GI tumors – colorectal, pankreas, biliary tract – and malignant melanoma

Eva Vegh MD MBA

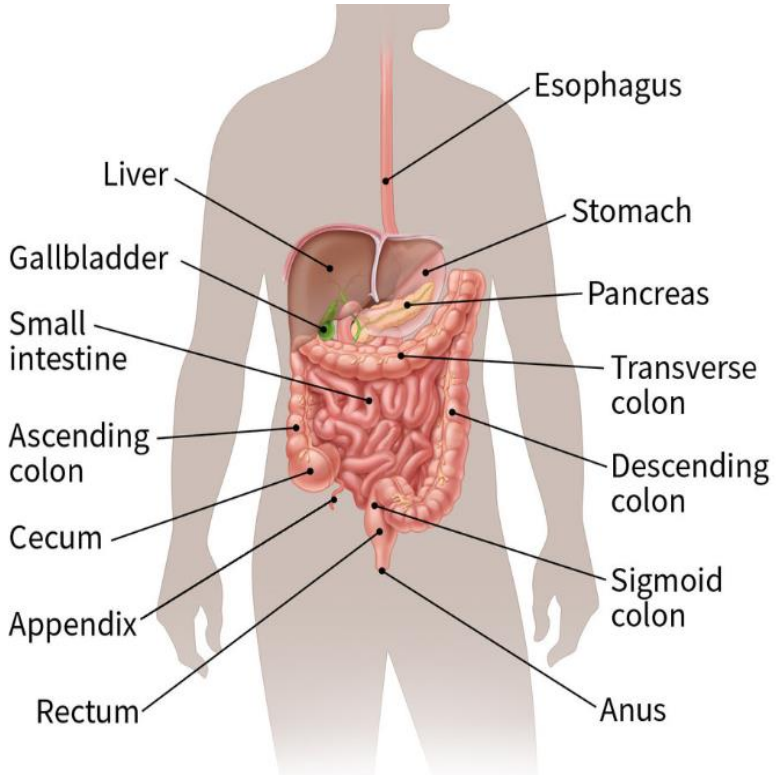
Central Hospital of Southern-Pest, National Institute of Hematology and Infectol

St. Laszlo Hospital, Department of Oncology, Budapest, Hungary

Gastrointestinal tumors

Gastrointestial tract cancer

- The gastrointestinal (GI) tract is along pathway that extends **from the mouth to the anus**
- **Gastrointestinal (GI) cancer** includes all cancers in the digestive tract:
  - Esophageal cancer
  - Stomach cancer (gastric cancer)
  - Small intestine cancer
  - Pancreatic cancer
  - Liver cancer
  - Gallbladder and biliary tract cancer
  - colon cancer (appendix, coecum, ascending, transverse descending, sigmoid colon
  - rectal cancer
  - anal cancer,



CRC: Colon cancer and rectal cancer are often grouped together because they have many features in common

Introduction

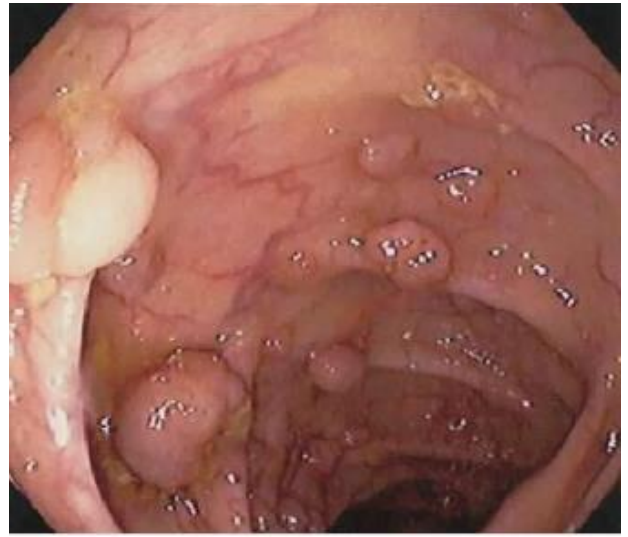
- Gastrointestinal cancer is common type of cancer wordwide, also in Central-Eastern Europe
- GI cancer acount for about **25% of cancer incidences** globally and **35% of all cancer-related death**[1] (estimated **4,8 million new cases** and **3,4 million death** globally
- Risk of GI cancer increases with age
- Treatments are more effective when the cancer is detected at an early stage – early detection is the first priority to prevent cancer death
- Diagnostic measures can clarify the specific type and the extent of the disease

