PARTNETS
Partnership in Neuroendocrine Tumors
23NOV2020

Hot topics to solve in the perioperartive setting

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- **Personal financial interests:** Novartis, Ipsen, Pfizer, Merck Serono, Advanced Accelerator Applications, MSD (Advisory board,public speaking)

- **Institutional financial interests:** Novartis, Ipsen, Merck Serono, MSD, Pharmacyclics, Incyte, Halozyme, Roche, Astellas, Pfizer (Clinical trial or research projects: principal investigator, steering committee member)

- **Non-financial interests:**
  - ESMO: Past coordinator of the Neuroendocrine, Endocrine neoplasms and CUP Faculty
  - ENETS: executive committee member
  - AIOM: Referee for ITALIAN NEN guidelines
  - ITANET: Scientific committee member

Adjuvant / neo-adjuvant therapy: when?

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- Moderate/high risk of recurrence

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- Locally advanced stage

Adjuvant / neo-adjuvant therapy: when?

- Moderate/high risk of recurrence

- Intermediate/high grade
- Locally advanced stage

- Pancreas
- Lung

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Neuroendocrine and Adrenal Tumors

NCCN Guidelines Index
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Discussion

PRINCIPLES OF SYSTEMIC ANTI-TUMOR THERAPY
Locoregionally Advanced and/or Metastatic Pancreatic Neuroendocrine Tumors

- Systemic therapy may not be appropriate for every patient with locoregionally advanced or metastatic disease. Consider multidisciplinary discussion to determine the best choice of treatment, including: observation for patients with stable disease with mild tumor burden, hepatic regional therapy for patients with liver-predominant metastases, cytoreductive surgery, or systemic therapy.
- Currently, there are no data to support a specific sequence of regional versus systemic therapy and no data to guide sequencing of the following systemic therapy options.
- There is no known role for systemic treatment in the adjuvant setting for PanNETs.
- Doses and schedules are subject to appropriate modifications depending on the circumstances.
- For management of hormone-related symptoms and complications with octreotide or lanreotide, see PanNET-1 through PanNET-5.

