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 vient d'être réactualisée en 2015 (1) (**Figure 1**).

Types et sous types-histologiques	**Code ICDO**
TUMEURS EPITHELIALES	
Adénocarcinome	8140/3
[…]	
Carcinome malpighien (ou épidermoïde)	8070/3
[…]	
Tumeurs 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
Tumeurs carcinoïdes	
Tumeur carcinoïde typique	8240/3
Tumeur carcinoïde atypique	8249/3
Lésion pré-invasive	
Hyperplasie neuroendocrine diffuse pulmonaire Idiopathique	8040/0
Carcinome à grandes cellules	8012/3
Carcinomes adénosquameux	8560/3
Carcinomes sarcomatoïdes	
[…]	
Autres carcinomes et carcinomes inclassés	
[…]	
Tumeurs de type glandes salivaires	
[…]	
Papillomes	
[…]	
Adénomes	
[…]	
Tumeurs mésenchymateuses	
[…]	
Tumeurs lymphohistiocytiques	
[…]	
Tumeurs d'origine ectopique	
[…]	

Figure 1 – **Classification histologique des tumeurs pulmonaires de 2015 (extraits focalisés sur les tumeurs neuroendocrines ; la classification complète figure en ANNEXE 2 du référentiel CBNPC)** (2)**.**

Parmi ces types de tumeurs bronchiques, 4 grands types histologiques représentent à eux seuls 95% de la totalité de ces tumeurs :

- les carcinomes épidermoïdes, les adénocarcinomes, les carcinomes indifférenciés à grandes cellules (classés en carcinomes non à petites cellules),
- et les carcinomes à petites cellules.

Au sein de ces types histologiques se distinguent **les tumeurs neuroendocrines bronchiques**. Cette catégorie de tumeurs est particulière et répond à des critères morphologiques, immuno-histochimiques et moléculaires distincts. **Il s'agit de tumeurs épithéliales qui expriment une différenciation neuroendocrine, pour lesquelles la classification a été réactualisée en 2015.**

Ces tumeurs classées **au sein des différentes catégories morphologiques de tumeurs épithéliales bronchiques** de la classification de l'Organisation Mondiale de la Santé, répondent à des critères très précis, qui ont conduit les anatomopathologistes à en distinguer **4 grands types** :

- **les carcinomes bronchiques primitifs à petites cellules (CBPC)**
- **les carcinomes bronchiques primitifs neuroendocrines à grandes cellules (CNEGC)**
- **les tumeurs carcinoïdes typiques (CT) et atypiques (CA)**

Les critères reconnus actuellement pour le diagnostic de ces tumeurs sont ceux de Travis *et al*.(1), non modifiés dans la classification WHO 2015 :

- **Tumeur carcinoïde typique** : tumeur à morphologie carcinoïde avec moins de 2 mitoses par 2 mm^2 (10 HPF), pas de nécrose, et mesurant au moins 0,5 cm.
- **Tumeur carcinoïde atypique** : tumeur à morphologie carcinoïde avec 2 à 10 mitoses par 2 mm^2 (10 HPF) et/ou nécrose (souvent punctiforme).
- **Carcinome neuroendocrine à grandes cellules** :
    - Architecture neuroendocrine : nids, travées, rosettes, palissades
    - Index mitotique élevé : ≥ 11 mitoses par 2 mm2 (10 HPF), moyenne de 70 par 2 mm^2 (10 HPF)
    - Nécrose (souvent de larges zones)
    - Cellules tumorales larges avec cytoplasme modéré à abondant
    - Nucléole fréquent
    - Un ou plusieurs marqueurs neuroendocrines positifs en immunohistochimie chromogranine, synaptophysine et CD56. Un marqueur est suffisant si > 50% cellules tumorales
    - Variant combiné : avec un autre carcinome non CBPC
- **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 : ≥ 10 mitoses par 2 mm^2 (10 HPF), moyenne de 80 par 2 mm^2 (10 HPF)
    - 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 + (10% cas négatifs). TTF1 + dans 90% des cas
- Il existe donc trois grades de prolifération tumorale de malignité croissante distinguant les carcinoïdes typiques, les atypiques et les tumeurs de haut grade de malignité regroupant les carcinomes à petites cellules et les carcinomes neuroendocrines à grandes cellules (3,4).

Remarques :

1- **La détermination du Ki67** est utilisée dans la classification OMS 2019 des tumeurs neuroendocrines (TNE) digestives, mais ne l'est pas en cancérologie thoracique. Elle peut être utile pour aider à déterminer l'agressivité d'une tumeur (5,6). En effet, le taux de Ki67 sera plus élevé pour le CBPC et le CNEGC alors qu'il sera bas pour les tumeurs carcinoïdes. Il est donc utile pour différencier le groupe des tumeurs de « haut grade » (CBPC et CNEGC) des tumeurs de « bas grade » (tumeurs carcinoïdes) (1). Cela est confirmé par une étude récente de tumeurs neuroendocrines bronchiques de tout grade avec un *cut-off* de 20% de Ki67 pour différencier les tumeurs neuroendocrines de bas de grade et de haut grade (7).

2- **La recherche de *MGMT*** (méthyl-guanine methyl transférase) en immuno-histochimie sur la tumeur pourrait aider à la détermination de la stratégie thérapeutique dans l'avenir (la surexpression est un facteur de moindre réponse aux alkylants en cancérologie neurologique). L'analyse de la méthylation du gène semblerait plus pertinente dans les TNE digestives (la méthylation de MGMT pourrait être un facteur prédictif de réponse aux alkylants) (8).
Une étude de type PHRC incluant les tumeurs carcinoïdes bronchiques est en cours actuellement sur la France (MGMT NET) pour confirmer ou non l'intérêt de la méthylation de MGMT dans la prédiction à la réponse des alkylants (NCT03217097).

3-Dans quelques études**, le profil génomique** des tumeurs neuroendocrines et leurs anomalies commencent à être analysés(9–11). Le profil moléculaire des CBPC et CNEGC semble proche. Les anomalies moléculaires sont plus fréquentes et plus hétérogènes pour les tumeurs neuroendocrines de haut grade que dans les tumeurs carcinoïdes (*PIK3CA*, *EGFR*, *KRAS*, *ALK* et *RET*, *TP53* et *RB1*).
Concernant **l'expression de PD-L1,** une étude de 227 patients porteurs d'une TNE pulmonaire retrouve une expression de 10,4% des CNEGC, 5,8% des CBPC, et aucune expression des tumeurs carcinoïdes (11) avec un *cut-off* de 1%. Deux autres études centrées, dont celle du GFPC (13), sur les TNE de haut grade et particulièrement les CNEGC retrouvent environ 10% d'expression PD-L1 (14).

LES CANCERS BRONCHIQUES PRIMITIFS A PETITES CELLULES

Les carcinomes bronchiques primitifs 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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