1 Arnold M, Abnet CC, Neale RE, Vignat J, Giovannucci EL, McGlynn KA, Bray F. Global Burden of 5 Major Types of Gastrointestinal Cancer. Gastroenterology. 2020 Jul;159(1):335-349.e15. doi: 10.1053/j.gastro.2020.02.068. Epub 2020 Apr 2. PMID: 32247694; PMCID: PMC8630546.

Aetiology of GI cancers

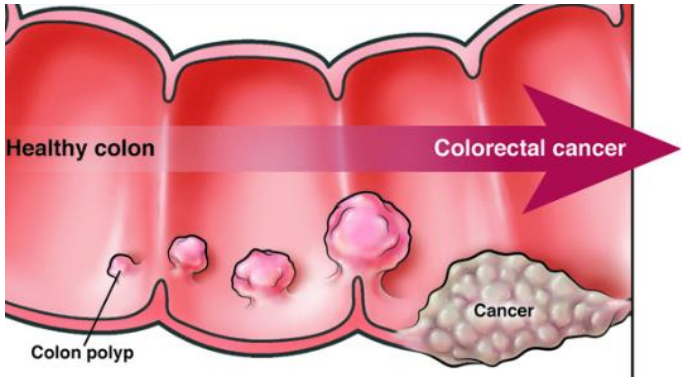
- GI tumors may result from **specific underlying conditions**, including:
  - gastroesophageal reflux disease in the esophagus,
  - Helicobacter pylori infection in the stomach,
  - hepatitis B or C virus infection or cirrhosis in the liver
  - Polyps.
- A small percentage of gastrointestinal cancers are **inherited** (~5% of the CRC cases):

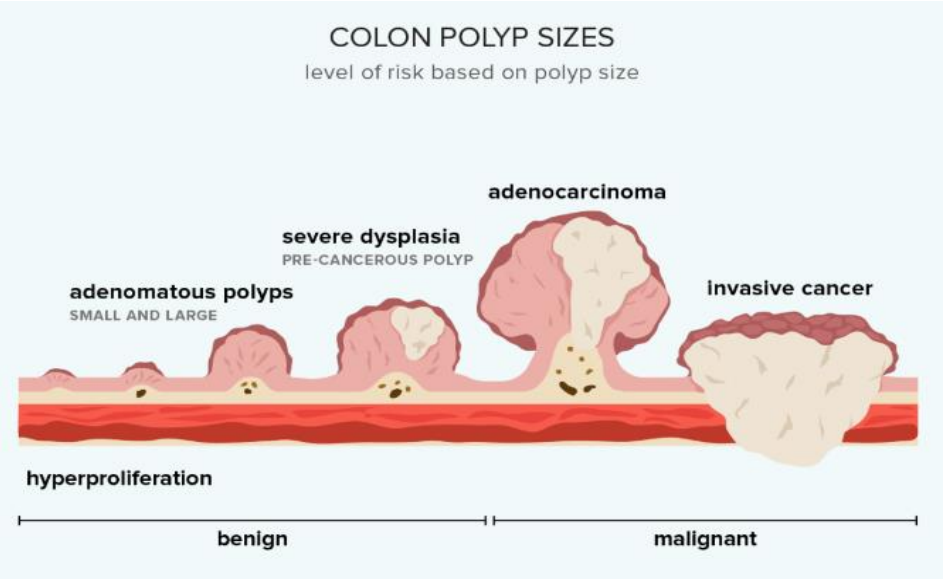
- most common: **Lynch syndrome** (i.e. Hereditary Nonpolyposis Colorectal Cancer /HNPCC/ - increased risk for colorectal, endometrial and other cancers)
- **FAP:** familial adenomatosus polyposis)



