Prognostic Significance of Pulmonary Multifocal Neuroendocrine Proliferation With Typical Carcinoid

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Running head: Multicentric bronchial typical carcinoids

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Abstract

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

Methods: A retrospective series of TC with long-term follow-up data prospectively collected from two institutions was evaluated, and the outcome comparison between TC alone and MNEP+TC was investigated. Several baseline covariates were imbalanced between the MNEP+TC and TC groups, therefore, we have conducted 1:1 propensity score matching and inverse probability of treatment weighting (IPTW) in the full sample. In the matched group, association of clinical, respiratory and work-related factors with group was determined through univariable and multivariable conditional logistic regression analysis.

Results: 234 TC patients have undergone surgery: 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%) of MNEP+TC group and in 7(3.6%) of TC group. After matching, in 36 pairs of patients a significantly higher 5-years progression-free rate was observed for TC group($p<0.01$). Similar results were observed using IPTW in the full sample. Odds of being in the 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 association with MNEP seems to represent a clinically and prognostic relevant factor in TC. Hence, careful pre-operative workup, systematic pathological evaluation, including non-tumorous lung parenchyma, and long-term postoperative follow-up should be recommended in these patients.

Synchronous multifocal microscopic pulmonary neuroendocrine proliferations (MNEP) represent a subgroup of neuroendocrine lesions of the lung, ranging from pulmonary neuroendocrine cell hyperplasia (PNECH) to tumorlets[1-4]. According to the 2015 WHO classification, idiopathic pulmonary neuroendocrine cell hyperplasia may be diffuse (DIPNECH) or localized (PNECH)[5]. Both can be associated with tumorlets and bronchial carcinoids[5,6] and are considered a preinvasive lesion[7]. Tumorlets are by definition well-differentiated pulmonary neuroendocrine micro-tumors measuring up to 0.5 cm[7,8].

PNECH 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[9-13]. The diagnosis of PNECH is purely histological, while DIPNECH requires clinical respiratory symptoms (dry cough, exertion dyspnea) correlated with the airflow obstruction secondary to peribronchiolar fibrosis and constrictive obliterative bronchiolitis and may be diagnosed with a thin slice CT-scan[8]. Untreated DIPNECH may evolve with progressive respiratory insufficiency. Both PNECH and DIPNECH may also be incidentally found at the histologic examination in asymptomatic patients after surgery for carcinoid tumors[14-17].

The biological significance of MNEP in association with well-differentiated pulmonary neuroendocrine tumors with low-grade proliferative features (also known as Typical Carcinoid tumor; TC) is still a matter of debate[18]. Furthermore, MNEP has been reported in sporadic cases, and their incidence and prevalence remain to be established along with their clinicopathologic significance, yet not evaluated in large series.

To answer these unresolved issues, we evaluated the clinical and prognostic significance of pulmonary neuroendocrine proliferations in association with TC in a large cohort of surgically resected patients.

Patients and Methods

We have analyzed the institutional database from the *Thoracic Surgery Department, University of Perugia, Perugia, PG, Italy* (Jan 1983-Dec 2013) and the *Division of Thoracic Surgery, University Health Network, Toronto, ON, Canada* (Jan 2000-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; ^{111}In-pentetreotide scan (OctreoScan™) was performed from 1996. Central lesions are by definition those located in segmental or larger bronchus and peripheral tumors those involved with the subsegmental bronchus or beyond[21]. 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 were carried out in patients with CT scan finding of mediastinal node enlargement. Endobronchial debridement 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 lymphadenectomy was carried out along with lobar or major resections.

Neuroendocrine differentiation was assessed based upon morphology and immunohistochemical reactivity according to the WHO classification; Ki-67 index was also evaluated[7]. Multiple forms of neuroendocrine proliferations including tumorlets in association with pulmonary neuroendocrine cell hyperplasia were carefully assessed by performing serial sections of lung parenchyma and immunohistochemical markers. The staging was established according to the 8th edition of the AJCC TNM staging system.

