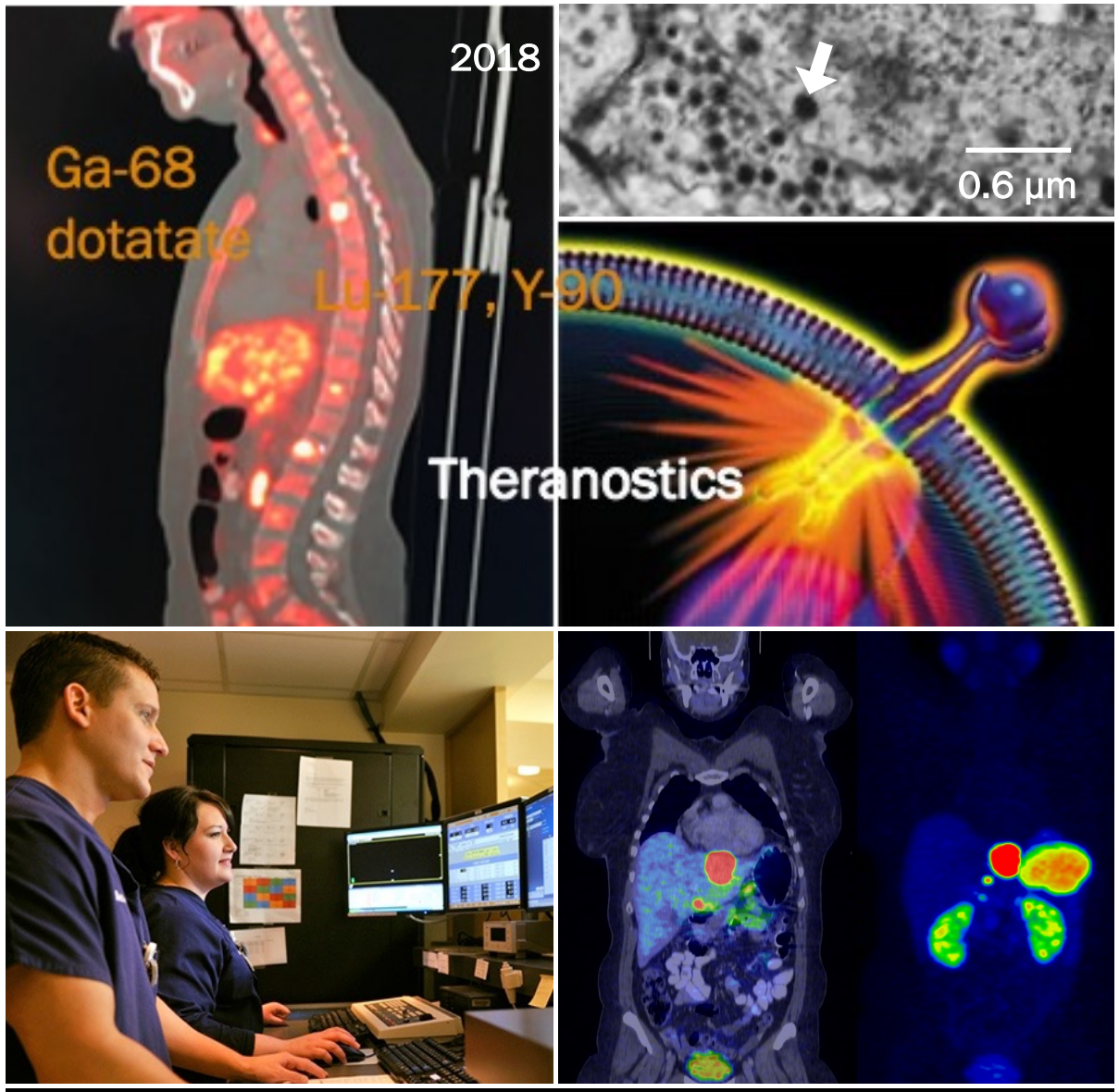

17th Annual New Orleans Summer Cancer Meeting
June 24-26, 2022

Neuroendocrine Tumors (NET): Novel Advances in Therapy

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UK HealthCare MARKEY CANCER CENTER

NCI Cancer Center
A Cancer Center Designated by the National Cancer Institute

Objectives

Review NETs Classification and Epidemiology

Define the clinical phenotypes

Discuss therapeutic options

Describe novel advances

NETs are a heterogeneous family of tumors

- NETs arise from neuroendocrine cells found throughout the body
- May involve GI tract, lung and pancreas

1. NET of the GI tract, lung, and thymus (carcinoid tumors)[1,2]

- Majority of NET in the United States

2. PNET[1,2]

- Approximately 6% of NET in the United States

Tumor origin of carcinoid tumors[3]

- Foregut
  - Lungs
  - Thymus
  - Stomach
  - Proximal duodenum
- Midgut
  - Small intestine
  - Appendix
  - Proximal colon
- Hindgut
  - Distal colon
  - Rectum

Yao et al. *J Clin Oncol* 2008; 26(18):3063; NCCN Guidelines 2015; Oberg *Ann Oncol* 2010; 21 (Suppl 7): vii72

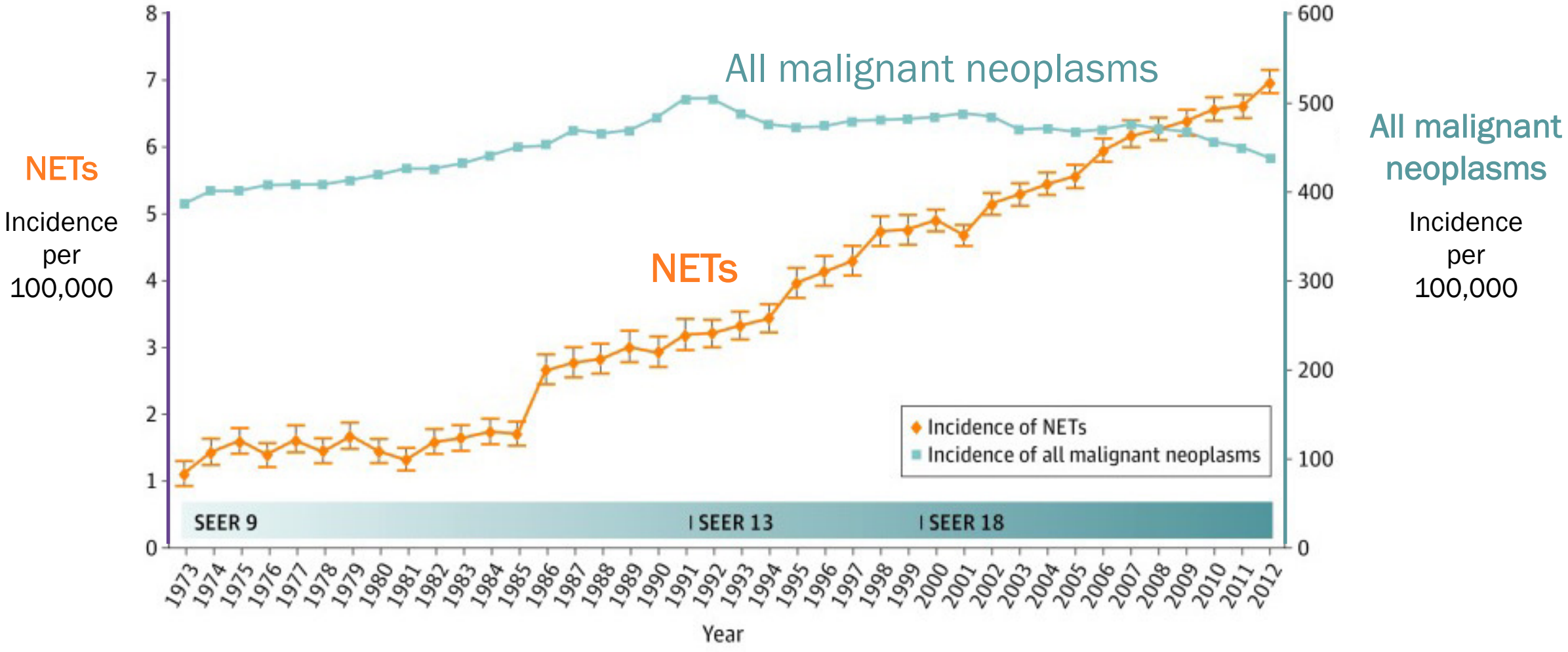
WHO (2019) classification and grading criteria for neuroendocrine neoplasms of the gastrointestinal tract and hepatopancreatobiliary organs