Polyps in CRC

- Some type of polips (called adenomas) can turn into cancer (if not removed),
- The most bowel cancers develop from adenoma polyps
- Very few polyps will turn into cancer
- It takes many years
- Routine colorectal screening markedly reduces the risk of colon cancer by finding and removing polyps before they have the chance to become cancerous





Laboratory examination – GI cancers

- Anaemia and/or low iron levels – due to occult bleeding
- Test to look for bleeding: stool-based tests:
  - guaiac fecal occult blood test (gFOBT)
  - fecal immunochemical test for hemoglobin (FIT),
- Septin-9 screening from blood) (FDA approved test)
- Tumor M2-PK can be measured in stool, can detect gastrointestinal cancer and polyps
- Elevated liver enzymes (transaminase, ASAT, ALAT)
- Elevated serum bilirubin
  - liver cancer – parenchymal damage
  - obstruction of biliary tract: biliary tract or gall bladder tumor, tumor of the pancreatic head, lymphnodes in the portal region, etc.
- Azotaemia (elevated BUN, serum creatinin) – mostly in case of locally advanced rectal cancer
- Tumor markers:
  - **CEA**: carcinoembrionic antigen, (colon, small intestinem biliary etc)
  - **AFP**: alfa-foetoprotein, - elevated level mostly indicates liver cancer
  - **CA 19-9** high levels often a sign of pancreatic cancer, but can be a sign also a gastric cancer or CRC

Diagnosis in GI cancer

- **X-ray, ultrasound**,
- **CT** (chest – abdominal-pelvic) **MRI** (mostly in rectal cancer for staging or examination of liver
- **Izotop** examination of bones (mets)
- **PET** (positron emission tormography) – functional imaging techniquee
- **Endoscopic examination** (upper panendoscopy, gastroscopy, colonoscopy sigmiodescopy,
- endoscopic ultrasound
- **ERCP:** Endoscopic Retrograde Cholangiopancreatography

BIOPSY

- Important procedure for correct diagnosis – often collected during endoscopic examination
- Obtain a sample of abnormal tissue and analyze it for the presence of cancer cells.
- Tissue sample from primary tumor or from metastasis
- FNAB (fine needle aspiration biopsy), core biopsy
- Ultrasound driven or CT driven sampling
- Abnormal tissue can be resected during a surgery (acute surgery due to obstruction/ileus)

Pathological examination

- Pathologist examines the tissue under a microscope to check for the presence of cancer cells
- IHC (immunochemistry) can help to set up correct diagnosis
- Nowadays biomarker examination help to set up modern therapeutic plan (KRAS, NRAS, BRAF, HER2, PDL-1, TMB, MSI etc.)
- Liquid biopsy (blood) – ctDNA – in initial phase – future development is expected!

Rare cancer of GI tract

- Neuroendocrin tumors (**NET and NEC**) (carcinoid tumors)
- **GIST:** gastrointestinal stromal tumor
- Lymphomas
- Sarcomas
- Etc.

