MEMETS
Middle East Neuroendocrine Tumor Society

1st World NEN Lives 2020 Congress
September 23—24, 2020

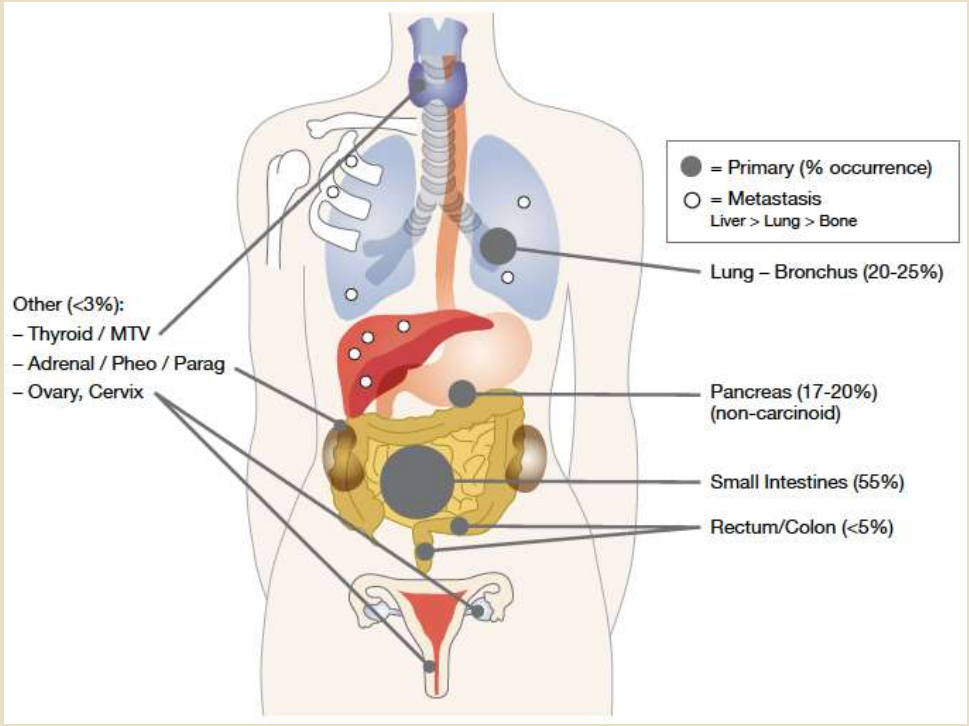
2020 STATE OF THE ART IN NEN DIAGNOSIS AND THERAPY

Marianne Ellen Pavel
Friedrich Alexander University Erlangen, Germany

ENETS
European Neuroendocrine Tumor Society

Neuroendocrine neoplasms (NEN) are rare and heterogenous

Anatomical distribution of neuroendocrine tumours



Predominant metastatic site:
- Liver
- Lymph nodes

More rare:
- Lungs, bone, peritoneum, others

Functional tumours (10–30%)
- Insulinoma
- Gastrinoma
- Glucagonoma
- VIPoma
- Others

- Carcinoid Syndrome

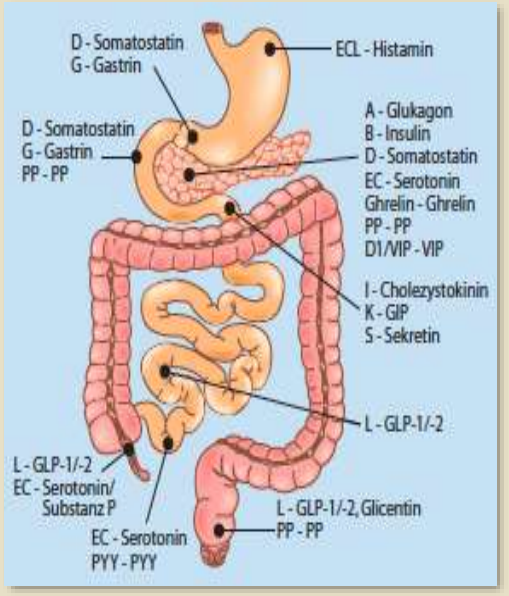
Non-functional tumours
(70–90%)

Sporadic NEN (90%);
Genetic background
MEN-1, VHL, TSC2 (≥5%)

Frilling A, et al. Endocr Relat Cancer 2012;19:R163–85. Lombard-Bohas C, et al. Neuroendocrinology 2009;89:217–22.

What is neuroendocrine cancer? University of Iowa Hospitals & Clinics. Available at: https://uihc.org/health-topics/what-neuroendocrine-cancer. Accessed August 2020*.

Neuroendocrine neoplasms arise from the disseminated endocrine cell system



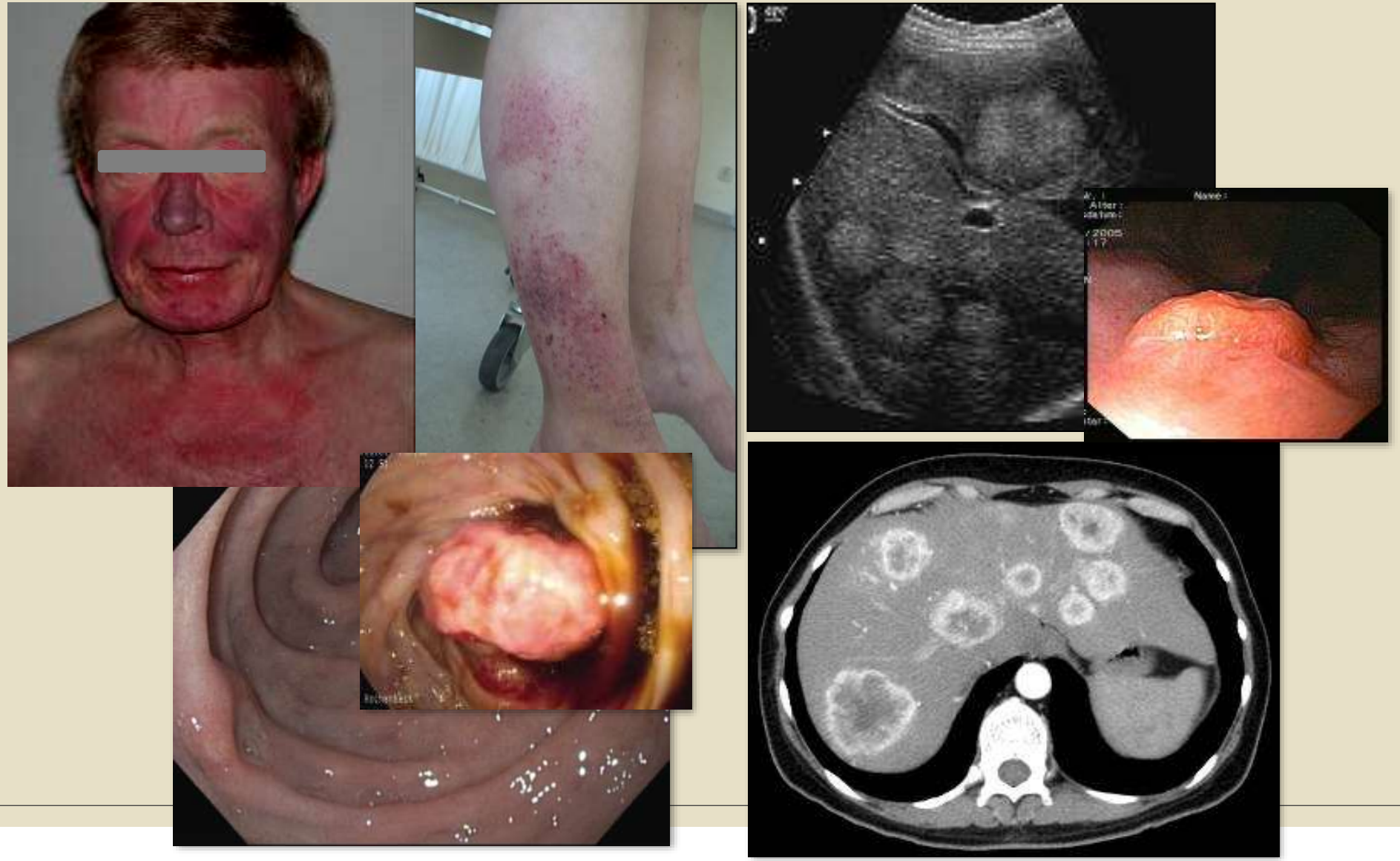
Neoplasm and cell type	Pancreas	Stomach		Small intestine			Appendix	Large intestine	
		Body fundus	Antrum	Duodenum	Jejunum	Ileum		Colon	Rectum
NET grade 1–2									
B	✓	–	–	–	–	–	–	–	–
A	✓	–	–	–	–	–	–	–	–
PP	✓	–	–	–	–	–	–	–	–
D	✓	–	–	✓	✓	–	–	–	–
EC	✓	✓	✓	✓	✓	✓	✓	✓	✓
ECL	–	✓	–	–	–	–	–	–	–
G	✓	–	✓	✓	✓	✓	–	–	–
L	–	–	–	✓	✓	✓	✓	✓	✓
P/D1	✓	✓	–	–	–	–	–	–	–
NEC grade 3									
S/L	✓	✓	✓	✓	✓	✓	✓	✓	✓

Hormones/ bioactive compounds

Insulin
Glucagon
Pancreatic polypeptide (PP)
Somatostatin
Serotonine
Histamine
Gastrin
“Enteroglucagon” (GLP-1/GLP-2, etc)

Rindi G, et al. *Nature Rev Endocrinol.* 2011;8(1):54-64.