Terminology	Differentiation	Grade	Ki-67 Index	Mitotic Rates
NET, Grade 1	WD	Low	<3%	<2
NET, Grade 2	WD	Intermediate	3-20%	2-20
NET, Grade 3	WD	High	>20%	>20
Small cell NEC	PD	High	>20%	>20
Large cell NEC	PD		>20%	>20
MiNEN	WD or PD	Variable	Variable	Variable

PD, poorly differentiated; WD, well differentiated

Nagtegaal et al. *Histopathology* 2020; 76 (2): 182-188

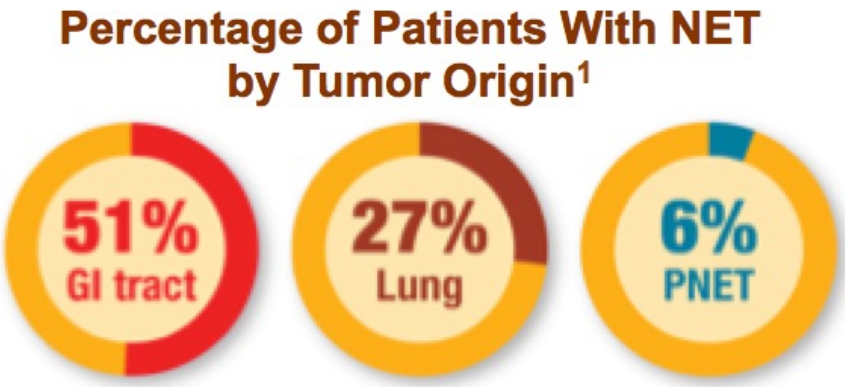
Incidence: SEER DATA

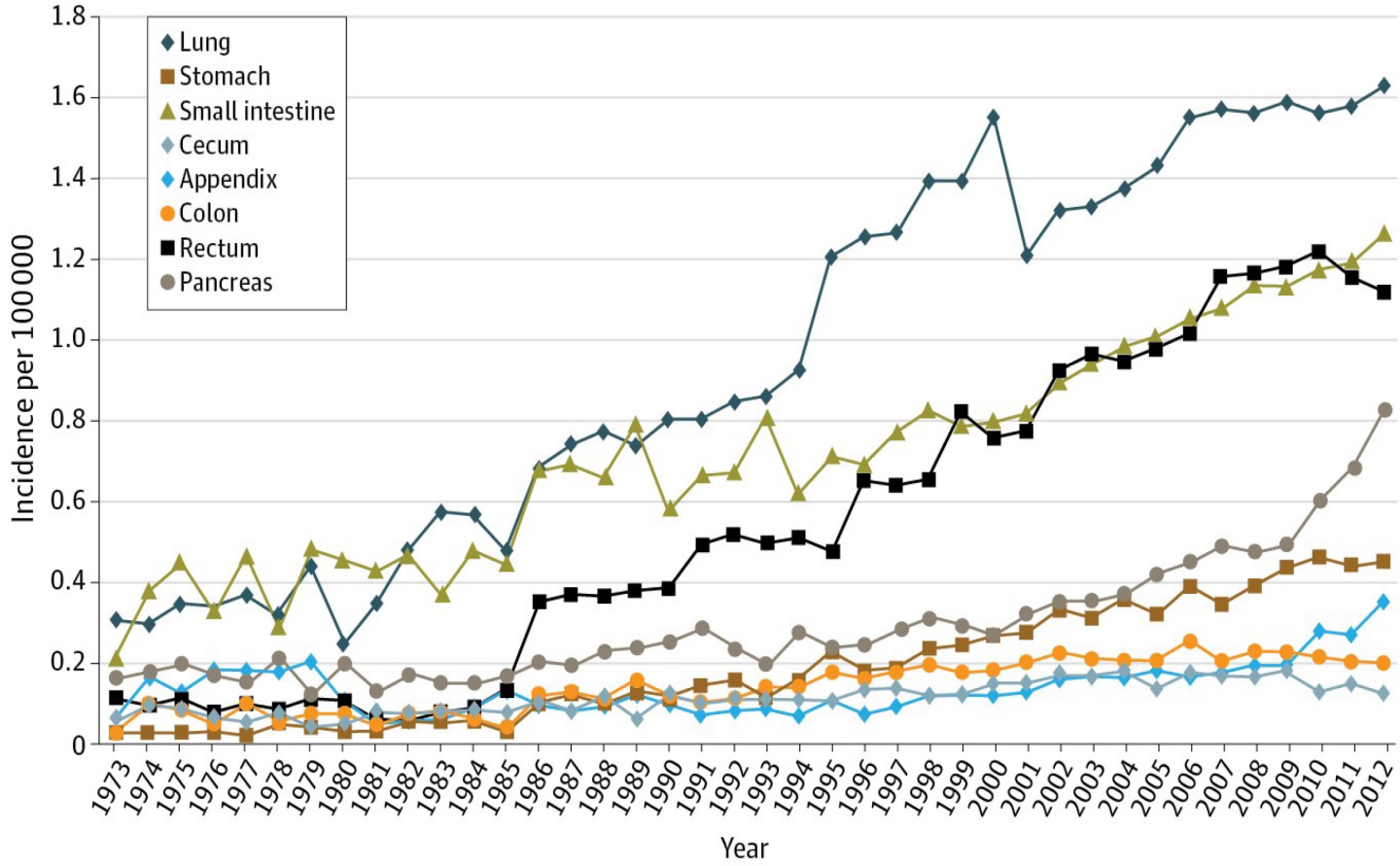


Dasari et al. *JAMA Oncol.* 2017; 3(10):1335-1342

NETs are rare but have increased in incidence during the past 3 decades

- Incidence is 5.25/100,000 people per year
- The increase in incidence may be due, in part, to technological advancements, leading to improved detection

