Alma Mater Studiorum – Università di Bologna

DOTTORATO DI RICERCA IN

SCIENZE CARDIO-NEFRO-TORACICHE

Ciclo XXXIII

Settore Concorsuale: 06/E1

Settore Scientifico Disciplinare: MED/21

PROGNOSTIC SIGNIFICANCE OF PULMONARY MULTIFOCAL NEUROENDOCRINE PROLIFERATION WITH TYPICAL CARCINOID

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Esame finale anno 2020

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1. INTRODUCTION

1.1 NEUROENDOCRINE TUMORS OF THE LUNG

Neuroendocrine tumors (NET) of the lung represent a distinctive family of lung tumors with shared characteristics. The four major categories of NET of the lung are small cell lung carcinoma (SCLC), large cell neuroendocrine carcinoma (LCNEC), typical carcinoid (TC) and atypical carcinoid (AC) [1]. While the first two are considered high-grade tumors, the last two are considered to be low and intermediate-grade malignant tumors respectively [2-4]. There is increasing evidence that TC and AC are morphologically associated more closely with each other than with LCNEC and SCLC. In fact, from a clinical standpoint, approximately 40% of patients with either AC or TC are non-smokers, while almost all patients affected by SCLC or LCNEC are heavy smokers. Moreover, unlike the high-grade lesions, both AC and TC can occur in 8% of patients with multiple neuroendocrine neoplasia type 1 (MEN 1) and show MEN 1 mutations in sporadic cases (40%) [5,6]. In addition, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH), with or without tumorlets, may be present in both typical and atypical carcinoids, for which it is considered a preneoplastic lesion, but is not a defined preneoplastic lesion for SCLC or LCNEC.

1.2 CARCINOID TUMORS OF THE LUNG

These are neuroendocrine epithelial malignancies, which can be divided in two categories: typical carcinoind (TC) with < 2 mitoses per $2mm^2$ with a diameter ≥ 0.5cm and lacking necrosis and atypical carcinoid (AC) with 2-10 mitoses per $2mm^2$ and/or foci of necrosis. These are relatively rare malignancies with an estimated age-adjusted incidence that ranges from <0.1 per 100.000 to 1.5 per 100.000, with TC accounting for 70-90% of cases. The incidence of carcinoid tumors is higher in Caucasian non-smokers females and aged <60 years old [7]. The mechanisms of

carcinoid tumors development and progression are not clear, although some cases are postulated to develop in the MEN1 setting; others are assumed to develop in the setting of DIPNECH and tumorlets [8]. Carcinoids are rarely associated with DIPNECH and may rarely produce a military pattern in the lung [9]. The cell of origin is unknown, although it was historically thought to arise from pulmonary neuroendocrine (Kluchitsky) cells. Carcinoid tumors of the lung most commonly arises in the central airways with peripheral forms accounting for 1/3 of cases and can be asymptomatic and incidentally detected. Most central carcinoids are found in mainstem or lobar bronchi, peripheral carcinoid tumors are more likely to be AC. Peripheral TC in particular may be associated with multiple tumorlets with or without DIPNECH. Clinical syndromes underlying a peptide production are uncommon and include carcinoid syndrome, acromegaly and Cushing syndrome. The classic VIII TNM staging system is applied to carcinoid tumors though lymphatic and distant haematogenous metastases are encountered more frequently with the AC form. Atypical carcinoid has a worse prognosis than TC with a 5-years survival rate that is approximately 90% for TC and 60% for AC [10,11]. Prognostic factors are considered also TNM stage and mitotic index. In resectable cases prognosis depends mostly on complete surgical resection.

1.3 PRE-INVASIVE NEUROENDOCRINE LESIONS OF THE LUNG

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) represents a generalized proliferation of pulmonary neuroendocrine cells (PNCs) that may be confined to the mucosa of airways (with or without luminal protrusion), may invade locally to form tumorlets, or may develop into carcinoid tumors (**Fig.1**) [1]. Indeed, tumorlets are defined as locally infiltrative (microinvasive) well differentiated pulmonary neuroendocrine micro-tumors measuring up to 0.5 cm and are considered potential precursor proliferations for TC and AC [1,12]. DIPNECH is often accompanied by mild chronic lymphocytic inflammation and fibrosis of the involved airways (in form of constrictive bronchiolitis). In fact, DIPNECH has been frequently associated with pulmonary fibrosis and bronchiectasis, suggesting that it may represent a hyperplastic response of

pulmonary neuroendocrine cells to airways impairment and hypoxia [13-19]. Cytokines and growth factors secreted by PNCs (such as bombesin, gastrin releasing peptide, and fibroblast growth factor), stimulate fibrosis and airway cell chemotaxis, which results in bronchiolar fibrosis and obstructive patters at pulmonary function tests [20]. In some cases, the presence of allergy-like symptoms has been reported from the patients for many years before diagnosis (pruritus, nasal congestion, lachrymation, asthma), probably as a consequence of the secretion of hormones and neuropeptides from pulmonary neuroendocrine cells of the so-called diffuse neuroendocrine system [21]. Moreover, DIPNECH can be diagnosed in two different clinical settings: the first, in symptomatic patients presenting with respiratory symptoms (dry cough, exertion dyspnea, and wheezing, often misdiagnosed as asthma) with a suspicious high resolution CT-scan, often evolving in progressive respiratory insufficiency; the latter, as an incidental finding at the histologic examination in asymptomatic patients after surgery for carcinoid tumors [21-24]. Pathological examination is the gold standard for the diagnosis, however when widespread PNCs proliferation is denoted in the non-neoplastic lung surrounding a TC but the diagnosis of DIPNECH is not certain, high-resolution CT may be useful, showing nodular bronchial wall thickening, mosaic attenuation caused by mucus plugging, airway obstruction, air trapping, and sometimes bronchiectasis [20]. DIPNECH probably arises in terminal bronchioles as a cluster of neuroendocrine cells; when tumorlets develop, invading the basal lamina, they extend through the bronchiolar wall. It is not known what proportion of DIPNECH patients eventually develop carcinoid tumors, but it is probably the minority. Most of tumors that develops in this context are TC, but occasional atypical carcinoids with more aggressive behavior have also been described.

1.4 MULTIFOCAL PULMONARY NEUROENDOCRINE PEOFLIFERATIONS

Synchronous multifocal microscopic pulmonary neuroendocrine proliferations (MNEP) represent a subgroup of diagnostic entities comprehending DIPNECH and well-differentiated pulmonary neuroendocrine micro-tumors (also known as tumorlets or micro-carcinoids) combining in different patterns [11,20,25-27] and possibly leading to the simultaneous formation of carcinoid tumors. As said, DIPNECH can show multifocal pulmonary neuroendocrine cell hyperplasia-to-neoplasia progression sequence characterized by multiple micro-neuroendocrine tumors (tumorlets) as well differentiated pulmonary neuroendocrine tumors [28,29], therefore it is considered a preinvasive lesion [1]. The multifocal combination of these complex, evolutive patterns defines MNEP (**Fig.1**). It should be emphasized that, in the setting of DIPNECH (and consequently MNEP), multiple carcinoid tumors should not be regarded as metastatic lesions, but as synchronous multiple primaries [22].

