Neuroendocrine Neoplasms (NENs)

What are Neuroendocrine Neoplasms (NENs)?

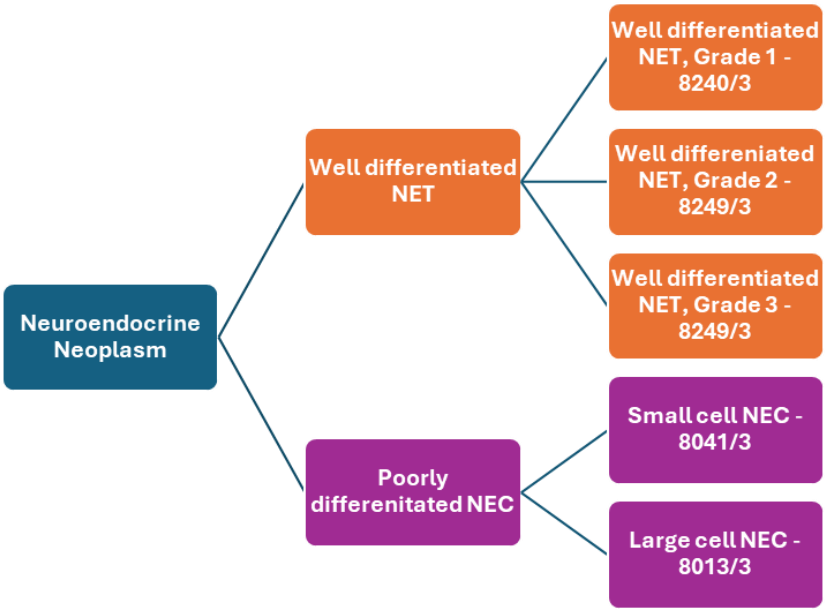
- Term "neuroendocrine" is applied to widely dispersed cells with "neuro" and "endocrine" properties
- Based on clinical behavior, histology, and proliferation rate, NENs are generally categorized as low-grade indolent tumors vs. high-grade aggressive carcinomas
    - Relevant for prognosis and treatment choices
        - However, distinctions aren't very clear
    - We know them typically as **neuroendocrine tumors** (NETs) and **neuroendocrine carcinomas** (NECs)

Neuroendocrine Tumors (NETs)

- These can develop anywhere endocrine cells are present
    - Endocrine cells help regulate various body functions and are distributed throughout the body
- Almost all NETs are considered malignant. There are just differences in how aggressive they are.

Neuroendocrine Carcinomas (NECs)

- These are rare and aggressive form of cancers that arise from neuroendocrine cells
- These are solid "sheetlike" proliferation of tumor cells with irregular nuclei, high mitotic features, and less cytoplasmic secretory granules
- Neuroendocrine component has to exceed 30% to be called an NEC



Are Neuroendocrine Tumors reportable?
In short, yes. However, be sure to follow reportability instructions in SEER Coding Manual.

A neuroendocrine tumorlet of lung and non-lung sites is not reportable. A tumorlet is a tumor of neuroendocrine differentiation, defined by size <5mm, mitotic count <2, and absence of necrosis.

Histologic Grade
Grade doesn't always correlate with clinical behavior for NENs.

- There is a subset of NENs with a low-histologic grade appearance that may behave aggressively with rapid growth and metastasis matching those of high-grade NEC.
- Grade for these tumors is not based on the cancer cells and how they resemble normal cells. This is an exception to how other tumors are graded.
    - NCCN recommends the inclusion of tumor differentiation, mitotic rate, and Ki-67 in the pathology report with specification of the particular classification and grading scheme to avoid confusion.

Assigning Grade:

- Some neuroendocrine histologies have a grade or differentiation as part of the actual ICD-O histologic term. This is describing something other than the differentiation of the tumor cells and is not used to assign grade.
    - Grade is based on mitotic count and/or Ki-67 (*Grade Table 07*)

Ki-67		Mitotic Rate	WHO Grade	Grade
< 3%	**AND**	< 2*	1	**1**
3-20%	**OR**	2-20	2	**2**
< 20%	**OR**	> 20	3	**3**

*Many times, if Ki-67 is less than 3, mitotic count is not done

    - For sites where *Grade Table 07* apply and you don't have Ki-67 or mitotic count or a stated WHO Grade (G1, 2, or 3), then assign **grade 9** (unknown).

How do I determine the correct histology?

1. Use the **Solid Tumor Rules** (use the most recent release).
2. If the histology isn't in the Solid Tumor Rules, then use the **ICD-O updates**. Personally, I prefer using the *Annotated Histology List* (https://www.naaccr.org/icdo3/).
3. If you still can't locate the histology, submit a question to **Ask a SEER Registrar**.

The following tables are for your reference and **NOT** to be used to determine the appropriate histology code, grade, or reportability.

Terminology		Grade Term	Ki-67	Histology
NET, G1	Well differentiated	Low	<3%	**8240**
NET, G2		Intermediate	3-20%	**8249**
NET, G3 [2021+]		High	>20%	**8249**
NEC, small cell type	Poorly differentiated	High	>20%	**8041**
NEC, large cell type				**8013**
NEC, NOS				**8246**
NEN	Poorly differentiated			**8246** (2021+)
NET	Moderately differentiated			**8249**

Site-Specific Neuroendocrine Histologies

Site	Terminology	Applicable years	Histology
C54_; C559	NEC, High Grade	2018+	**8041**
C50_	NEC, Poorly Diff	2018+	**8041**
C25	Pancreatic NET, nonfunctioning/Clear cell NET, non-functioning pancreas	2021+	**8150**
C301	Middle Ear NET	2026+	**8240**
C44_	NEC, primary cutaneous	2021+	**8247**
C721	Cauda equina NET	2023+	**8693**
C751	PitNET (pituitary neuroendocrine tumor)	2023+	**8272**

Resources:

https://www.upmc.com/services/endocrinology/conditions/neuroendocrine-carcinomas

https://pmc.ncbi.nlm.nih.gov/articles/PMC5678742/

https://cancerbulletin.facs.org/forums/node/124336