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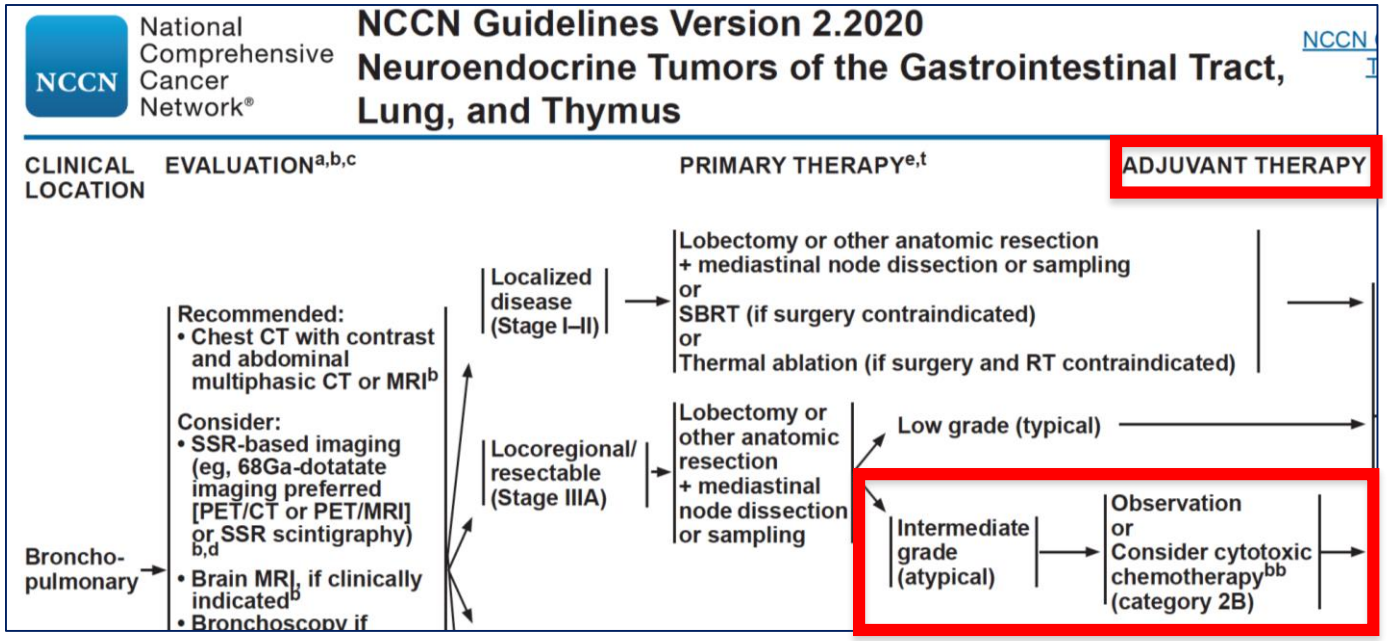
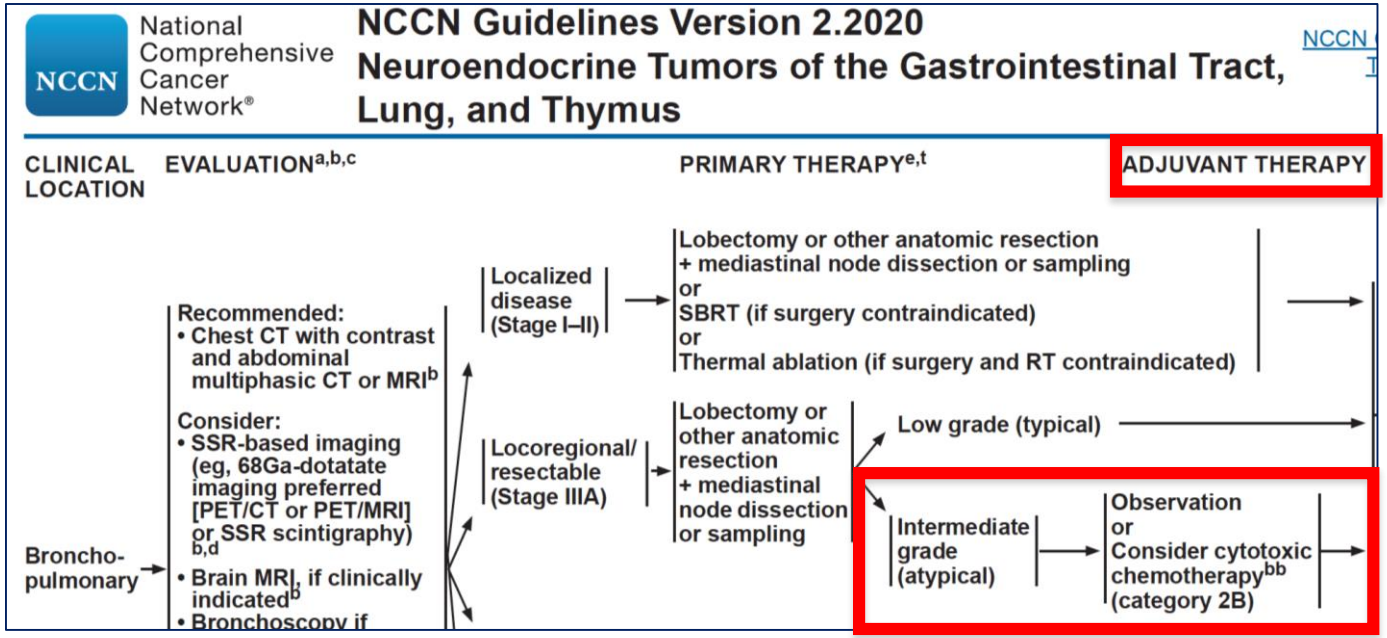
PRINCIPLES OF SYSTEMIC ANTI-TUMOR THERAPY
Locoregionally Advanced and/or Metastatic Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus

- Systemic therapy may not be appropriate for every patient with locoregionally advanced or metastatic disease. Consider multidisciplinary discussion to determine the best choice of treatment, including: observation for patients with stable disease with mild tumor burden, hepatic regional therapy for patients with liver-predominant metastases, cytoreductive surgery, or systemic therapy, which may be appropriate considerations.
- Currently, there are no data to support a specific sequence of regional versus systemic therapy, and no data to guide sequencing of the following systemic therapy options.
- There is no known role for systemic treatment in the adjuvant setting for NETs.
- Doses and schedules are subject to appropriate modifications depending on the circumstances.
- For management of hormone-related symptoms for GI tumors, see NET-11. For management of carcinoid syndrome, see NET-12.