Neuroendocrine Neoplasms have many disease facets



Frequent symptoms – rare diseases

- Diarrhea, increased bowel movements
- Flushing
- Peptid ulcer disease
- Low blood sugar
- Skin lesions

Carcinoid syndrome

Verner Morrison syndrome VIPOMA

Zollinger Ellison Syndrome

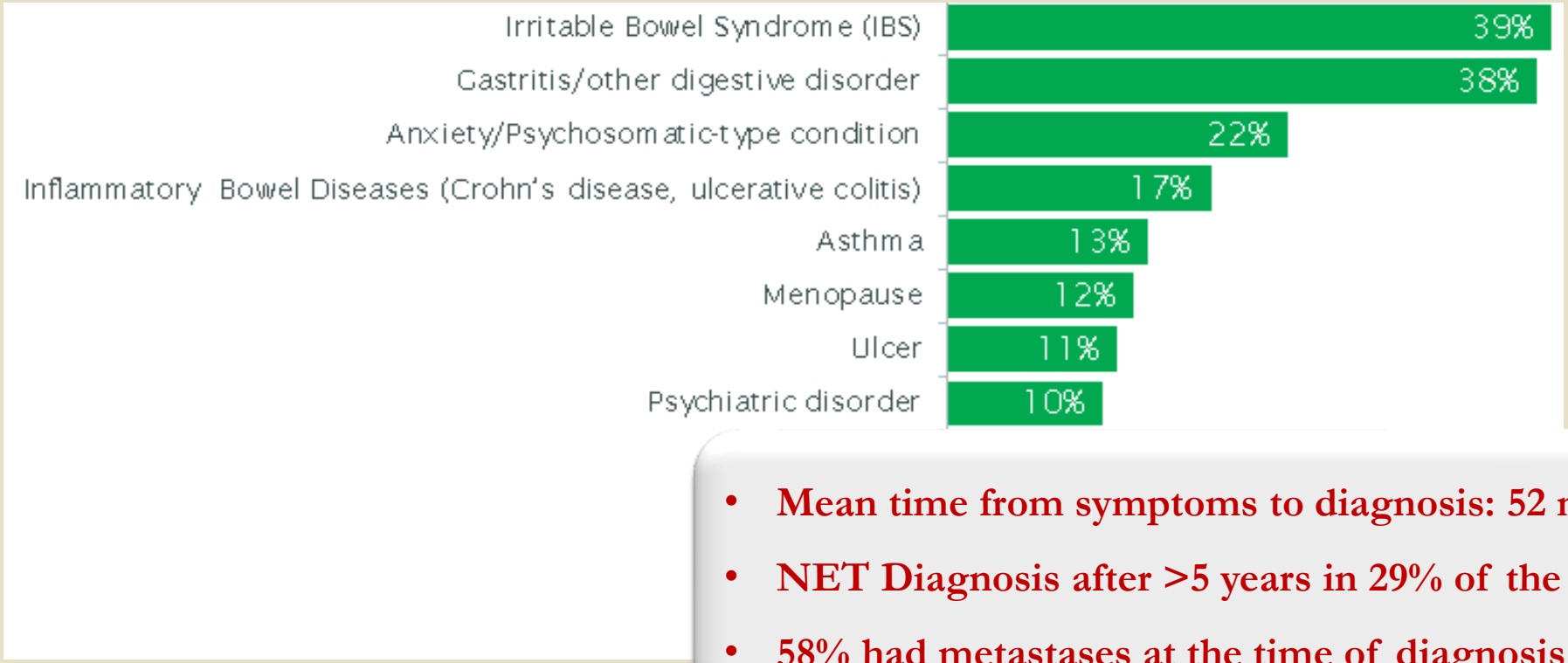
Hypoglycemic Syndrome

Glucagonoma Syndrome

Early detection is a challenge Symptoms may be subtle or absent particularly in non secreting /non functioning tumors

Diagnoses before NET Diagnosis

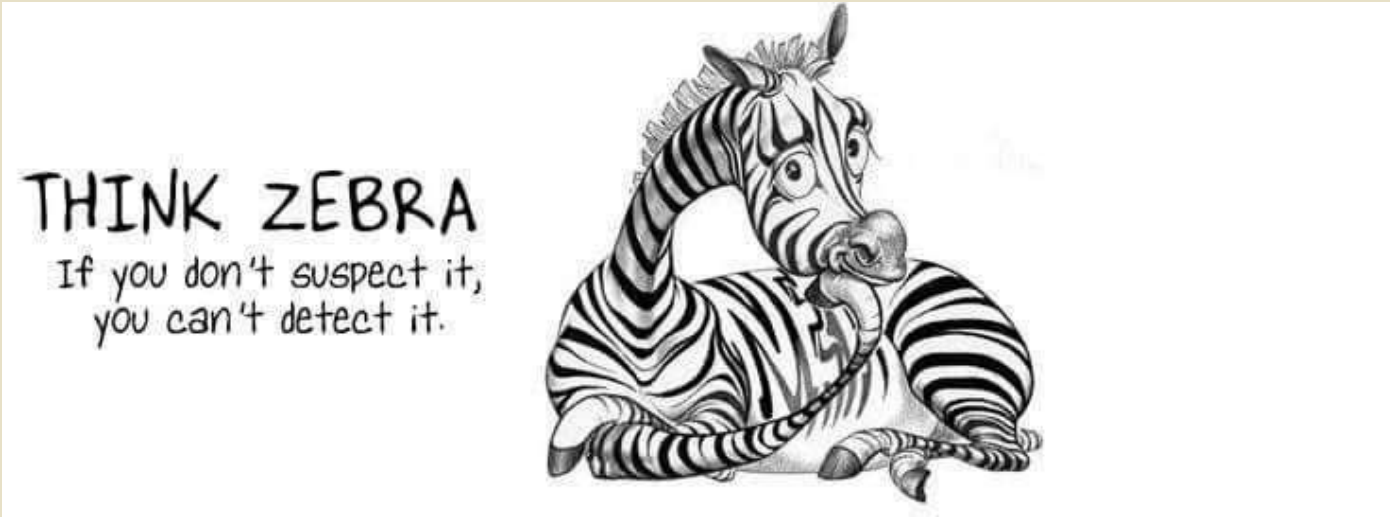
Analysis in 1928 patients with NET from more than 12 countries (USA, Asia, Europe, Australia)



- **Mean time from symptoms to diagnosis: 52 months**
- **NET Diagnosis after >5 years in 29% of the patients**
- **58% had metastases at the time of diagnosis**

Singh et al J Glob Oncology 2017, Pavel et al ENETS Annual Meeting 2015

“if you hear the clatter of hooves, it's probably horses, not zebras”



Diversity and heterogeneity of neuroendocrine tumors

Incidental finding of a small NET

- Appendix
- Stomach
- Rectum
- Pancreas

Unspecific Symptoms

- Bowel obstruction
- Gastrointestinal Bleeding
- Jaundice
- Weight loss

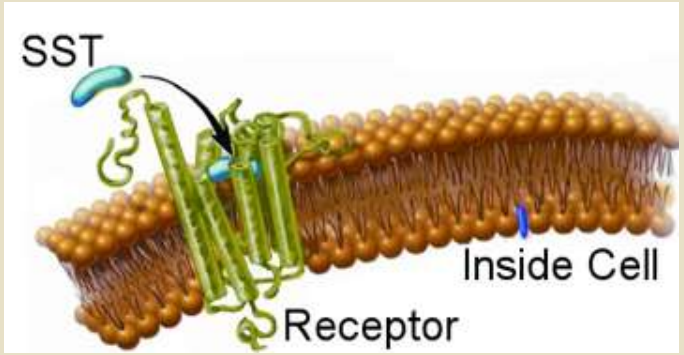
Specific Symptoms

- Flushing
- Diarrhoea
- Exanthema/ Skin lesions

Special features of NET

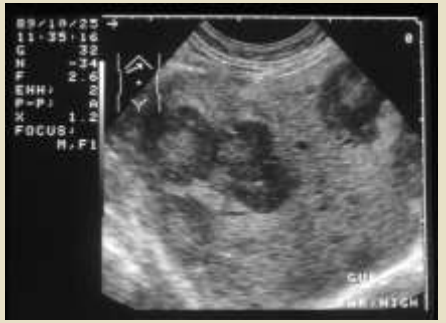
- Broad range of various tumors with variable course and clinical picture
- Some are indolent . Cure after resection
- Some are advanced at diagnosis , e.g. intestinal NET

