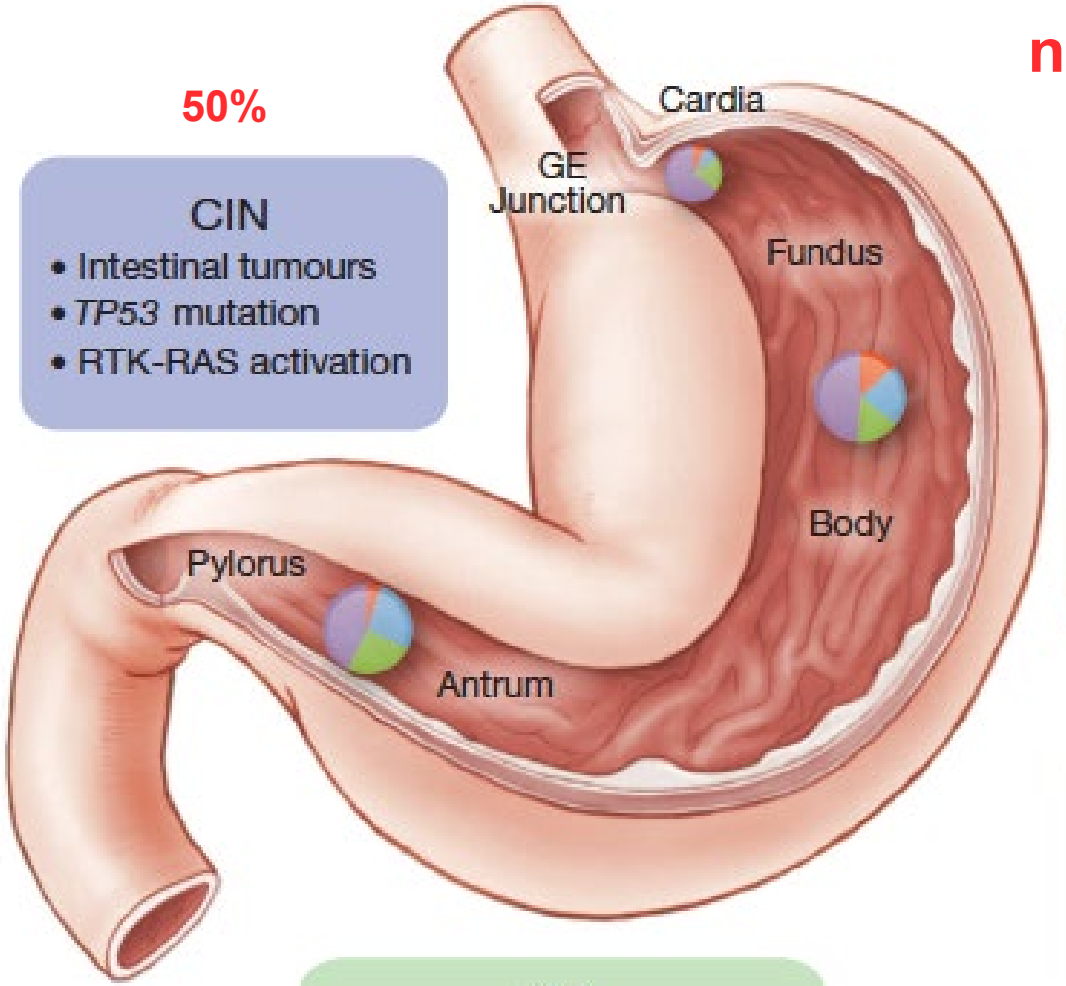
Unlike SCC esophagus, CRT does not generally cure adenocarcinoma.

Adding **neoadjuvant chemoradiotherapy** or **perioperative chemotherapy** to surgery in adenocarcinoma oesophagus improves survival and is recommended

n=295

50%

CIN
- Intestinal tumours
- *TP53* mutation
- RTK-RAS activation



9%

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

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

22%

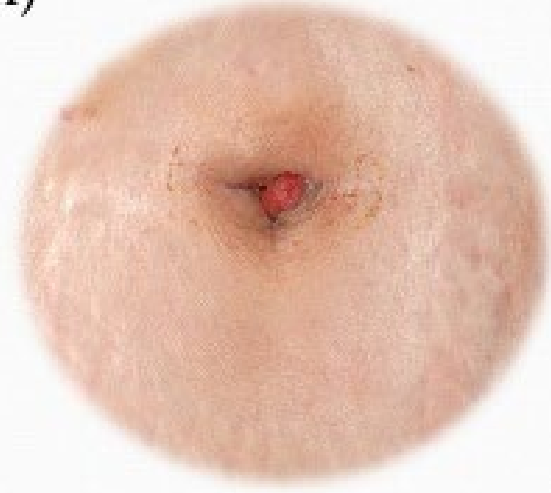
GS
- Diffuse tumours
- *CDH1, RHOA* mutations
- *CLDN18–ARHGAP* fusion
- Cell adhesion

20%

TCGA GC-EGJC Nature 2014

Signs

- Palpable abdominal mass: most common physical finding
- If cancer spreads via lymphatics...
  - Left supraclavicular node (Virchow's)
  - Periumbilical node (Sister Mary Joseph)
  - Left axillary node (Irish)
  - Enlarged ovary (Krukenberg's tumor)
  - Ascites



PREOP EVALUATION

- CTS
- EUS (T1-T2)
- PET/CT SCAN
- TUMOR MARKERS
- STAGING LAPAROSCOPY PREOP IN T2-T4 AND LN+

UNRESECTABILITY

- DISTANT METS
- MAJOR VESSELS
- OCCLUSION OF HEPATIC ARTERY/RPOXIMAL SPELIC ARTERY
- LINITIS PLASTICA
- BULKY ADENOPATHY FIXED TO PANCREATIC HEAD NEES WHIPPLE
- POS PERITINEAL CYTOLOGY→ M1

GASTRIC ADENOCARCINOMA

Management of early/locally advanced disease: recommendations

Endoscopic resection is recommended for very early gastric cancers (T1a) if they are clearly confined to the mucosa, b) well-differentiated G1-2, c) ≤2cm and d) non-ulcerated .

For stage IB-III gastric cancer, **radical gastrectomy** is indicated.

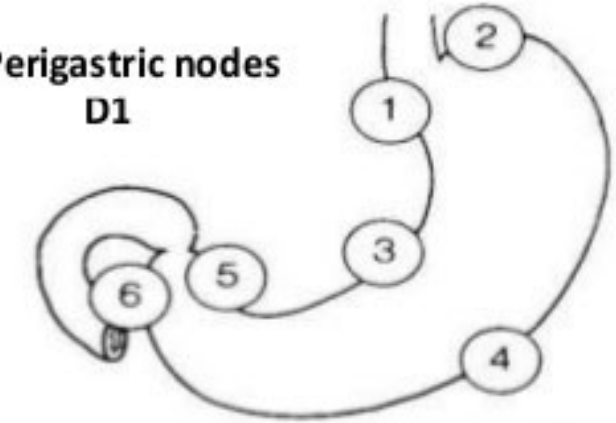
Adding **perioperative chemotherapy** before and after surgery in gastric adenocarcinoma improves survival and is the preferred approach in Europe.

For patients who do not have perioperative chemotherapy before surgery **adjuvant chemotherapy** or adjuvant chemoradiotherapy can be considered

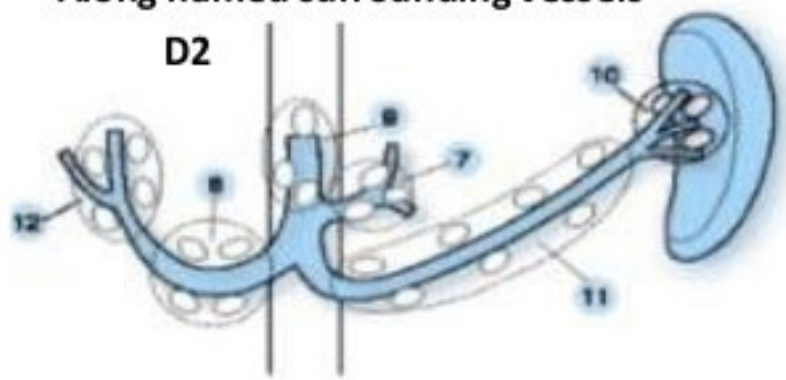
D2 Lymphadenectomy

	LN group	
D1	1	R cardiac
	2	L cardiac
	3	Lesser curvature
	4	Greater curvature
	5	Suprapyloric
	6	Infrapyloric
D2	7	L gastric artery
	8	Common hepatic artery
	9	Celiac artery
	10	Splenic hilar
	11	Splenic artery

Perigastric nodes
D1



Along named surrounding vessels
D2



TREATMENT OF ADVANCED ESOPHAGEAL CANCER

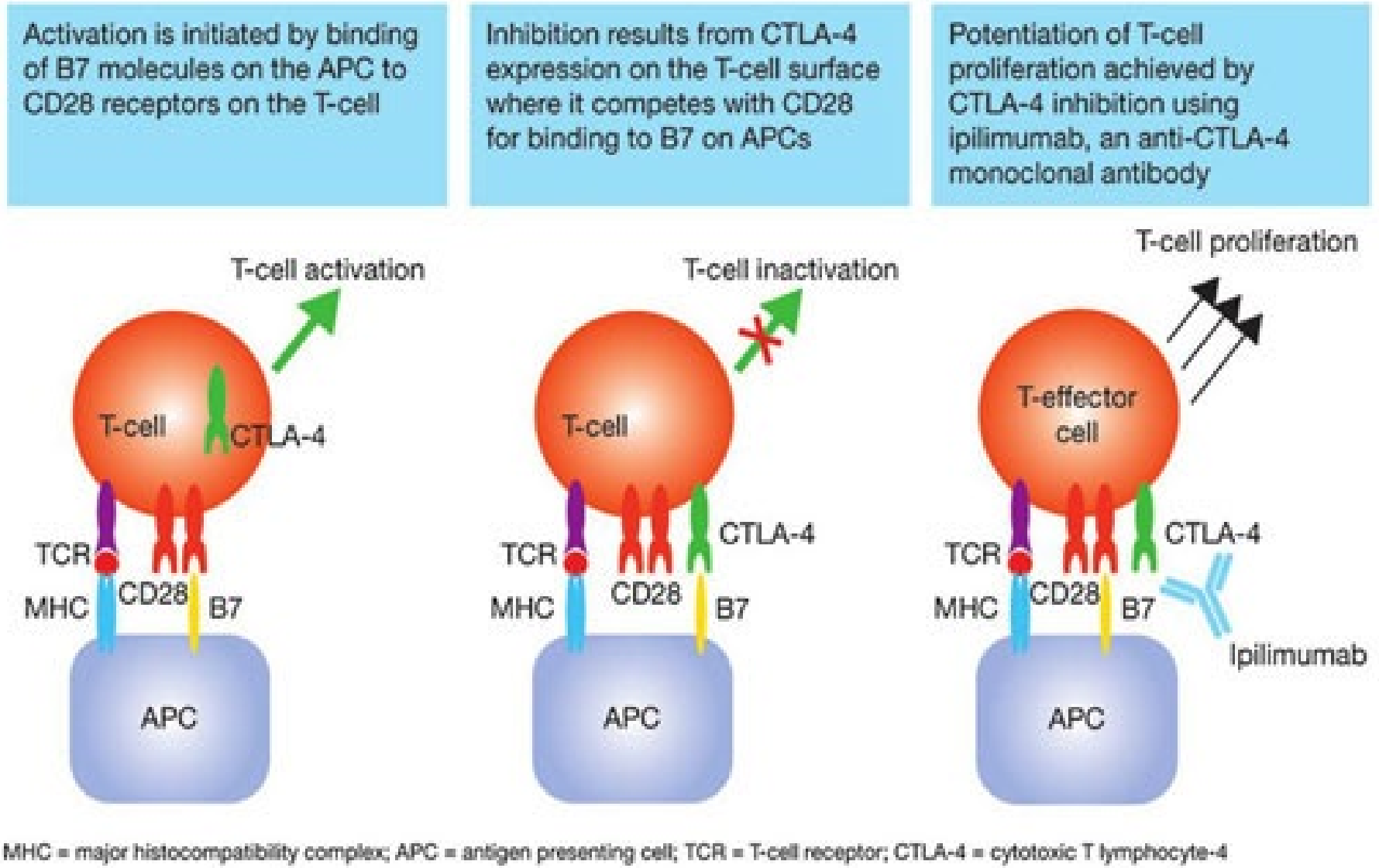
Esophageal Squamous Cell Cancer 1L treatment

Standard first line chemotherapy for ESCC is a **platinum and fluoropyrimidine doublet**.

Most randomised trials have been conducted in adenocarcinoma and data are extrapolated to ESCC, however multiple phase II studies support platinum and fluoropyrimidine treatment in an ESCC population.

Data from trials in locoregionally advanced ESCC suggest **equivalence for cisplatin and oxaliplatin** based regimens.

The **GO-2** trial also recruited older and more frail ESCC patients with advanced cancer and demonstrated equivalent outcomes and reduced toxicity for **dose reduced** oxaliplatin and capecitabine chemotherapy.