The follow-up protocol included a clinical interview with a physical examination, chromogranin A measurements, and post-operative chest-abdomen CT scan according to the ESMO and ENETS Guidelines for at least 15 years. Fiberoptic bronchoscopy was performed every 3 years for patients with central tumors and every five years for peripheral TC.

Parameters related to patient's demographics (age at the time of surgery, gender) and clinical history (smoking history, 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. 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), 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 for analysis. A total of 234 patients affected by primary lung TC were enrolled; among these 41 (17.5%) had MNEP along with single TC (MNEP+TC) and 193 (82.5%) had only TC. Overall Survival (OS) was calculated from the date of surgery to the last date of follow-up or the date of death. Progression-free rate (PFR) was calculated from the date of surgery to the date of recurrence. The study design is displayed in **Figure 1**.

Statistical Analysis

Data on categorical variables were reported as frequencies and percentages. Continuous variables were described as means +/- standard deviations, along with median values. In the unmatched dataset, patient characteristics between MNEP+TC and TC groups were compared using Chi-square test or Fisher's exact test for categorical variables and Student's t-test for continuous data. A number of baseline variables were different between the groups and we have conducted 1:1 propensity score (PS) matching to adjust the imbalance between the groups (MNEP+TC vs TC) and compared the OS and the PFR between matched groups. PS matching enables one to estimate

the effect of the MNEP+TC vs. TC under the condition that the cohorts are similar with respect to variables of interest[20]. Therefore, PS matching analysis estimates the average treatment effect among the treated (ATT).

Apart from PS matching, the following three techniques were used as sensitivity analyses to account for confounding in the full sample 1) Inverse probability of treatment weighting (IPTW) by the propensity score 2) Cox proportional hazard model adjusted for PS 3) Multivariable analysis using Cox proportional hazard model. A detailed description of the aforementioned techniques is reported in the **Supplementary file 1**.

Institutional review board approvals were obtained for both the centers: *Comitato Etico Aziende Sanitarie Umbria Prot. 8579/16/L, Perugia, PG, Italy* and *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.

Results

Amongst 41 patients with MNEP+TC, we identified 5 patients with PNECH, 16 patients with tumorlets and 20 patients affected by tumorlets 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 the **Supplementary file 2**.

Recurrence and overall 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 six patients in MNEP+TC group with radiologically evident micronodules in the different lobe or the contralateral lung, one lessened in size, four remained stable, and one increased in size. This patient underwent lingulectomy six years after the 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%) ($p<0.001$). In the competing risk approach, probability of 10-year progression was 15.9% in the MNEP+TC and 3.8% in the TC group. The 10-years OS was better for TC patients (93.5%) compared to MNEP+TC patients (71.9%;$p<0.001$). The OS, PFR and probability of progression curves are shown in **Figure 2**. **Figure 3** displays the estimated results pooled by two groups.

Uni-multivariable analysis

The univariable regression analysis demonstrated that MNEP+TC was the only prognostic factor influencing negatively the progression [p=<0.001, HR 7.34; 95%CI:2.62-20.5]. 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 4.23; 95%CI: 1.95-9.19] was confirmed to be an independent prognostic factor.

Propensity score match analysis

Among the 41 patients in the MNEP+TC group, 36 patients could be matched in the TC group. This resulted in 36 matched pairs for MNEP+TC vs TC comparison. **Table 1**

reports the baseline characteristics of patients in the propensity score matched sample, along with the associated standardized differences in the matched sample, unmatched sample and IPTW approach. The standardized differences were all smaller in the matched sample and IPTW approach compared to the original sample, except for gender in IPTW approach. The largest standardized difference in the matched sample and IPTW approach was 0.17 and 0.20 for gender, and the largest standardized difference in the original sample was 0.54 for location. Primary variables of interest that were matched between MNEP+TC and TC groups were age, stage, location, smoking history and follow-up time, apart from side, primary tumour diameter and centre of the study. All primary variables of interest had standardized difference less than or equal to 0.15 in the matched sample and IPTW approach.

Among the 36 matched pairs, tumor progression was recorded in 8 patients of the MNEP+TC group (22.2%). 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 univariable 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 ratio (HR) 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%), HR: 2.78 (95%CI:0.84-9.3, p=0.095). The OS and PFR curves for the matched groups are shown in **Figure 4**.