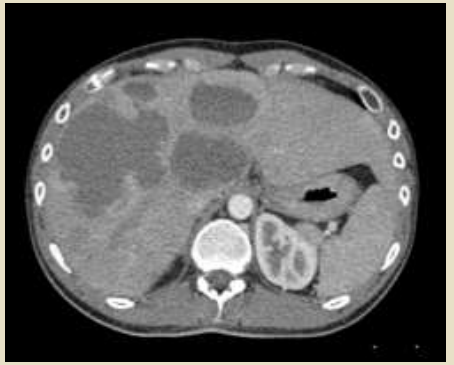
- Often slow growth (some exceptions)
- Secretion of hormones and other bioactive compounds
- May have few symptoms (most are non functional)
- Somatostatin receptor expression

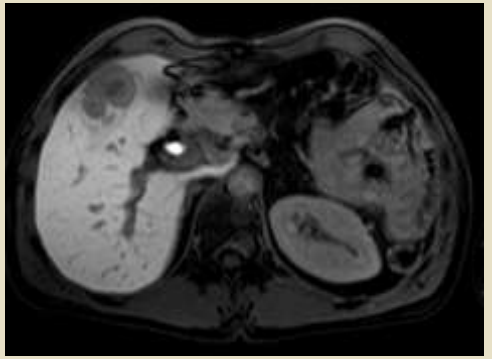


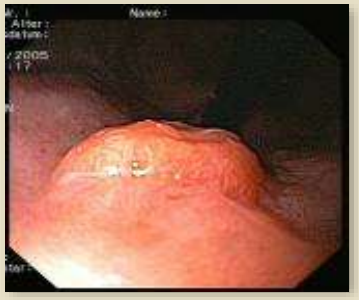
Diagnosis of NET

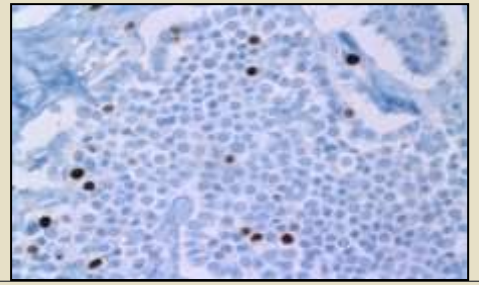
- **Clinical suspicion** (unexplained symptoms…)
- **Hormonal assessment** (peptide hormones, serotonin in plasma, 5-HIAA in urine)
- **Imaging**
  - Ultrasonography
  - Computed tomography
  - Magnet resonance imaging (MRI)
  - Somatostatin receptor imaging
  - Endoscopy
- **Histology**



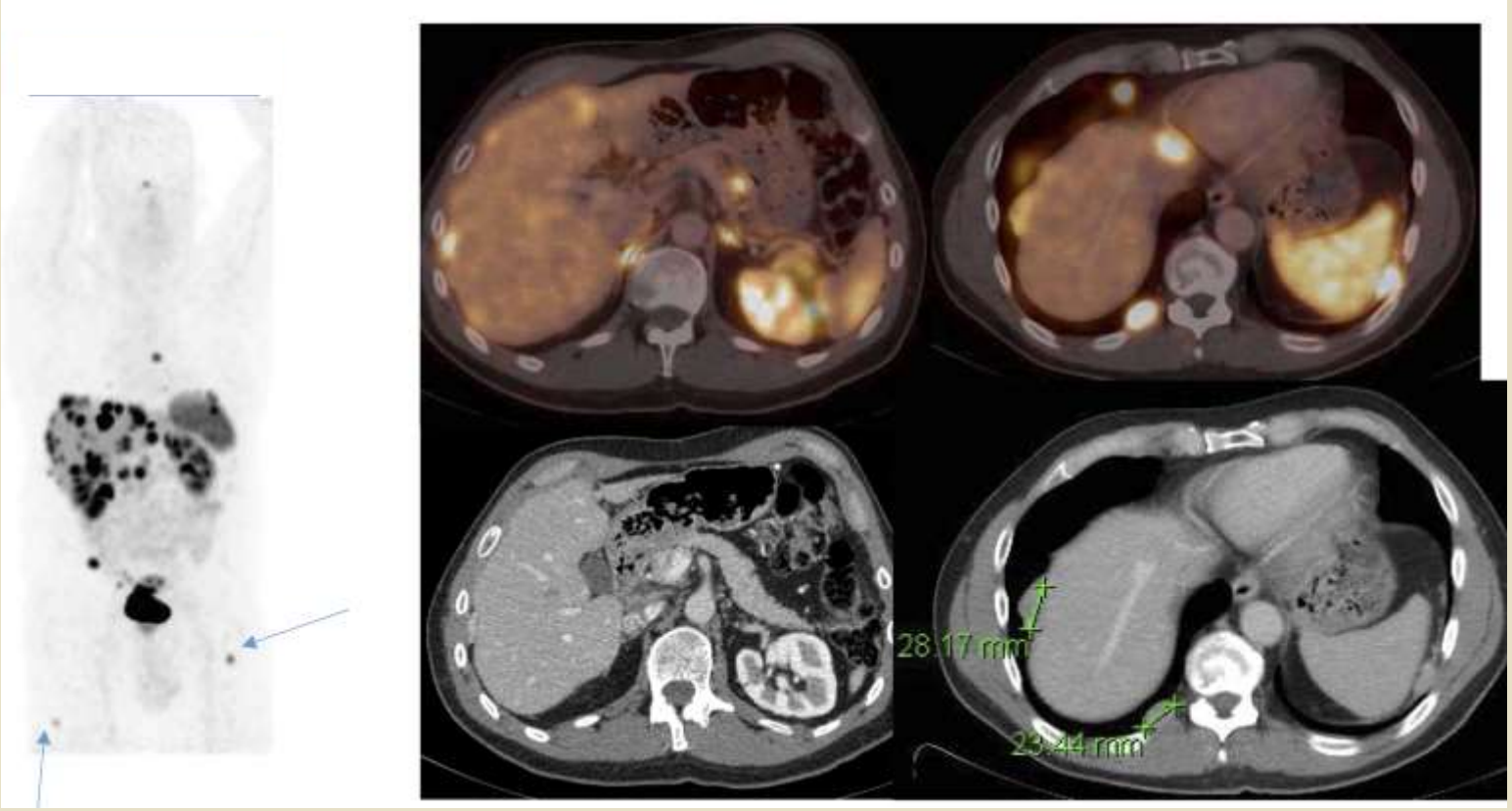








Somatostatin receptor imaging – the value of Ga-DOTA-PET/CT



- Identifies **additonal metastases** in more than 1/3 of the patients compared to CT
- Detects metastases particularly in **bone, peritoneum, other rare disease sites**
- May identify the **primary tumor**

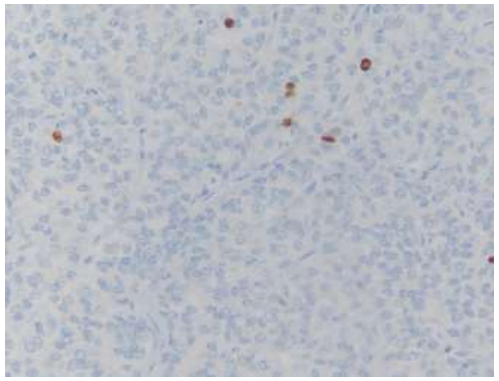
Arrows indicate bone lesions, additional finding of thoracic lesion and peritoneal metastases next to liver metastases

