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ORIGINAL ARTICLE

# Histological Diagnosis and Frequency of Primary Endocrine Tumors (ETs) and Neuroendocrine Tumors (NETs) According to WHO Classification

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**The new WHO classification provides the foundation for tumor diagnosis, patient treatment and tools for clinico-epidemiological research. This study was conducted to determine the frequency and update the histological aspects of different endocrine and neuroendocrine tumors for clinical significance and to minimize unclassified lesions.**

**Materials and Methods: Five hundred biopsies were analyzed in the Pathology Department of King Edward Medical University from 1st June 2004 to 31st December 2005. Tumors were diagnosed with light microscopy using the new WHO classification.**

**Results: Following 500 biopsies, 145 (29%) Endocrine(ET) and Neuroendocrine Tumors (NET) were found; majority of the former, ET, n=112 (77.2%), were in the thyroid, of which 84 (75%) were follicular adenomas and 28 (25%) were carcinomas, of the 28 carcinomas, the frequencies were: papillary carcinoma (PC) 21 (75%); anaplastic(AC) 4 (14.28%); follicular(FC) 2 (7.14%); and medullary (MC) 1 (3.57%). Of the 145, 33 (22.8%) were neuroendocrine tumors (NET), with the following types and frequencies: adrenal 13 (39.5%); pituitary 10 (30.5%); pancreatic 4 (12%); parathyroid 3(9%); appendix 1 (3%); and rectum 1 (3%). One NET detected in the thyroid region was a well-differentiated neuroendocrine carcinoma (WDNEC). Among adrenal NETs, of 13 only 2 (14.4%) were malignant and diagnosed as a cortical and a neuroblastoma respectively, while all others were benign NETS, as follows: cortical adenoma 2 (15.38%); pheochromocytoma 7 (53.8%) and 1 (7.69%) ganglio neuroblastoma, and ganglioneuroma each respectively. All pituitary, parathyroid and pancreatic NETS were benign in nature. NETS of the appendix and rectum were WDNETS, while that of the lung was a WDNEC.**

**Findings of this study confirm that the WHO classification provides uniform, simple, reproducible and practical criteria for diagnosis of ETs and NETS.**

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## Introduction

Endocrine cancer is a rare malignancy worldwide (1.5% in males and 3.5% in females), including Pakistan (1.2% in males and 2.0% in females). The most commonly affected endocrine organ is the thyroid gland representing 80-92% of all endocrine malignancies (0.8% in males and 1.8% in females in Pakistan and 1.0% in males and 3.3% in females worldwide)[1,2]. Although thyroid no-

dules are relatively common, being present in 4-7% of the adult population, less than 1% of all thyroid nodules are malignant.[3-7]

Human thyroid neoplasia represents a variety of lesions starting from well-differentiated benign tumors to anaplastic malignant cancers. According to the simplified classification of primary thyroid tumors, modified from the World Health Organization (WHO) classification in 2001, histologically malignant tumors are divided into two groups, nonmedullary and medullary thyroid cancer of hereditary or nonhereditary origin. Nonmedullary thyroid cancers include papillary cancer, follicular carcinoma, poorly differentiated and anaplastic cancer.[8,9]

Before the new WHO classification, the tumors of the disseminated endocrine system were referred to as" carcinoids.[10] This term was used for the first time in 1907 by Oberndorfer, for those epithelial tumors with a relatively monotonous structure and less aggressive behavior than carcinomas.[11] Neuroendocrine and endocrine tumors of the gasterointestinopancreatic system were classified by WHO in 2000; a distinction was made between well-differentiated endocrine tumors, which show benign behavior or uncertain malignant potential, well-differentiated endocrine carcinomas characterized by less aggressive malignant behavior, and poorly differentiated endocrine carcinomas of high-grade malignancy.[12,13,14] This system of classification has so many pitfalls that the reproducibility of this grading system and its prognostic importance are in question.[15]

A number of clinicopathologic criteria for the endocrine tumors have proven to be useful predictors of their malignant behavior; these include site of origin, tumor type, tumor size, invasion of nearby tissue or deep wall invasion, angioinvasion and invasion of perineural spaces, presence of spotty necrosis, overt cellular atypia, more than two mitoses in 10 HPFs, Ki-67 index of more than 100/10 HPFs, or more than 2% loss of chromogranin A immunoreactivity and nuclear p53 accumulation. The predictive value of these criteria needs further research and still remains to be proven for tumors, other than those of the pancreas and stomach.[16-18]