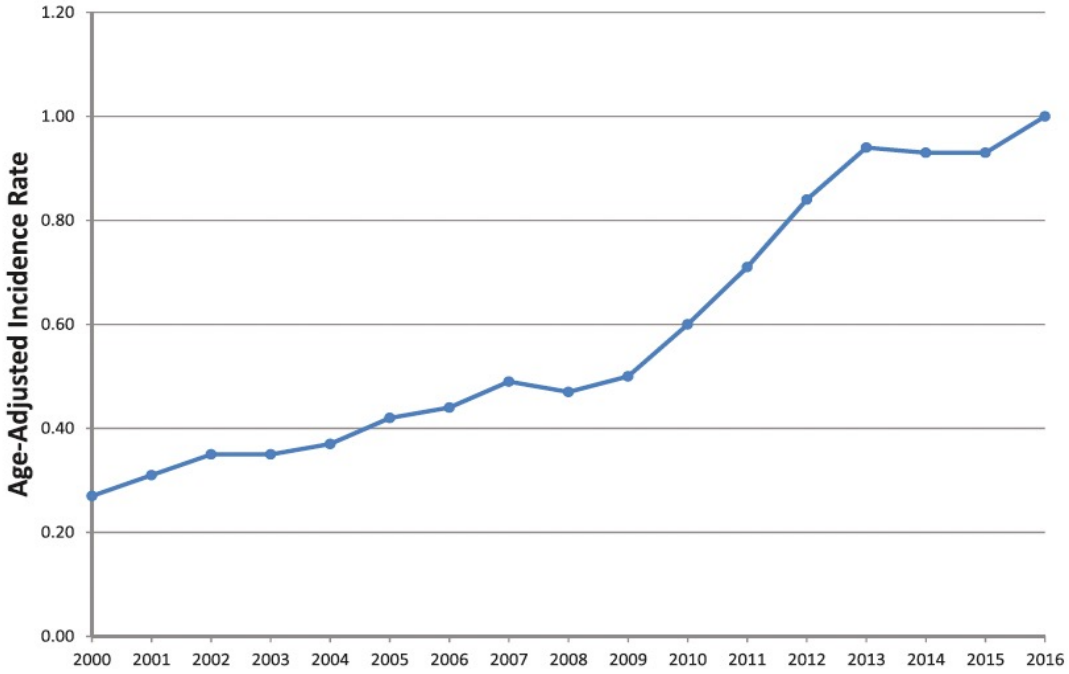




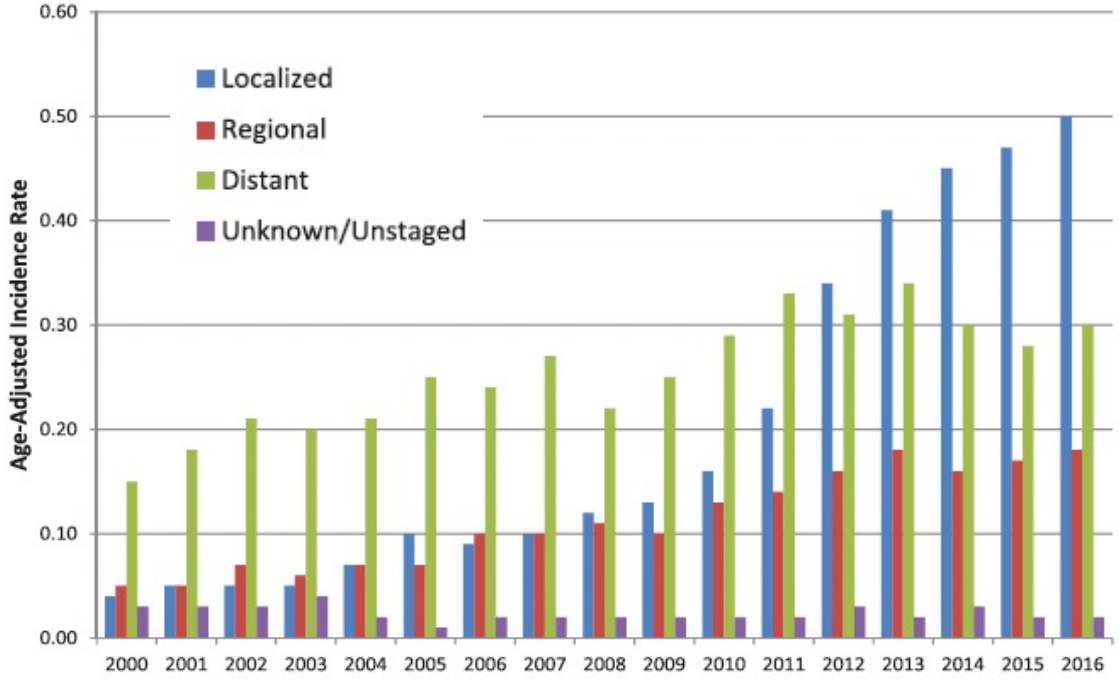
Yao JC et al. J Clin Oncol 2008;26(18):3063-3072

Increasing incidence of pNETs (2000-2016)
SEER Database Analysis (N~9K)