GI cancer treatment

SURGERY

RADIOTHERAPY

ANTITUMOR DRUGS:

- Chemotherapy
- Targeted therapies
- Immuno-oncological treatments

Surgery

- Optimal surgery involves complete removal of the tumor, along with surrounding tissue and regional lymphnodes.
  - **R0 R1 R2 resection** (no tumor involvement, microscopic or macroscopic tumor residuum)
- To restore function (esophagus, stomach, colorectal tract etc) - anastomosis may be performed to connect the remaining healthy portions of the organ.
- Liver resection of hepatocellular cancer, liver transplantation in rare cases
- **Metastasectomy** – liver, lung, mostly in CRC (In 50% of CRC cases occur liver metastases. (900.000 CRCLM worldwide each year)
- Palliative surgery: complete tumor removal is not feasible – restore GI tract function

Radiotherapy

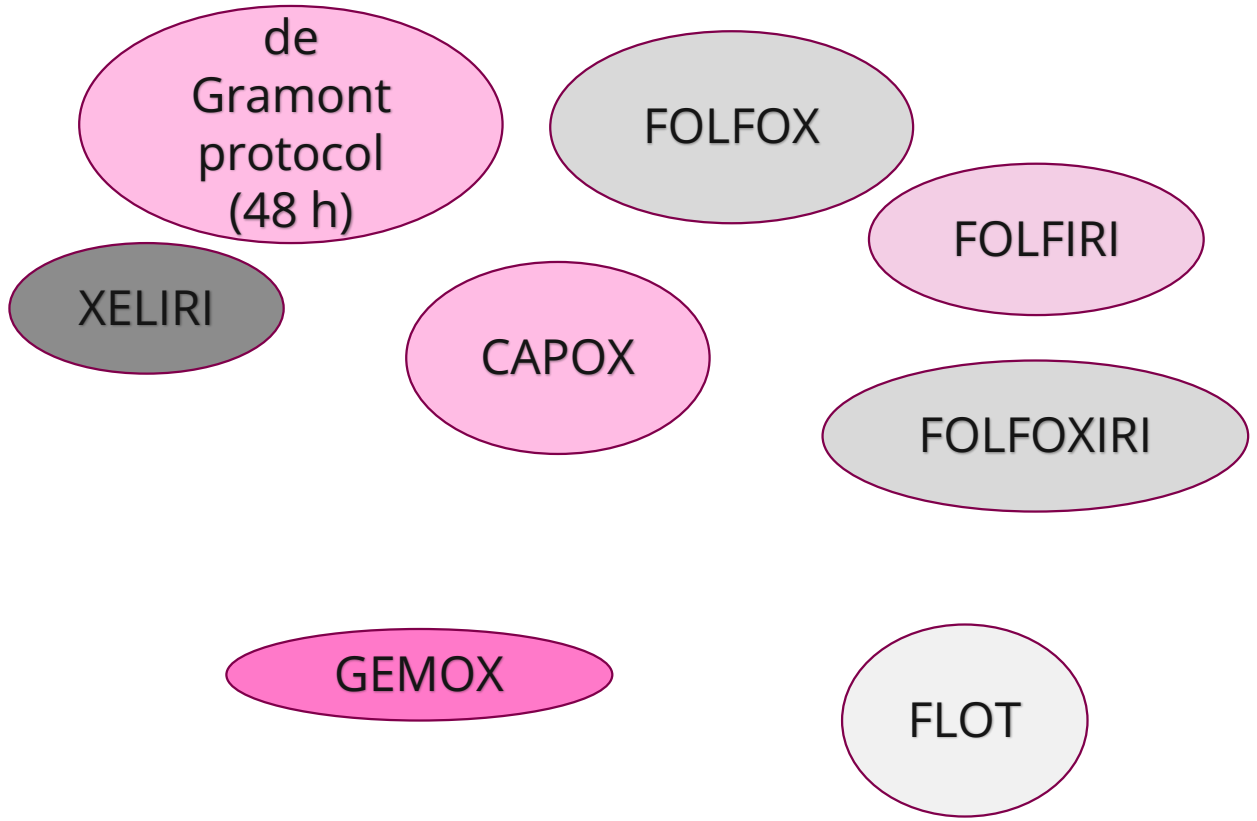
- Neoadjuvant/adjuvant radiotherapy of rectal cancer (reducing the local recurrance rate): traditional long course (25-30 days) or RAPIDO (5 days)
- Stomach, pancreas
- Radiochemoterapy of the anal cancer
- Palliative radiotherapy of bone metastases, brain mets