1.5 AIM OF THE STUDY

The biological significance of MNEP in association with well-differentiated pulmonary neuroendocrine tumors with low-grade proliferative features (TC), is still a matter of debate [13,30]. Therefore, MNEP has been reported in sporadic cases, and their incidence and prevalence remain to be established along with their clinic-pathological significance, yet not evaluated in large series. To address this knowledge gap, we analyzed the clinic-pathological features of a comprehensive series of surgically treated well-differentiated pulmonary neuroendocrine tumors. Aim of the study was to assess the prevalence of MNEP and to define the prognostic value of MNEP in patients who underwent pulmonary resection for TC. Meanwhile, the association between MNEP and the underlying chronic lung inflammatory disease and the potential role of inhalant exposure in our study population has been described.

2. PATIENTS AND METHODS

2.1 STUDY DESIGN

We have analyzed the institutional database from the *Thoracic Surgery Department, University of Perugia, Perugia, PG, Italy* (between Jan 1983 and Dec 2013) and the *Department of Thoracic Surgery, University Health Network, Toronto, ON, Canada* (between Jan 2000 to Dec 2013) including over 350 patients operated for well-differentiated pulmonary neuroendocrine tumors.

Patients with atypical carcinoid tumor, presence of synchronous or previous primary/metastatic tumor, biopsy or isolated bronchoplasty specimens with pulmonary neuroendocrine tumors, as well as lung transplants, patients with a follow-up period of less than 5 years and patients with neoadjuvant chemo/radiotherapy were excluded.

Standard diagnostic workup included chest-abdomen CT scan and fiberoptic bronchoscopy. 111In-pentetreotide scan (OctreoScan) was performed from 1996 and ^{18}FDG/PET-CT from 2004. We defined central lesions those located in segmental or larger bronchus and peripheral tumors those involved with the subsegmental bronchus or beyond. Preoperative histologic diagnosis was achieved by bronchial biopsy in centrally-located lesions and by fine needle aspiration biopsy or by video-assisted wedge resection in peripheral lesions. Mediastinoscopy or endobronchial ultrasound (EBUS) were carried out in patients with CT scan finding of mediastinal node enlargement or in those glucose avid at 18FDG/PET-CT. Endobronchial debridment in rigid bronchoscopy was performed pre-operatively to assess tumor location and treat obstructive pneumonia in selected cases. Surgery consisted of sub-lobar, lobar, bronchial sleeve lobectomy and pneumonectomy. Nodal sampling was usually performed during sub-lobar resections, while systematic or lobe-specific lymphadenectomy were carried out along with major resections.

NE differentiation was assessed on the basis of morphology and immunohistochemical reactivity for panneuroendocrine markers Neuron Specific Enolase (NSE), Chromogranin A,

Synaptophysin. In each case, the presence of necrosis, number of mitoses, and Ki-67 index were evaluated. Multiple forms and tumorlets were carefully researched by performing serial sections of lung parenchyma.

Staging was established according to the 8th edition of the AJCC TNM staging system.

The follow-up protocol included clinical interview with physical examination, chromogranine A measurements, chest-abdomen CT scan at 6 months, 1 year and 2 years after surgery. Then annual chest X-ray, abdomen ultrasonography and biochemistry profile were performed; chest-abdomen CT scan was indicated every 2 years for at least 15 years. Fiberoptic bronchoscopy was performed yearly for the first 2 years and then every 3 years for patients with central tumors and every 5 years for peripheral TC.

Parameters related to patient's demographics (age at the time of surgery, gender) and clinical history (smoking history, body mass index, gastro-esophageal reflux disease, chronic obstructive pulmonary disease, Charlson co-morbity index, occupational exposure to inhalants gas, dust or fumes, respiratory symptoms related to asthma or bronchitis) were collected. Theragnostic considered imaging details (tumor location, absence or presence of synchronous micronodules on the preoperative chest CT); the type of surgical procedure (sub-lobar, lobar, bronchial sleeve lobectomy and pneumonectomy); the type of lymphadenectomy (systematic, lobe-specific, sampling and no lymphadenectomy); along with histopathological data (tumor size, nodal status, tumor stage, status of non-tumorous lung parenchyma by analysis of chronic inflammation, fibrosis, emphysema and bronchiolitis) were considered.

The OS was calculated from the date of surgery to the last date of follow-up (for alive patients) or the date of death. The PFS was calculated from the date of surgery to the date of recurrence.

A total of 234 patients affected by primary lung TC were enrolled; among these 41 (17.52%) had MNEP along with single TC (MNEP+TC) and 193 had only TC. The two groups were compared.

Given the heterogeneity of a number of baseline variables between groups, a 1:1 propensity score matching was used to compare the long-term survival data between TC and MNEP+TC. Age at time of diagnosis, tumor stage, smoking history, location, follow-up time, patients' clinical management site (Toronto vs Perugia), side and size of the primary tumor were entered as independent variables in the logistic regression model. The study design is displayed in **Figure 2**.

2.2 STATISTICAL ANALYSIS

Unmatched Data

Data on categorical variables were reported as frequencies and percentages. Continuous variables were described as means +/- standard deviations, along with median values. Summary statistics are reported on the whole cohort and also on patients with or without hyperplasia individually. Statistical significance was reported using Chi-square test for categorical variables and student's t-test for continuous data. Kaplan-Meier method was used to estimate the probability of OS and PFR, and log-rank test was used to report significance between groups. Cox regression model was used to identify significant independent predictors of the OS. The statistical significance level was chosen at a *p* value of 0.05 or less. SAS v9.3 (SAS Institute, Cary NC, USA) or R version 3.3.3 (R Core Team,2013; R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria, EU; URL http://www.R-project.org/) was used for statistical analysis.

Matched Data

Among the 41 patients in the MNEP+TC group, 36 patients could be matched with TC group. This resulted in 36 matched pairs for the comparison of patients with MNEP+TC and TC. Patients then were matched on the logit of the propensity score using a caliper of 0.2 standard deviations of the logit of the propensity score. The percentage of GMATCH propensity score macro developed by the Division of Biostatistics at the Mayo Clinic was used for propensity score matching [31].

To assess the balance between matched samples, standardized differences were calculated and used in this report [32]. Some authors have suggested that standardized differences of less than 0.1 (10%) likely denote a negligible imbalance between treated and untreated subjects [33].

The OS and PFR were compared between matched groups, by using a robust variance estimator in univariable Cox regression model. In the matched group analysis, association of clinical, respiratory and work-related factors with group category (MNEP+TC *vs* TC) was determined through univariable and multivariable conditional logistic regression analysis and the associated p-values were reported.

