INTRODUCTION

De nombreuses modifications des différentes classifications histologiques des tumeurs bronchiques ont été effectuées ces dernières années. La classification histologique de l'Organisation Mondiale de la Santé pour les tumeurs bronchiques a été réactualisée en 2021 (1) (**Figure 1**).

Types et sous types-histologiques	**Code ICD -O**
NEOPLASIES NEUROENDOCRINES PULMONAIRES	
Lésions pré-invasives	
Hyperplasie neuroendocrine pulmonaire diffuse idiopathique	8040/0
Tumeurs neuroendocrines	
Tumeur carcinoïde NOS / tumeur neuroendocrine NOS	8240/3
Tumeur carcinoïde typique / tumeur neuroendocrine de grade 1	8240/3
Tumeur carcinoïde atypique / tumeur neuroendocrine de grade 2	8249/3
Carcinomes neuroendocrines	
Carcinome à petites cellules	8041/3
Carcinome à petites cellules composite	8045/3
Carcinome neuroendocrine à grandes cellules	8013/3
Carcinome neuroendocrine à grandes cellules composite	8013/3

Figure 1 – Classification histologique OMS des tumeurs pulmonaires de 2021 (extraits focalisés sur les tumeurs neuroendocrines ; la classification complète figure en ANNEXE 1 du référentiel CBNPC) (2)**.**

Les néoplasies neuroendocrines bronchiques (NNE) (ou en anglais *neuroendocrine neoplasms, NEN*) sont des tumeurs épithéliales présentant une différenciation neuroendocrine sur le plan morphologique et immuno-phénotypique. Elles peuvent être distinguées en fonction de leur grade de malignité croissante (3,4) de la manière suivante :

- Les tumeurs neuroendocrines (TNE) (ou en anglais *neuroendocrine tumors*, NETs) sont bien différenciées :
  - Les carcinoïdes typiques (CT) : tumeur de bas grade (G1)
  - Les carcinoïdes atypiques (CA) : tumeur de grade intermédiaire (G2)
- Les carcinomes neuroendocrines (CNE) (ou en anglais ou en anglais *neuroendocrine carcinomas*, NECs) sont peu différenciés et de haut grade de malignité :
  - Les carcinomes neuroendocrines à grandes cellules (CNEGC)
  - Les carcinomes à petites cellules (CPC).

Enfin, l'hyperplasie neuroendocrine pulmonaire diffuse idiopathique (DIPNECH) est reconnue comme la lésion pré invasive des TNE et est associée à ces derniers dans 60 à 75% des cas.

Les critères reconnus actuellement pour le diagnostic de ces tumeurs sont ceux de Travis *et al.*(5), non modifiés dans la classification OMS 2021 :

- **Tumeur carcinoïde typique** (CT) : tumeur de morphologie NE (ou organoïde) avec moins de 2 mitoses par 2 mm^2, pas de nécrose, et mesurant au moins 0,5 cm.
- **Tumeur carcinoïde atypique** (CA) : tumeur de morphologie carcinoïde avec 2 à 10 mitoses par 2 mm^2 et/ou nécrose (souvent punctiforme).
- **Carcinome neuroendocrine à grandes cellules** :
  - Architecture neuroendocrine : nids, travées, rosettes, palissades
  - Index mitotique élevé : ≥ 11 mitoses par 2 mm2, moyenne de 70 par 2 mm^2
  - Nécrose (souvent de larges zones)
  - Cellules tumorales de grande taille avec cytoplasme modéré à abondant
  - Nucléole fréquent

- Un ou plusieurs marqueurs neuroendocrines positifs en immunohistochimie : chromogranine, synaptophysine et CD56. Un seul marqueur est suffisant s'il est exprimé de façon diffuse.
- Variant combiné : avec un autre carcinome non CPC

- **Carcinome à petites cellules** :
  - Petite taille des cellules (en général < au diamètre de trois petits lymphocytes)
  - Peu de cytoplasme
  - Chromatine granuleuse, nucléoles absents
  - Déformation (*moulding*) nucléaire
  - Index mitotique élevé : ≥ 11 mitoses par 2 mm², moyenne de 80 par 2 mm^2
  - Nécrose fréquente, souvent en larges plages
  - Variant combiné : avec un autre carcinome
  - En IHC :
    - Kératine AE1/AE3 souvent en dots.
    - Marqueurs neuroendocrines (CD56, chromogranine et synaptophysine) souvent positifs (10% cas négatifs).
    - TTF1 positif dans 90% des cas

L'hyperplasie neuroendocrine pulmonaire diffuse idiopathique des cellules neuroendocrines pulmonaires (*Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia*, DIPNECH) :

- Elle est définie par la prolifération généralisée ou multifocale des cellules neuroendocrines pulmonaires pouvant se répartir de manière linéaire le long de la membrane basale ou sous forme de minuscules agrégats nodulaires pouvant bomber dans les voies aériennes (6,7).
- Le plus souvent confinée à l'épithélium bronchique ou bronchiolaire, cette prolifération peut franchir la membrane basale et former des *tumorlets* (agrégats de cellules neuroendocrines de moins de 5mm envahissant le tissu pulmonaire adjacent) ou des tumeurs carcinoïdes (5 mm ou plus).
- La DIPNECH peut être accompagnée de signe de bronchiolite constrictive fibrosante. L'expression "syndrome DIPNECH" a été proposée pour désigner les cas de patients symptomatiques associés à la description d'une bronchiolite constrictive (8).