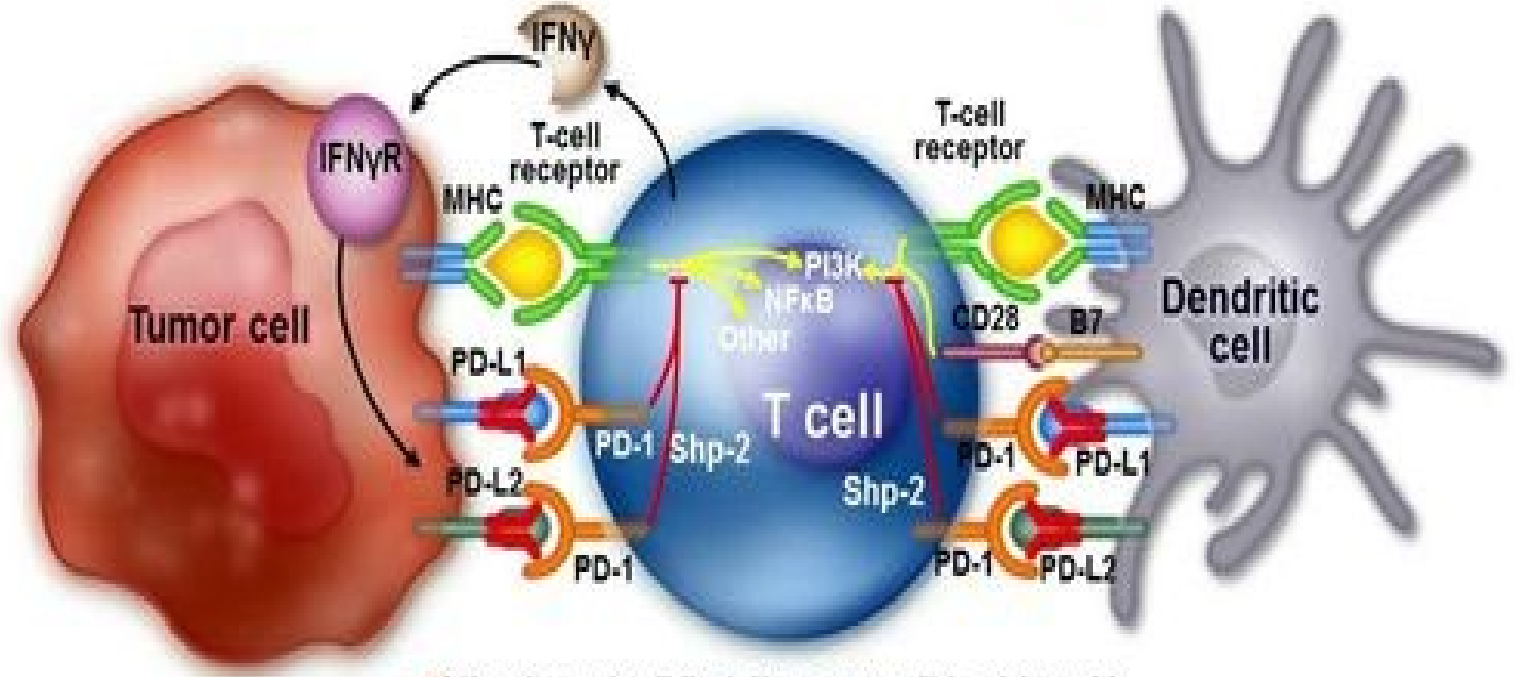


MHC = major histocompatibility complex; APC = antigen presenting cell; TCR = T-cell receptor; CTLA-4 = cytotoxic T lymphocyte-4

FIG. 1. T-cell activation and mechanism of action of ipilimumab (adapted with permission from Weber[51]). APC, antigen presenting cell; CTLA-4, cytotoxic T lymphocyte antigen-4; TCR, T-cell receptor; MHC, major histocompatibility complex.

Nivolumab Mechanism of Action

- PD-1 expression on tumor-infiltrating lymphocytes is associated with decreased cytokine production and effector function[11]
- Nivolumab binds PD-1 receptors on T cells and disrupts negative signaling triggered by PD-L1/PD-L2 to restore T-cell antitumor function[12–14]



TAKE HOME MESSAGES GEA ADVANCED DISEASE

First line

- Chemotherapy improves OS and QoL
- More is not better – doublet > triplet for most. Oxali is safer and better tolerated. Dose reductions in elderly/frail.
- Trastuzumab added to chemotherapy in patients with HER2 positive patients
- Addition of nivolumab to chemotherapy in CPS ≥ 5 patients improves OS

Second line

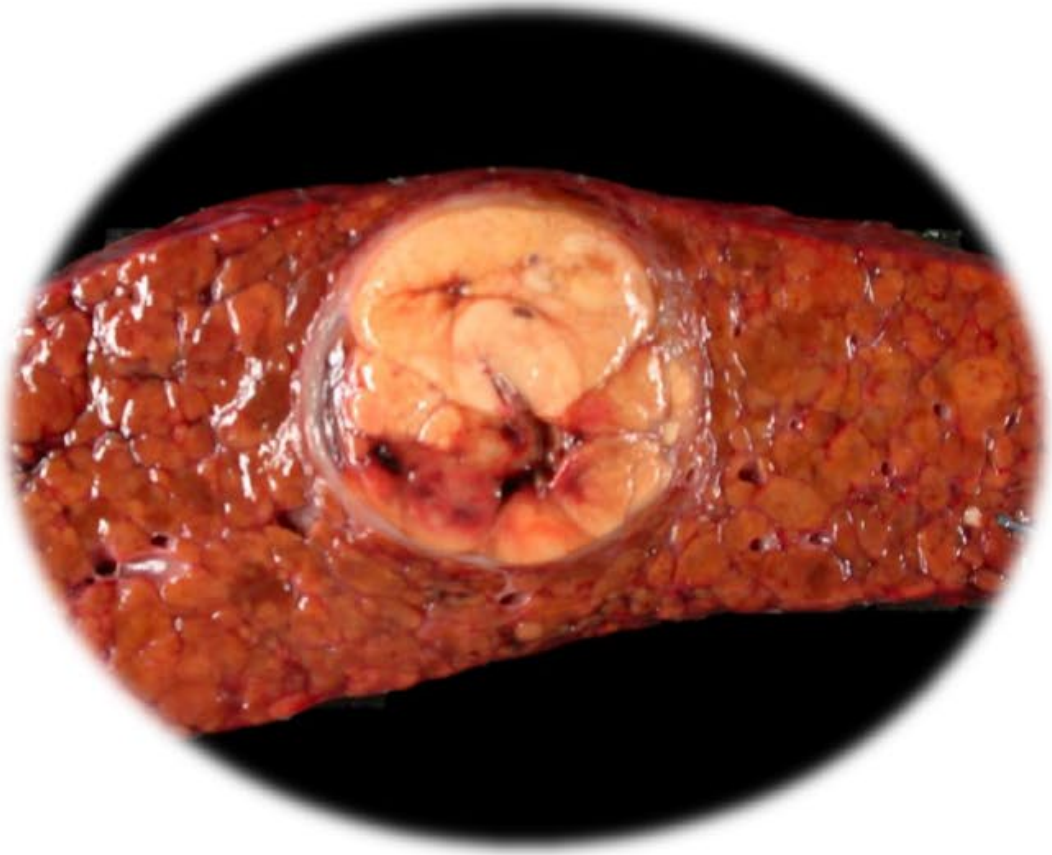
- Small benefit on average for chemotherapy, better for chemosensitive patients
- Ramucirumab added to chemotherapy improves outcomes

Third line

- Similar OS benefit to Lonsurf as 2L chemo
- In Asia and US, anti-PD-1 is standard, not EMA approved

ΗΠΑΤΟΚΥΤΤΑΡΙΚΟ ΚΑΡΚΙΝΩΜΑ

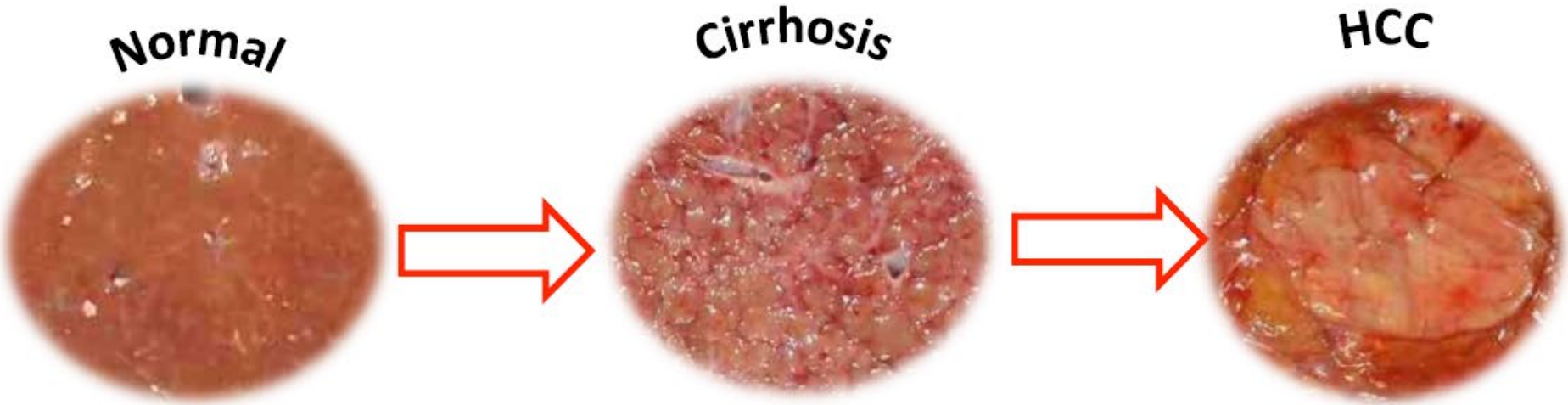
HCC: Magnitude



- The most frequent primary malignancies of the liver (5th most common cancers)
- 4th most common cause of cancer-related death worldwide
- Increasing overall burden of liver cancer worldwide over time

HCC Development: A multistep process

- Arise in > 80% of cases in the context of chronic liver diseases



Changes in the major risk factors

HBV

- HCC annual incidence of 0.42%
- NAs associated with risk reduction, but not elimination of HCC in patients with CHB

HCV

- HCC annual incidence 0.5-10%, considerable (50%–80%) and steady HCC risk reduction over time of *de novo* HCC among pts achieving DAA-related SVR
- Absolute risk of HCC persisted in patients with DAA-induced SVR

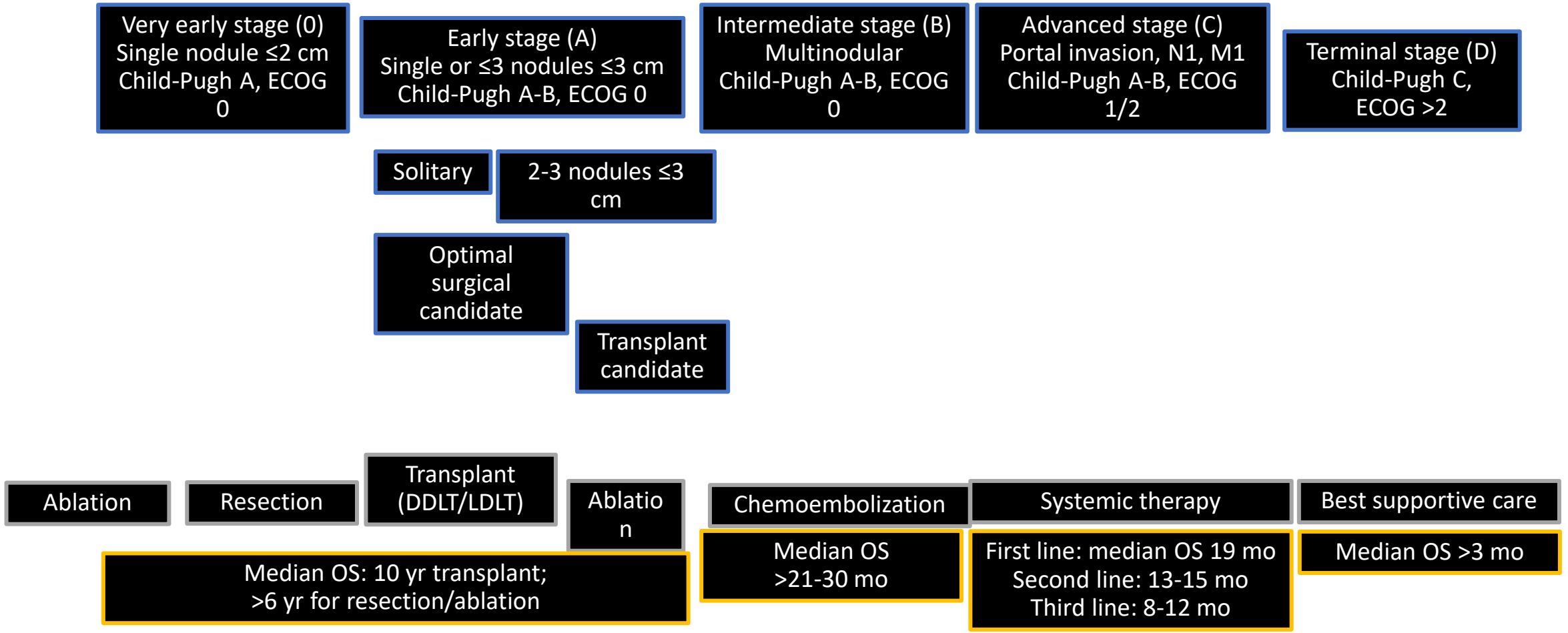
Alcohol consumption

- Remains a significant risk factor, two- to three-fold lower risk of HCC than patients with cirrhosis due to viral hepatitis
- Significant increased risk of 4% per 10 g alcohol intake per day