2.3 INSTITUTIONAL REVIEW BOARD APPROVAL

IRB approvals were obtained for both data sites from the department of Thoracic Surgery, University of Perugia (*Comitato Etico Aziende Sanitarie Umbria Prot. 8579/16/L, Perugia, PG, Italy)* and for the Department of Thoracic Surgery at the Toronto General Hospital (*Research Ethics Board 12-5628-TE, University Health Network, Toronto, ON, Canada*). All patients signed the permission for anonymous use of their clinical data for scientific purposes; a formal informed consent from participants was not obtained because the retrospective study design.

3. RESULTS

Amongst 41 patients with MNEP+TC, we identified 5 patients with PNECH, 16 patients with tumorlets and 20 patients affected by tumorlets/microcarcinoids along with PNECH. Eleven of 41 patients had preoperative evidence of micronodules on imaging studies, and 6 of them were radiologically evident in different lobe or in the controlateral lung. Patients in the MNEP+TC group were characterized by older age (63±1 years vs 54±1 years, $p<0.001$), peripheral tumors (76% vs 50%, $p=0.0032$), smaller tumor size (16.2±10.9 mm vs 21.3±11.7 mm, $p=0.011$) and lymph-nodal spread ($p=0.02$) in comparison with TC group. Clinical and pathological features of the 234 patients are displayed in **Table 1**.

3.1 RECURRENCE AND SURVIVAL

The mean follow-up period was 9.6±5.2 years (range 1.4-31.3 years). Fifteen people had relapse: 8 in the MNEP+TC group (19.5%) and 7 in the TC group (3.6%). The pattern of relapse was the following: liver (8), endobronchial (3), bones (4), brain (2) and lung (1). Among the 6 patients in MNEP+TC group with radiologically evident micronodules in different lobe or in the controlateral lung one regressed, 4 remained stable and one increased in size; this patient underwent lingulectomy 6 years after right upper lobectomy. Two hundred six patients were alive and 28 died: 4 disease related out of 12 MNEP+TC patients (33.3%) and none disease related out of 16 TC. The 10-years PFR was higher in the TC group (96.1%) than in the MNEP+TC group (83.8%) ($p<0.001$). The 10-years OS was better for TC patients (93.5%) compared to MNEP+TC patients (71.9%) ($p<0.001$).The OS and PFR curves are shown in **Figure 3**. **Figure 4** graphically displays, in a Forest Plot, the estimated results pooled by two groups (MNEP+TC vs TC).

3.2 UNI-MULTIVARIABLE ANALYSIS

The univariable regression analysis demonstrated that MNEP+TC was the only prognostic factor influencing negatively the PFR [p=0.0017, HR 5.8 95%CI 1.93-17.4]. This was confirmed also by comparing each sub-group analyses: Perugia-MNEP+TC versus TC alone [p=0.0044, HR 0.13 95% CI 0.03-0.53] and Toronto-MNEP+TC versus TC alone [p=0.027, HR 0.18 95% CI 0.04-0.82]. With regard to OS, the univariable regression analysis revealed that MNEP+TC [p<0.001, HR 4.78 95%CI 2.23-10.23] and age older than 65 years [p=0.022, HR 2.41 95%CI 1.14-5.11] were poor prognostic factors. At the multivariable analysis only MNEP+TC [p<0.001, HR 3.71 95%CI 1.08-12.68] confirmed to be independent prognostic factor.

3.3 PROPENSITY SCORE MATCH ANALYSIS

Among the 41 patients with MNEP+TC, 36 patients could be matched with the TC group on the basis of age, stage, location, smoking history and follow-up time (**Figure 2)**. This resulted in 36 matched pairs for the comparison of MNEP+TC vs TC groups. **Table 2** summarizes the baseline characteristics of patients in the propensity score matched sample, along with the associated standardized differences in both the matched sample and the initial sample. The standardized differences were all smaller in matched sample compared to the original sample. The largest standardized difference in the matched sample was 0.17 for gender, and the largest standardized difference in the original sample was 0.54 for location. Primary matched variables of interest between TC and MNEP+TC groups included age at time of diagnosis, tumor stage, tumor location, smoking history and follow-up time. All primary variables of interest had standardized difference less than or equal to 0.15 in the matched sample. Amongst the 36 matched pairs, tumor progression was recorded in 6 patients of the MNEP+TC group (16.6%). Thirty-two patients were alive in the TC group as opposed to 24 in the MNEP+TC group. The 5-years PFR was higher in the TC group (100%) than in the MNEP+TC group (93.4%).When a univariate Cox proportional hazards model

was fit and robust variance estimator was obtained, the associated p-value for the comparison of MNEP+TC with TC was <0.001. However, hazard ratios could not be obtained, as the TC group did not have any events.The 5-years OS was similar for TC patients (91.3%) and MNEP+TC patients (93.8%). When a univariate Cox proportional hazards model was fit and robust variance estimator was obtained, the associated hazard ratio for MNEP+TC compared to TC was 2.78 (95% CI=0.84-9.3, p=0.095). The OS and PFR curves for the matched groups are shown in **Figure 5**.

In the matched population, the univariable conditional logistic regression analysis demonstrated that the odds of belonging to MNEP+TC group was higher with the different following factors. Occupational exposure to inhalant gas, dust or fumes [p=0.008; OR 5.33; 95%CI 1.55-18.30]. Presence of respiratory symptoms-related to asthma/bronchitis[p=0.002;OR795%CI2.09-23.47]. Bronchiectasis/Fibrosis/Emphysema/Granuloma/Pneumonitis (BFEGP) pattern [p=0.032; OR 4; 95%CI 1.13-14.18]. Finally, the presence of micronodules on the pre-operative chest CT scan [p=0.039; OR 3.25; 95%CI 1.06-9.96].

Conversely, the odds declined with the presence of an increased oxygen partial pressure in the arterial blood gas analysis [p<0.036; OR 0.95; 95%CI 0.91-0.99]. At the multivariable analysis, we considered two types of conditional logistic regression analysis: clinical (MODEL-1) and pathological (MODEL-2). In MODEL-1 the occurrence of respiratory symptoms-related to asthma or bronchitis [p=0.009; OR 6.94; 95%CI 1.60-30.1] and presence of micronodules on the pre-operative chest CT scan [p=0.043; OR 4.54; 95%CI 1.05-19.6] resulted to be independent predictors of MNEP.

In MODEL-2 work exposure to inhalant gas, dust or fumes [p=0.026; OR 5; 95%CI 1.21-20.5] the presence of micronodules on the pre-operative chest CT scan [p=0.042; OR 4.86; 95%CI 1.06-22.2] and BFEGP patterns [p=0.03; OR 5.96; 95%CI 1.18-29.9] resulted to be independent predictors of MNEP.