Adrenal tumors arise from the cortex (adenoma and carcinoma), and medulla (pheochromocytoma and neuroblastoma, ganglioneuroma and ganglioneuroblastoma). Adrenal carcinoma and neuroblastoma are malignant tumors which invade nearby tissues and metastize. Pheochromocytoma, ganglioneuroma and adrenal cortical adenoma are benign tumors with no metastasis or local tissue invasion, while ganglioneuroblastomas exhibit an intermediate degree of differentiation neuroblastomas and ganglioneuromas.[1,19-21]

Among adrenal gland tumors, the most common is the pheochromocytoma, popularly referred to as the "ten percent tumor" because they do many things about ten percent of the time.[22,23] Adrenocortical carcinoma is a rare tumor originating from the adrenal cortex, with an estimated annual incidence of 0.5% to 2% per 1 million patients.[24]

Parathyroid carcinoma is a rare tumor that is responsible for <1% cases of hyperparathyroidism in most parts of the world. Most patients with carcinomas present with marked hypercalcemia and are more likely to have associated bone and renal disease than those with adenomas.[25]

Endocrine pancreatic tumors are uncommon tumors occurring in approximately 1 in 100,000 of the population, representing 1-2% of all pancreatic neoplasms.[26,27]

Although rare, insulinomas are the most common functioning islet cell tumour of the pancreas. Recognition of the key neuroglycopenic symptoms should trigger the initial investigation, and biochemical proof of endogenous hyperinsulinemic hypoglycemia establishes the diagnosis. The tumours are usually small, single, benign, well-circumscribed, and evenly distributed throughout the pancreas; it may be a part of the multiple endocrine neoplasia type 1 (MEN-1) syndrome, in which case the tumours are almost always multiple.[28]

Pituitary tumors represent 10% to 25% of all intracranial neoplasms in adults but are rare in children. Based on biological behavior, these are divided into three groups, i.e., benign adenomas (17%), invasive adenomas (35%), and carcinomas (01-0.2%).[29-34]

This study was conducted to determine the frequency and the histological aspects of different ETs and NETs for clinical significance and to help establish diagnosis of unclassified lesions.

## Materials and Methods

This was a descriptive cross sectional study, conducted at the Department of Pathology, King Edward Medical University, Lahore, in collaboration with the four major surgical units and two Ear Nose and Throat (ENT) units of Mayo Hospital, Lahore, Pakistan. All samples, submitted and documented between 1st June 2004 and 31st Dec 2005 to the Department of Pathology, King Edward Medical University, Lahore were included in this study. Hematoxylin and eosin stained sections were diagnosed by two expert histopathologists.

The relevant scans and laboratory investigations of the patients were correlated in this study, and written consent was obtained from all patients for ethical reasons.

### Histological criteria for ETs and NETs

The histologic features of vascular space invasion and capsular penetration as criteria for distinguishing follicular adenoma thyroid from minimally invasive carcinoma noted by Graham were used regarding thyroid neoplasms. The gold standard for diagnosis of papillary thyroid carcinoma was conventional histology, the essential element being the characteristic ground glass nuclear features, regardless of whether papillary structures were present or not.[1]

### Criteria of malignancy for NETs

NETs are classified on the basis of light microscopy only, which provides a potential widespread and worldwide application of this classification system accepted by WHO.

According to WHO criteria, these tumors are divided into three main categories. All the tumors with benign morphology, no invasion, small size (<2 cm) and low proliferarive index (Ki-67 with <2%), and no or spare (<2.10 hpf) mitosis were diagnosed as Well Differentiated Neuroendocrine Tumors (WDNET); tumors showing malignant features but no pleomorphism and with moderate increase in proliferative index (proliferation index, >2% but <15%), mitosis rare (>2 but <10.10 hpf) as Well Differentiated Neuroendocrine Carcinoma (WDNEC), while tumors with pleomorphism, necrosis, brisk mitotic (10.10 hpf) activity and with high proliferative index (>25%) were categorized as Poorly Differentiated Neuroendocrine Carcinoma (PDNEC) either with small cell or large cell morphology.[35] Malignant NETS were confirmed on Chromogranin A and their behaviour was confirmed by Ki-67.

### Data analysis and statistics

Data, obtained through specially designed proforma, was analyzed using SPSS; mean age and standard deviation was calculated. The statistical analysis involved calculation of the percentage of tumors for each group and comparisons.