Metabolic syndrome / NAFLD

- The most common liver disease and a major risk factor for HCC in most developed countries
- Irrespective of NAFLD, obesity and diabetes increase HCC risk

BCLC Staging and Treatment Strategy for HCC



Chronic Liver Disease Assessment - Child-Pugh Score

Parameters		Score		
		1	2	3
Albumin		> 35 g/L	28 – 35 g/L	< 28 g/L
Ascites		Absent	Slight	Moderate
Bilirubin		< 34.2 µmol/L	34.2 – 51.3 µmol/L	> 51.3 µmol/L
Encephalopathy		None	Grade 1 – 2	Grade 3 – 4
PTT	Seconds over control	< 4	4 – 6	> 6
	INR	< 1.7	1.7 – 2.3	> 2.3

Score	Class	Description	1-Year Survival (%)	2-Year Survival (%)
5 – 6	A	Well-compensated disease	100	85
7 – 9	B	Significant functional compromise	80	60
10 – 15	C	Decompensated disease	45	35

Reference:

1. Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973; 60:646.
2. Child CG, Turcotte JG. The Liver and Portal Hypertension, WB Saunders Co, Philadelphia 1964.
3. Trey C, Burns DG, Saunders SJ. Treatment of hepatic coma by exchange blood transfusion. NEJM 1966; 274:473.

Early and very early stages
1b – surgery: liver transplantation

- Patients awaiting liver transplantation:
  - No treatment, but observation with imaging follow-up
  - If waiting list > 6 mo: bridging to transplant
    - TACE ? RE ? RFA ? Resection ?
- Down-staging policies for HCC exceeding criteria:
  - If down staging successful: consider transplantation;
  - Optimal treatment for down-staging: ?
  - What waiting period after down-staging: ?
  - Living donor transplantation ?

1. Heimbach J, et al Hepatology 2017
2. EASL-EORTC guidelines J Hepatol 2012

Options for Second-line Therapy

Atezo + Bev | Sorafenib | Lenvatinib

Based on RCTs

Based on nonrandomized trials or lacking prospective trial data

Regorafenib | Cabozantinib | Ramucirumab

Nivolumab* | Pembrolizumab | Nivolumab + ipilimumab

*April 2021: FDA Oncologic Drugs Advisory Committee voted 5 to 4 against continuing the indication of nivolumab monotherapy for patients with HCC who previously received sorafenib.

Slide credit: clinicaloptions.com

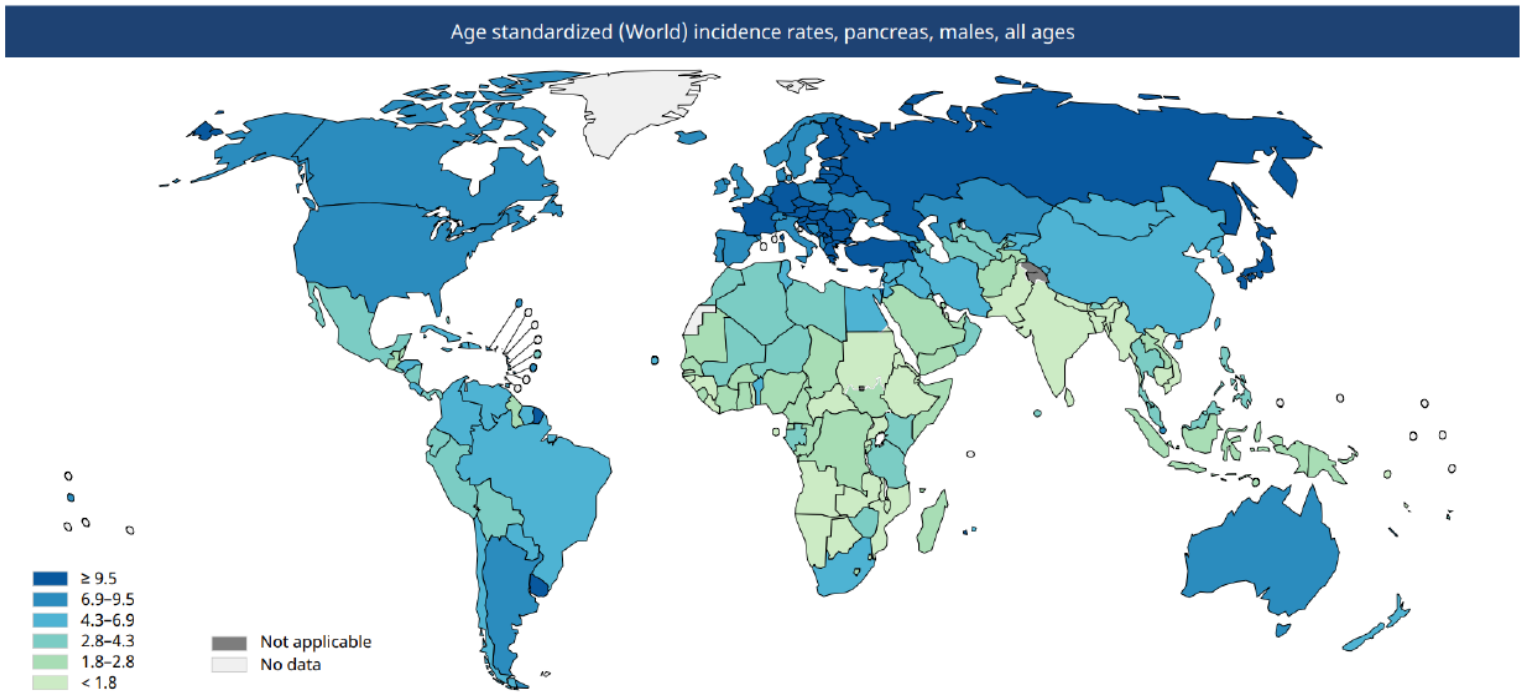
Τοπικά προχωρημένο-Μεταστατικό HCC

- Βάσει της θεραπείας η ανοσοθεραπεία-αναστολείς τυροσινικών κινασών
- Πολλές θεραπείες δεν μπορούν να δοθούν λόγω Child-Pugh B ή C

ΚΑΡΚΙΝΟΣ ΠΑΓΚΡΕΑΤΟΣ

PANCREATIC CANCER

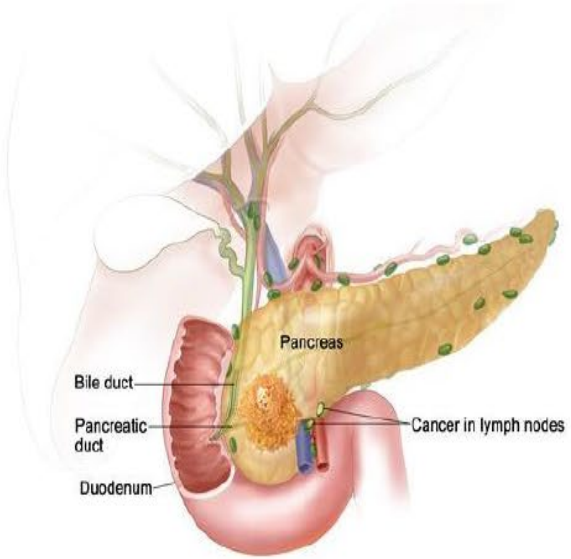
Epidemiology



https://gco.iarc.fr/today/data/factsheets/cancers/13-Pancreas-fact-sheet.pdf

PANCREATIC CANCER

Risk factors

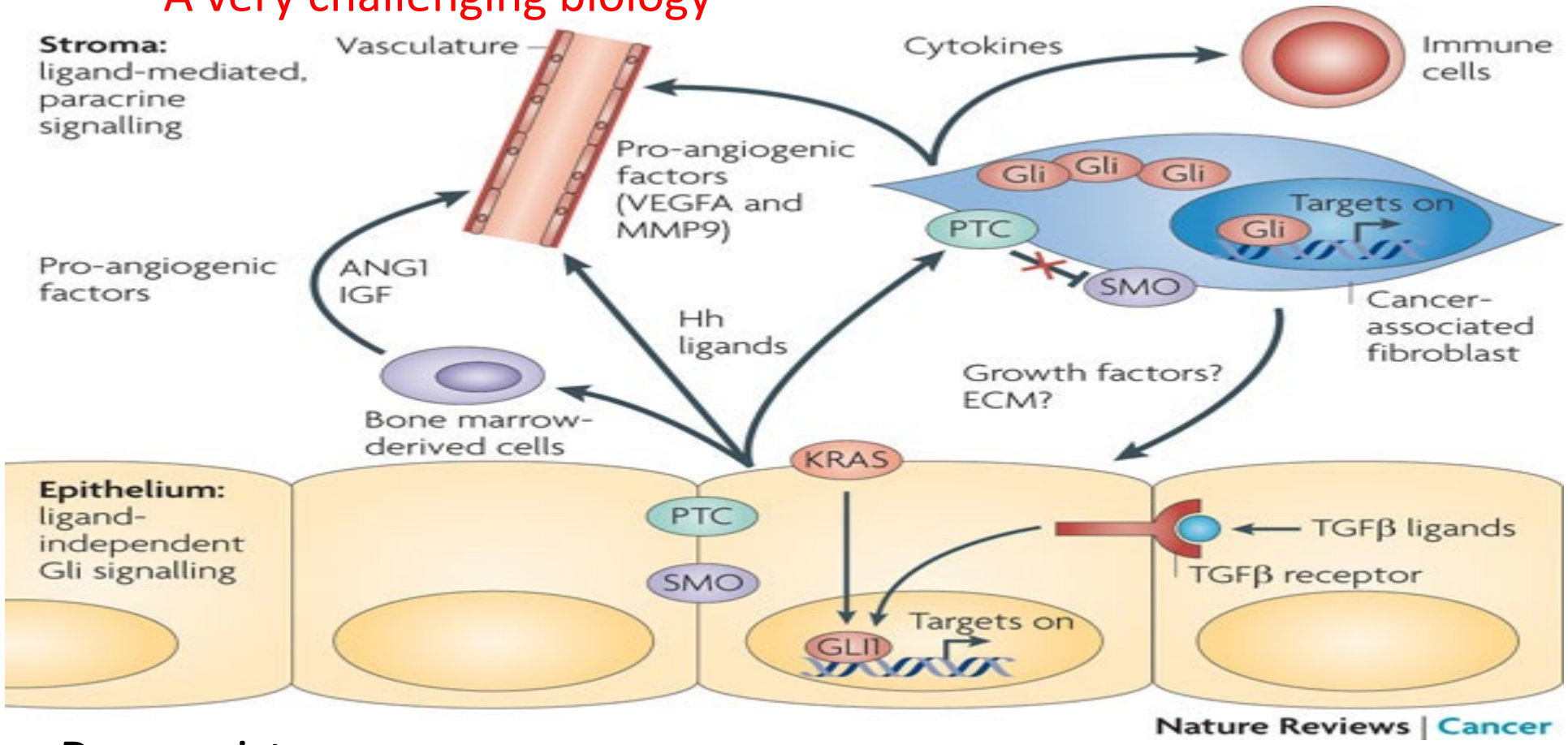


http://www.cancer.gov/images/cdr/live/CDR742418-571.jpg

- **Tobacco smoking**
- **Dietary habits**
  - Heavy alcohol drinking
  - Obesity
  - Chronic pancreatitis
  - Diabetes mellitus
  - Red meat intake
- **5-10% of pancreatic cancers are due to germline genetic alterations**
  - BRCA2, p16, ATM, STK11, PRSS1/PRSS2, SPINK1, PALB2, and DNA mismatch repair genes

ESMO Guidelines Committee. *Annals of Oncology* 26 (Supplement 5): v56–v68, 2015

A very challenging biology



- Drug resistance
- Stroma as a barrier to drug delivery
- Complex and poorly understood microenvironment
- Multiple gene mutations
- Non-druggable tumor suppressor genes
- No biomarkers