Systemic anti-cancers treatments

- pharmaceutical agents/drugs to treat cancer
- Different type/timing of treatments
  - **Neoadjuvant:** to shrink the tumor before planned surgery –
  - **Adjuvant treatment:** additional cancer treatment given after the primary treatment (in most cases after surgery), to reduce the risk that the cancer will come back (relapse)
  - **Palliativ cancer treatment:** non-curative treatment of recurrant/metastatic cancer to optimize symptom control, improve QoL and ideally to improve survival – mostly combined treatments
    - **First-, second-, third-, multiple line**

Chemotherapy

- Most frequently used medicines in GI cancers:
  - fluorouracil
  - irinotecan
  - oxaliplatin
  - capecitabine
    - Doublet-triplet chemotherapies
  - trifluridine/tipiracil tablets (TAS)
  - Gemcitabine
  - Taxans: paclitaxel/nab-paclitaxel/docetaxel
  - Carboplatin, mitomycin (anal cancer)



Targeted therapy in GI cancers (1)

Drug name	Target	Indication in GI cancers
cetuximab	EGFR inhibitor	CRC
panitumumab	EGFR inhibitor	CRC
trastuzumab	ERBB2 (HER2)	Gastric cancer
bevacizumab	VEGF inhibitor	CRC

Targeted therapy in GI cancers (2)

Drug name	Target	Indication in GI cancers
erlotinib	Tyrozine kinase (TK)	Pancreatic cancer
sorafenib	Multikinase inhibitor	hepatocellular carcinoma
ramucirumab	VEGFR-2	gastric cancer, CRC
regorafenib	Multikinase inhibitor	CRC, GIST
imatinib	TK (BCR-ABL, c-KIT, PDGFR)	GIST
sunitinib	TK (VEGFR, PDGFR, c-KIT, FLT3)	GIST, NET
everolimus	mTORC1, VEGF	neuroendokrin
sunitinib	TK (VEGFR, PDGFR, c-KIT, FLT3)	GIST, NET
aflibercept	VEGFR (1/2)	CRC

Immunotherapy in GI cancers

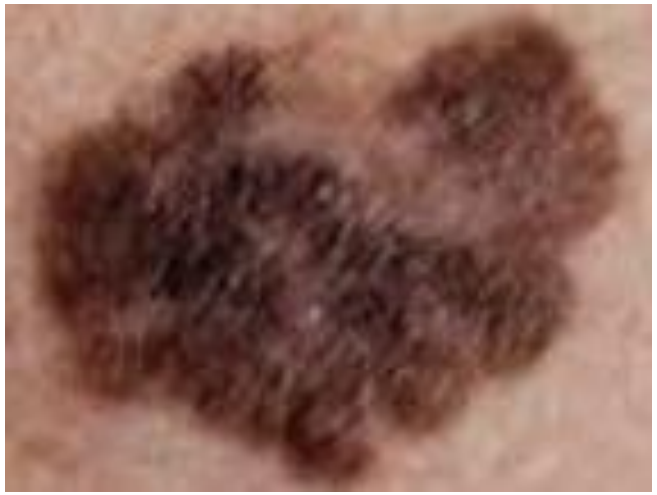
GI cancer		
Colorectal cancer	Mismatch repair deficien (dMMR) or high mikrosatellita instabile (MSI-H)	Pembrolizumab, nivolumab, ipilimumab
Gastric cancer		atezolizumab, pembrolizumab, nivolumab
Esophageal cancer	squamous cell carcinoma	nivolumab
GEJ and esophagus	adenocarcinoma	nivolumab
Cholangiocellular carcinoma		ipilimumab, pembrolizumab, nivolumab, durvalumab
Hepatocellular carcinoma		atezolizumab pembrolizumab nivolumab

Supportive and palliative treatment

- Erytropoetins, CSF (colonia stimulating factors) blood transfusion, thrombocyta replacement, reducing side effects of active onco treatments, etc
- BSC: best supportive care - mostly symptomatic treatment at the end of life (palliative care) – pain killers, parenteral fluid replacement, laxatives, decubitus prevention etc.