Incidence by Year of Diagnosis

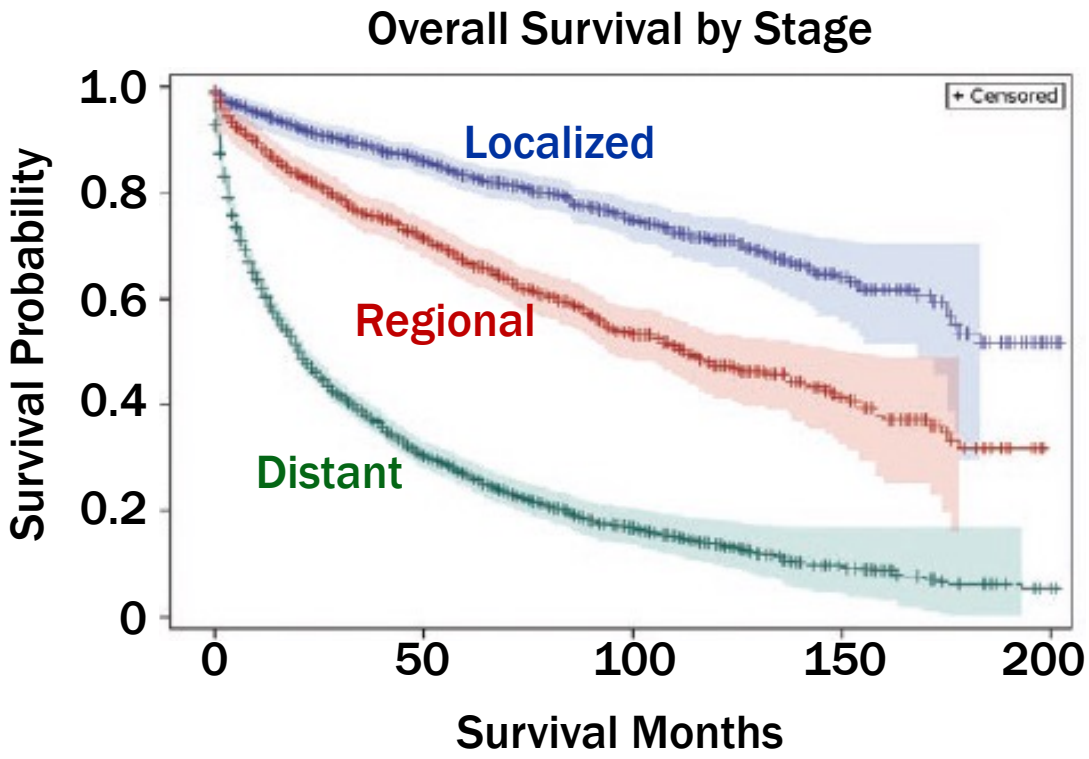


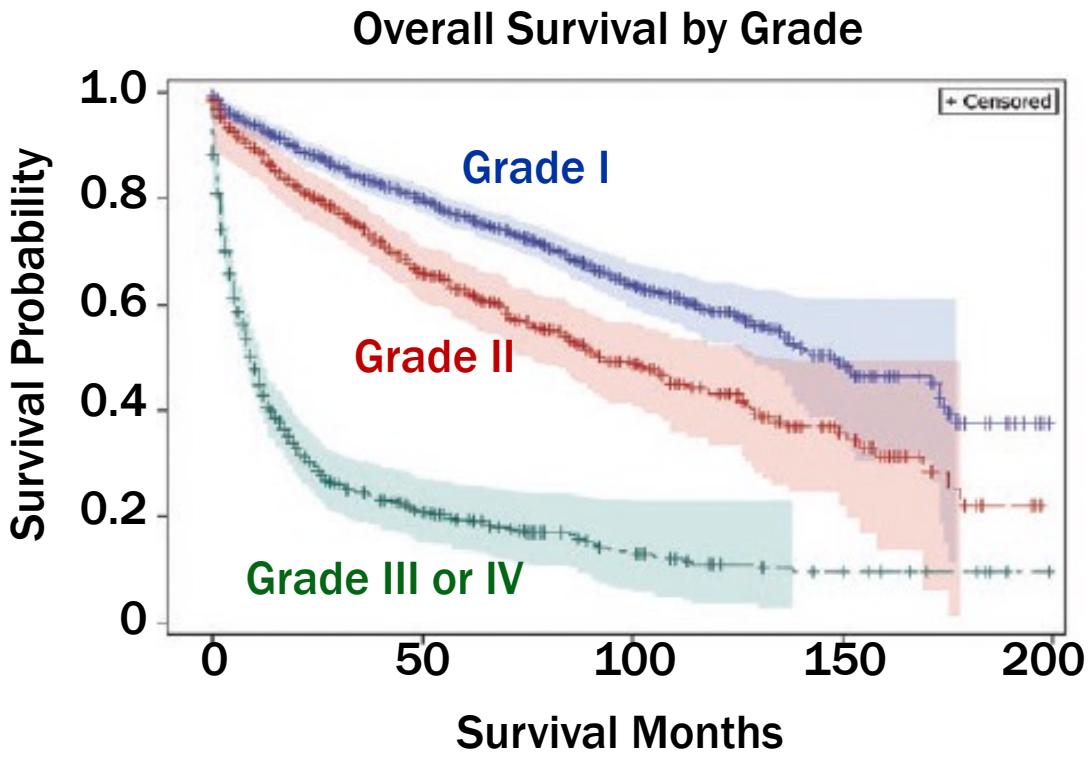
Incidence by Stage



Sonbol et al. *The Oncologist* 2022

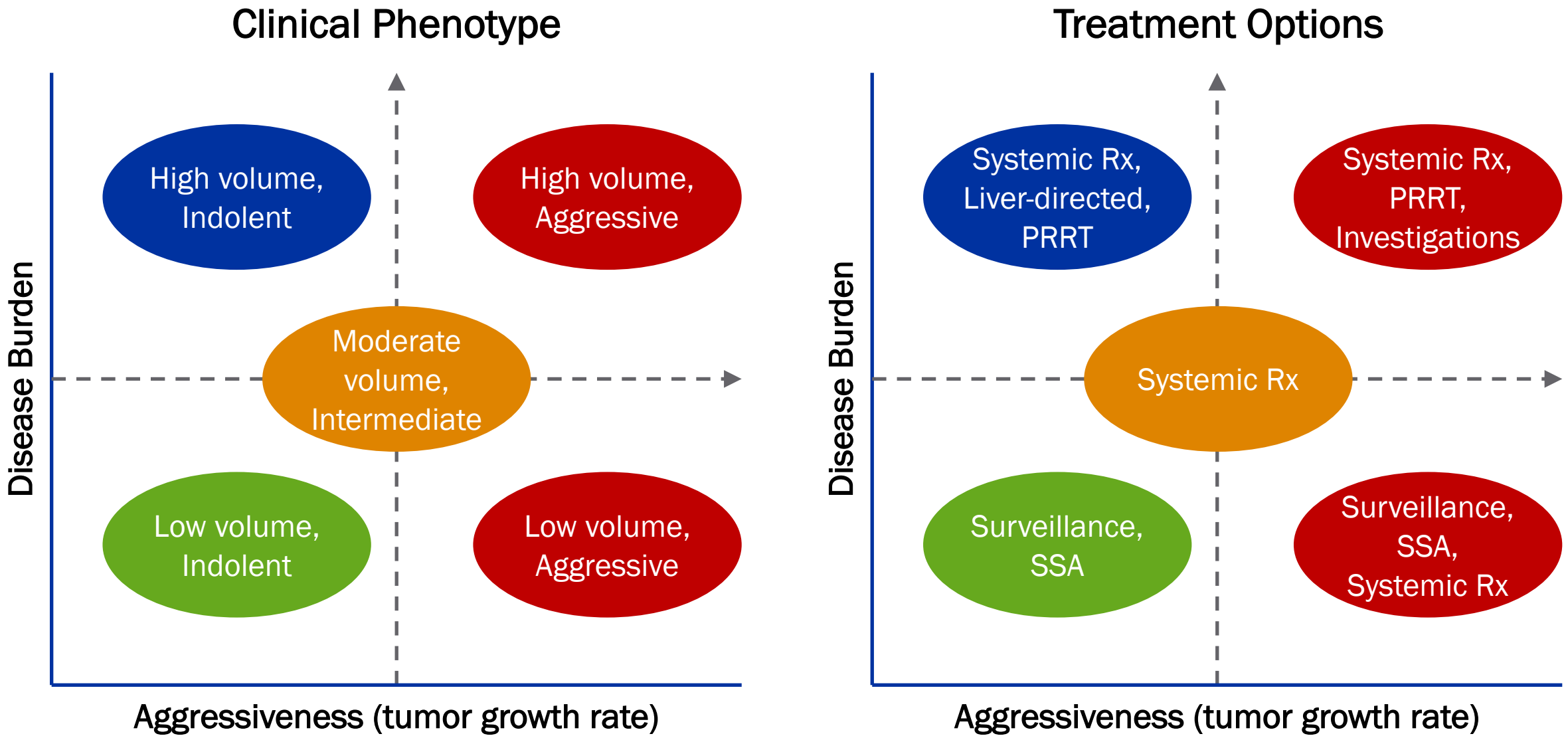
Increasing incidence of pNETs (2000-2016) SEER Database Analysis (N~9K)