Genetic Alterations in Pancreatic Ca

Gene Mutation/ Deletion

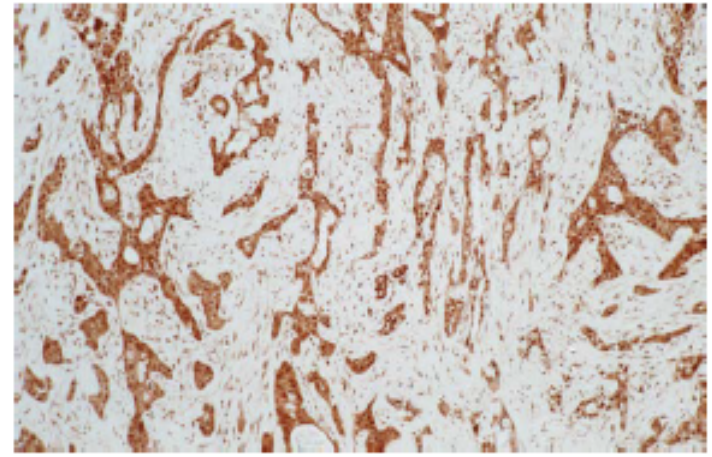
- p16 80%
- K-ras (B-raf) 90%+
- p53 70%
- SMAD4/ TGFβR1+2 55%
- BRCA 1, 2, PALB2 5-8%
- Mismatch repair genes 4%
- STK11 (Peutz-Jeghers) 5%
- MKK4 5-13%
- FANCC/ FANCG 5%

Amplification/ Overexpression

- PI3K/ Akt, c-myc, Shh/ Gli, Notch, etc (10-30%)

Other Genetic Changes

- Telomere shortening
- Widespread allelic loss



Infiltrating pancreatic ca

Syndromes Associated with Pancreatic Adenocarcinoma

Syndrome	Relative Risk of PC	Gene
Familial Atypical Multiple Mole Melanoma (FAMMM)	13-22 fold	p16
Familial Breast and Ovarian	< 5 fold	BRCA1 or 2
Fanconi Anemia, Breast CA	Unknown	PALB2
FAP	5 fold	APC
Hereditary Non-polyposis Colon Cancer (HNPCC)	1.5-9 fold	MLH1, MSH6 MSH2, PMS2
Peutz-Jeghers Syndrome	Up to 100 fold	STK11/LKB1
Hereditary Pancreatitis	53 fold	PRSS1
Cystic Fibrosis	2.6 to 32 fold	CFTR
Ataxia - telangiectasia	Unknown	ATM

Courtesy of Randall Brand

Diagnostic tools

Lab studies

– Tumor markers i.e.CA19-9 (5-10% not expressed)

✓Associated with prognosis, precedes relapse

– Glucose intolerance

Imaging modalities

– CT scan

– ERCP (choledocholethiasis, stent insertion)

– MRI/MRCP (if ERCP cannot be done)

– Staging laparoscopy

Biopsy

- Not needed in resectable disease
- EUS-FNA

✓90% sensitivity

✓Less likely to cause intraperitoneal spread

- Percutaneous biopsy

✓Dissemination of cells

Treatment-Clinical grouping

1. Metastatic disease
2. Resectable disease
3. Borderline Resectable disease: definition issues

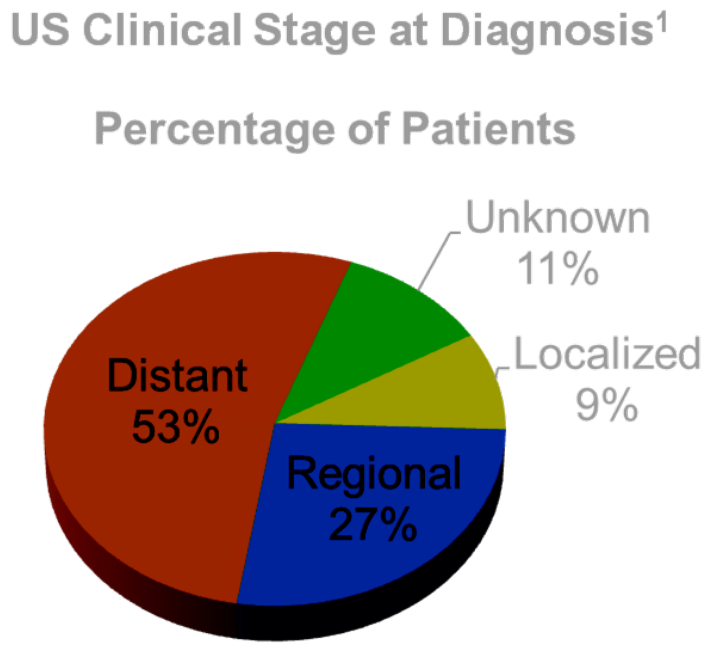
Neoadjuvant treatment

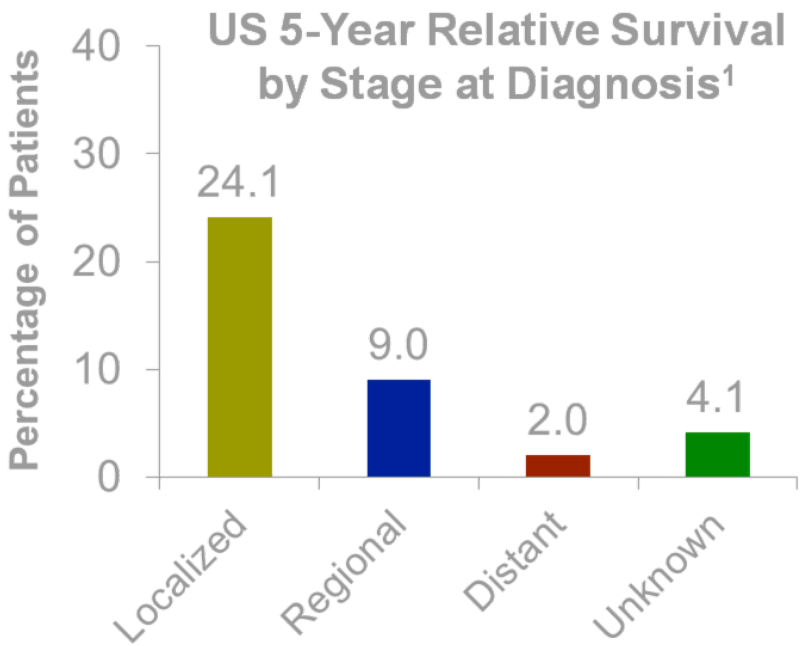
a. CHT

b. CHT-RT

4. Locally advanced, but clearly not resectable disease

Pancreatic Cancer Survival Rates by Stage





Majority of patients have inoperable disease at time of diagnosis[1]

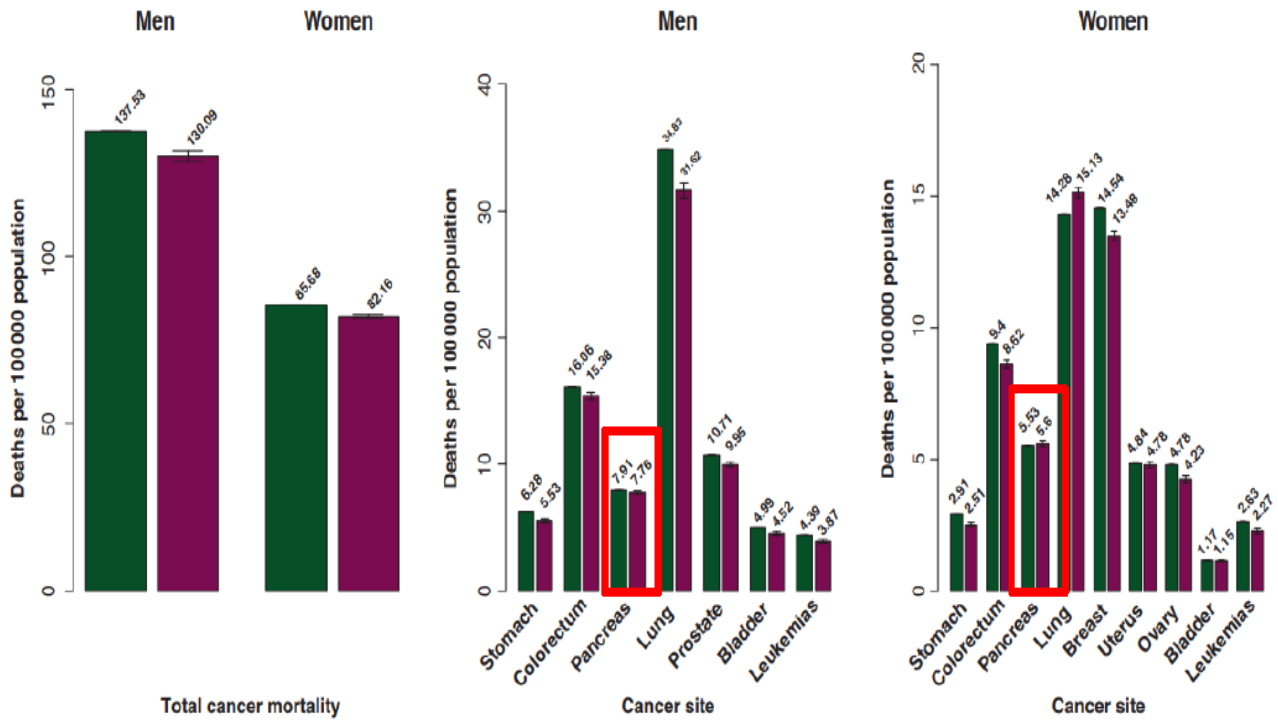
ΟΙ ΠΕΡΙΣΣΟΤΕΡΟΙ 53% ΜΕ ΑΠΟΜΑΚΡΥΣΜΕΝΕΣ ΜΕΤΑΣΤΑΣΕΙΣ ΣΤΗ ΔΙΑΓΝΩΣΗ

1 *Figures 2013*. Atlanta: American Cancer Society; 2013.

PANCREATIC CANCER

Any progress?

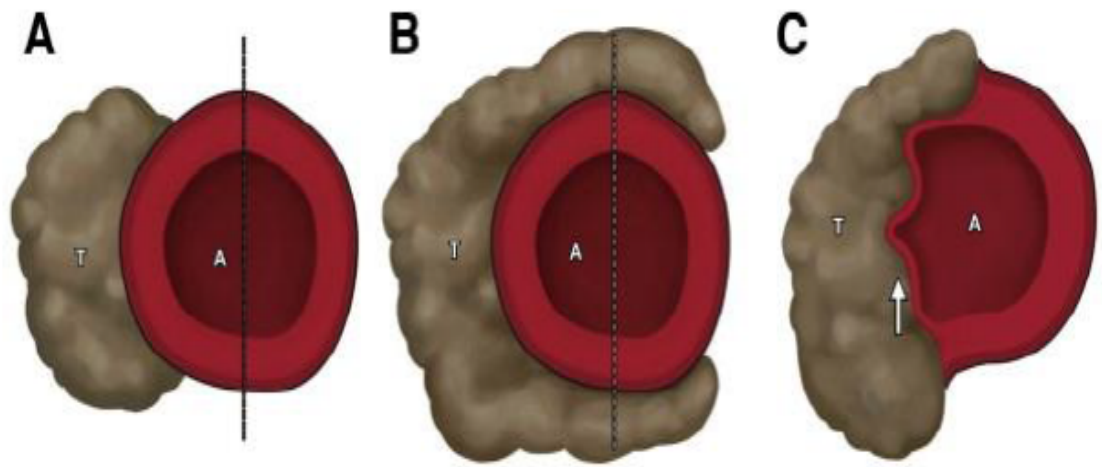
Death rates per 100 000 persons for the year 2015 (left columns) and predicted rates for 2020 (right columns) with 95% prediction intervals for total cancers and 10 major cancer sites in EU men and women.