Malignant melanoma (MM)

Malignant melanoma

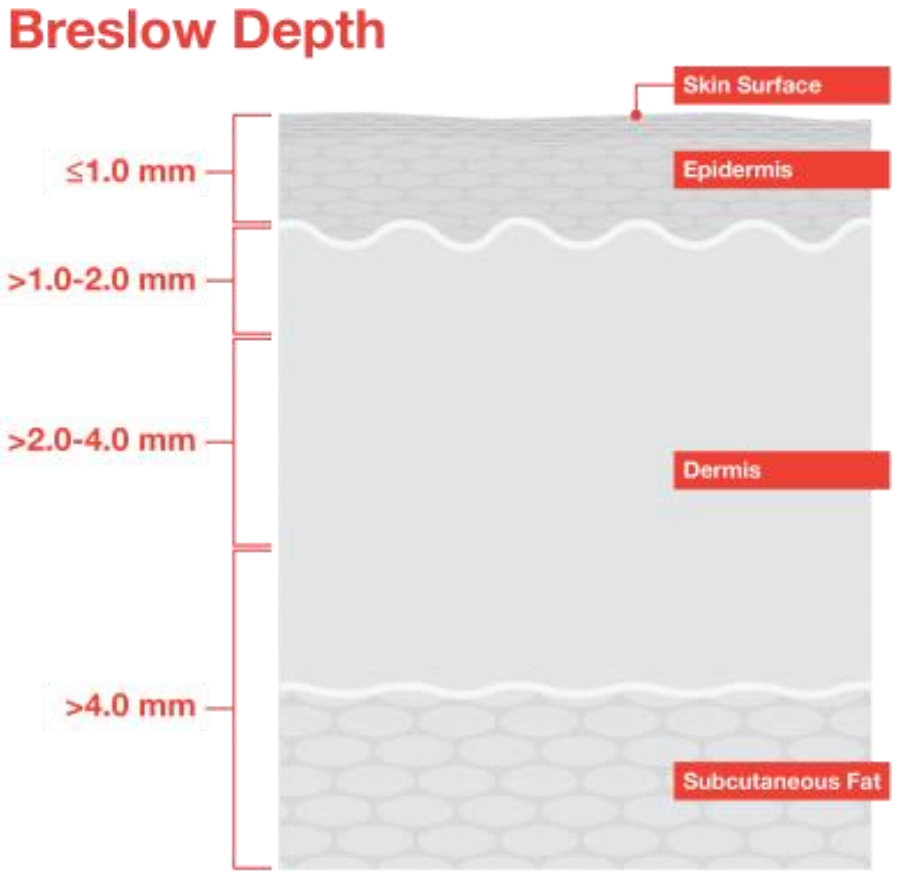


- Type of skin cancer
- develops from melanocítes (pigment producing cells).
- Melanoma subtypes:
  - cutaneus,
  - uveal,
  - mucosal melanoma, (intestines, mouth, genital region).
- Occurs more frequently in men than in women
- Risk factors: Personal or family history of melanoma; atypical, large, or numerous (>50) moles; ultraviolet radiation (sunlight or indoor tanning); History of excessive sun exposure (including sunburns); Sun sensitivity (eg, sunburn easily or have natural blond or red hair color); immunosuppression