## Results

Five hundred samples were collected to assess the clinical presentation, morphological diagnosis and frequency of primary endocrine and neuroendocrine tumors, of which only 145 (29%) cases revealed different types of endocrine tumors (ETs) (n=112, 77.25%) or neuroendocrine tumors (NETs) (n=33, 22.75%); most of the tumors, 113 (78%) were benign. Of the 145 cases, all tumors were more common in females 101 (69.6%) as compared to males 44 (30.4%). Male to female ratio was 1:1.58; age range was 12-82 years, with a mean age of 48.54±12.23 years (Fig.1).

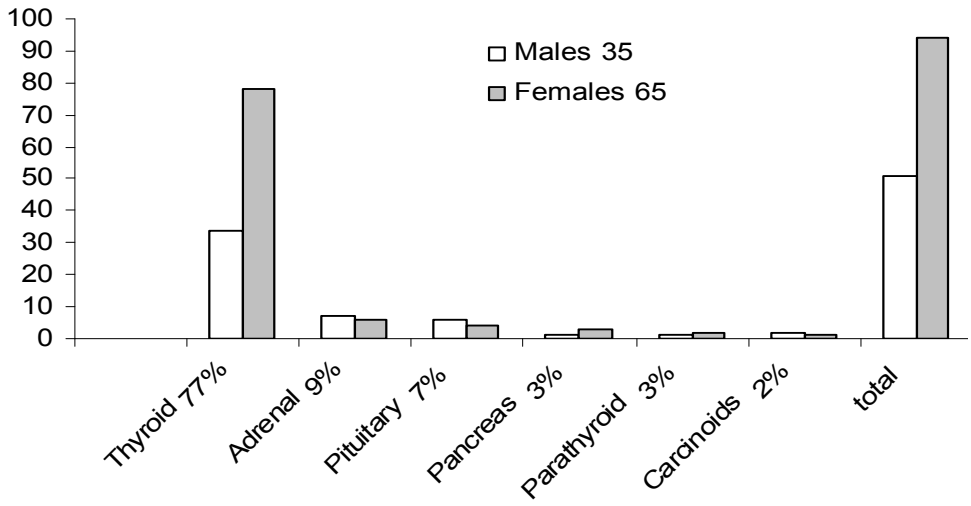


**Fig.1 Sex Distribution of Endocrine and Neuroendocrine Tumors**

The overall frequency of endocrine and neuroendocrine tumors in the thyroid was 112 (77.25%); 33(23.15%) were seen in other organs, of the thirty-three 13 (39.5%) were in the adrenal glands; 10 (30.5%) were in the pituitary gland, 4 (12%) in the pancreas, 3 (9%) in the parathyroid 1 (3%) in the appendix, 1 (3%) in the rectum, and 1 (3%) in the lung (Table 1).

**Table 1. Types of endocrine and neuroendocrine tumors in glands other than the thyroid**

| Tumors (n=33) | Numbers | Total | (%) |
|---|---|---|---|
| Adrenal | 13 | 13 | 39.5 |
| Pituitary (Adenomas) | 10 | 23 | 30.5 |
| Pancreas (Inslinomas) | 4 | 27 | 12 |
| Parathyroid (Adenomas) | 3 | 30 | 9 |
| Appendix (well differentiated neuroendocrine tumors = carcinoid) | 1 | 31 | 3 |
| Rectum (Well differentiated neuroendocrine tumor) | 1 | 32 | 3 |
| Lung (Well differentiated neuroendocrine carcinoma =atypical carcinoid) | 1 | 33 | 3 |

Most of the patients with thyroid neoplasms presented with solitary cold nodules, while some presented with multinodular goiters and thyroid cysts. Eighty-four of these thyroid neoplasms were follicular adenomas and 28 were carcinomas. Details of thyroid tumors, (Table 1 and Figures 2 & 3), placed in the classification of NETs, was diagnosed as well differentiated neuroendocrine carcinoma (MC).