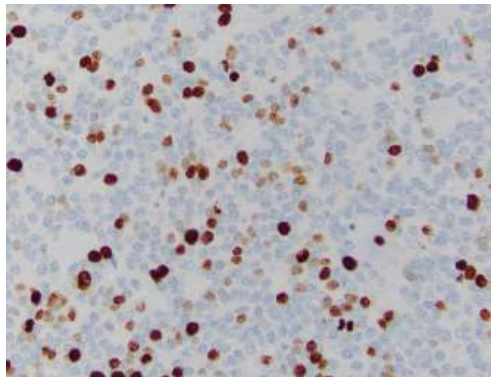
Merola et al JCEM 2017

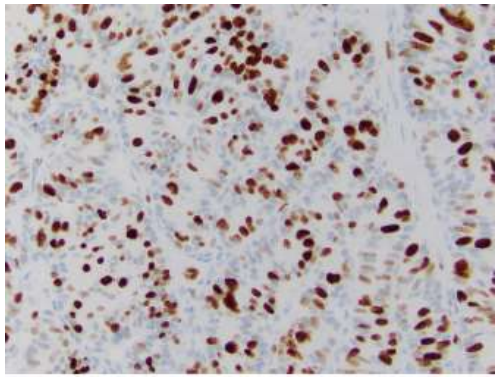
Ruf et al Neuroendocrinology 2010

Diagnosis – the importance of tissue analysis

Siegfried Oberndorfer







Ki-67	<3%	3–20%	>20 %
Grade	G1	G2	G3

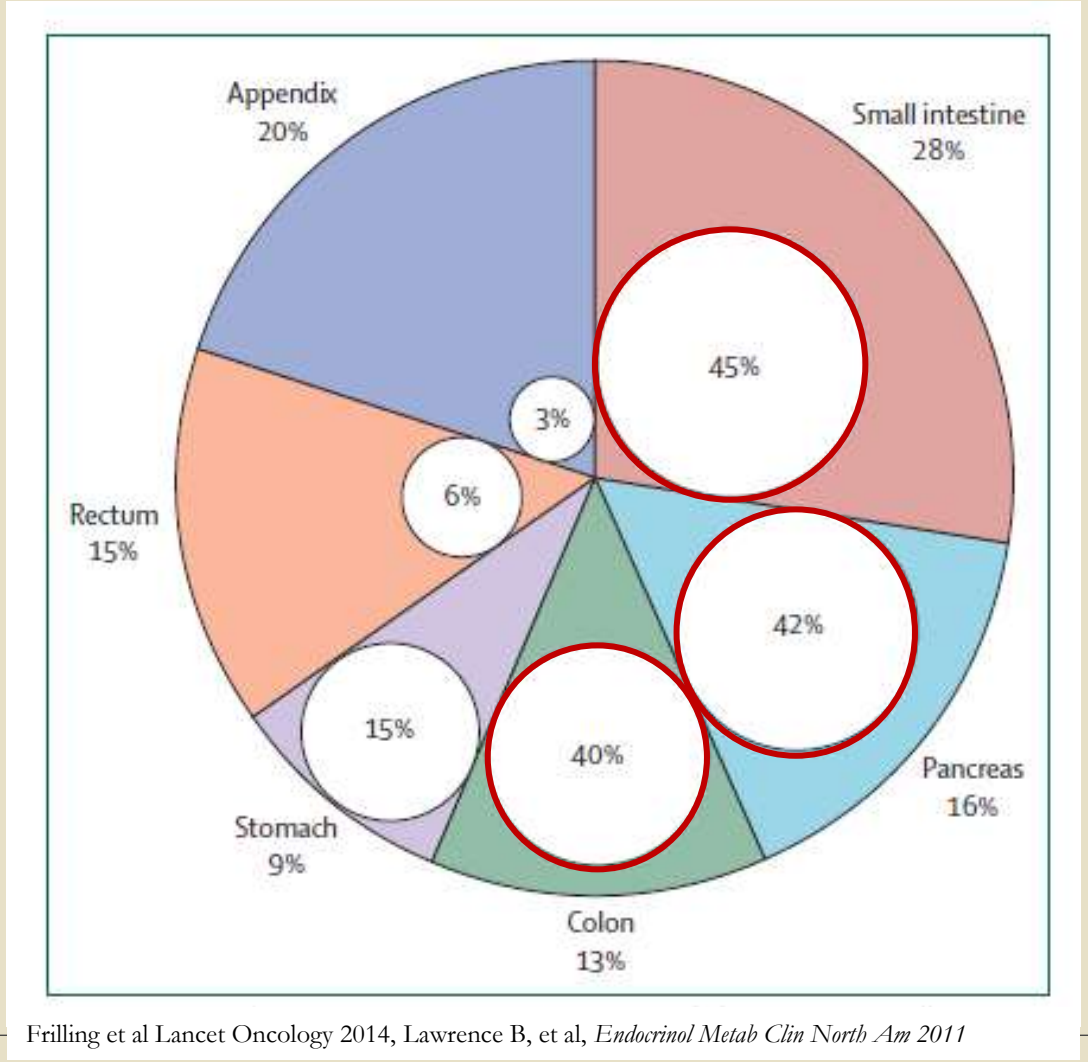
Impact on prognosis, choice of diagnostics and therapy

Images adapted from Rindi G, et al. Mod Pathol. 2018;31:1770–86

Frequency of metastases according to primary site

Local therapies

(systemic therapies)

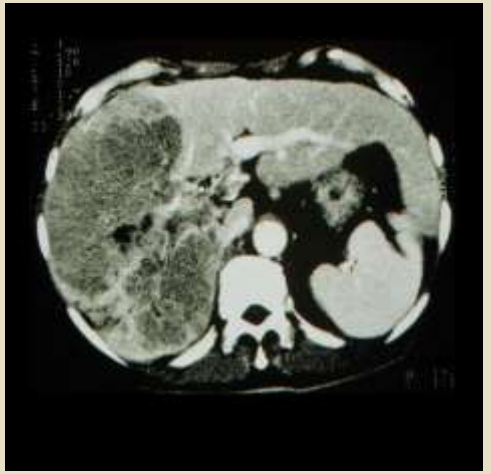


Frilling et al Lancet Oncology 2014, Lawrence B, et al, *Endocrinol Metab Clin North Am 2011*

Systemic therapies in advanced disease

white circles indicate frequency of metastases

Role of surgery



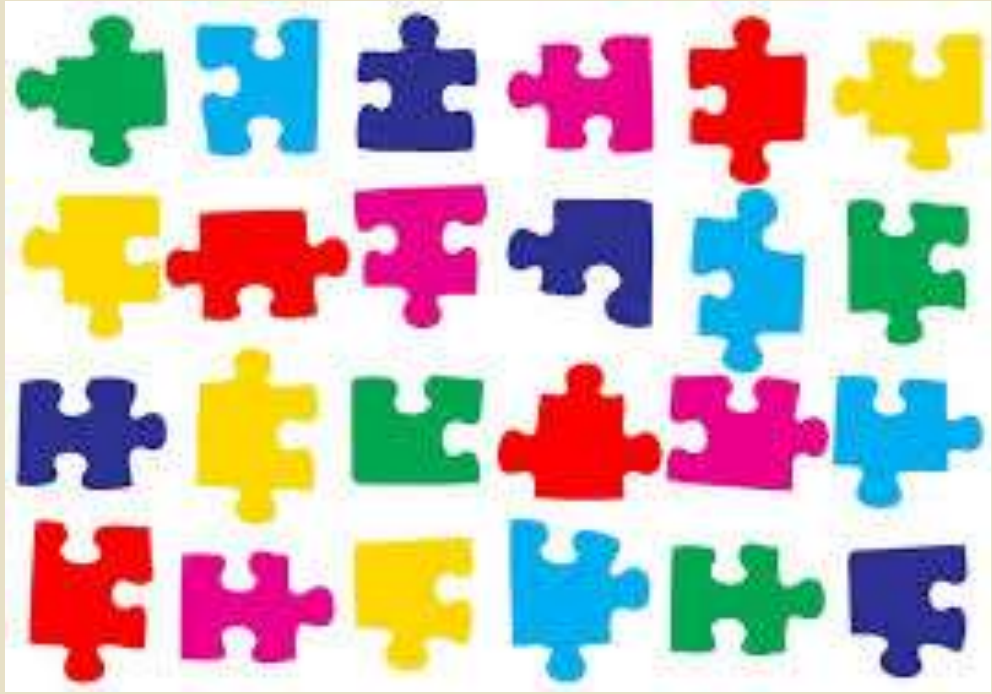
- Cure in patients with „limited disease“
- Debulking surgery in patients with syndromatic NET (VIPoma, insulinoma….)
- Removal of the primary tumor and lymph nodes (e.g. intestinal NET)
- Prevention of complications (e.g. ischemia, bleeding)

Decision making in NET….

Localized disease NET G1/ G2

→ Surgery

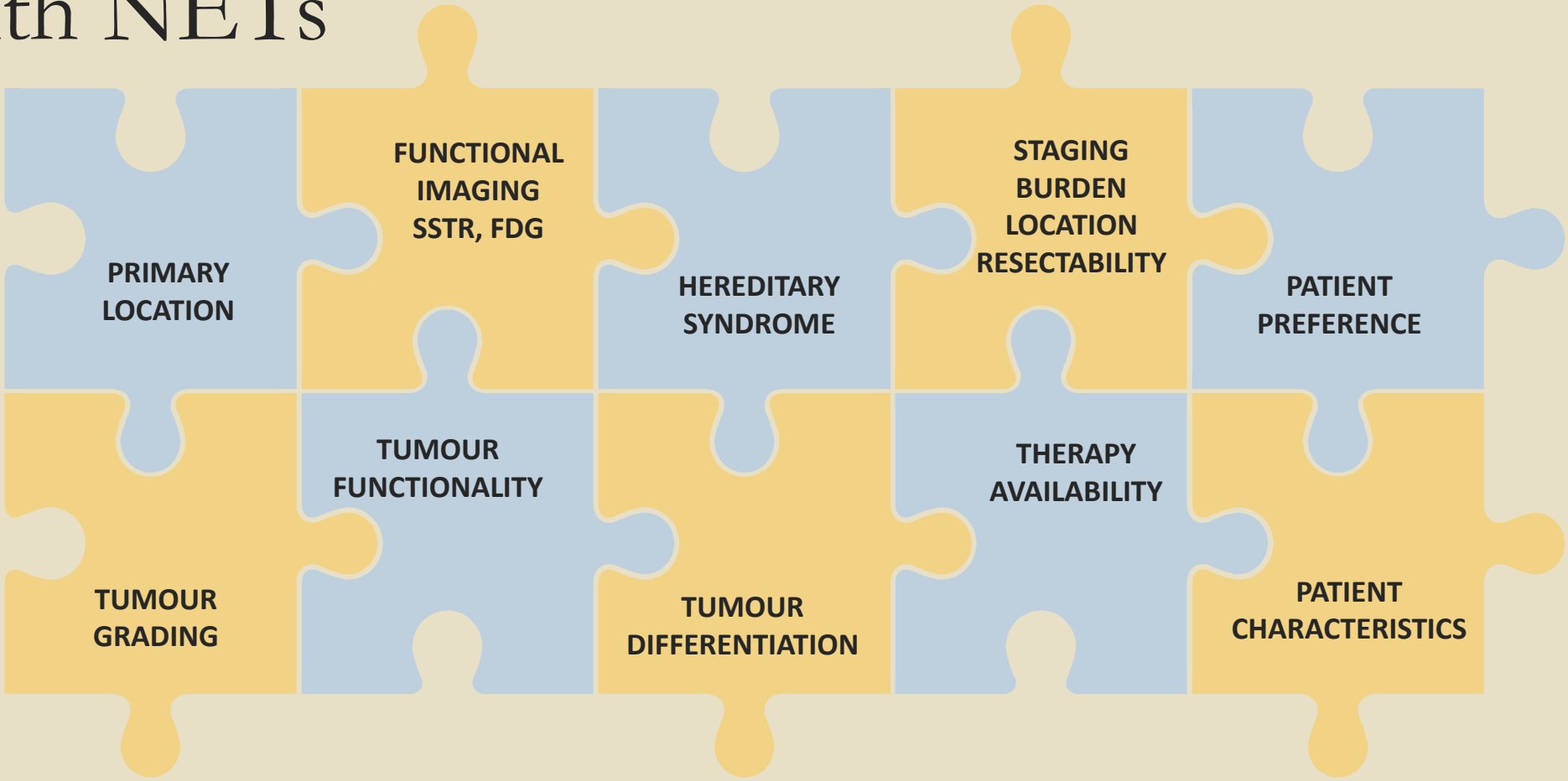
Advanced disease/ distant metastatic disease: tumor site, hormonal activity, growth, Somatostatin receptor expression….