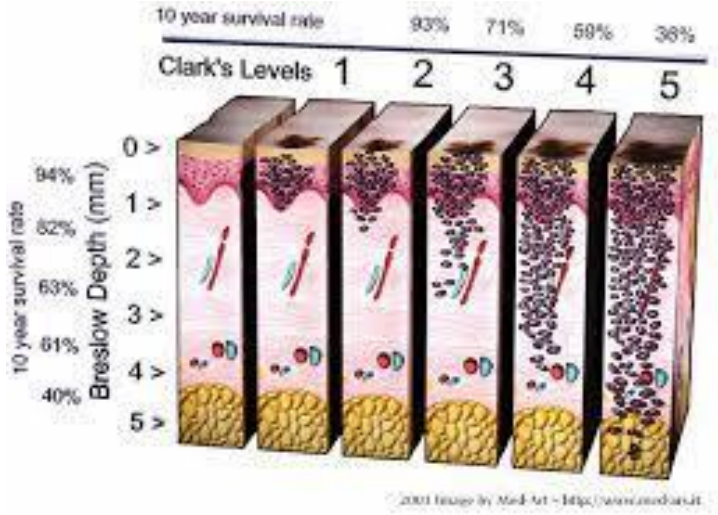
Epidemiology

- **~ 325,000 new cases per year worldwide[1]**
- 57,000 deaths per year worldwide[1]
- The 5-year survival rate is 92% for all stages, 90% for local disease, 63% for regional disease, and 20% for distant metastasis

Breslow depth and Clark level



Clark Level	Histological tumour characteristics
Level 1	Confined to the epidermis; "*in situ*" melanoma
Level 2	Invasion of the papillary dermis
Level 3	Filling of the papillary dermis but not extending to the reticular dermis
Level 4	Invasion of the reticular dermis
Level 5	Invasion of the deep, subcutaneous tissue



Important prognostic factors

- Localized melanoma cases: pathological subtype, tumor thickness (Breslow thickness), mitotic rate, ulceration[1]
- Unresectable disease, prognostic factors for poor survival[2,3]
  - Older age at diagnosis
  - Elevated LDH (lactate dehydrogenase)
  - Elevated serum albumin levels
  - ECOG performance status 2
  - Number of visceral metastatic sites
  - CNS (central nervous systeme) metastases

1. Balch CM et al. *J Clin Oncol*. 2009;27:6199-6206. 2. Bedikian AY et al. *Cancer Invest*. 2008;26:624-633.
3. Gershenwald JE et al. *CA Cancer J Clin*. 2017;67:472-492.

Treatment options

Stage (per TNM staging criteria)	Standard treatment option
Stage 0 melanoma (in situ melanoma)	Excision
Stage I melanoma	Excision +/– lymph node management
Stage II melanoma	Excision +/– lymph node management
Resectable stage III melanoma	Excision +/– lymph node management Adjuvant therapy
Unresectable stage III, stage IV, and recurrent melanoma	Intralesional therapy Chemotherapy Palliative local therapy Immunotherapy Signal-transduction inhibitors

National Cancer Institute. Melanoma treatment (PDQ)–health professional version. https://www.cancer.gov/types/skin/hp/melanoma-treatment-pdq#section/_885. Accessed September, 2022.

Melanoma therapy

- Surgery – wide excision and if necessary re-excision of the primary – sentinel lymph node (SLNB) – correct staging
- Radiotherapy- mostly palliative (bone, braind mets)
- Immunotherapy – in case BRAF V600 mutation
- Targeted therapy – possible also in mutant and wild type BRAF V600
- Tebentafusp: registered for uveal melanoma
- Chemotherapy – dacarbazin, vincristin, bleomycin etc.

Widely used systemic treatments

Checkpoint Inhibitor Therapy

- Ipilimumab
- Nivolumab
- Nivolumab+ ipilimumab
- Pembro-lizumab

Targeted Therapy

- Vemurafenib
- Dabrafenib
- Dabrafenib + trametinib
- Vemurafenib + cobimetinib
- Encorafenib + binimetinib

Thanks for your attention!