Sonbol et al. *The Oncologist* 2022

Clinical assessment and decision making in Stage IV NETs

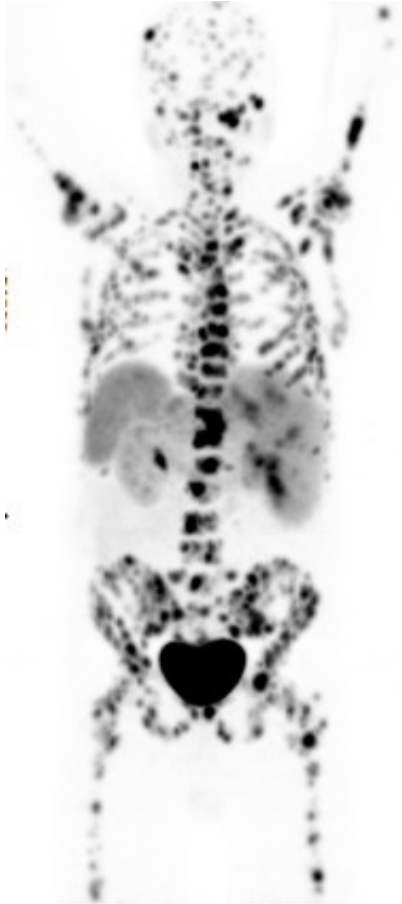


Anthony et al. In press

Clinical Classification of Stage IV NETs using somatostatin receptor scintigraphy with 64Cu- or 68Ga-dotatate PET/CT