If cure is not feasible, we need to define the needs of the patient….

- Symptom control (e.g. insulinoma, VIPoma)
- Tumor growth control (stable vs. progressive vs. unknown)
- Pain relief (e.g. tumor burden, bone lesions)
- Prevention of complications (hormone-related, local invasion, heart disease …)

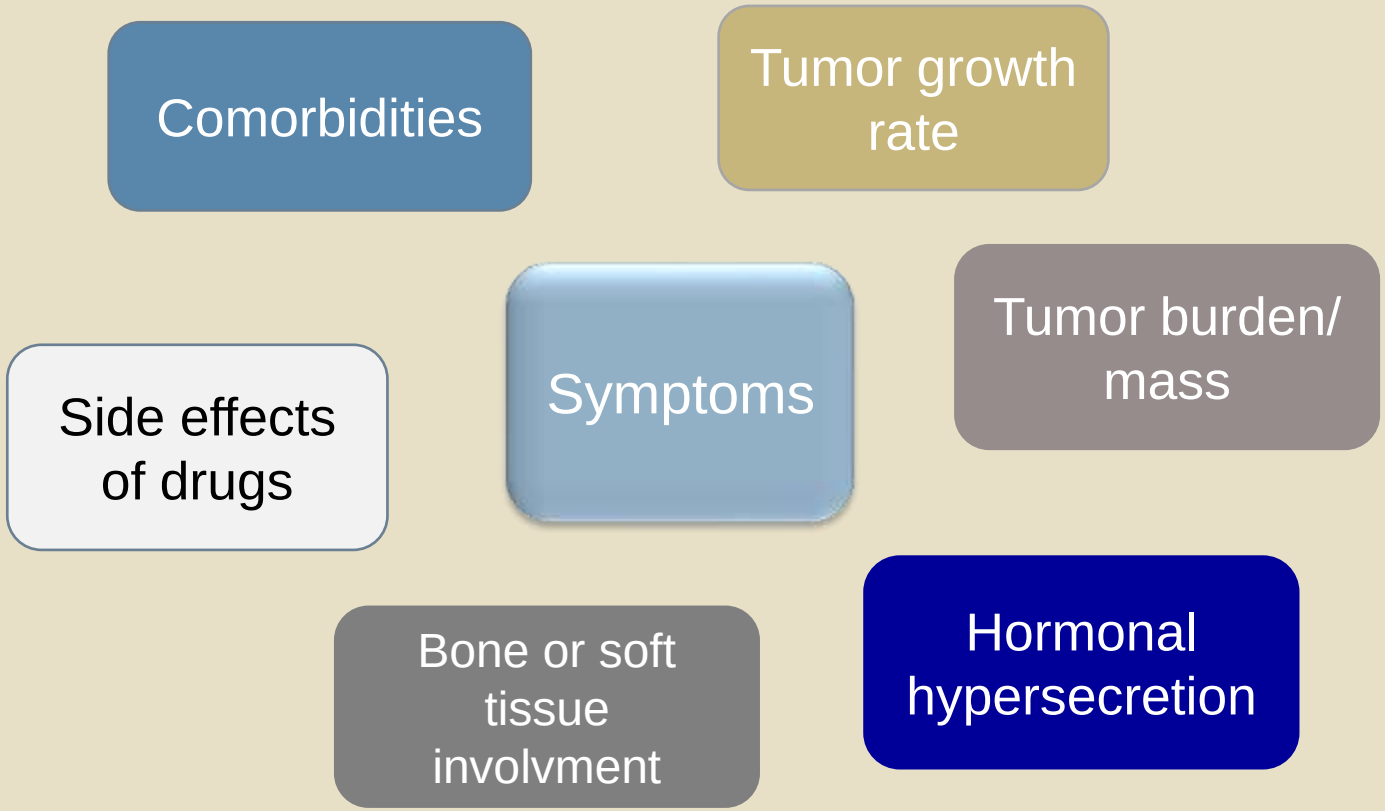
Decision-making on treatment for patients with NETs



FDG, fluorodeoxyglucose; NET, neuroendocrine tumour; SSTR, somatostatin receptor.

Disease burden in NET

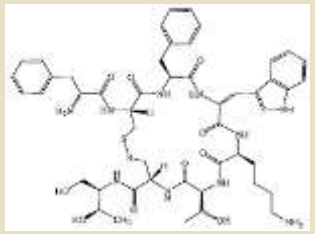
High prevalence of moderate-to-severe patient-reported symptoms



Hallet et al, Oncologist 2019, Leyden et al, Asia Pac J Clin Oncol. 2018, Beesley et al Supportive Care in Cancer 2018

Evolution of therapies – the 80s

First description of carcinoid in small intestine by Sigfried Oberndorfer



Octreotide
in carcinoid syndrome
Functional PnnNET

- Long acting somatostatin analog
  - Developed by Bauer 1982
  - → Clinical trials in patients with carcinoid syndrome