4. DISCUSSION

The knowledge gap regarding to the incidence and clinical significance of MNEP in association with TC and their clinico-pathologic correlates in larger series was one of the main drivers of this study. After the first description of DIPNECH [34], small series and case reports have been published in Literature (**Table 3**), but the complex pathophysiology and the real clinical meaning remain to be better clarified [35-37]. The current surgical series identified MNEP in 17.5% of patients with TC. In the MNEP+TC group older age ($p<0.001$), peripheral tumors ($p=0.0032$), smaller tumor size ($p=0.011$) and lymph-nodal spread ($p=0.02$) were observed in comparison with TC group. The findings of this cohort also showed that this pattern was significantly associated with adverse outcome in affected patients as represented by a trend of progressively reduced 10-year OS and PFR rates when compared to patients with TC: the 10-years progression-free survival were 96.1% in TC and 83.8% in MNEP+TC groups ($p<0.001$). Also in the matched population the 5-year PFR in the group with MNEP+TC resulted to be significantly lower compared to patients of TC group ($p<0.01$). Moreover, relapses occurred in 8 patients (19.5%) in the MNEP+TC group and in 7 (3.6%) of the TC group. Another important highlight from the current series is the presence of statistically significant association of asthma/bronchitis, work exposure to inhalant agents, emphysema, fibrosis and inflammatory status and respiratory insufficiency with MNEP+TC. Specifically, the significance in MNEP+TC group was higher with work-related exposure to inhalant agents ($p=0.008$), asthma/bronchitis ($p=0.002$), emphysema, fibrosis and inflammatory status ($p=0.032$), micronodules on the chest CT-scan and respiratory insufficiency ($p=0.036$).

To discuss this issue properly, we articulate our concepts in four distinct paragraphs.

The role of the thin slice CT and Nuclear medicine imaging in preoperative diagnosis and postoperative follow-up

Assessment of preoperative imaging studies and risk factors as well as the evaluation of clinical symptoms may be crucial to rise the suspect in the preoperative workup of pulmonary neuroendocrine tumors [37-39]. The concomitant presence of multifocal microscopic pulmonary neuroendocrine proliferation should warn the surgeon to program a close radiological follow-up with the oncological support in case of lymph nodal metastatic involvement [22]. In the PNECH setting, high resolution CT scan with espiratory study plays a role in detecting mosaic attenuation, bronchial wall thickening, air trapping and bronchiectasis in association to pulmonary nodules [20,24,39,40]. In our case series, only 11 of 41 patients with multicentric forms had multiple nodules in the preoperative CT scan; this data confirms that CT scan is insufficient to establish a definitive diagnosis, as radiological findings are aspecific, thus histology is always required [39]. Concerning nuclear medicine imaging, ^{18FDG}PET/CT may fail to detect multifocal proliferations and nodal involvement as TC are characterized by low proliferation index [22]. Since most patients with TC express somatostatin receptors, techniques with radiolabeled somatostatin analogs instead are helpful both for staging and to predict the response to peptide receptor radiotargeted therapy [41], furthermore ^{68Ga}DOTATATE-PET/CT is preferable to Octreoscan because it is characterized by higher sensitivity and specificity [42]. In the present paper, TC with MNEP are characterized by higher rates of nodal involvement and worst prognosis; this data suggests to perform nuclear imaging studies whenever multifocal forms are suspected.

The operative strategy in MNEP

Surgical resection, more or less conservative, along with lymph-nodal dissection is considered the gold standard for typical lung carcinoid [26]. Although lobectomy or bilobectomy are the predominant choices among the other available techniques, there is a tendency towards conservative surgery. The main concern in surgical treatment of TC is to avoid unnecessary removal of functioning pulmonary tissue. However, sublobar resections performed electively, are questionable because satisfactory lymphadenectomy cannot be achieved particularly of the intraparenchymal nodes.

In our multicenter experience, if the surgical resection was performed with lymphadenectomy (92%) we sought a significant result compared to the absence of it ($p=0.035$). Due to the absence of pathological lymph-nodes during the pre-operative radiological workup and to the frequency of sub-lobar resections, we performed more often sampling (39.3%) compared to the systematic (26.9%) and lobe-specific (26.1%). MNEP entails a more complex pattern of multiple synchronous pre-invasive/invasive lesions, a higher risk of lymphatic spread, and the worst prognosis according to our results. Therefore, when diagnosed pre-operatively, it should consider more conservative lung resections to maintain a proper respiratory function in PNECH patients and the view of possible future surgical resections. Likewise, an adequate lymph-nodal dissection should be considered crucial in this setting.

The pathological assessment of the specimen

A high standard pathology practice is required to diagnose MNEP, with routine detailed examination of the non-tumorous parenchyma away from the TC [43,44]. TC and tumorlets arising in the background of PNECH (and consequently MNEP) should not be regarded as a metastatic spread, but as synchronous multiple primaries [16,22]. Moreover, the presence of a PNECH to tumorlet progression sequence is also reassuring of a primary multifocal disease. Pathological examination is considered the gold standard for the diagnosis, anyways when widespread pulmonary neuroendocrine cells proliferation is denoted in the non-neoplastic lung surrounding a TC but the diagnosis of DIPNECH is not certain, a high-resolution CT may be useful [20].

Post-operative follow-up strategy and tools in case of MNEP

From a clinical standpoint our results may suggest that potential underlying triggers leading to MNEP, seem to play a role in the tumor aggressiveness despite their overall small tumor size, earlier tumor stage and low-grade proliferative features. Thus, even in well-differentiated pulmonary neuroendocrine tumors, an accurate follow-up plays a crucial role [45]. In addition, the frequent association with peripheral tumor location and advanced age is of clinical interest. Detection of such patients with smaller tumor size and earlier tumor stage may be explained due to frequent respiratory symptoms as seen in patients with DIPNECH. In contrast to isolated TC, which may be diagnosed in the third decades, the low frequency of central tumors and the latency of the underlying potential triggers leading to TC and MNEP may also explain the fact that the diagnosis of patients with MNEP+TC occurs more frequently in advanced age.

Moreover, the current series showed the presence of statistically significant association of asthma/bronchitis, work exposure to inhalant agents, emphysema, fibrosis and inflammatory status and respiratory insufficiency with MNEP+TC. The lack of association for smoking and GERD also distinguishes such manifestations.

While the role of previous triggers remains to be further validated in other series, the well-known role of pulmonary neuroendocrine cells as chemo- and baroreceptors [45,46] may explain the relationship of some previous clinical states with the occurrence of MNET+TC. It remains to be determined whether there is a causal relationship with the development of fibrosis and hypoxic respiratory failure. Moreover, the release of fibrotic factors from the hyperplastic NE cells like histamine, serotonin, bradykinin, gastrin-releasing peptide-bombesin and other, needs to be further investigated.

The complex analysis of the action of different professional inhalant, and their ability to increase the release of neuroendocrine secretory pattern and in particular of histamine may be also regarded as a possible co-factor in the development of respiratory symptoms, fibrosis and pulmonary insufficiency [15-18].