ESMO ACADEMY

Carioli G et al. Ann Oncol. 2021 Apr;32(4):478-487

“Resectable”: Tumor-vessel contract / deformity



Abutment
≤ 180°

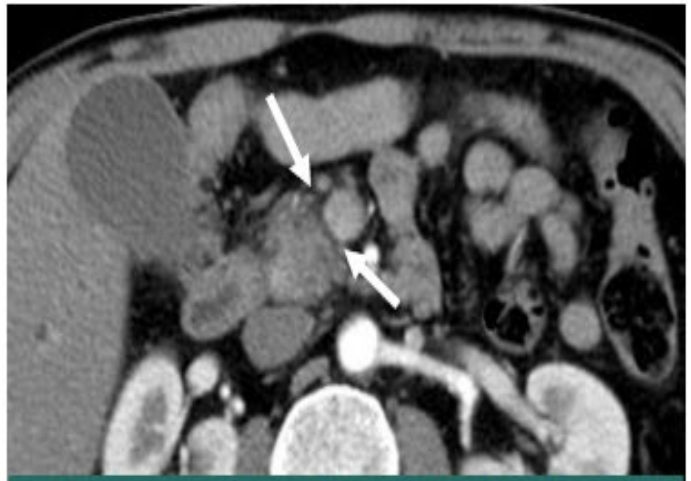
Encasement
> 180°

Deformity

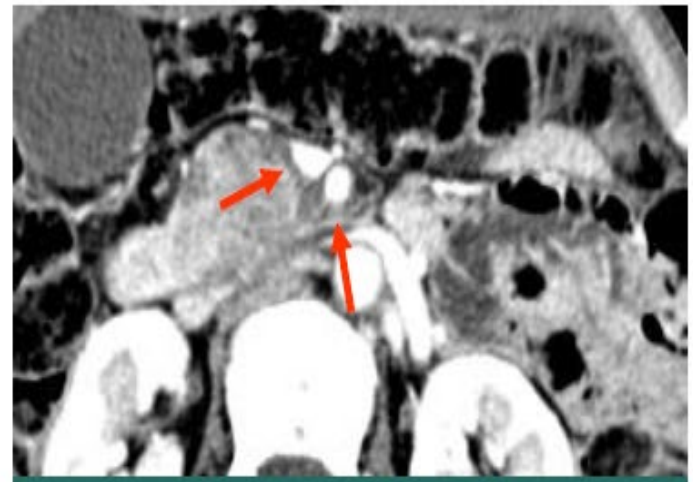
Gray zone

Highly specific for vascular invasion
PPV 89% ~100%

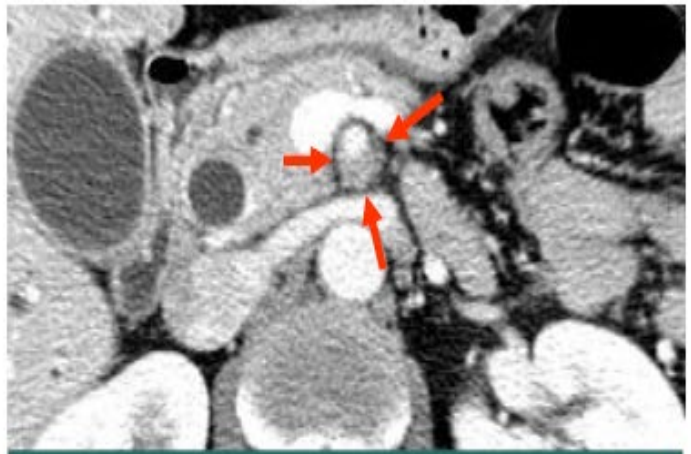
Ex) Pathologic PV Invasion (+) in 51%



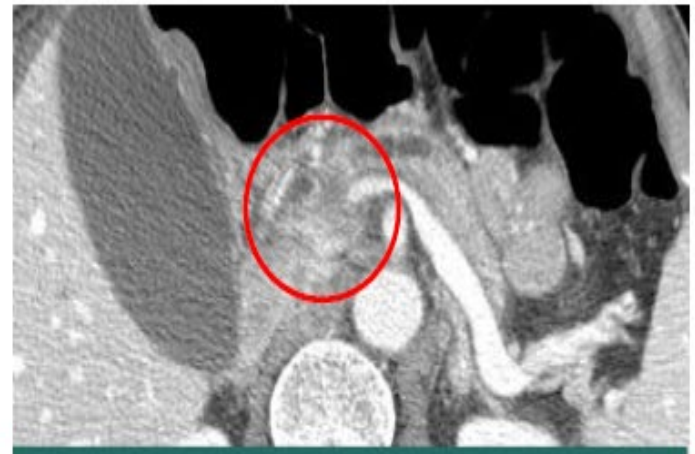
No invasion (intact fat plane)



Abutment (≤180º)

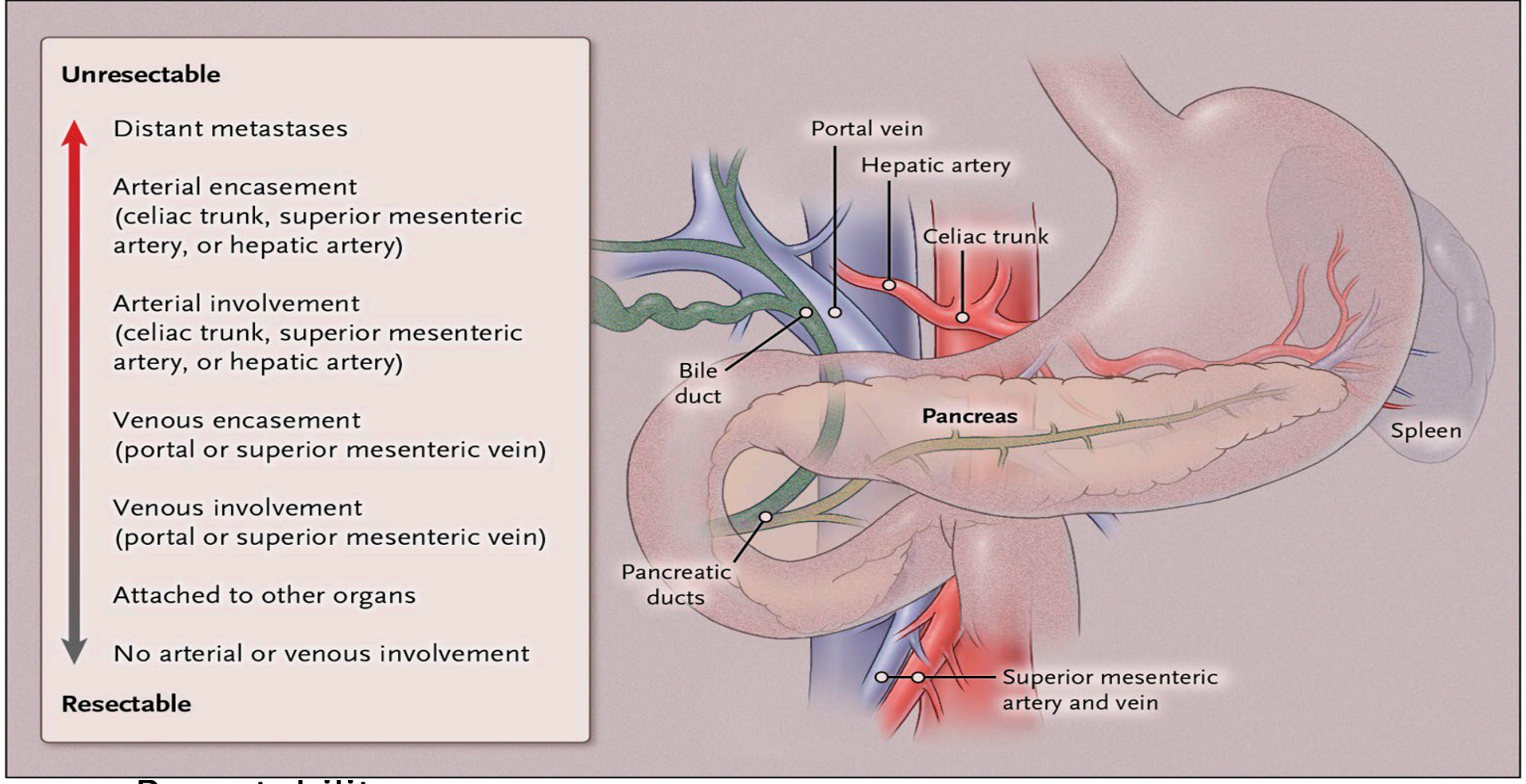


Encasement (>180º)



Encasement/ occlusion

Strongly suggestive of vascular invasion



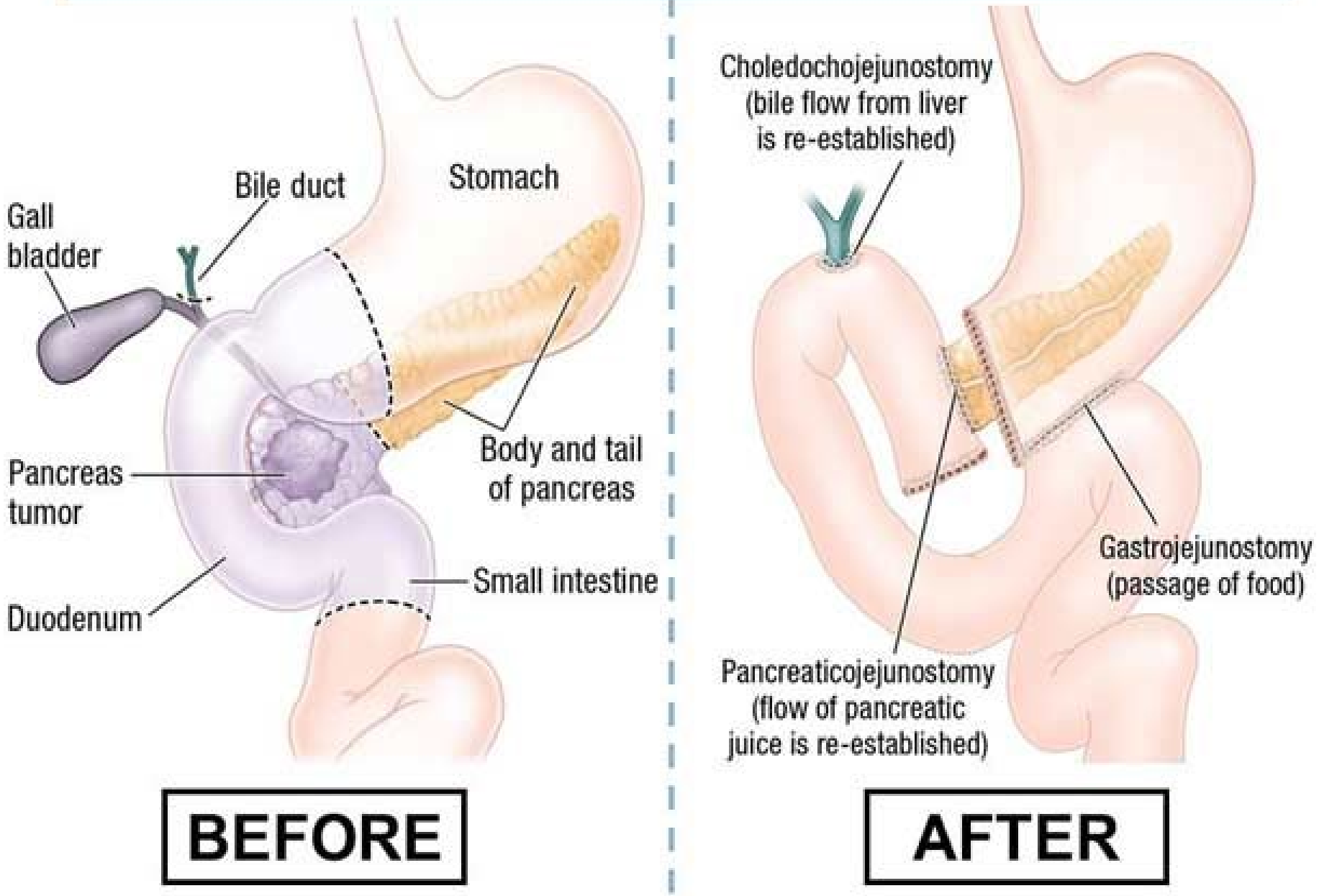
- Resectability

➢No distant mets

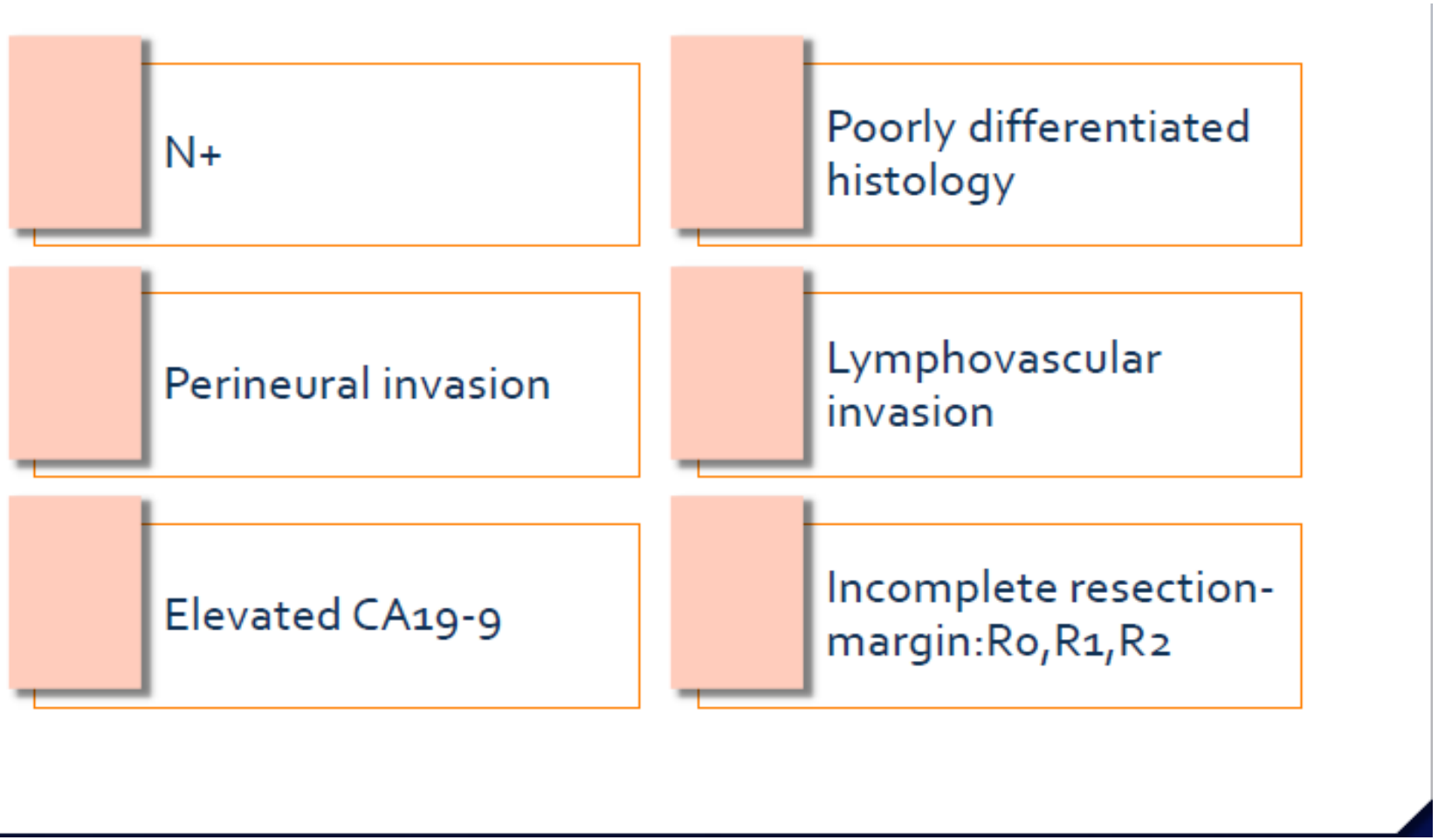
➢No superior mesenteric vein/portal vein distortion