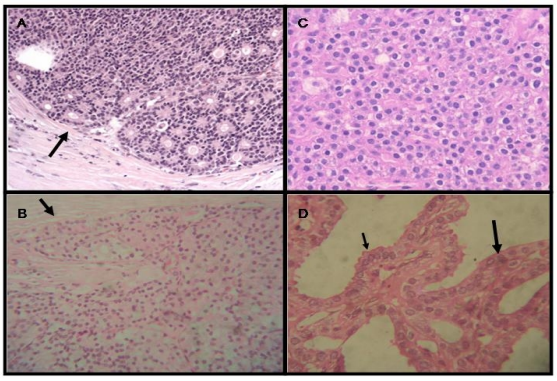


**Fig. 2. Photomicrograph (H &E 40x) of thyroid follicular adenoma (A), Arrow showing no invasion of capsule, B; Follicular carcinoma (H & E 40x) with capsular invasion (arrow), C; Parathyroid adenoma with homogenous proliferation of cells with uniform nuclei, D. of Papillary carcinoma thyroid (H & E 40x), showing papillary processes, overlapping of cell with clear pale staining nuclei having intranuclear inclusions and groove (arrows).**

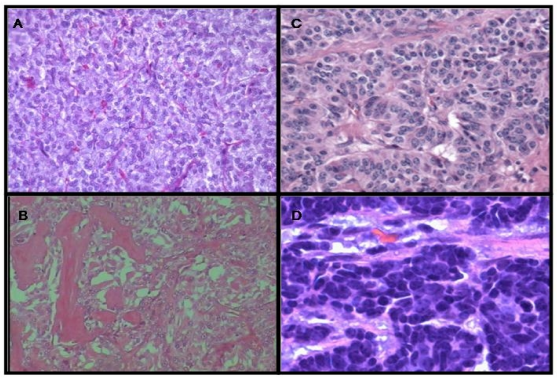


**Fig. 3. Photomicrograph (H&E 40x) of Pheochromocytoma (A), B; Medullary carcinoma with amyloid deposits (H&E 40x), C; Well differentiated (carcinoid). Neuroendocrine tumors of appendix (H&E 40x) with uniform nuclei, <2.10hpf mitosis. Well differentiated (atypical carcinoid) neuroendocrine carcinoma lung (H&E 40x) with pleomorphism and mitosis >2 but <10.10hpf and focal necrosis.**

Patients with adrenal benign tumors, presented with an abdominal mass; most of them were young and in their teens with no significant sex difference. Patients with pheochromocytoma presented with a history of hypertension, recurring episodes of sweating, headache, and a feeling of anxiety (Table 3). In the adrenal cortex, 2 cases were WDNEC (cortical carcinoma and neuroblastoma), while the remaining were WDNETs. These tumors were strongly positive for Chromogranin A.

Pituitary neuroendocrine tumors were benign (WDNETs) and only very few were symptomatic, no local invasion being seen. Functional criteria were also used to define tumors in terms of their endocrine activity. Prolactinomas were the most common pituitary adenoma accounting for 50% of all the pituitary neoplasms, followed by the adrenocorticotropic hormone (ACTH) secreting adenoma and growth hormone (GH) adenomas, each representing 10% of the cases. In addition there were 30% cases of non functioning adenomas (Table 2).

**Table 2. Types of thyroid neoplasms according to WHO histopathological criteria**

| Thyroid Tumors | Gender M:F=1:1.54 | | Total number | Percentage |
|---|---|---|---|---|
| | M 34.112 (30.35) | F 78.112 (69.65) | | |
| Adenomas (follicular adenoma) | 23 (27.3)* | 61 (72.7) | 84 | 75 |
| Thyroid carcinoma | 11.28 (39.2) | 17.28 (59.8) | 28 | 25 |
| Papillary carcinoma | 7 (33.3) | 14 (66.7) | 21 | 75 |
| Anaplastic carcinoma | 2 (50) | 02 (50) | 04 | 14.28 |
| Follicular carcinoma | 1 (50) | 01 (50) | 02 | 7.14 |
| Medullary carcinoma | 1 (100) | 0 | 01 | 3.57 |

Note: The frequency of endocrine tumors was 112 (77.25%) and was found most the in thyroid. According to WHO classification medullary carcinoma was included in neuroendocrine tumors.* Numbers in paranthesis denote percent

**Table 3. Type of adrenal tumors according to WHO histopathological criteria**

| Adrenal Tumors (n=13) | Gender M:F=1:1.1 | | Total Number |
|---|---|---|---|
| | M | F | |
| Cortical adenoma | 01 | 01 | 02 |
| Cortical carcinoma | 01 | 0 | 01 |
| Pheochromocytoma | 03 | 04 | 07 |
| Neuroblastoma | 01 | 0 | 01 |
| Ganglioneuroblastoma | 0 | 01 | 01 |
| Ganglioneuroma | 01 | 0 | 01 |
| Total | 07 | 06 | 13 |

All pancreatic nueroendocrine tumors were also well differentiated neuroendocrine tumors (benign insulinomas). They presented with an abdominal mass, fasting hypoglycemic attacks with low fasting blood sugar levels (≤50mg/dL (Fig. 1).