1907 1982 1984 1996

Prof Öberg
Uppsala 1983

Interferon
in carcinoid syndrome

Prof Moertel
Mayo Clinic
Rochester, USA

Chemotherapy

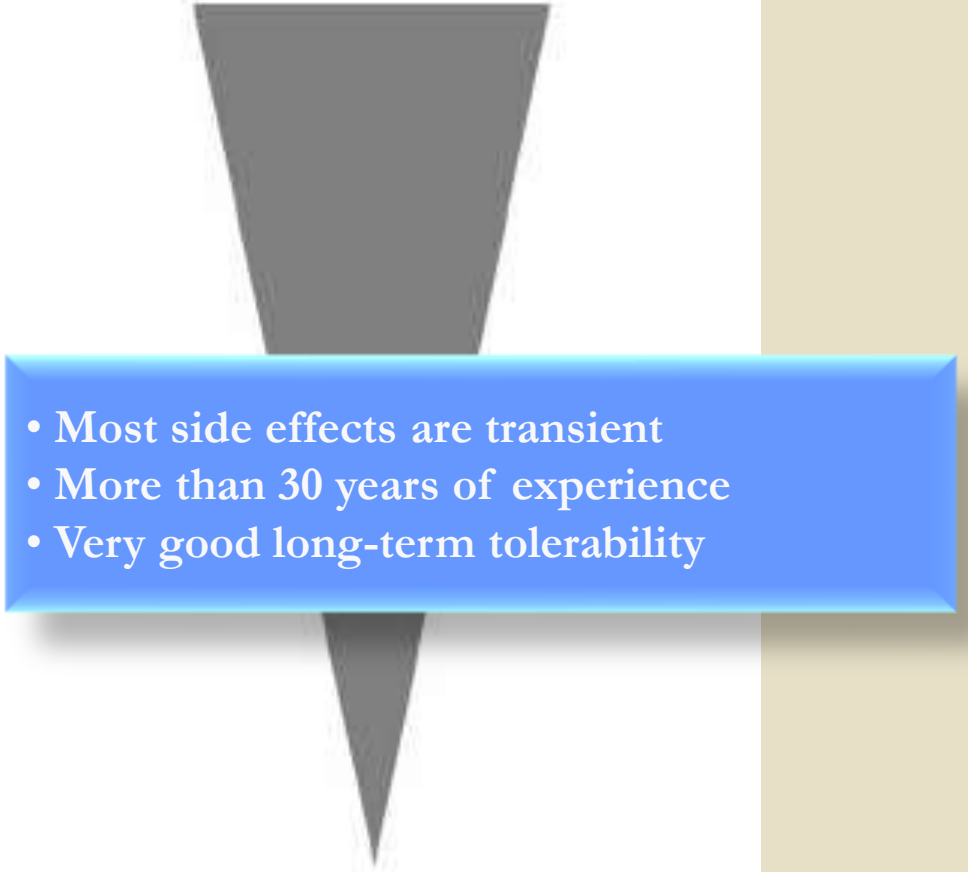
1st use of PRRT

Peptide receptor radionuclide therapy

Surgery and loco-regional therapies

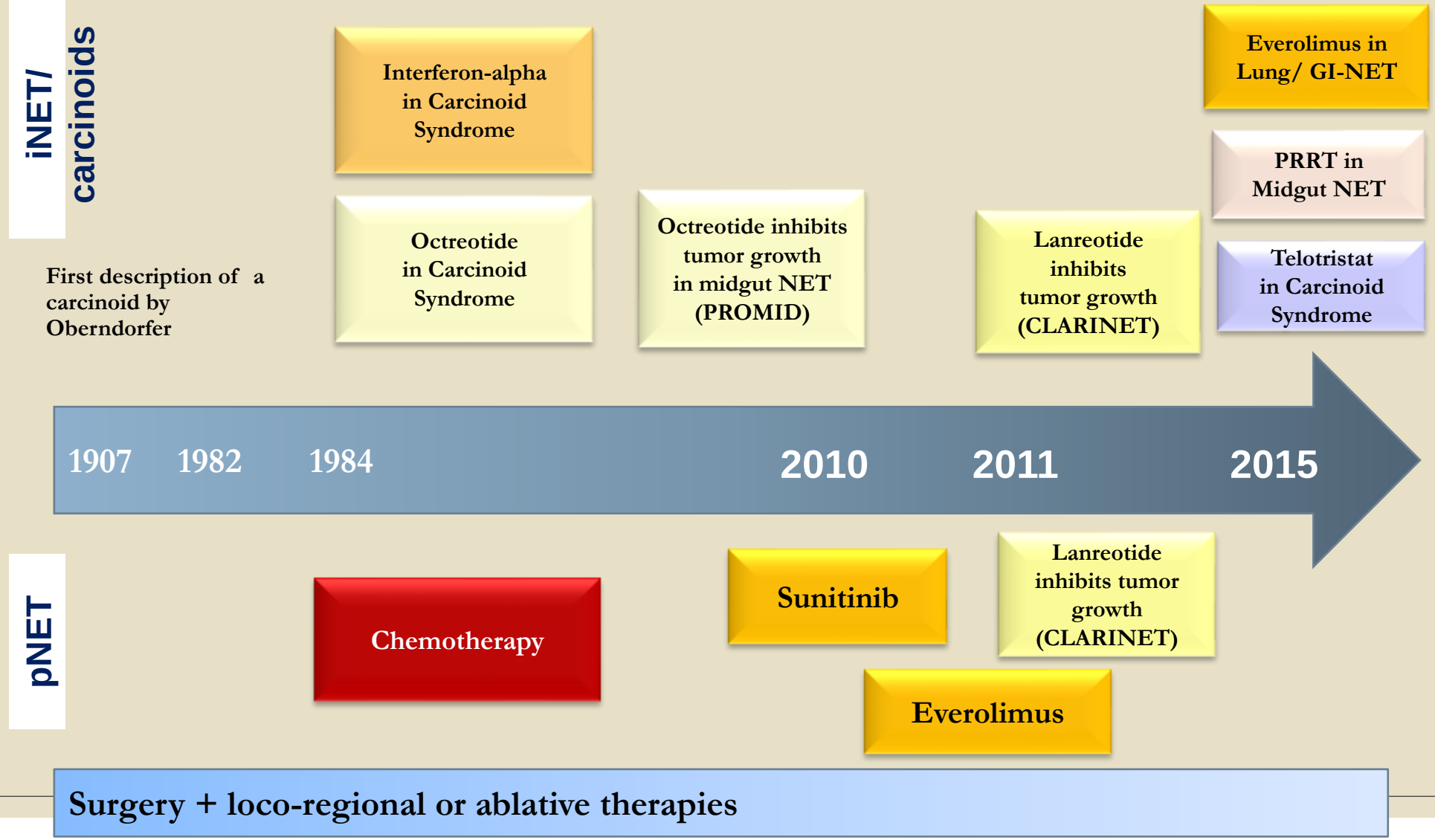
Tolerability of Somatostatin Analogs

• Diarrhoea:	37,3%
• Steatorrhoea:	39,3%
• Flatulence:	28,1%
• Pain at injection site:	28,1%
• Gall stones:	17,9%
• Emesis:	11,5%
• Hyperglycaemia:	10,8%
• Bradycardia:	4,3%
• Cholangitis:	4,3%
• Septicaemia:	<1%



Review Shah & Caplin, 2005: *Best Pract Res Clin Gastroenterol.* 2005 Aug;19(4):617-36. Arnold et al, Gut 1996, Öberg et al, *Acta Oncol* 1991, Trendle et al, Cancer 1997.

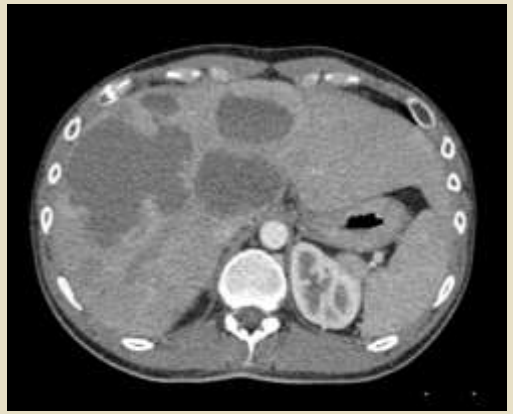
Evolution of Therapies in neuroendocrine tumors



Systemic therapies in NEN

- **Somatostatin analogs**
- Interferon –alpha
- **Peptide receptor radionuclide therapy (PRRT)**
- **Targeted drugs**
  - Everolimus
  - Sunitinib
- **Systemic chemotherapy** (in fast growing tumors, Pan-NET, G3)
- Immunotherapy ?
- Other: Telotristat Ethyl

Management of the Carcinoid Syndrome



Symptoms
(Flushing, Diarrhoea; Endocardial fibrosis)

Increasing lack of response

Growth

Debulking Surgery

Increasing tumor

and/or

First line

TAE TACE

Interferon-alpha

Telotristat Ethyl

PRRT

SSA (Octreotide LAR /Lanreotide AG) +/ - dose increase

Pavel et al. ESMO Guidelines Ann Oncol 2020

What is the best treatment to control tumor growth ?

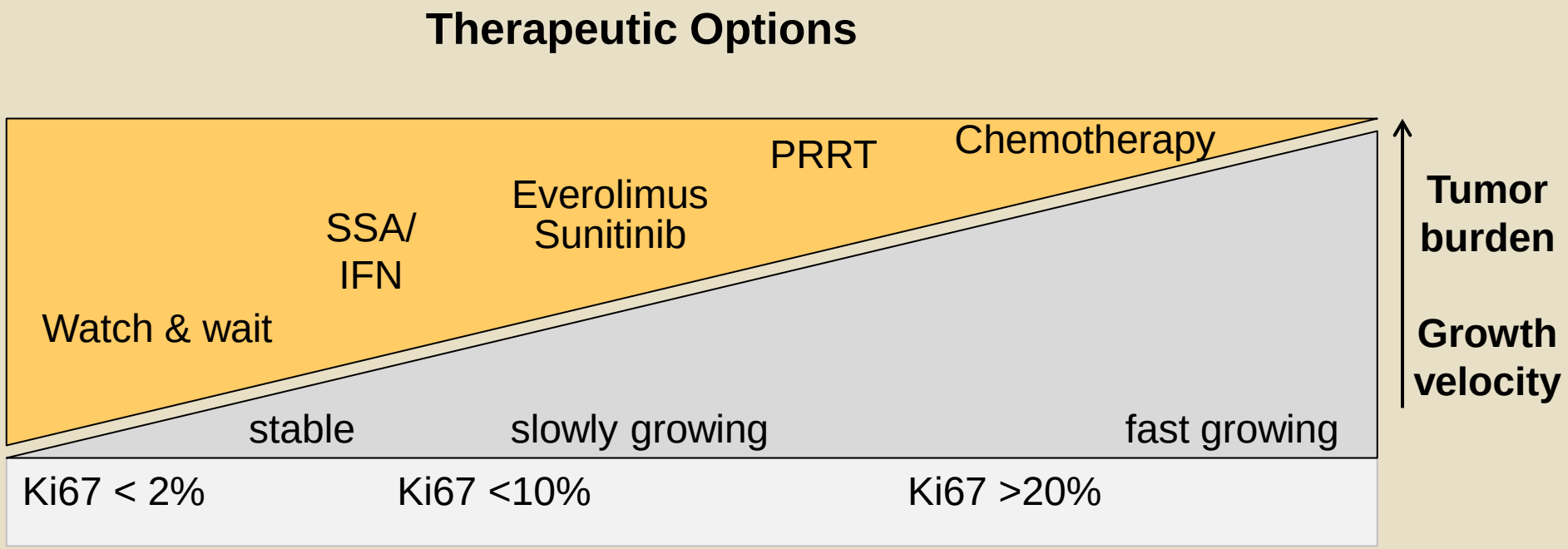
Individualized treatment approach

that takes into consideration all disease facets

and aims at prolongation of survival

while quality of life is maintained or improved

Natural tumor biology of advanced NET matters for therapy selection



Others: Functionality, Symptoms, SSTR expression profiles, side effects, safety, accessability/ approval of drugs, comorbidities

Individualized treatment to find the best strategy

Interdisciplinary Management !