From a surgical standpoint, the concomitant presence of MNEP should warn the surgeon to program a close and protracted follow-up though the modality and timing of examinations are not standardized [22,26]. Although most patients with MNEP remain stable over many years, few of them experience disease progression, which can be managed with the administration of somatostatin analogs or redo surgery [22,39]. In our case series, one patient underwent lingulectomy for MNEP progression six years after right upper lobectomy; in this setting, indeed, parenchymal-sparing surgery should be preferred to lobar resection. Eventually, in selected patients with radiological and clinical DIPNECH evolution with severe airflow obstruction, lung transplantation may be indicated [24,39]; in the current series, five patients underwent bilateral lung transplantation, but they were excluded from the study because of the residual absent native parenchyma to investigate at the follow-up. Of them, three still alive at 10 and 11 years from surgery.

4.1 CONCLUSIONS

MNEP in association with a synchronous TC seems to be a negative prognostic factor and close postoperative surveillance should be advised. Since the preoperative confirmation of MNEP can be challenging, pathologists provide additional value for the dynamic risk stratification of patients with well-differentiated pulmonary neuroendocrine tumors by performing a careful assessment of the non-tumorous lung parenchyma. However, the suspicion of MNEP during the pre-operative setting should be careful evaluated enabling possible changes in the surgical strategy. The association MNEP + TC appears to have distinct clinicopathological correlations in elderly patients with respiratory symptoms and may result in early tumor detection. The significant involvement of inhalant exposure rather than active/passive smoking history and GERD, might be considered as a predictor of MNEP.

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6. ICONOGRAPHY

Figure 1

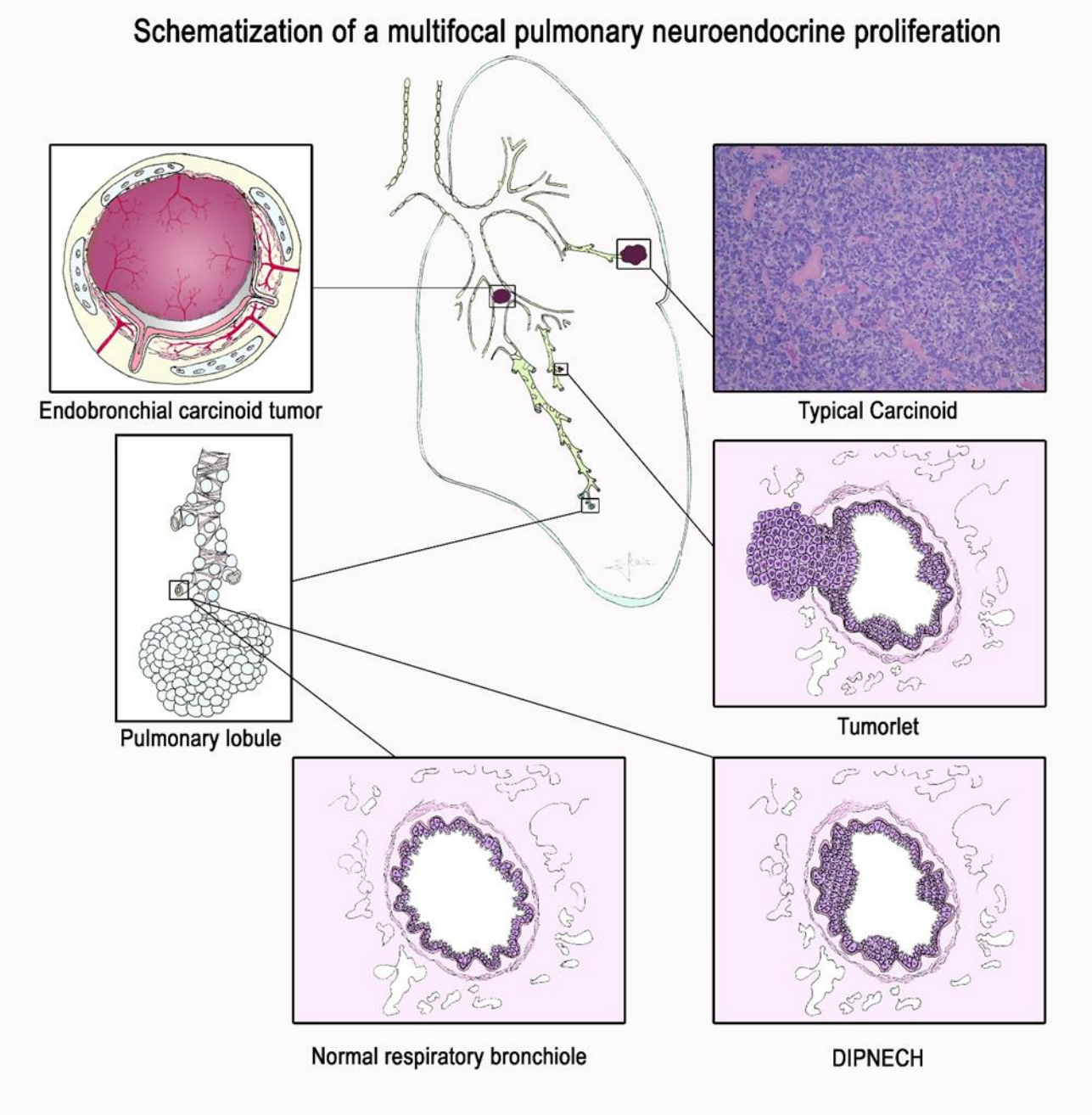

Fig.1 Schematization of a theoretical MNEP along with DIPNECH hyperplasia to neoplasia progression