➢Clear fat planes around celiac axis, hepatic artery and superior mesenteric artery

THE WHIPPLE PROCEDURE



Prognostic features of resected pancreatic cancer



Adjuvant therapy

- Should start 4-6 weeks post surgery
- Baseline CTs and Ca19.9 prior to initiation
- Elevated Ca19.9?
- Systemic relapse in >80%, local relapse in >20%

Metastatic PC

- Median survival of patients with metastases without treatment is only about 3 mos
- Often rapid symptomatic progression: optimal palliative care is crucial
  - Cachexia, anorexia
  - Joundice: bile duct obstruction
  - Gastric outlet obstruction
  - Pain
- Patients with metastatic pancreatic cancer should have a full assessment of symptom burden, psychological status, and social support as early as possible, preferably at the first visit. In most cases, this assessment will indicate a need for a formal palliative care consultation and services (ESMO and ASCO guidelines)
- Chemotherapy: modest progress

Συμπεράσματα

- Ο καρκίνος γαστρεντερικού είναι μείζον πρόβλημα για την παγκόσμια υγεία
- Ο καρκίνος παχέος εντέρου/ορθού τρίτος σε συχνότητα και θνητότητα παγκοσμίως
- Ο καρκίνος παγκρέατος 4^{ος} σε θνητότητα παγκοσμίως
- Καρκίνος παχέος εντέρου: μεγάλη αύξηση τα τελευταία έτη και σε νέους < 45 ετών, πολύ σημαντικός ο προσυμπτωματικός έλεγχος με κολονοσκόπηση στα 45 έτη, πρωτογενής πρόληψη (επεξεργασμένα κρέατα, κάπνισμα)
- Καρκίνος στομάχου (αδενοκαρκίνωμα): λιγότερος συχνός, διαγιγνώσκεται αργά λόγω μη εμφάνισης συμπτωμάτων, σημαντική η λαπαροσκοπική σταδιοποίηση σε τοπικά προχωρημένους καρκίνους, προεγχειρητική χημειοθεραπεία στην Ευρώπη, περισσότερο επικουρική στην Ασία, χημειοανοσοθεραπεία στα μεταστατικά στάδια
- Καρκίνος οισοφάγου: αδενοκαρκίνωμα (οισοφάγος Barrett), πλακώδες (κάπνισμα, αλκόολ), προεγχειρητική χημειο-ακτινοθεραπεία σε χειρουργήσιμα στάδια

Συμπεράσματα

- ΗΚΚ: HBV, HCV, αλκόολ, επιλογή θεραπείας με BLCC κριτήρια χειρουργείο/τοπικές θεραπείες σε αρχικά στάδια, μεταμόσχευσή ήπατος σε κίρρωση, ανοσοθεραπεία/στοχεύουσες θεραπείες σε μεταστατικά στάδια
- Καρκίνος παγκρέατος: μεγάλη αύξηση, πολύπλοκη βιολογία, σημαντικός ο ρόλος του στρώματος, πολύ περιορισμένη θεραπευτική προόδος τα τελευταία έτη

Screening

- Ανίχνευση αιμοσφαιρίνης στα κόπρανα (FOBT)
- FIT (fecal immunochemical test): όπως FOBT αλλά με διαφορετική μέθοδο (αντισώματα)

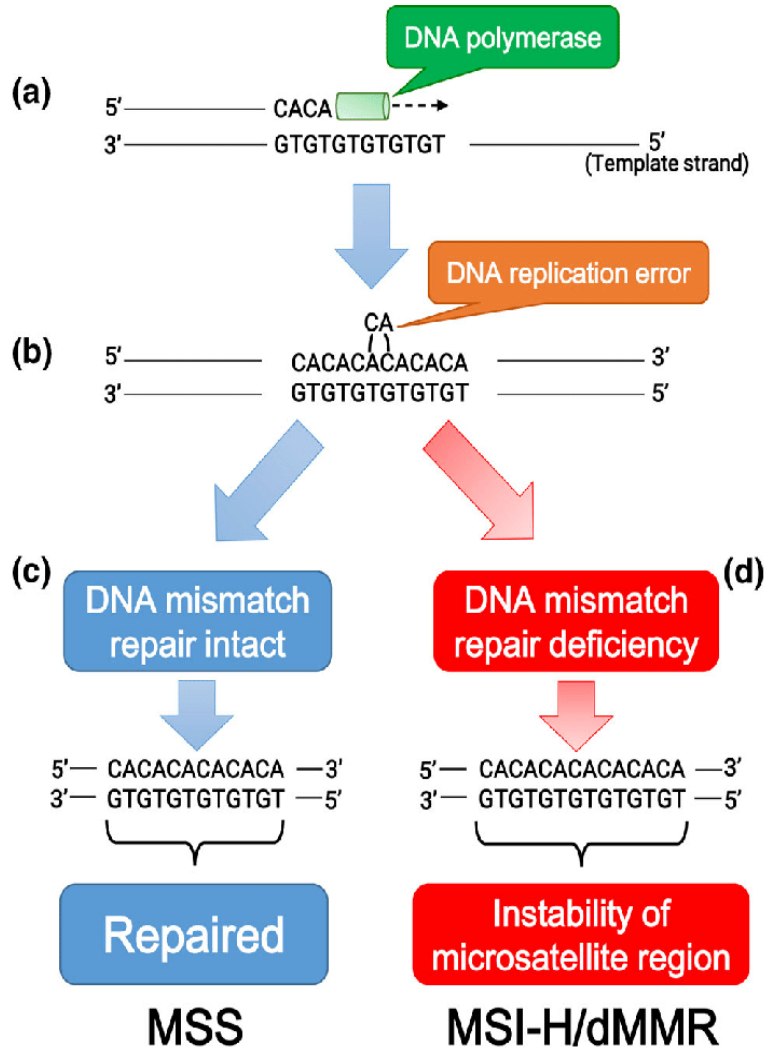
-δε χρειάζεται περιορισμούς στη δίαιτα

-πιο ακριβές

- Ορθοσιγμοειδοσκόπηση, Κολονοσκόπηση
- FOBT, FIT,κολονοσκόπηση, ορθοσιγμοειδοσκόπηση, βάριο → μείωση θνησιμότητας
- FOBT+ σιγμοειδοσκόπηση:μείωση θνησιμότητας αλλά χάνονται 8% των distal και ολοι οι proximal Cas
- Stool DNA: ανιχνεύει γενετικές αλλαγές στα κόπρανα

MSI

- Εν σειρά επαναλήψεις αλληλουχιών 2 – 5 βάσεων είναι γνωστές ως μικροδορυφορικό DNA.
- Η αστάθεια του μικροδορυφορικού DNA είναι ένα φαινόμενο που προκύπτει από την ανεπάρκεια του επιδιορθωτικού μηχανισμού λανθασμένου ζευγαρώματος βάσεων του DNA και αφορά ουσιαστικά σε ελλείψεις ή προσθήκες επαναλαμβανόμενων νουκλεοτιδίων στις αλληλουχίες του μικροδορυφορικού DNA.
- Αυξημένη συσσώρευση μεταλλαγών σε γονίδια-στόχους οπότε η εξαλλαγή του πολύποδα γίνεται γρήγορα (εντός 2-3 ετών)
- Οι ασθενείς με ορθοκολικούς καρκίνους με MSI σταδίων I-III έχουν **καλύτερη πρόγνωση** συγκριτικά με τους ασθενείς με ορθοκολικούς καρκίνους με CIN (MSS) και πιθανότατα **αντιδρούν διαφορετικά στην επικουρική χημειοθεραπεία** (προτιμάται η irinotecan έναντι των αλκυλιωτικών παραγόντων ή της 5-FU).



Prognostic determinants

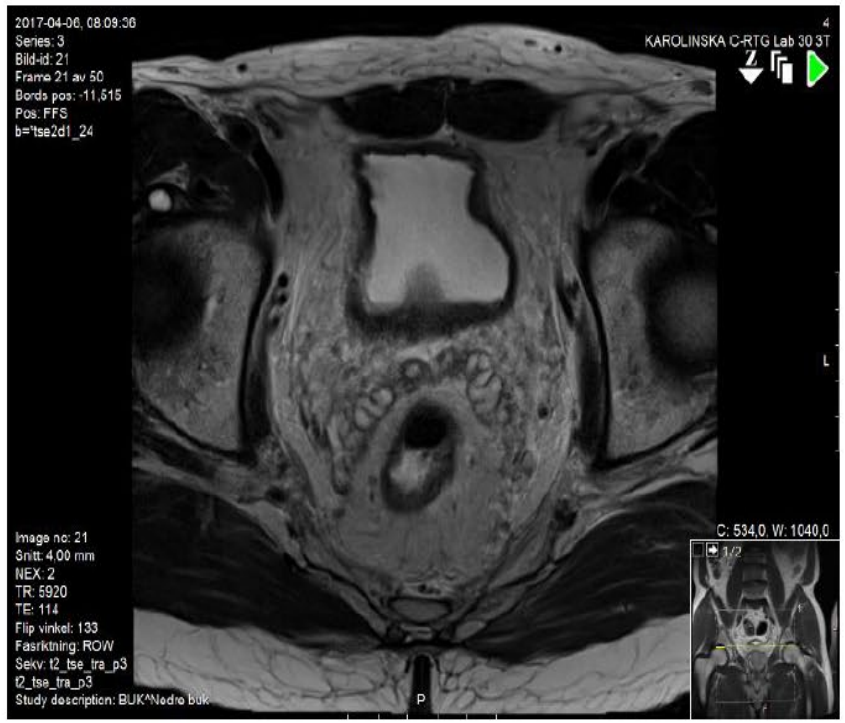
- Local tumor extent (local peritoneal involvement)
- Regional LNs: at least 12
- Nodal micromets (< 0,2 mm): χειρότερο OS
- Mesenteric LNs (discrete nodules in perirectalpericolic fat or adjacent mesentery): χειρότερη πρόγνωση
- LVSI (high risk II)
- Περινευριδιακή διήθηση (high risk II)
- Residual tumor
- Poorly differentiated (adverse prognosis if no MSI)
- Tumor regression post chemoRT (rectal)
- Microvessel density (tumor-induced angiogenesis: χειρότερη πρόγνωση
- TILs (καλύτερη πρόγνωση)
- NET component (κακή πρόγνωση)
- Preop CEA > 5
- Εντερική απόφραξη/ διάτρηση
- MSI high (καλύτερη πρόγνωση)

Personalizing Treatment in mCRC: Considerations

- Extent of disease
- Intent of treatment (palliative vs potentially curative)
- Performance score
- Age
- Comorbid illnesses
- Previous adjuvant therapy within 1 yr
- Molecular markers
- Organ function: hepatic and renal
- Risks for toxicity: active CAD/CVD, proteinuria, active bleeding, nonhealed wound, allergy to mAb, neuropathy, IBD, ILD, Gilberts
- Convenience
- Cost/resources
- Patient preferences and goals

CRUCIAL INFORMATION AT MDT

Focus on locoregional disease



- ✓ Tumour height from anal verge
- ✓ mrT-stage
- ✓ mrN-stage
- ✓ Enlarged lateral lymph nodes
- ✓ Extramural Vascular Invasion (EMVI)
- ✓ **Relation to Mesorectal Fascia (MRF):**

LR rate <10% if MRF >1 mm vs 30% if MRF ≤ 1 mm

5-y DFS 70% if MRF >1 mm vs 50% if MRF ≤ 1 mm

MERCURY study: Taylor et al, J Clin Oncol 2014

DECISIONS AT MDT

Treatment intent

Type of surgery aimed for (sphincter preservation or APE)

Any neoadjuvant therapy?
If ”Yes” – what neoadjuvant therapy?