Liver Dominant

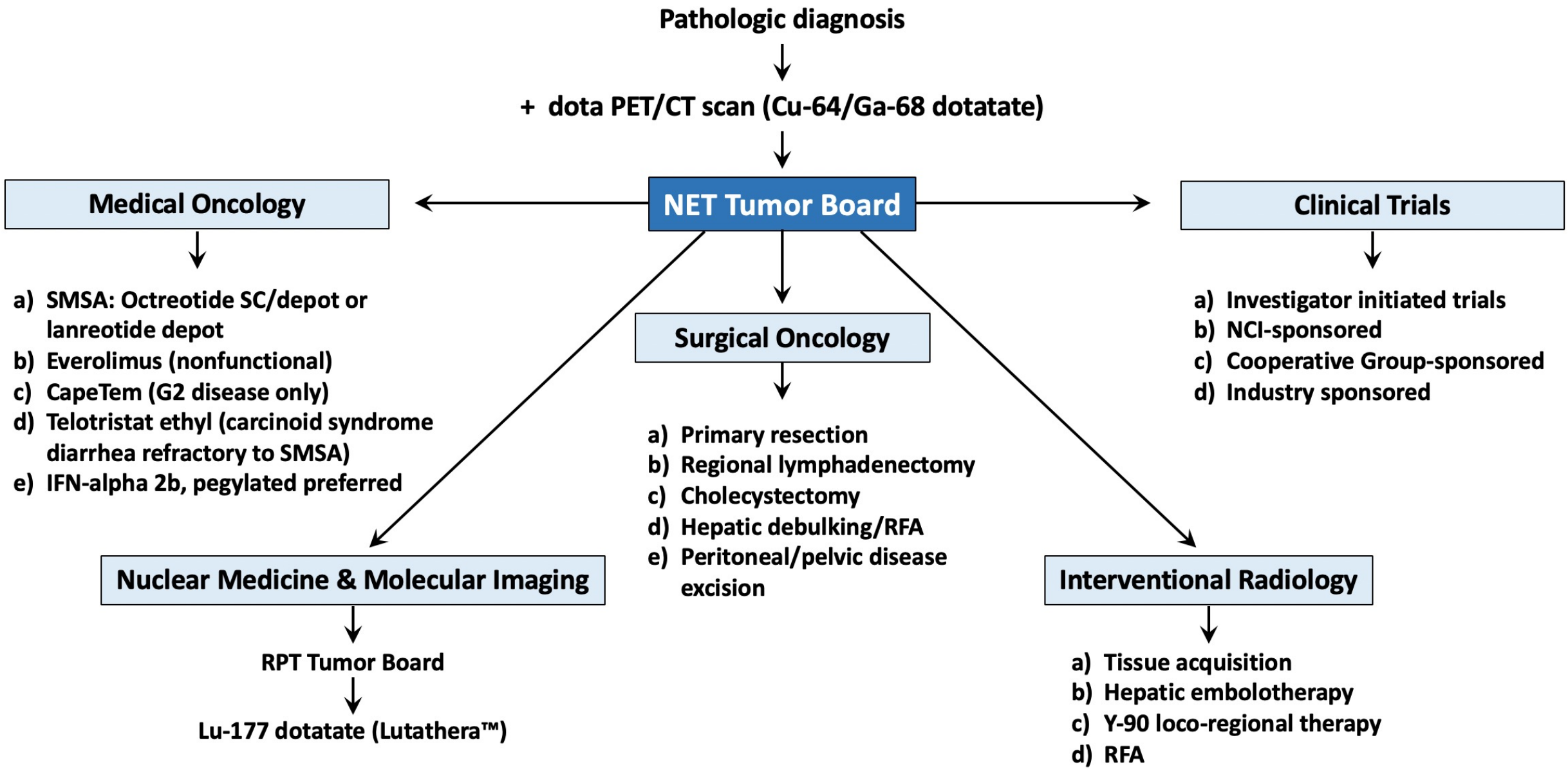
Extrahepatic Dominant



Hepatic and Extrahepatic

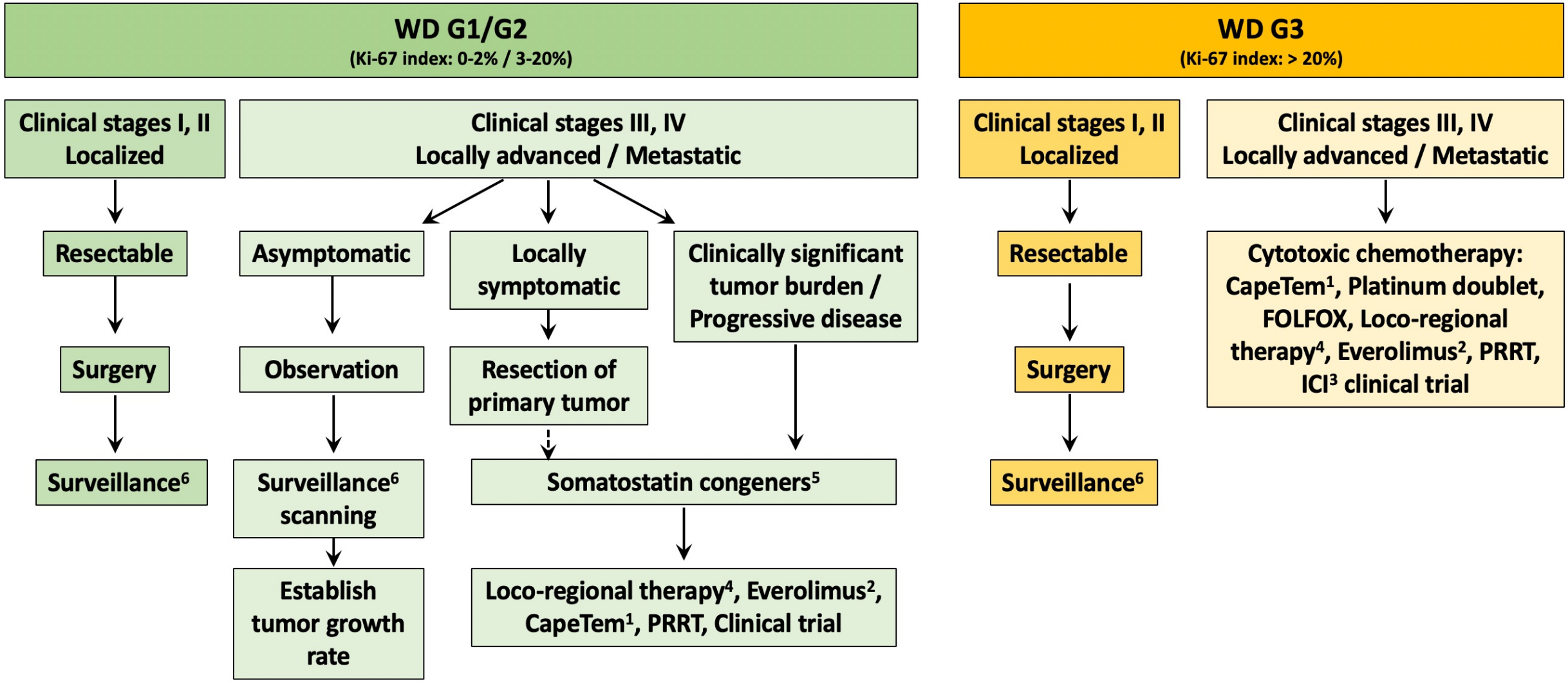
Anthony et al. In press

Multi-Disciplinary Neuroendocrine Oncology Clinical Program
G1, G2 WD Intestinal NETs



Anthony et al. In press

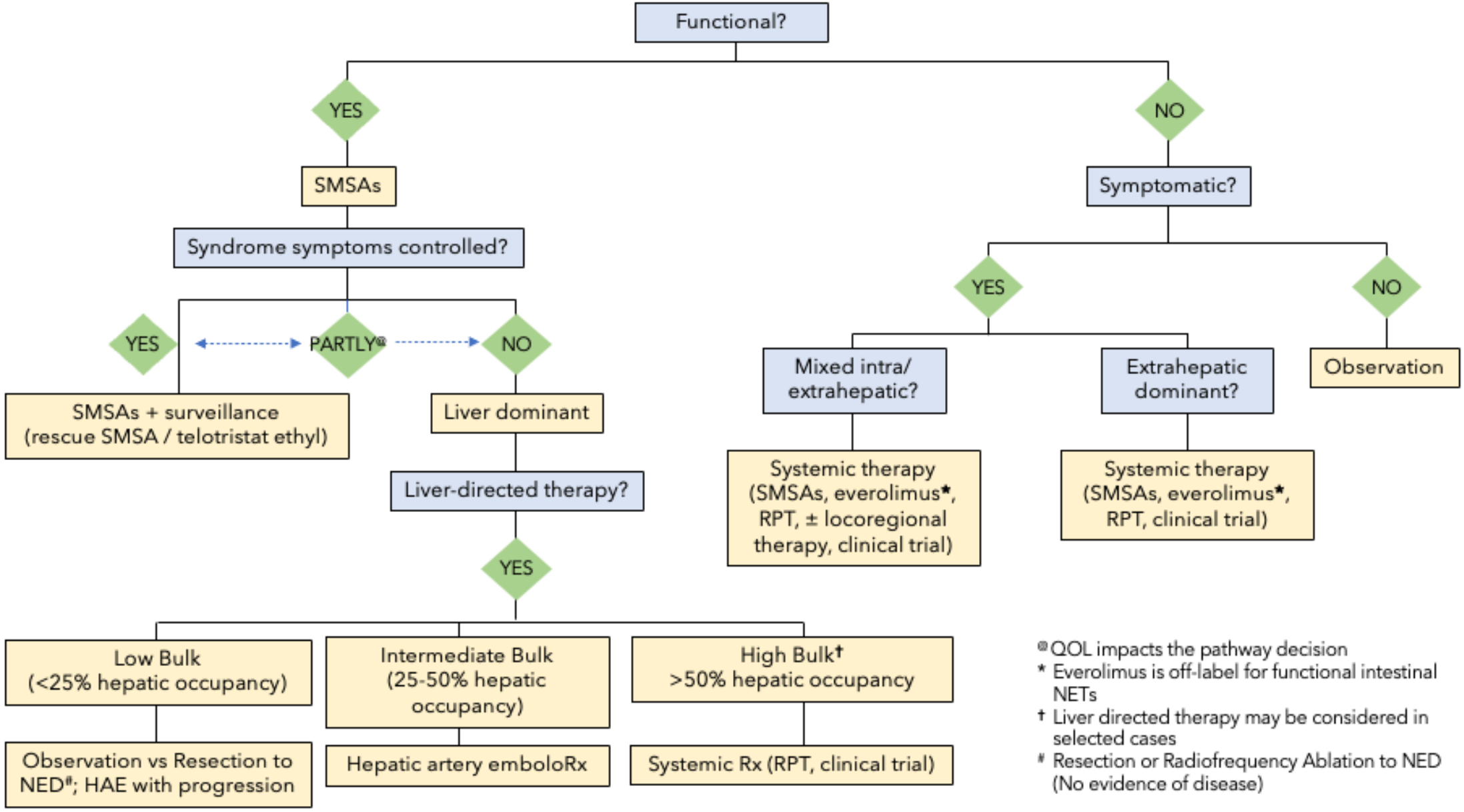
Intestinal NET Management Paradigm



[1]CapeTem: Capecitabine, temozolomide for G2/G3 disease *ONLY ;* [2]Everolimus: Indicated for non-syndromic patients (RADIANT-4 clinical trial); [3]ICI: Immune checkpoint inhibitors for MSI-H, TMB > 10; [4]Loco-regional therapy: Includes surgery, hepatic artery embolotherapy, radiofrequency ablation; [5]Somatostatin congeners: Octreotide and lanreotide are more likely to benefit sst2+ disease, syndromic (flushing, secretory diarrhea), slows progressive disease; [6]Surveillance: Adjuvant clinical trial in progress