Figure 2

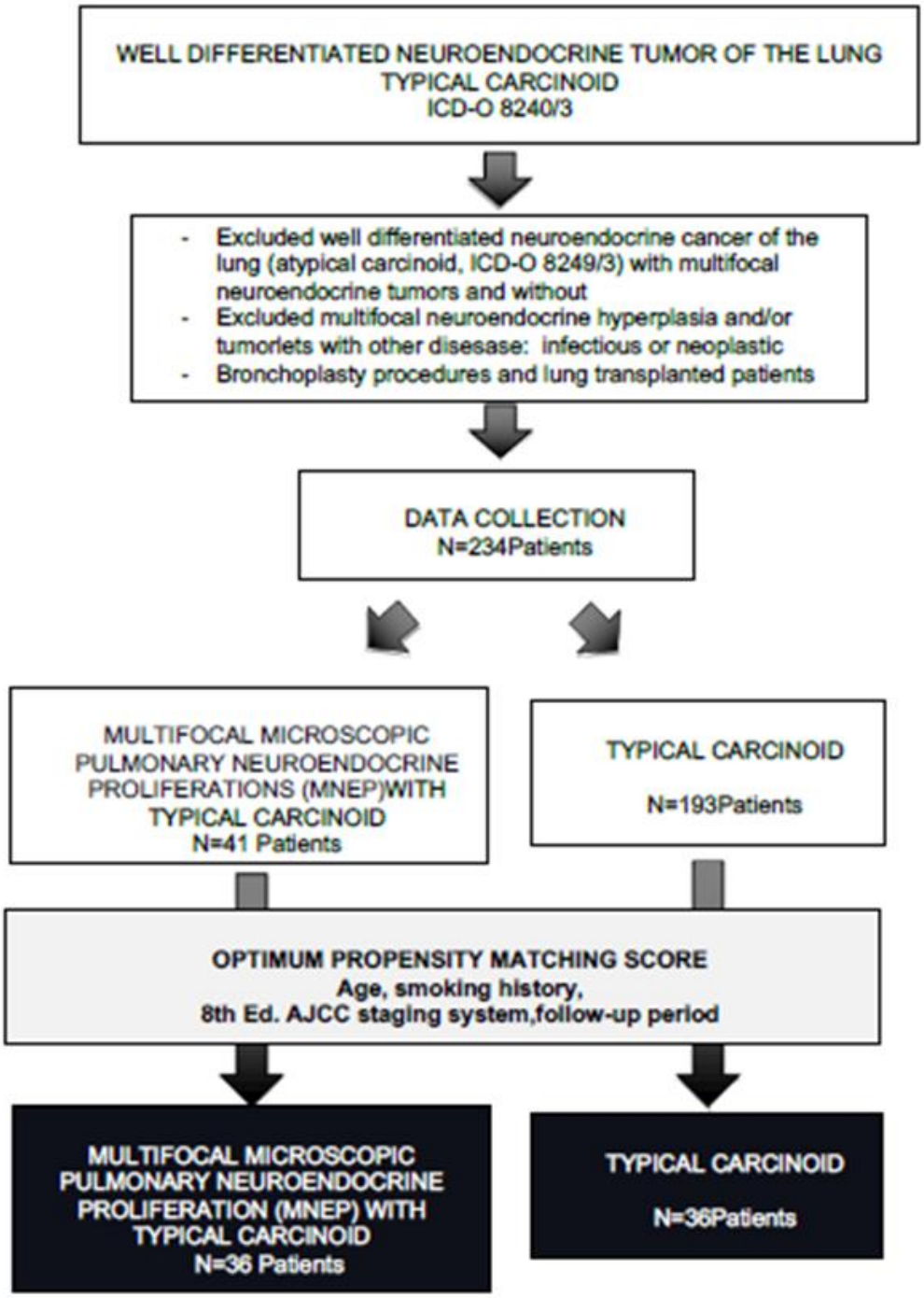

Fig. 2 Flow chart of the patient's selection. In this study, 36 patients with multifocal microscopic pulmonary neuroendocrine proliferations along with primary typical carcinoid were matched with 36 typical carcinoid patients.

Table 1

Covariate	Full Sample (n=234) N(%)	TC (n=193) N(%)	MNEP+TC (n=41) N(%)	p-value
Centre				0.39
Perugia	135(58)	114(59)	21(51)	
Toronto	99(42)	79(41)	20(49)	
Age categories				**0.022**
<=65	155(66)	133(69)	22(54)	
>65	79(34)	60(31)	19(46)	
Age at diagnosis				**<0.001**
Mean+/sd	56+/15	54+/15	63+/11	
Median Min-Max	59 15-88	57 15-83	63 34-88	
Sex				0.3
Female	136(58)	109(56)	27(66)	
Male	98(42)	84(44)	14(34)	
Smoke				0.15
No	80(35)	70(37)	10(24)	
Yes	149(65)	118(63)	31(76)	
Missing	5	5	0	
Tumor location				**0.0032**
Central	106(45)	96(50)	10(24)	

Peripheral	128(55)	97(50)	31(76)	
Primary tumor location				0.24
Bronchus	12(5)	10(5)	2(5)	
Lower	104(44)	89(46)	15(37)	
Middle	47(20)	34(18)	13(32)	
Upper	71(30)	60(31)	11(27)	
Surgery				0.12
Lobar + Bronchoplastic/Sleeve	187(79)	159(83)	28(68)	
Pneumonectomy	12(5)	10(5)	2(5)	
Wedge + Sub-lobar	35(15)	24(12)	11(27)	
Lymphadenectomy				**0.035**
No	19(8)	12(7)	7(17)	
Yes Systematic Lobe-specific Sampling	215(92) 63(26.9) 61(26.1) 92(39.3)	181(94) 51(26.4) 57(29.5) 73(37.8)	34(83) 12(29.6) 4(9.7) 19(46.3)	
Pt				**0.011**
Mean+/-sd	20.4+/-11.7	21.3+/-11.7	16.2+/-10.9	
Median Min-Max	19 5-110	20 5-110	15 6-71	
pN+	20(8.5)	14 (7.2)	6 (14.6)	**0.02**
N1	13(5.5)	6(3.1)	4(9.7)	

N2	10(4.2)	8(4.1)	2(4.8)	
8th AJCC staging				**0.041**
I/II	204(87)	172(89)	32(78)	
III	11(5)	9(5)	2(5)	
X	19(8)	12(6)	7(17)	

Tab.1 Clinical and pathological features of the 234 TC patients with (41 patients) and without (193 patients) MNEP.

Figure 3

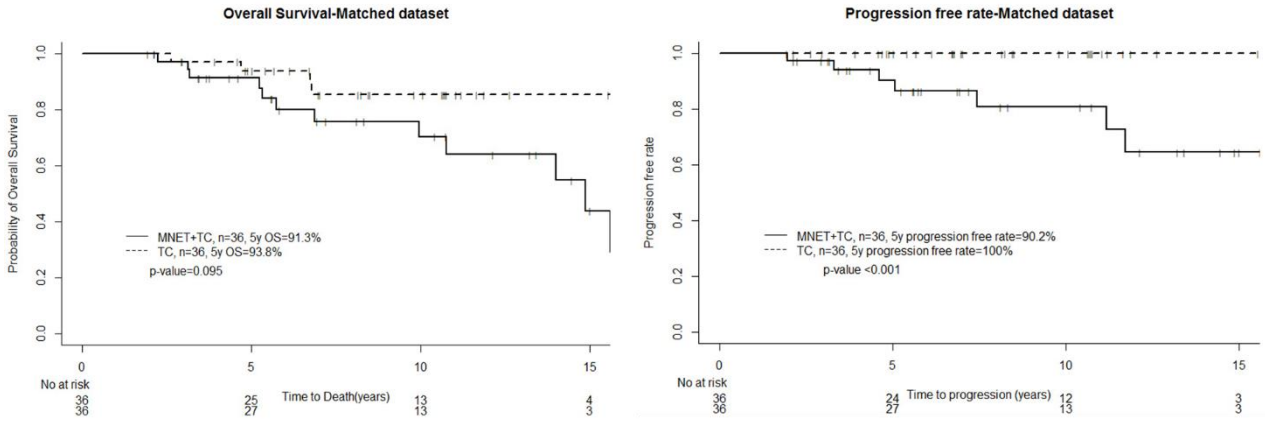

Fig.3 The overall survival and progression free rate curves for MNEP+TC (dashed line) and TC (continuous line) in the unmatched population.