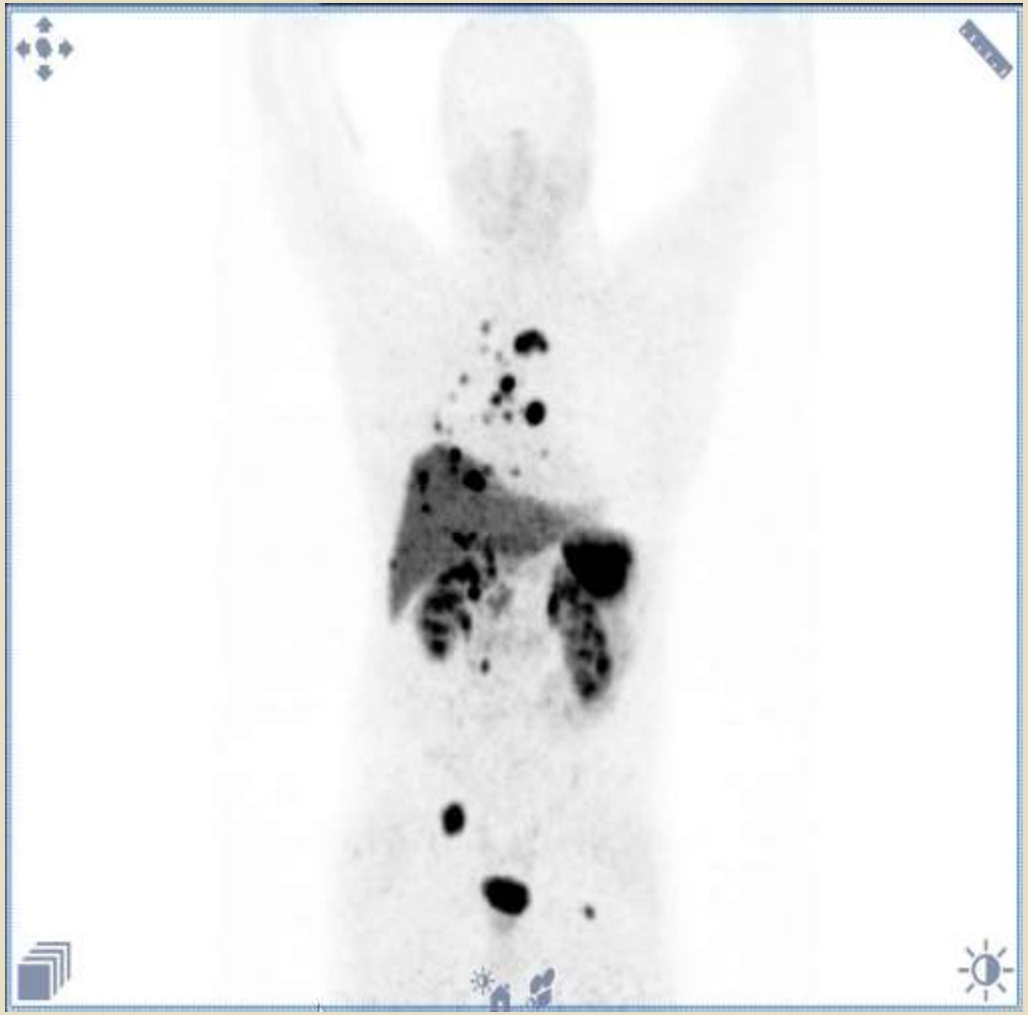
One of my first patients diagnosed in 1987 at the age of 34 yrs with a lung carcinoid

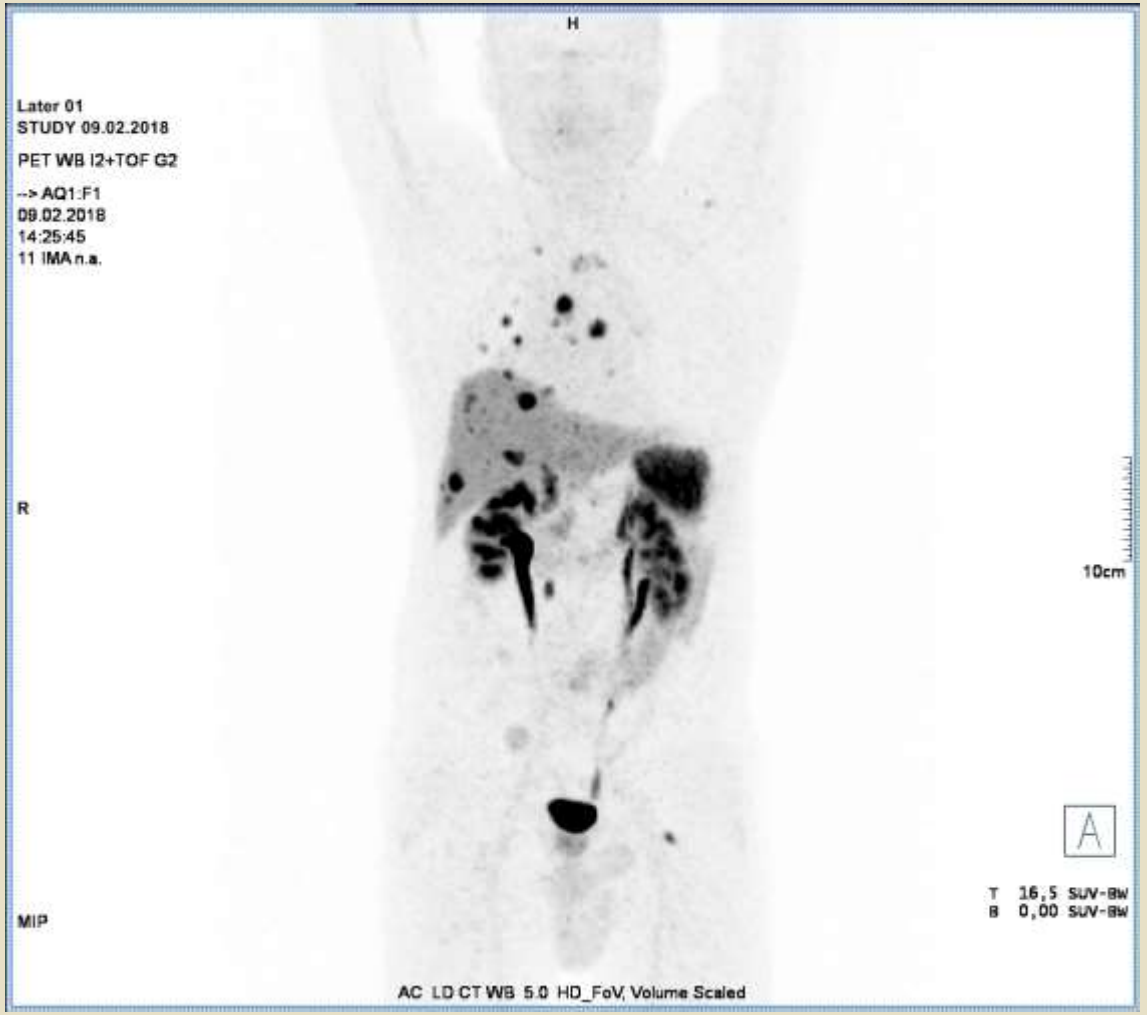
- - Patient had cough, CT revealed a nodule in the lung
- - **surgical resection** of **primary tumor in the middle lobe** Sep 1987
- - **pneumonectomy** for loco-regional recurrence; March 1994 and **partial liver resection** for **liver metastases**
- - **Metastases in the thyroid** → **thyreoidectomy** May 1998
- - 4 cycles Yttrium-**PRRT** 1998 (**mediastinal lesion** progressive, painful **bone metastases**→ pain relief)
- - 2 cycles Yttrium-**PRRT** 2001
- - **Somatostatin analogs** (Sandostatin LAR 20 mg per month) since 2001

- **Patient is now 67 years old, fully asymptomatic, ECOG 0, active, working**

Disease spread
Lung
Bone
Liver
Thyroid
Muscle

Patient with lung carcinoid
Ga-SR -PET/CT 02/2007 and 02/2018



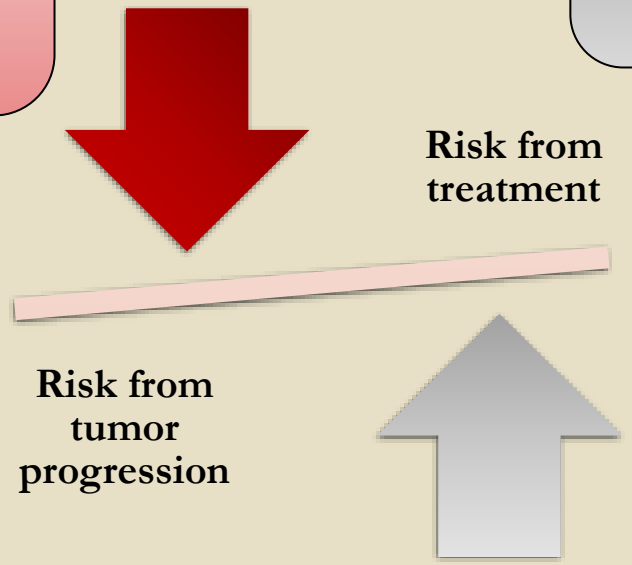


Courtesy Dr Michael Beck, Nuclear Medicine, FAU Erlangen

Risks and benefits of treatment

Tumor features
- Symptoms: Pain, weight loss etc
- Tumor volume: any risk if tumor grows?
- Tumor aggressiveness: Ki-67; growth rate, biomarkers