Remarques :

1- La détermination du Ki67 est utilisée dans la classification OMS 2019 des TNE digestives, mais ne l'est pas en cancérologie thoracique. Bien qu'il n'y ait pas de valeur seuil reconnue pour le Ki67, il est admis qu'une tumeur NE avec un Ki67 > 5% est probablement un carcinoïde atypique (CA), et qu'une tumeur avec un Ki67 > 30% est probablement un carcinome NE de haut grade (9). Le rôle principal du Ki67 est dans les échantillons de cytologie ou de biopsie écrasés d'exclure les CPC ou CNEGC (10). **Des travaux supplémentaires sont nécessaires pour étudier la signification clinique et le rôle de l'indice Ki67 dans l'évaluation pronostique des néoplasies neuroendocrines pulmonaires** (9,11–14)**.** Le KI67 ne doit pas être utilisé dans le cas de métastases car toutes les études ont été menées sur des pièces opératoires. Dans ces cas-là, il convient d'utiliser le terme de « métastase de TNE » sans spécifier CA ou CT, mais de mentionner l'index mitotique et la présence de nécrose.

2- L'existence de TNE ayant la morphologie d'un carcinoïde typique mais un compte de mitoses > 10 pour 2 mm2 ou avec un Ki67 > 30% a été rapportée. Ces tumeurs sont très rares et sont en cours de caractérisation. Elles pourraient correspondre comme pour le pancréas à des TNE de grade 3 (15).

3- Le **profil génomique** des TNE et des CNE semble différent (16–18). Les CPC se caractérisent par une double inactivation des gènes *TP53* et *RB1*, et des mutations inactivatrices des gènes *NOTCH* dans 25% des cas. Les CNEGC présentent un génotype soit proche de celui des CPC, soit proche des autres carcinomes non NE avec des mutations de *KRAS, STK11* ou *KEAP1*. Les carcinoïdes ne présentent généralement pas ces anomalies moléculaires, mais plutôt des mutations des gènes de remodelage de la chromatine ou du complexe SWI/SNF (dont *MEN1*, *PSIP1* et *ARDI1A*).

4- Dix à 20% des carcinomes non à petites cellules (adénocarcinome, carcinome épidermoïde ou carcinome à grandes cellules) expriment en immunohistochimie un ou plusieurs marqueurs NE mais sans morphologie NE (19). On les considère comme des carcinomes « à différenciation NE » sans indication à les traiter comme des CNEGC. C'est pourquoi, en l'absence de morphologie NE, il ne faut pas rechercher les marqueurs neuroendocrines en IHC.

5- Concernant **l'expression de PD-L1,** une étude de 227 patients porteurs d'une NNE pulmonaire retrouve une expression de PDL1 chez 10,4% des CNEGC, 5,8% des CBPC, et aucune expression des tumeurs carcinoïdes (20) avec un *cut-off* de 1%. Deux autres études centrées, dont celle du GFPC (21), sur les CNE et particulièrement les CNEGC retrouvent environ 10% d'expression PD-L1 (22).

Tableau 1- Récapitulatif des critères diagnostiques des différents néoplasmes neuroendocrines bronchiques (inspiré de la classification OMS 2021)

	CT	**CA**	**CNEGC**	**CPC**
Mitoses par 2mm²	<2	2-10	>10 (médiane : 70)	>10 (médiane : 80)
Nécrose	Non	Si oui, focale	Oui	Oui
Morphologie NE	Oui	Oui	Oui	Oui
Index Ki67	Jusqu'à 5%	Jusqu'à 30%	30-100%	30-100%
Expression TTF1	Positive dans la plupart des tumeurs périphériques, négatif dans la plupart des tumeurs centrales	Positive dans la plupart des tumeurs périphériques, négatif dans la plupart des tumeurs centrales	Positive (70%)	Positive (85%)
Expression p40	Négative	Négative	Négative	Négative
Variant combiné avec CBNPC	Non	Non	Jusqu'à 25% des CNEGC réséqués	Jusqu'à 25% des CPC réséqués

Avertissement et remarques générales :

Hormis les CPC, les néoplasies neuroendocrines (NNE) sont des tumeurs rares, de diagnostic difficile sur de petites biopsies, donnant lieu à des séries publiées de petite taille, souvent rétrospectives, avec un faible niveau de preuve scientifique. Plusieurs études de la littérature n'ont plus de valeur aujourd'hui en raison de critères histologiques différents, regroupant CNEGC et carcinoïdes atypiques ou bien mélangeant les CNEGC et les carcinomes indifférenciés à grandes cellules. Nous avons essayé de privilégier autant que possible les études prospectives lorsqu'elles existent et les études rétrospectives de grande taille.

LES CANCERS BRONCHIQUES A PETITES CELLULES

Les carcinomes bronchiques à petites cellules font l'objet d'un référentiel spécifique et ne seront donc pas traités ici (➔ référentiel Cancers Bronchiques à Petites Cellules).

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