Carcinoid tumors of the appendix, rectum and lungs were well differtiated NETs and well differentiated NECs respectively, based on WHO criteria classification, one case each was found in the rectum, appendix and lung. Tumors from the appendix and rectum were asymptomatic and benign. Whereas carcinoid of the lung was histologically aggressive, there were no metastases and this was classified as a WDNEC (atypical carcinoids). Ki-67 in appendiceal and rectal WDNET was less than 5% and 8% respectively and 15% in lung WDNEC.

Only three (age range 20-30 years) cases of parathyroid adenomas were diagnosed, of which one patient had a history of renal stones while the other two were symptomless; however all three patients were hypercalcaemic with a mean serum calcium level of 13.33±0.97 mg/dL (Fig. 1).

## Discussion

Endocrine and neuroendocrine tumors are relatively uncommon, but they represent an important group of potentially treatable cancers. The frequency of endocrine tumors in our study is 29%, which because of a lack of information regarding the overall incidence of endocrine tumors cannot be compared to those of other geographical areas; our frequency is one of a unicentric study and could be different from other cohort or national studies.

The demographic characteristics of our patients with endocrine cancers are comparable to those documented in western literature; however the clinical presentation is somewhat different and more aggressive than the

data mentioned. The morphological features in our patients of differentiated endocrine cancer are almost the same as discussed in worldwide literature and have been reported previously from several studies.[2,36-40]

Thyroid carcinoma is the most common form of endocrine cancers described in world literature, accounting for ~1% of all new malignant diseases (~0.5% of cancers in men and ~1.5% of cancers in women).[41]

In our study, most of the endocrine and neuroendocrine tumors were found in the thyroid, while the frequency of these tumors in other places was low. As compared to malignant ones, more benign tumors of the thyroid were seen. The most common malignant thyroid tumors were papillary carcinoma (PC), anaplastic carcinoma (AC), follicular carcinomas (FC) and medullary carcinoma (MC) in descending order. MC of the thyroid was placed in NET and was diagnosed as Well Differentiated Neuroendocrine Carcinoma (WDNEC).

The male to female ratio for endocrine tumors in our study was 1:1.58 while the ratio for thyroid tumors was 1:2, showing a female predominance, similar to results of other national and international studies In a study, conducted in Pakistan, by Shah et al,[2] a total of 8541 malignant tumors were diagnosed over a period of 3 years, including 103 (1.2%) cases of thyroid cancer. Papillary carcinoma (69%) was the most common histological type of thyroid tumor, followed by FC (11.6%), MC (9.7%), AC (5.9%), non-Hodgkin`s lymphoma (2.9%) and unclassified tumors (0.9%) in order of frequency; PC was the most common histological variant of thyroid cancer found in our study, in both sexes. It was more prevalent in the third, fourth and fifth decades of life, while follicular and AC were more frequent after the fourth decade of life. The age incidence seems to be decreasing regarding thyroid cancers. Age, sex and clinical presentations are similar to previous studies from Pakistan. The frequency of PC is high in our data (75%) followed by AC (14.28%); this could be due to a rise in the incidence of PC or clinicopathological findings or attributed to histological reclassification. No case in our study was associated with multiple endocrine neoplasms, which could be due to our limited data from a unicentric study or could be due to the low occurrence of this disorder in Pakistan.

AC of the thyroid, the most aggressive solid tumor known,[42] constituted 14.28% of all thyroid carcinoma cases in this study. In contrast to previous studies, the incidence of AC was higher. This could again be due to unicentral information and could be reinvestigated on a larger scale in the future; however these findings are consistent with those of Agrawal et al.[43]

In our study, the incidences was 7.14% for FC and 3.51% for medullary carcinoma. The findings are not consistent with the results of Shah et al,[2] Bhurgri et al[36] and Werk et al.[5]

The second most common NETs, in our study were those of the adrenal gland (9%). Pheochromocytoma led in this group (53.84%), its frequency and other characteristics are similar to those reported in earlier studies by Kimura et al.[23] All these tumors were reclassified as WDNETs. Two tumors were malignant in adrenal samples, one was cortical carcinoma and other was neuroblastoma, the tumors being reclassified as WDNEC.