Stage IIIA	T1-2	N2	M0
	T3	N1-2	M0
	T4	N0-1	M0

[bb] Cytotoxic chemotherapy options include **cisplatin + etoposide, carboplatin + etoposide, or temozolomide**. There are limited data on the efficacy of chemotherapy for stage III atypical bronchopulmonary NET.



Stage IIIA	T1-2	N2	M0
	T3	N1-2	M0
	T4	N0-1	M0

[bb] Cytot
etopos
temozo
of chem
broncho

- ✓ Why cis/carboplatin/etoposide ?
- ✓ Why not also oxaliplatin-based?
- ✓ Why not everolimus?
- ✓ How long?

Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids

M. E. Caplin[1*], E. Baudin[2], P. Ferolla[3], P. Filosso[4], M. Garcia-Yuste[5], E. Lim[6], K. Oberg[7], G. Pelosi[8], A. Perren[9], R. E. Rossi[1,10] & W. D. Travis[11] the ENETS consensus conference participants[†]

Annals of Oncology 26: 1604–1620, 2015

Which proliferation index threshold ?

Which one ? How long?

adj

Currently, there is no consensus on adjuvant therapy in PCs after complete resection. Indeed, both prognostic studies and trials in the adjuvant setting are lacking. Only patients with AC with positive lymph nodes, especially if there is a high proliferative index, should be considered for adjuvant therapy and discussed on an individual patient basis in the context of multidisciplinary tumor board meeting. Clinical trials are needed in this setting.

Studies investigating predictors for recurrence after curative surgery of panNET

Limitations:

The majority of these studies include patients with distant metastases, hereditary syndromes or high grade neuroendocrine carcinoma

Genc et al., Ann Surg 2017

211 pts with resected G1-G2 panNET - mFup 51 months

Recurrence rate = 17%

Lymph node involvement
G2
Perineural invasion

} Predictors of recurrence

DSS = 98% at 5y and 84% at 10y

Genc et al., Ann Surg 2018

Ann Surg Oncol. 2018 Aug;25(8):2467-2474. doi: 10.1245/s10434-018-6518-2.
Epub 2018 May 22.

Recurrence of Pancreatic Neuroendocrine Tumors and Survival Predicted by Ki67

C G Genç [1], M Falconi [2], S Partelli [2], F Muffatti [2], S van Eeden [3], C Doglioni [4], H J Klümpen [5], C H J van Eijck [7], E J M Nieveen van Dijkum [8]

3 centers – 1992-2016 – 241 pts with resected G1-2 panNET

Recurrence rate = 14% with Ki-67 </= 5% (median 34 months)
41% with Ki-67 6-20% (median 16 months)

Int J Surg. 2020 Feb;74:86-91. doi: 10.1016/j.ijsu.2019.12.034. Epub 2020 Jan 9.

Novel scoring system for recurrence risk classification of surgically resected G1/2 pancreatic neuroendocrine tumors – Retrospective cohort study

Siyi Zou [1], Yu Jiang [1], Weishen Wang [1], Qian Zhan [1], Xiaxing Deng [1], Baiyong Shen [2]

Single-center – 245 pts with G1-2 panNET

Table 4
Risk scoring system for recurrence risk estimation of resected G1/2 pancreatic neuroendocrine tumors.

	Points	3y recurrence risk	5y recurrence risk	mDFS (m, 95%CI)
Lymph node metastatic (LNM)	No = 0 Yes = 4.9			
Tumor size (cm)	cm*1.8			
WHO grade	G1 = 0 G2 = 16			
Total points* and risk classification	Low risk (< 15.4);	0.8%	4.3%	NR
	Intermediate risk (> 15.4, < 24.5);	11.6%	21.4%	70 (70-NR)
	High risk (> 24.5)	37.3%	68.7%	49 (32-NR)

mDFS(m): median disease-free survival (month); 95%CI: 95% confident interval; NR: not reached.
Total points = (LNM, if yes = 4.9; if no = 0) + (1.8 tumor size in cm) + (WHO grade, if G1 = 0; if G2 = 16).