Anthony et al. In press

Medical decision making:
sst2+ metastatic WD G1/G2 intestinal NETs, primary resected or asymptomatic



Anthony et al. In press

Lanreotide autogel/depot (LAN) in patients with advanced bronchopulmonary (BP) neuroendocrine tumors (NETS): Results from the phase III SPINET study

Table: 10960	DB		
	LAN (n=51)	PBO (n=26)	HR [95% CI][a]
PFS (TC & AC), median (95% CI), mths	16.6 (11.3–21.9)	13.6 (8.3–NC)	0.90 [0.46–1.88]
ORR, % (95% CI)	14.0 (5.8–26.7)	0 (0.0–13.7)	–
TTF, median (95% CI), mths	13.3 (5.6–14.1)	9.8 (5.4–13.6)	0.86 [0.50–1.50]
	DB		OL-LAN
TEAEs, n (%)[b]	LAN (n=51)	PBO (n=26)	All pts (n=40)
Any	49 (96.1)	25 (96.2)	26 (65.0)
Related	38 (74.5)	14 (53.8)	13 (32.5)
Grade			
1	44 (86.3)	23 (88.5)	25 (62.5)
2	37 (72.5)	19 (73.1)	14 (35.0)
3	13 (25.5)	8 (30.8)	3 (7.5)
4	1 (2.0)	0	0
5	1 (2.0)	0	0
Leading to study treatment withdrawal	2 (3.9)	3 (11.5)	0
Serious AEs	10 (19.6)	7 (26.9)	1 (2.5)
Related	2 (3.9)	1 (3.8)	0

[a]LAN vs PBO; [b]Excludes death/progression (part of PFS assessment) TEAE, treatment-emergent adverse event.

Conclusions

- **SPINET, the largest prospective study to date with an SSA in SSTR-positive BP-NETs, suggests that LAN 120 mg could be an appropriate treatment option, *especially for typical carcinoid*.**

ANNALS OF ONCOLOGY driving innovation in oncology
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
Baudin et al. *Ann Oncol.* doi.org/10.1016/j.annonc.2021.08.178

A Randomized Study of Temozolomide or Temozolomide and Capecitabine in Patients with Advanced Pancreatic Neuroendocrine Tumors: Final Analysis of Efficacy and Evaluation of MGMT as a Predictive Biomarker (ECOG-ACRIN E2211)

BACKGROUND: Retrospective and small prospective studies suggest that the combination of capecitabine and temozolomide is associated with **high response rates and relative long PFS**

METHODS: E2211 was a multicenter, randomized, phase II trial comparing TEM vs. CAPTEM in patients with advanced progressive (>12 mos) pancreatic NETs

Agent	Dose	Day
TEM	200 mg/m^2 PO QD	1-5
CAPTEM	750 mg/m^2 PO, BID 200 mg/m^2 PO QD	1–14 10–14

RESULTS (see table):

- 144 patients were enrolled from 4/2013–3/2016 to TEM or CAPTEM; the efficacy analysis population included **133 eligible patients**.
- Interim analysis (1/2018): Median PFS was sufficient to reject the null hypothesis (stratified log rank p=0.022).
- Final analysis (5/2021): CAPTEM associated with better median OS; higher rates of grade 3-4 AEs; and more MGMT deficiency (defined as low IHC or positive promoter methylation), which was associated with greater odds of response

Time	Char.	TEM	CAPTEM	Stat.
Enrollment	N	72	72	
Interim analysis	Median PFS (mo)	14.4	22.7	HR=0.58
Final analysis	Median OS (mo)	53.8	58.7	HR=0.82 P=0.42
	RR	34%	40%	P=0.59
	Gr. 3-4 AE	22%	45%	P=0.005
	MGMT deficiency	9.79 (1.09-87.71)	6.38 (2.19-18.60)	OR (95% CI)

CONCLUSION: E2211 is the first prospective randomized trial of CAPTEM and shows the **longest PFS and highest RR reported for patients with pancreatic NETs** in a prospective randomized study. MGMT deficiency was associated with greater odds of objective response.

Kunz, et al. Abstract 4004, ASCO 2022 Annual Meeting (June)

Efficacy of Capecitabine and Temozolomide in Small Bowel (Midgut) Neuroendocrine Tumors

BACKGROUND: The capecitabine/temozolomide regimen has **proven significant activity in pancreatic NETs**, however data are limited in NETs of the small bowel (midgut).

METHODS: Retrospective study of patients with metastatic midgut NETs treated with CAPTEM between 1/2008 and 6/2019.

RESULTS:

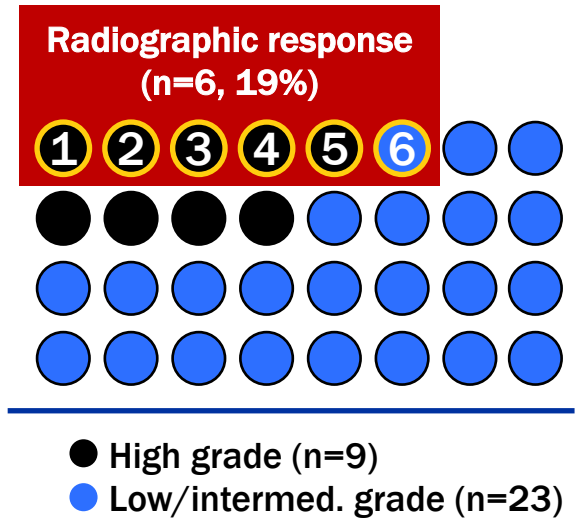
- 32 patients with small bowel NETs: 6 had radiographic response (19%), 5 of whom had high-grade (well-differentiated) disease.
- Only 1 patient among 23 with low/intermediate grade disease responded (4%), whereas the response rate for patients with high-grade disease was 56%.
- Among patients with low/intermediate-grade disease, 44% discontinued for poor tolerability.

CONCLUSION: The CAPTEM regimen appears to have activity in patients with WD high-grade small bowel NETs and is largely inactive in patients with low/intermediate grade tumors.

"CAPTEM use should largely be reserved for midgut NET patients with high-grade disease."

Agent	Dose	Day
Capecitabine	750 mg/m^2 PO, Twice daily	1–14
Temozolomide	200 mg/m^2 PO, Once daily	10–14

1 cycle = 28 d



Al-Toubah et al. Abstract 158, NANETS 2021 Annual Meeting (November)

Treatment Response and Clinical Outcomes of Well-differentiated (WD) High-grade (HG) Neuroendocrine Tumors (NETs) to ^{177}Lu-DOTATATE

BACKGROUND: ^{177}Lu-DOTATATE is an approved therapy for SSTR-positive GEPNETs. Little data are available on response and outcomes for WD HG NETs treated with ^{177}Lu-DOTATATE.

METHODS: Patients with progressive WD HG NETs treated with ^{177}Lu-DOTATATE from 2018-2020.