Patient features
- Functional status
- Comorbidities
- Preferences

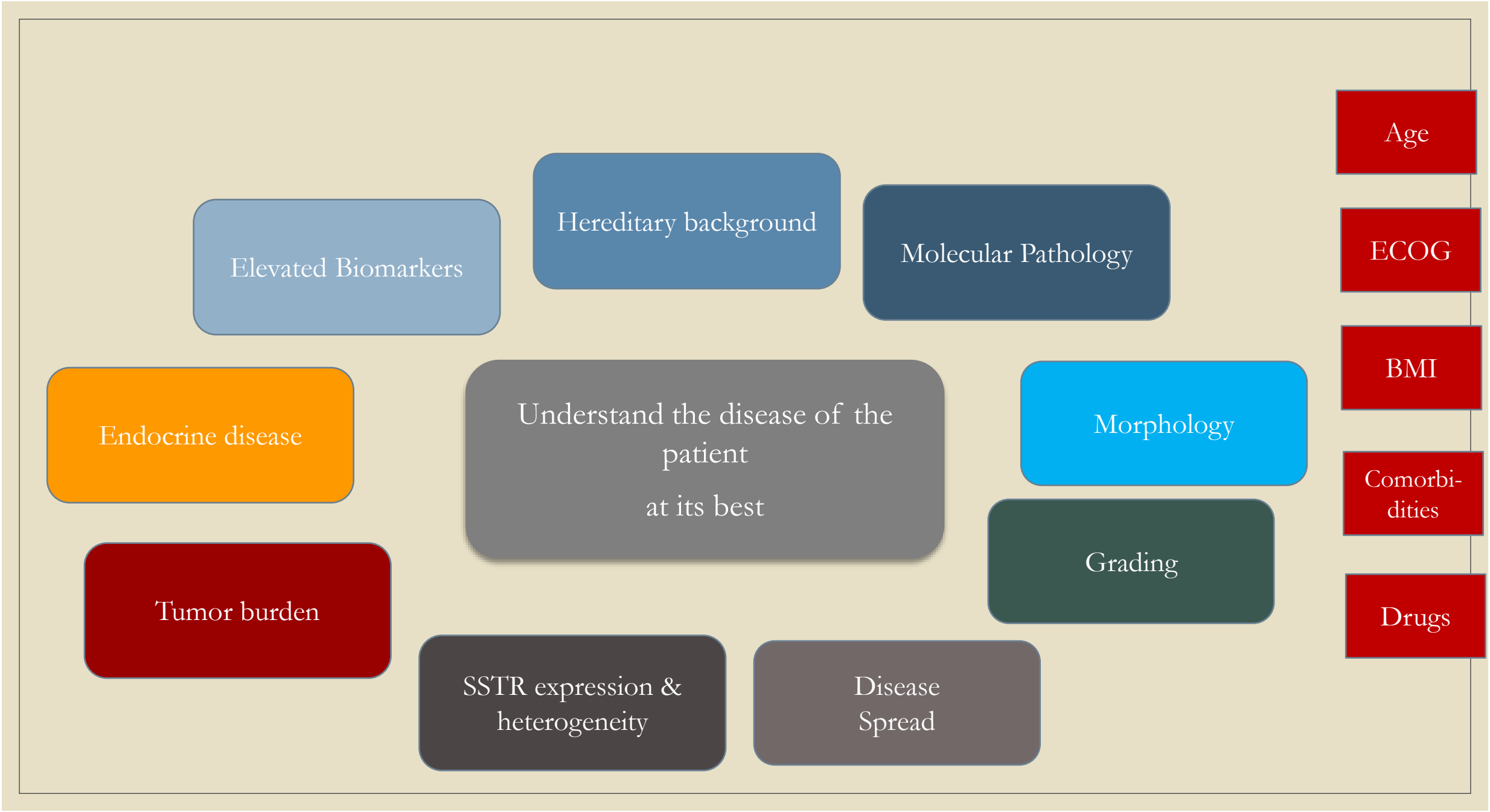


Always weighing benefits and risks

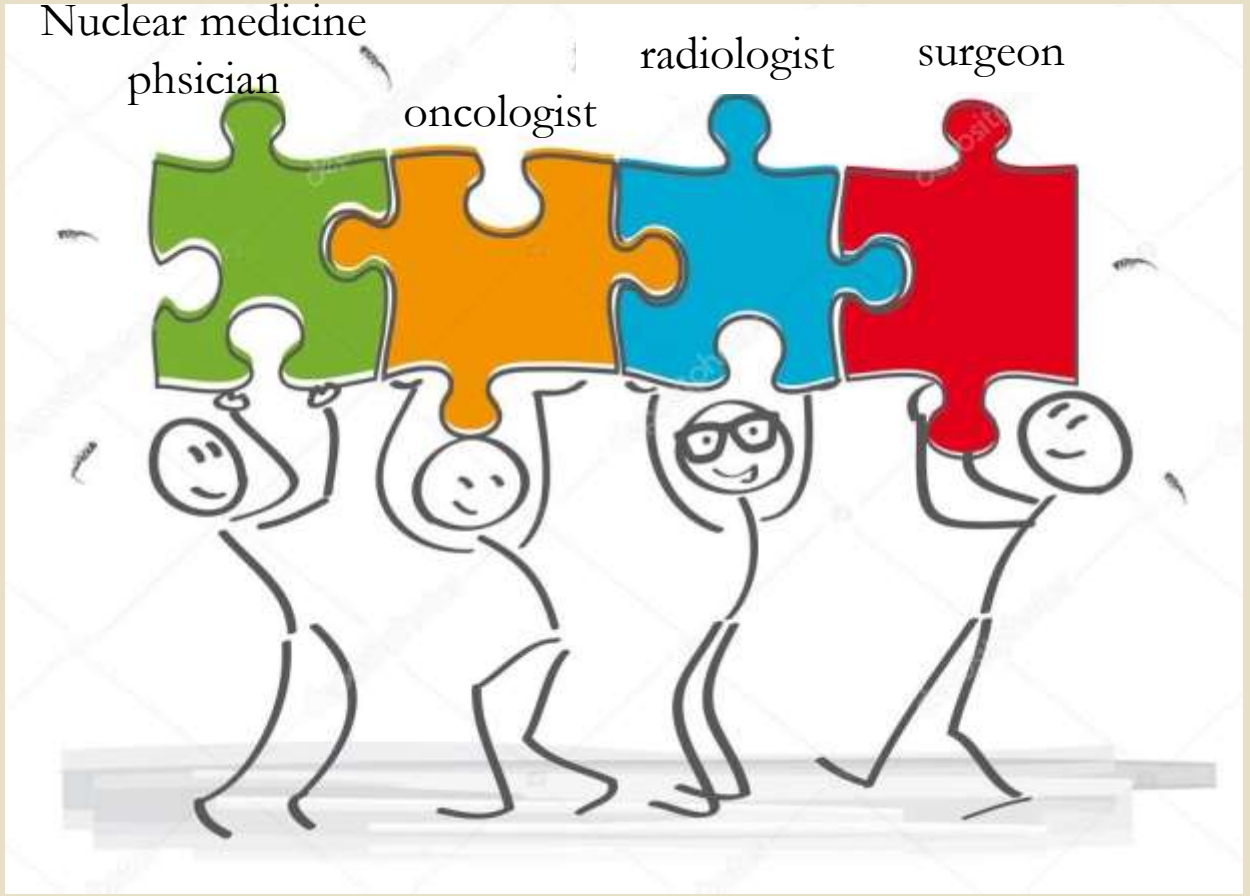
Treatment features
- Short term risks, long-term risks
- Reversibility of AEs ?

Improving Outcomes

- Combination therapies
- Sequential therapies
- Maintenance therapies (e.g. SSA after Chemotherapy)
- Exploration of novel drugs
- Biomarker driven therapies (tissue, blood)


Age
ECOG
BMI
Comorbi-dities
Drugs
Hereditary background
Molecular Pathology
Elevated Biomarkers
Endocrine disease
Understand the disease of the patient
at its best
Morphology
Grading
Tumor burden
SSTR expression & heterogeneity
Disease Spread

A team of experts is needed to achieve the best outcome for the patients



ENETS CoE World Map

Improving education translates in quality of care…

60 CoEs today

Thanks to MENETS and INCA and all support groups for patients

Give advice on disease facets,

Inform with flyers, booklets, patient meetings

Support studies

Give advice on clinical trials

Give guidance on where to find a specialist…

Plovdiv 2019

Building bridges between patients and caregivers

Thank you

תודה רבה

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