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Pancreatology. 2018 Apr;18(3):313-317. doi: 10.1016/j.pan.2018.02.008. Epub 2018 Feb 21.

Is radical surgery always curative in pancreatic neuroendocrine tumors? A cure model survival analysis

Claudio Ricci [1], Riccardo Casadei [2], Giovanni Taffurelli [2], Davide Campana [2], Valentina Ambrosini [3], Carlo Alberto Pacilio [2], Donatella Santini [3], Nicole Brighi [3], Francesco Minni [2]

Single-center – 143 resected panNET

TNM and grading = two independent factors related to cure fraction

JAMA Netw Open. 2020 Nov 2;3(11):e2024318. doi: 10.1001/jamanetworkopen.2020.24318.

Evaluation of Outcomes Following Surgery for Locally Advanced Pancreatic Neuroendocrine Tumors

Ashley L Titan [1], Jeffrey A Norton [1], Andrea T Fisher [1], Deshka S Foster [1], E John Harris [1], David J Worhunsky [2], Patrick J Worth [1], Monica M Dua [1], Brendan C Visser [1], George A Poultsides [1], Michael T Longaker [1], Robert T Jensen [3]

99/249 patients with T3/T4 panNETS and no distant metastatic disease

Thirty-five patients (35%) developed recurrent disease; most of which (20 [57%]) were seen in the liver.

Lymph node involvement
Additional organ resected
Male sex

} Greater probability of tumor recurrence

- MEN-1 = lower risk of recurrence
- Functioning tumors = not higher risk of recurrence

«Patients had an excellent overall survival at 5 years of 91%, with an associated good quality of life, as indicated by low ECOG scores, and an overall recurrence rate of only 35%. Our findings suggest that surgical resection of locally advanced PNETS without distant metastatic disease is indicated.»

Vascular involvement was also not associated with an increased risk of recurrence, further suggesting that vascular resection and reconstruction is warranted

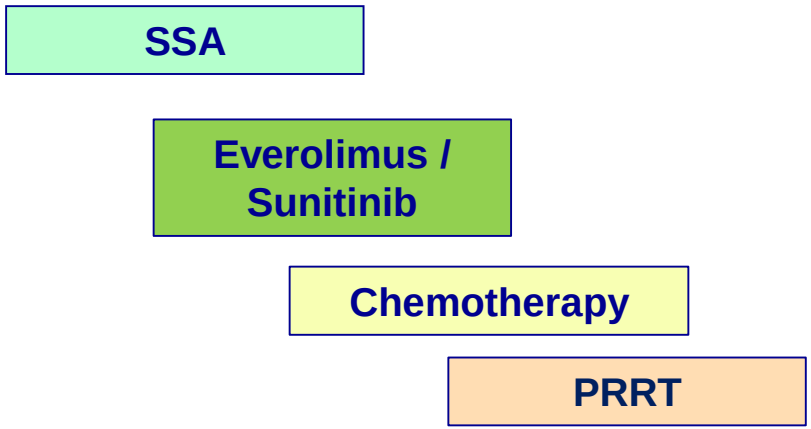
Titan et al., JAMA Netw Open, Nov 2020

CAVEAT

1. High risk of recurrence does not necessarly mean efficacy of an adjuvant therapy

2. A prognostic factor of relapse is not necessarly a predictive factor of response to an adjuvant therapy

- What systemic therapy should we use in adjuvant setting for a panNET?
- Should we base the decision on the metastatic setting evidence?
- What about duration?



Adjuvant / neo-adjuvant therapy for intermediate grade pancreatic / lung NETs: further issues

- Pathological characterization of the disease may be different between preop and postop
- What did systemic staging include? (morphological; functional (SSTR + FDG?)
- Which setting → Neo-adjuvant or adjuvant approach?

Concluding remarks

- ✓ Adjuvant therapy could be useful for a minority of radically resected pancreatic NET and atypical lung carcinoids
- ✓ No adjuvant therapy is justified outside clinical trials for pancreatic or lung NETs
- ✓ The neo-adjuvant setting can be an interesting context for proof-of-concept studies
- ✓ Adjuvant therapy trials should be designed in specific subgroups of panNETs on the basis of the hypotheses came out from several retrospective studies

IEO NEN MDT

European Institute of Oncology, IRCCS, IEO, ENETS CoE