RESULTS:

- 19 patients (see table). All tumors were *SSTR+ on Ga68-DOTATATE*.
- *Best response* by radiographic report (17 evaluable patients): 12 (71%) partial response, 5 (29%) disease progression. 3 patients with response received additional cycles of 177Lu-DOTATATE at progression.
- *Median PFS:* 11.8 months (95% CI 10.6–18.6). 5 patients (26%) experienced dose modifying toxicity.

CONCLUSION: We observed a meaningful disease response of 71% during WD HG NET treatment with ^{177}Lu-DOTATATE. In this heavily pre-treated population, more than half of patients received all 4 treatment cycles. Rx-related toxicities were largely bone-marrow.

Patient characteristics	N=19
Mean age	54 years
Female	63%
Pancreatic NET	14 (74%)
Median Ki-67	32% (22-56)
Median # prior systemic/liver-directed treatments	4 (2-7)
Completed all 4 cycles	13 patients (68%)
Incomplete treatments	6 patients (3 toxicities, 3 clinical progression)

Coffman et al. Abstract 178, NANETS 2021 Annual Meeting (November)

Incidence of Psychiatric Illness in Neuroendocrine Tumor Patients: A Comparative Population-Based Analysis

HYPOTHESIS: Diversion of tryptophan to hormonal production has been suggested to result in increased prevalence of psychiatric illnesses in NET patients.

METHODS: We linked population-based healthcare data to match adults with NET 1:1 to CC (2000-2019). Psychiatric illnesses was defined by mental health diagnoses (depression, psychosis, anxiety, schizophrenia) and mental health use after cancer diagnosis and categorized as severe, other, and none. Cumulative incidence functions accounted for death as a competing risk.

RESULTS:

- There was no difference in pre-cancer psychiatric illnesses between groups.
- There was no difference in post-cancer psychiatric illnesses by NET primary site or metastases.
- In sub-groups of small bowel and lung NETs and of confirmed functional NETs, 5-year cumulative incidences of severe and other psychiatric illnesses were statistically higher; however, absolute differences were small (<1.5% for severe; 3.5% for other)

CONCLUSION: Patients with NETs did not have higher incidence of psychiatric illnesses after cancer diagnosis compared to CC, except marginally in sub-groups of small bowel and lung NETs and confirmed functional NETs. These data did not substantiate the hypothesis of a relationship between psychiatric illnesses and NETs.

Characteristic	NETs Patients	Controls	P-value
N	11,223	11,223	
Median follow-up (IRQ, months)	49 (18-95)	45 (19-92)	
5-year cumulative incidence of severe psychiatric illnesses (95% CI)	7.7% (7.2-8.2%)	7.6% (7.2-8.2%)	0.50
5-year cumulative incidence of other psychiatric illnesses (95% CI)	32.9% (32.0-33.9%)	31.6% (30.8-32.6%)	0.0053

Hallet et al. Abstract 74 NANETS 2021 Annual Meeting (November)

Concurrent Everolimus with Hepatic Transarterial Bland Embolotherapy [Evero-Embo] in Patients with Bulky and/or Progressive Metastatic Well Differentiated NET

HYPOTHESIS: Continuing everolimus during and after bland TAE, hepatic mPFS will be greater than 18 months.

METHODS: A review of clinical and radiographic data was conducted for all sequential patients who underwent evero-embo between September 2016 and September 2020. An independent radiologist performed response evaluation criteria in solid tumors (RECIST) measurements. To be included in this study, patients were required to have had systemic everolimus for ≥1 month prior to embolization and to be on everolimus immediately post procedure. Patients with at least 20 months post procedure follow-up were included for mPFS analysis.

RESULTS:

- 96 TAEs with concurrent systemic everolimus were performed in 51 NET patients.
- 30/51 patients had 24 or more months of follow-up post-procedure. The median hepatic free progression (hPFS) was 30+

CONCLUSION: Evero-embo results in a median hPFS exceeding that of bland or chemoembolization. A prospective clinical trial is planned to confirm the efficacy and safety of combining everolimus with hepatic bland embolotherapy.

Gupta et al. Abstract 193 NANETS 2021 Annual Meeting (November)

A Prospective Study of Carcinoid Crisis with No Perioperative Octreotide

- **BACKGROUND:** **Octreotide has been used prophylactically to reduce crisis rates as well as therapeutically to treat crises that still occur.** However, multiple **retrospective studies using prophylactic octreotide still report crisis rates of 24-30%.** Average crisis duration with octreotide use range from 8.9-19 minutes and 8-24% last > 10 minutes. ***A recent prospective study showed there is no massive release of hormones during crisis, greatly weakening the argument for octreotide***. Before recommending cessation of octreotide use, the incidence ,duration and complications from crisis need to be studied when it is not used.

- **METHODS:** Patients with NETs undergoing operations between 2017-2020 with no perioperative prophylactic or therapeutic octreotide were prospectively studied. Crisis was declared by agreement of surgeon and anesthesiologist if sudden hemodynamic instability was observed with no plausible alternative explanation. Clinicopathologic data were compared by chi-squared test for discrete and Mann-Whitney U test for continuous variables.

- **RESULTS:** **171 patients underwent 195 operations**. **Crisis was documented in 49 operations** (25%). Median crisis duration was 3 minutes, and none lasted >10 minutes (0%). Crises correlated with small bowel primary ($p=0.012$), grade 2 tumor ($p=0.015$), older age ($p=0.021$), and carcinoid syndrome ($p<0.0001$), but there was no significant difference in outpatient long-acting somatostatin analog use. Patients with crisis were more likely to receive vasopressors ($p=0.04$), intraoperative transfusions ($p=0.006$), and have major postoperative complications ($p=0.003$). **Complication rates were not higher than previous reports using octreotide.**

- **CONCLUSIONS:** ***Completely eliminating perioperative octreotide did not result in increased rate or duration of crisis, or major complication rates*** compared to previous studies using it. We conclude that perioperative octreotide use may be safely stopped due to inefficacy and lack of scientific grounds. Because crisis of even short duration is associated with increased risk of major complications, the search for an effective prophylactic agent should continue.

Pommier et al. *Abstract 163*, NANETS 2021 Annual Meeting (November)

Summary

1. NETs are heterogeneous
2. NETs incidence is increasing across primary sites
3. Classification is both pathologically and clinically determined
4. Medical Decision Management: “*personalizing treatment options with individual patient variables*”

Summary

5

Lanreotide may be efficacious in typical bronchial carcinoid

6

Advanced pNETs: CAPTEM associated with better median OS; higher rates of grade 3-4 AEs

7

CapeTem only for WD G3 intestinal NETs

8

Lu-177 dotatate may have efficacy in HG NETs (Ki-67 index >20%)

Summary

9

Psychiatric disease is no greater in a serotonin producing tumor population

10

Continuing everolimus during bland hepatic artery embolotherapy increases hepatic PFS

11

Octreotide prophylaxis prior to surgical procedures is ineffective

Worldwide NET Cancer Awareness Day

Thank you!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