Figure 4

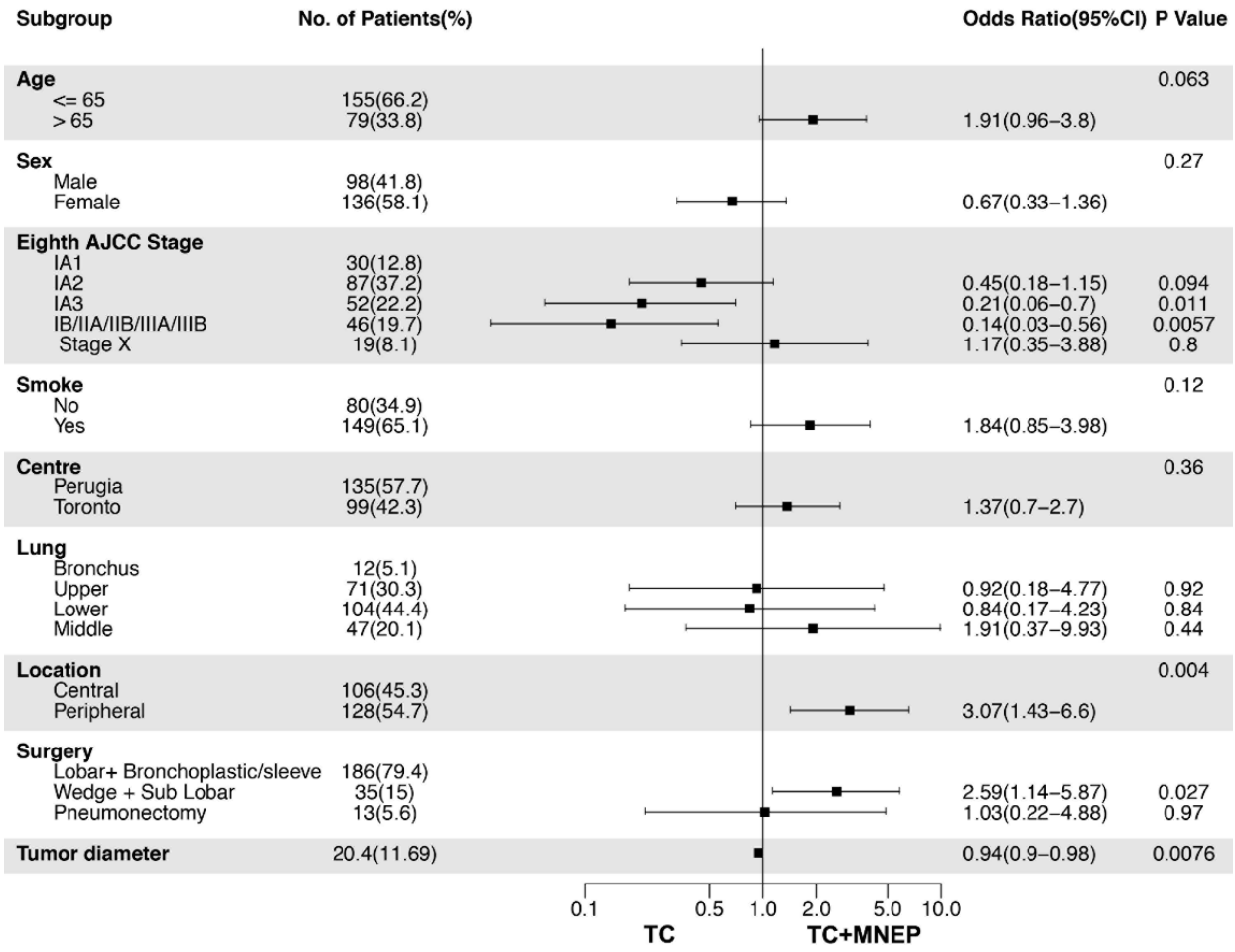

Fig.4 The Forest Plot displays the estimated results pooled by two groups (MNEP+TC vs TC). MNEP+TC: multifocal microscopic pulmonary neuroendocrine proliferations and typical carcinoid; TC: typical carcinoid.

Table 2

Covariate	TC (N=36) N (%)	MNEP+TC (N=36) N (%)	Standardized difference (Matched sample)	Standardized difference (Original Unmatched sample)
Centre			0.056	0.158
Toronto	17(47.2)	18(50.0)		
Perugia	19(52.8)	18(50.0)		
Age Category				0.317
<=65	23(63.9)	21(58.3)	0.114	
>65	13(36.1)	15(41.7)		
Gender			0.171	0.193
Female	20(55.6)	23(63.9)		
Male	16(44.4)	13(36.1)		
Smoking			0.000	0.281
No	9(25.0)	9 (25.0)		
Yes	27(75.0)	27(75.0)		
Location			0.063	0.544
Central	9(25.0)	10(27.8)		
Peripheral	27(75.0)	26(72.2)		
Primary Tumor Diameter			0.103	0.454
Mean (sd)	16.5+/-6.8	17.4+/-11.0		
Median (Min, Max)	15(6-35)	16.5(6-71)		
Grouping				
8th AJCC Stage	29(80.6)	30(83.3)	0.072	0.302
I/II	2(5.6)	2(5.6)	0.000	0.010
III/IV	5(13.8)	4(11.1)	0.084	0.364
X				

Tab. 2 Clinical and pathological features of the 72 matched TC patients with (36 patients) and without (36 patients).