Although in worldwide literature, pituitary tumors are very common but in our study the frequency was very low (6.9%), which could be due to calculation of its frequency from an endocrine group in contrast to others who compared them with intracranial tumors.[29] We found them to be the third most common endocrine neoplasms. The clinical presentation of our patients is not as aggressive as that reported in literature, but in our patients morphological features are comparable to previous reports by Singh et al and Ezzat et al.[32,44] We suggest that all these tumors should be classified, based on WHO criteria, for ET and NET, the entire benign tumor

should be named WDNET and malignant pituitary tumors should be classified as WDNEC and PDNEC.

Only three parathyroid adenomas were detected in our study, of which one presented with renal stones while the other two were symptomless, however all the three patients, age range 20-30 years, were hypercalcaemic with a mean serum calcium level of 13.33±0.97 mg/dl. In our study, the frequency, clinical and morphological presentation of parathyroid tumors is the same as that described in previous literature, however ours is higher compared to the results of the DeLellis study.[25]

Endocrine tumors of the pancreas represent 1% to 2% of all pancreatic neoplasms. The tumors tend to have an indolent behavior, and long-term survival is common. There is no gender or age predilection. Patients can present with symptoms due to hormonal overproduction. These tumors were rare in our study, comprising 2.7%, findings consistent with those of Oberg et al,[26] but higher than those of another study.[45] All the pancreatic NETs were classified as WDNETs and all these were previously diagnosed as insulinoma; in our study these were not associated with any syndrome as has been described in previous literature. This could be due to the low number of registered cases given coverage at our center.

Carcinoids were also classified on basis of criteria mentioned, like all other NETs, named as WDNET in the appendix and rectum, and as WDNEC (atypical carcinoid) in lung. In the new WHO classification for lung tumors, atypical carcinoid has also been accepted, whereas for tubular and other NET, the terms carcinoid, atypical carcinoid, malignant carcinoid or metastatic carcinoids are no longer used.[35] The frequency and features of these NET neoplasms were also comparable with those documented worldwide; however the lung neuroendocrine carcinoma observed in our study, was histologically more aggressive, while others were well differentiated NETs.

Malignant NETS were confirmed on Chromogranin A and their behaviour was confirmed by Ki-67. Ki-67 in appendiceal and rectal WDNET was lower than lung WDNEC, findings consistent with those of Jirasek[16] and Aslan et al.[46]

**Critical review of WHO classification**

Poorly differentiated thyroid carcinoma (PDTC), the insular variant, is now recognized by most anatomical pathologists as a separate entity and accepted in revised WHO classification; we suggest that the entity, showing insular, solid, squamous differentiation, evidence of mucin or combination of these features or occupying a position which is intermediate between well differentiated PC, FC and MC and undifferentiated (atypical) carcinomas should be proposed as PDTC. For further classification help may be taken from its immunohistochemistry; we also suggest that the spindle cell variant of papillary carcinoma with focal spindle and giant cell carcinoma components, be placed in PDTC, and its clinical behavior should be investigated. In our opinion, hurthle cell tumors should be kept in separate group as in the previous classification. MC is a variant of neuroendocrine carcinoma and should be classified according to the neuroendocrine carcinoma of lung or GIT into well differentiated neuroendocrine carcinoma and poorly differentiated neuroendocrine carcinoma. Recently, a new classification of NETs has been proposed and adopted by the World Health Organization (WHO). In order to explain the natural history of NETs more adequately, this classification is based on a series of histopathological and biological behaviour, cellular grading, primary size of the tumor and site, proliferation markers, local or vascular invasion, and the production of hormones. The main categories of tumour are well differentiated endocrine tumours, well differentiated endocrine carcinomas and poorly differentiated endocrine carcinomas. This classification facilitates easy diagnosis of neuroendocrine tumours in the gastroenteropancreatic

tract, but unfortunately is not applicable for lung tumours. Recent terminology used in the new classification has caused some confusion in the routine application and interpretation of some NETs, especially those of intermediate grade (which underwent major changes in the new classification). New diagnostic criteria pose some difficulties for the histopathologist (e.g. correct diagnosis on small biopsy fine needle aspirate cytology), use of Ki-67 and also to the clinician (choice of the appropriate therapy for single histological types. Finally, apart from pure endocrine tumors, NE differentiation occurs also in non-endocrine tumors in different organs, which the recent classification does not facilitate.

WHO classification was applied for all NET and ET to facilitate uniform for diagnosis and to remove the pitfalls of previous reporting systems for these tumors, and help in the proper management of the patients and to assess their prognosis. In spite of its shortcomings and pitfalls, the WHO classification of ETs and NETs has provided a uniform platform for the diagnosis of these tumors to assess their prognosis and to check the predictive value of their treatment.

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