Up-front therapy aiming at non-operative management??

However: ”No decisions about me without me”

MOLECULAR PATHOLOGY AND PREDICTORS

Oesophageal SCC Adenocarcinoma

SCC: PD-L1 positivity is defined as TPS ≥1% in the case of first-line treatment with nivolumab and nivolumab–ipilimumab

SCC + AC: PD-L1 positivity is defined as CPS ≥10 in the case of first-line treatment with pembrolizumab or CPS ≥ 5 for treatment with nivolumab

GEJ and Gastric Cancer

- HER 2 overexpression or amplification
- PD-L1 overexpression: CPS ≥ 5
- MSI .high/dMMR
- Other investigated predictive markers: MET, Claudin 18-2, FGFR fusion

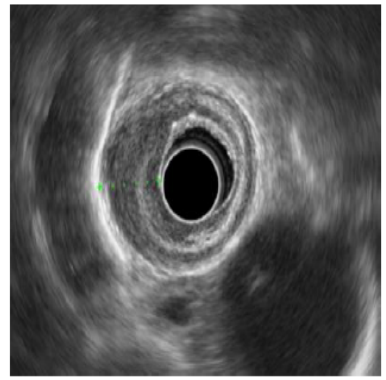
Sun JM, *Lancet*. 2021;
Bang YJ. Lancet. 2010
Janjigian YY. Lancet. 2021
Böger C. Oncotarget. 2016
Pietrantonio F. J Clin Oncol. 2019

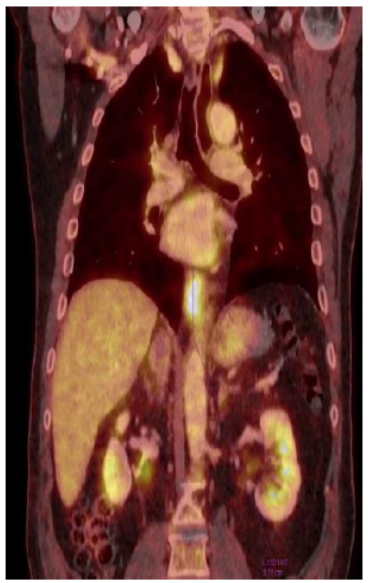
DIAGNOSIS

- Endoscopy
- Endoscopic ultrasound- most useful in early or late tumours, and to biopsy lymph nodes
- CT scan of chest and abdomen
- **Oesophageal:** [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG)PET-CT scan
  - most useful in early or late tumours, and to biopsy lymph nodes
- Biopsy (≥6-8 representative biopsies of the lesion)
- Laparoscopy± washing- in locally advanced (T3/T4) ACs of the OGJ infiltrating the anatomical cardia and gastric cancer- to rule out peritoneal metastases (15%)

- In patients who are candidates for surgery, an assessment of **medical fitness** is recommended

- **Nutrition assessment** and early **intervention** (ESPEN guidelines) improve outcomes.





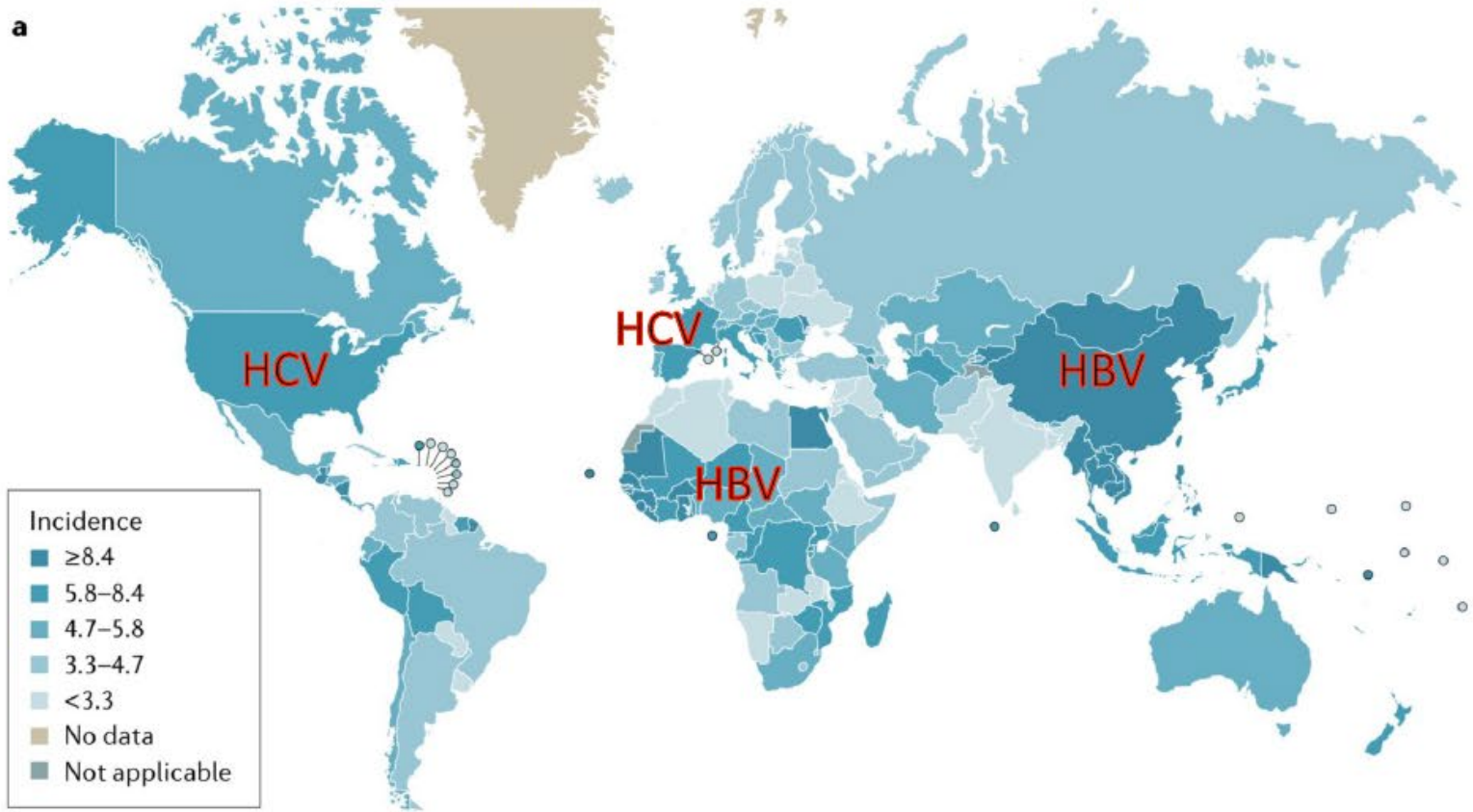
Obermannová R,...Smyth EC. Annals of Oncology. 2022. In Print

Risk Factors for gastric cancer

- Diet
  - nitroso compounds
  - low fruit/vegetable, high fried foods/processed meat
  - High salt intake
- Obesity
- Smoking (HR 2-3)
- ? Alcohol
- H. Pylori
- Low socioeconomic status
- Hereditary diffuse gastric cancer
  - 40-67% lifetime risk for men, 60-83% for women
- Immigrants from endemic areas
  - maintain native country risk, risk to offspring similar to new homeland

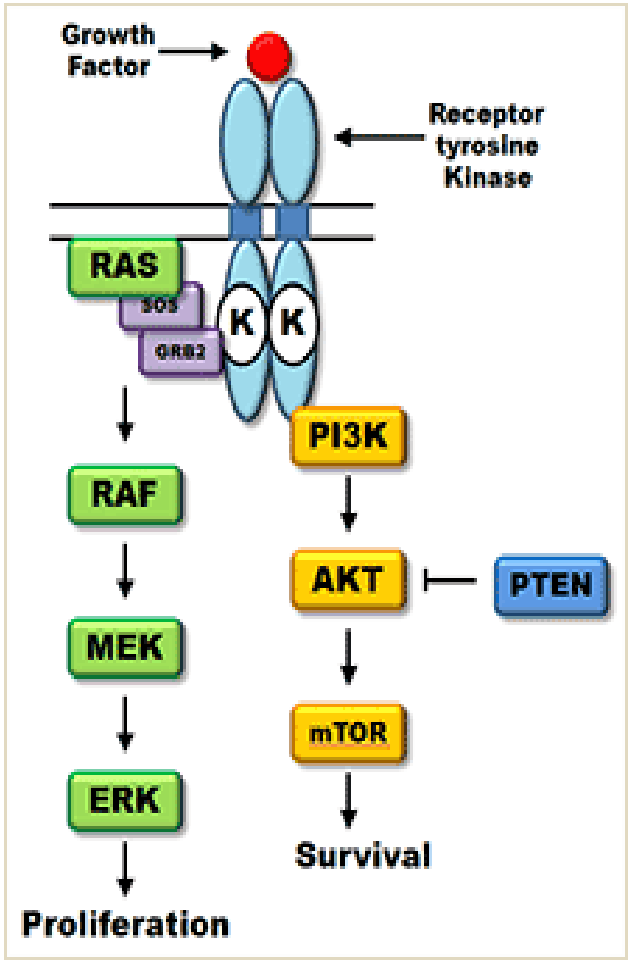
HCC: Incidence

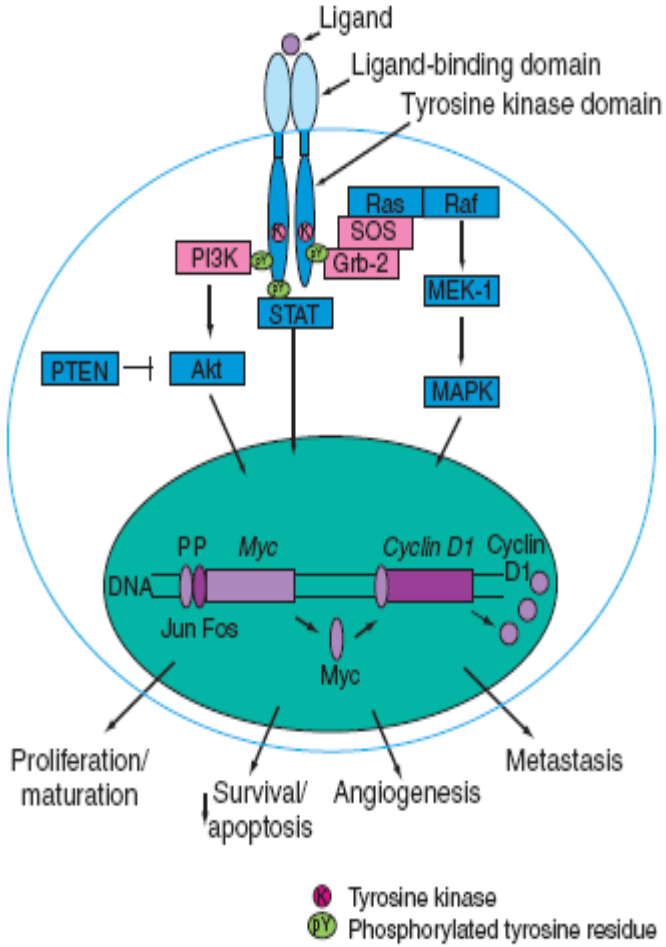
- High geographical divergence
- Later occurrence in Japan, North America and European countries