Figure 5

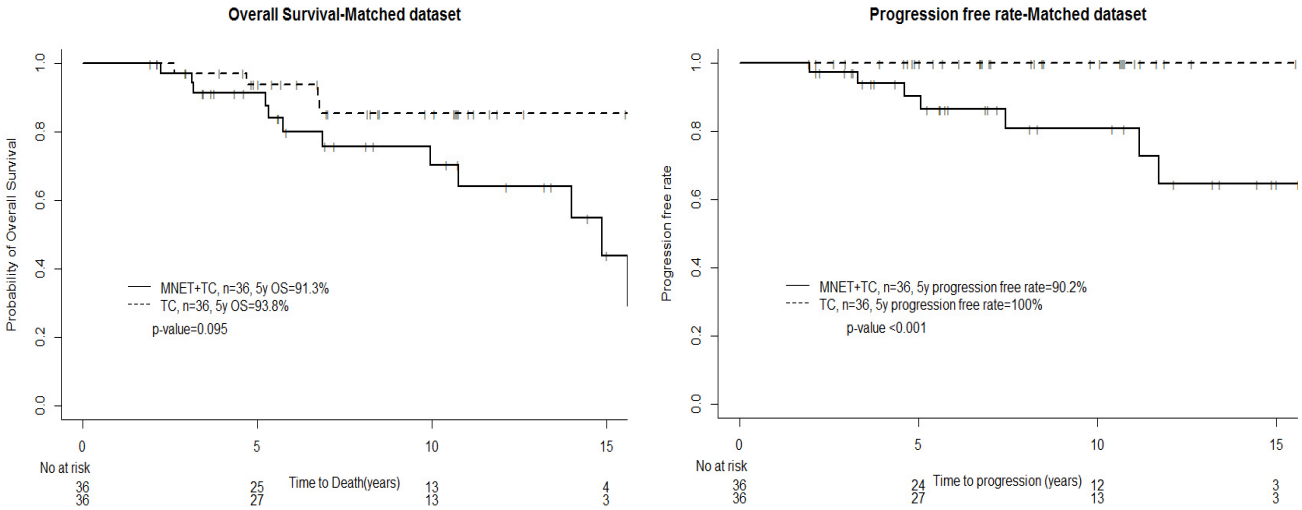

Fig. 5 The overall survival and progression free rate curves for MNEP+TC (dashed line) and TC (continuous line) in matched population.

Author	Year	Main topic	Statistical analysis method	N° of cases	M/F	Location	Clinical setting	Smoke	COPD	Additional CT scan nodules	N+	OS 10 years	Outcome	Descriptive conclusion
Miller RR	1995	Pathology	Descriptive	19/25 (76%)	2/17	Peripheral	incidental finding	5	6	4	na	na	na	Multicentric neuroendocrine cell proliferation is common in patients with peripheral carcinoid tumor of the lung
Aubry MC	2007	Surgery Clinical	Descriptive	19/28 (67.8%)	2/26	96% peripheral	43% cough, 2 Cushing Syndrome	13	19	na	3	na	7 improved 10 stable, 2 declined,	Most patients with tumorlets discovered in surgical lung specimens have associated peripheral carcinoid tumors.
Davies SJ	2007	Clinical	Descriptive	13/19 (68.4%)	4/15	na	Dyspnea, cough, pain, hemoptysis	17	8	na	na	na	11 stable 1 declined	DIPNECH seems to be more common than thought and may be associated with atypical carcinoids.
Rizvi SMH	2009	Pathology	Fisher exact text	41/144 (28.5%)	na	62% central 43% peripheral	Na	10	21	na	na	na	na	There is a statistically significant increase in the frequency of NEH in TCs when compared to other lung tumors.
Ferolla P	2009	Clinical	Kaplan-meier + Cox regression	14/123 (11.4%)	59/64	62 central 61 peripheral	Na	68	na	na	17	90% TC 67% AC	na	A statistically significant negative impact of multicentric forms on overall survival was evidenced
Nassar AA	2011	Review	Descriptive	10/25 (40%)	2/23	na	Cough, dyspnea, wheezing	8	13	15	na	na	6 improved 7 stable 4 declined	The majority of patients diagnosed with DIPNECH are middle-aged females presenting with obstructive symptoms.
Marchevsky AM	2015	Clinical Pathology	Chi-square	30/70 (42.8%)	9/61	na	Dyspnea, cough, wheezing	na	6	23	1	na	21 stable 5 declined	The presence of 5 or more NE cells, singly or in clusters, located within the basement membrane of the bronchiolar epithelium of at least 3 bronchioles, combined with 3 or more carcinoid tumorlets can be used to consistently diagnose DIPNECH.
Wirtschafter E	2015	Review	Descriptive	109/199 (54.8%)	na	na	Cough, dyspnea, others	53	6/30	na	na	na	13 improved 114 stable 30 declined	In patients with DIPNECH who present with carcinoid tumor, tumorlets and NECH, it is logical to assume that the condition is probably preneoplastic and that the carcinoid tumor evolved from a intraepithelial NECH.
Trisolini R	2016	Clinical Pathology	Descriptive, Student t test, Fisher exact test	13 (100%)	11/2	na	Cough, dyspnea, incidental finding	9	8	6	na	na	na	Symptomatic patients with DIPNECH are younger and have a higher number of foci of linear neuroendocrine proliferation and tumorlets. Incidental DIPNECH is commonly found in patients diagnosed with pulmonary adenocarcinoma.
Mengoli MC	2018	Clinical Pathology	Fisher exact text, Mann-Withney, Kruskal-Wallis test	151 (100%)	77/74	82 central 69 peripheral	Dyspnea, cough, other	50	36	10	3	na	na	DIPNECH with airway disease differs significantly from sporadic carcinoids with or without NECH in terms of demographical, clinical, radiological and immunopathological findings.
Al-Toubah T	2020	Clinical	Logistic regression, categorical response models	28/42 (66.6%)	2/40	na	Cough, dyspnea, fatigue	10	na	na	na	na	32 mproved with SSA	In patients with DIPNECH who have respiratory symptoms that are uncontrolled by conventional medications, SSA treatment palliates symptoms in most cases with a relatively low rate of toxicity.

Tab. 3 All reported cases in the Literature of multifocal microscopic pulmonary neuroendocrine proliferations (more than 10 cases).

Bibliography to Table 3

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ABSTRACT

Background. Clinical significance of multifocal pulmonary neuroendocrine proliferations (MNEP), including tumorlets and pulmonary neuroendocrine cell hyperplasia, in association with Typical Carcinoid (TC), is still debated.

Methods. A large retrospective series of TC with long-term follow-up data prospectively collected from two institutions was evaluated. Recurrence or new TC development was followed-up. Patients with TC alone and MNEP+TC were compared.

Results. 234 TC patients undergone surgery were included: 41 MNEP+TC (17.5%) and 193 TC alone (82.5%). In the MNEP+TC group older age ($p<0.001$), peripheral tumors ($p=0.0032$), smaller tumor size ($p=0.011$) and lymph-nodal spread ($p=0.02$) were observed in comparison with TC group. Relapses occurred in 8 patients (19.5%) in the MNEP+TC group and in 7 (3.6%) of the TC group. The 10-years progression-free survival were 96.1% in TC and 83.8% in MNEP+TC ($p<0.001$). After matching, in 36 pairs of patients a significantly higher 5-years progression-free survival was calculated for TC group ($p<0.01$). Furthermore the odds of belonging to MNEP+TC group was higher with work-related exposure to inhalant agents ($p=0.008$), asthma/bronchitis ($p=0.002$), emphysema, fibrosis and inflammatory status ($p=0.032$), micronodules on the chest CT scan and respiratory insufficiency ($p=0.036$).

Conclusions. The identification of MNEP requires careful pathological examination and postoperative follow-up. MNEP seems to be an adverse prognostic factor in patients with synchronous TC. Therefore, suspicion of MNEP during the pre-operative assessment should not be underestimated, enabling changes in the surgical strategy.