Yang JD Nature Reviews GE 2019

Main Signaling Cascades in Cancer relevant for targeted therapies

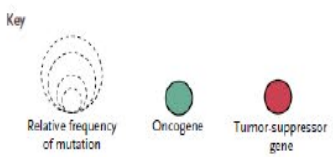


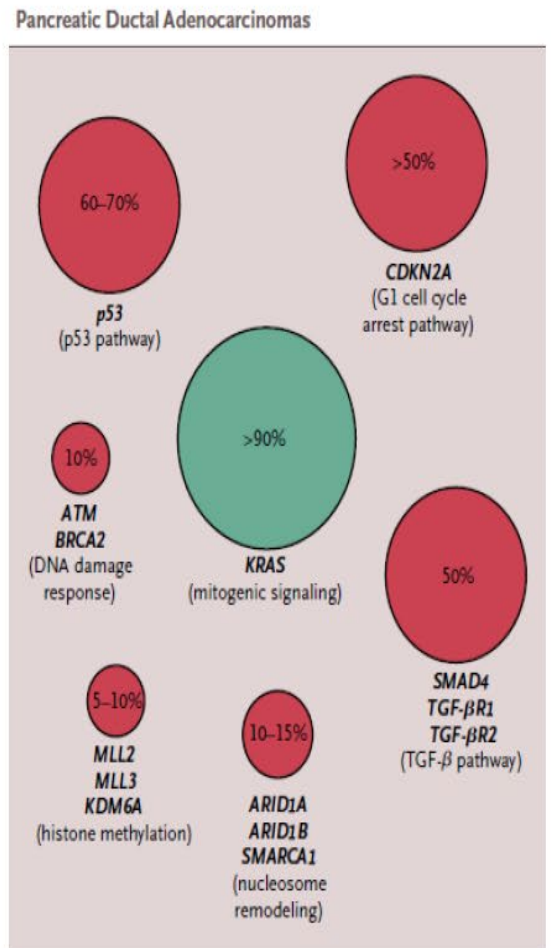


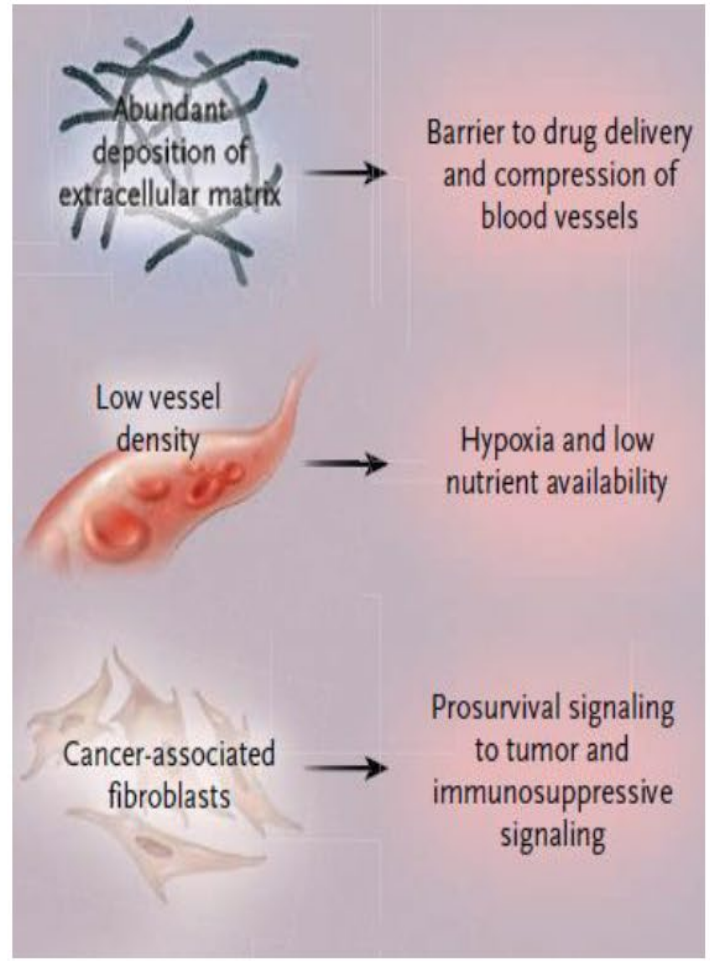
Baselga J. Oncol. 2002;7(suppl 4):2-8; Lynch TJ, et al. N Engl J Med. 2004;350:2129-2139; Rosell R, et al. N Engl J Med. 2009;361:958-967, MyCancerGenome.com

PANCREATIC CANCER

Biology

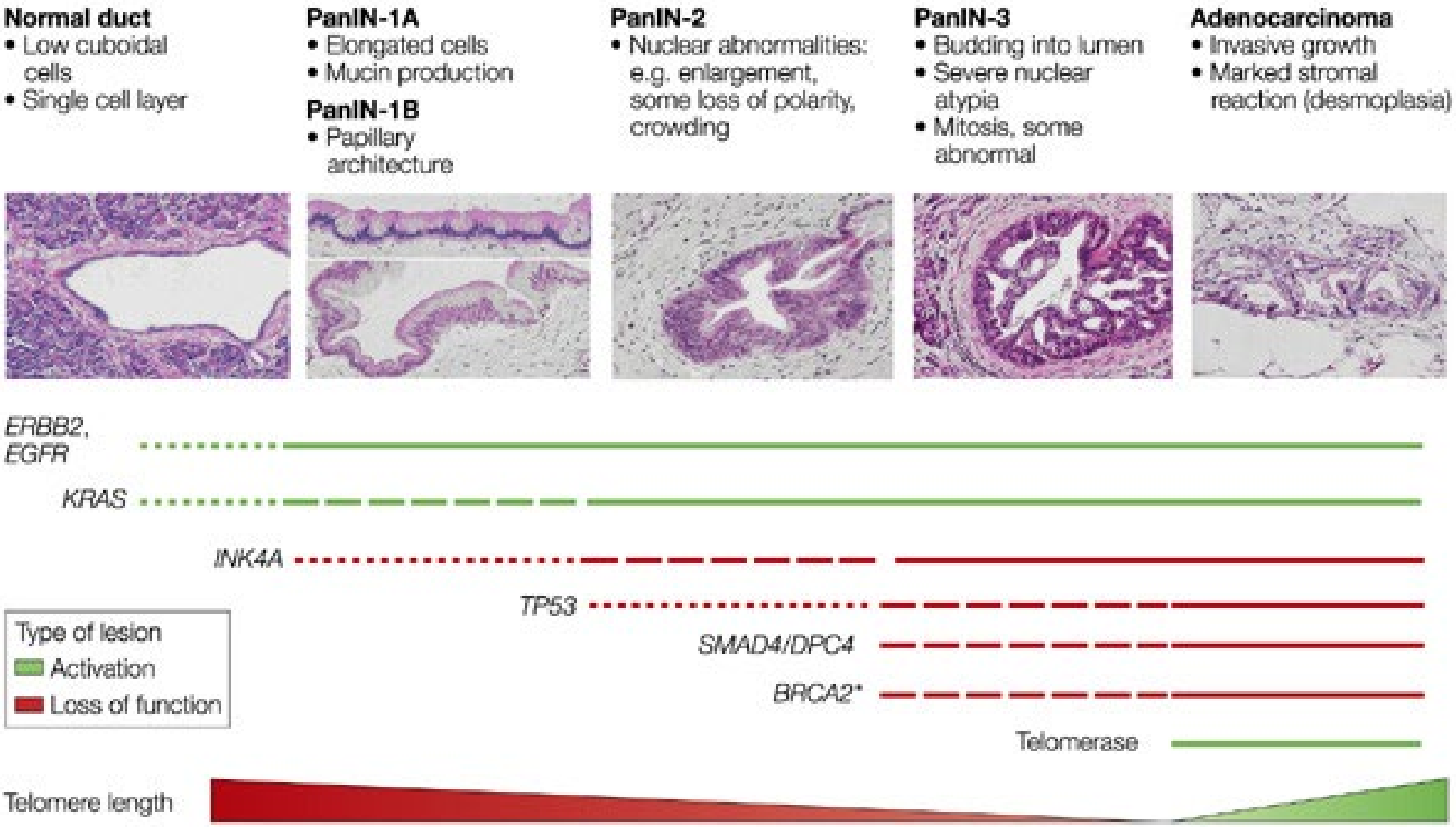




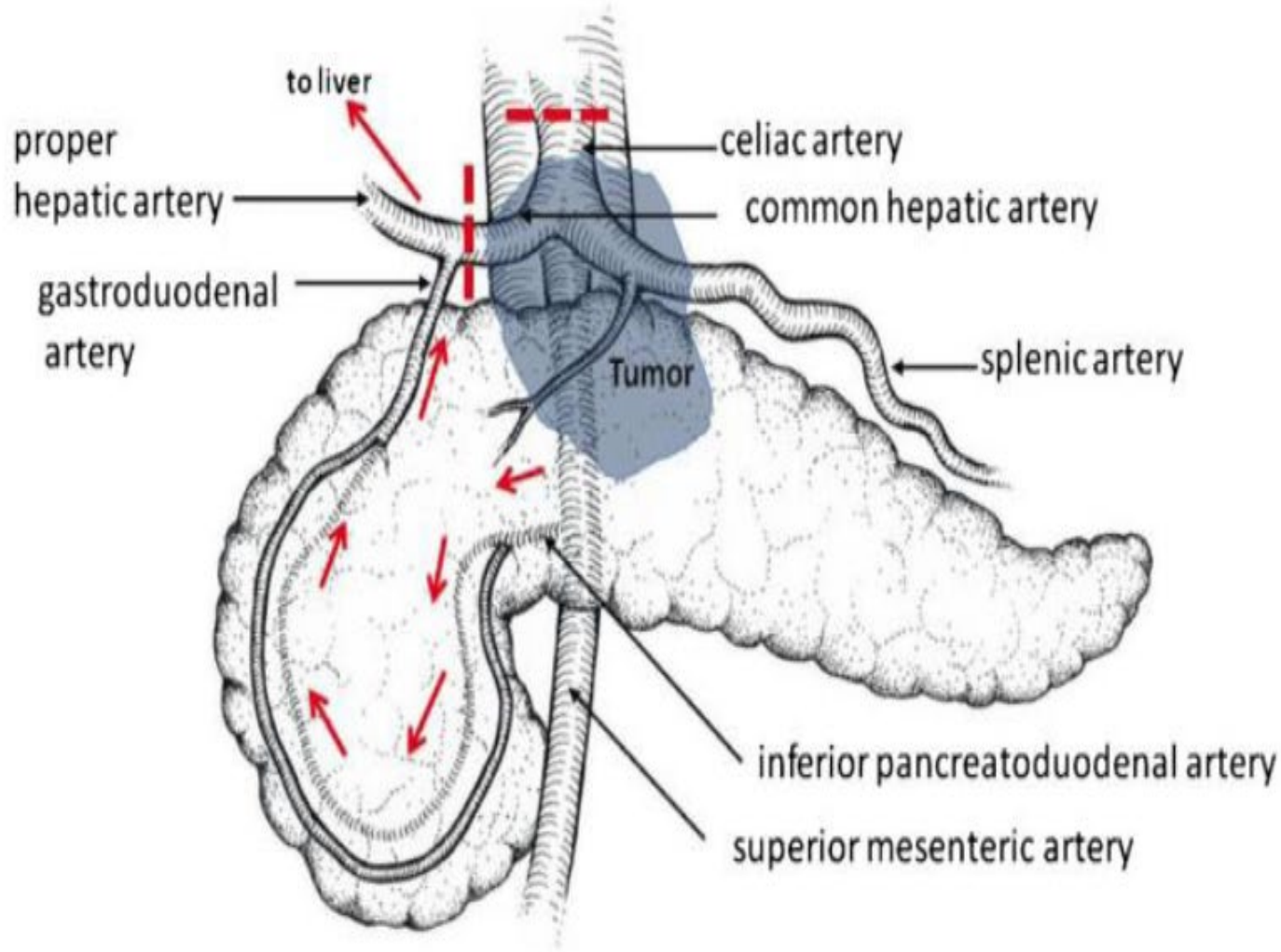


Ryan et al., N Engl J Med 2014; 371: 1039-49

Molecular pathogenesis



Nature Reviews | Cancer



Strasberg SM and Fields R. Cancer J. 2012 Nov-Dec

“Resectable”

- MD (Multi-Detector) CT > MRI: vessel invasion

	CT	MRI
Resolution	Better	Worse
Motion artifacts	Better	Worse
3D reconstruction	Better	Worse
Soft tissue contrast	Worse	Better

Recent Randomized Trials document Impact of EARLY Palliative Care

- Benefits of OUTPATIENT concurrent palliative care:
  - Avoided admissions and readmissions, increase referral to hospice,
  - Better communication and satisfaction
  - Equal or lowered costs to the health system
  - Equal or better symptom management
  - Equal or improved quality of life
  - Equal or LONGER survival
  - Not a single trial showed harm, added cost, or burden

Supportive and Palliative Care

- Start supportive and palliative care as soon as diagnosis is suspected – pancreatic cancer is an EMERGENCY
- Assess symptoms and their speed of development
- Consider pain, weight loss, exocrine pancreatic insufficiency, jaundice*, delayed gastric emptying*, VTE, depression, etc.

* Biliary obstruction: endoscopic stent placement

* Duodenal obstruction: endoscopic metal stent placement

- Pain
  - Assess at every visit including response to analgesics
  - May be neuropathic and require co-analgesics
  - RT or Celiac Plexus Block
- VTE
  - Four- to seven-fold higher in pancreatic cancer than in other common adenocarcinomas, risk highest in first months after diagnosis and increased by chemotherapy
  - Prophylaxis with LMWH reduces VTE but does not improve OS in outpatients- those with previous VT/E - lifelong LMWH
- Anxiety and Depression
  - 1/3 -2/3 of patients
  - Use validated instruments or “Are you depressed?”
  - Duloxetine or Venlafaxine co-treat neuropathic pain

Anorexia - Cachexia

- Weight loss and Anorexia – loss of appetite – is common and multifactorial, but in many cases reversible
  - Dysgeusia, xerostomia
  - Poor appetite
  - Poor GI transit/ motility or absorption
  - Early satietey (ascites, hepatomegaly)
  - Weight loss > 5% correlates with worse mortality
- Cachexia is characterized by
  - Excessive loss of lean body (skeletal muscle) mass
  - Cytokine activation and chronic inflammatory response
  - Increased basal metabolic rate / ‘hypermetabolic state’
  - Far more than poor caloric intake
  - Correlates with poor prognosis, directly linked to severity