Results from various analysis approaches are presented in **Tables 2** and **3**.

In the matched population (**Supplementary File 3**), the univariable conditional logistic regression analysis demonstrated that the odds of belonging to MNEP+TC group was

higher with: 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 or bronchitis [p=0.002; OR 7 95%CI: 2.09-23.47],

Bronchiectasis/Fibrosis/Emphysema/Granuloma/Pneumonitis (BFEGP) pattern [p=0.032; OR 4; 95%CI:1.13-14.18] and 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]. In the multivariable analysis we considered two types of models: 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] were 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] were independent predictors of MNEP.

Comment

The knowledge gap regarding the epidemiology, the clinicopathological and prognostic significance of the association of MNEP in patients with surgically resected pulmonary TC were among the leading drivers of the present study. After the first description of DIPNECH[21], small series and case reports have been published in Literature (**Supplementary File 4**).

The current surgical series identified MNEP in 17.5% of patients with TC. Hence, this series strengthens the message that in the presence of respiratory symptoms, PNECH should always be actively investigated. In the present study, the association with asthma/bronchitis, work exposure to inhalant agents, emphysema, fibrosis, inflammatory status and respiratory insufficiency in patients with MNEP+TC has been frequently observed.

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[15,22] may explain the relationship of some previous clinical states with the occurrence of MNEP+TC. It remains to be determined whether there is a causal relationship between 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 has been hypothesized.

Another reason for the research of PNECH, reinforced by this study, is the observation that multicentric forms in association with TC were significantly associated with adverse outcomes, as represented by a significant impact on 10-year OS and PFR rates when compared to patients with TC alone. Therefore, the complex pathophysiology and the real clinical meaning of MNEP with TC remain to be better clarified[23-25].

The assessment of preoperative imaging studies, risk factors, and clinical symptoms may be crucial to confirm the clinical suspect in pulmonary neuroendocrine tumors[25-27]. In the PNECH setting, a high-resolution CT scan with an expiratory study plays a role in detecting mosaic attenuation, bronchial wall thickening, air trapping, and bronchiectasis in association with pulmonary nodules[2,16,27,28]. However, 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 may be non-specific. Thus, histology is always required[27] to confirm the clinical suspect definitively.

Concerning nuclear medicine imaging, 18FDGPET/CT may fail to detect multifocal proliferation, and nodal involvement as TC are, by definition, characterized by a low proliferation index[14]. The role of 68GaDOTATATE-PET/CT in this subgroup of patients remains to be established since most of the nodular lesions are at the limit of the detection of the methods[29]. For the same reasons, most of the nodular lesions may not be revealed by the less sensitive Octreoscan™[30]. Nevertheless, long-acting somatostatin analogs have been proposed by some authors in limited series for the impact on clinical symptoms and stabilization of the disease. However, long-acting somatostatin analogs have been presented by some authors in small series for the effect on clinical symptoms and stabilization of the disease. The possible repercussions in delay the progression of the respiratory symptoms represents a discussion beyond the scope of this study[11,14].

Surgical resection, more or less conservative, and lymph-nodal dissection are considered the gold standard for typical lung carcinoid[4]. Although lobectomy or bi-lobectomy are the predominant choices among the other available techniques, there is a tendency towards conservative surgery. The main concern in the surgical treatment of TC is to avoid unnecessary removal of functioning pulmonary tissue. However, sub-lobar resections, performed electively, are questionable, because adequate lymphadenectomy cannot be achieved, particularly intraparenchymal nodes. Due to the absence of pathological lymph nodes during the pre-operative radiological workup and the frequency of sub-lobar

resections, we performed more often systematic (58%) than sampling (42%) lymphadenectomy. 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, more conservative lung resections should be considered, in order to maintain a proper respiratory function and in view of possible future surgical resections. Likewise, an adequate lymph-nodal dissection should be considered crucial in this setting.

This series include only patients surgically resected, this should be remembered as a part of the patients with PNECH may be unsuitable for surgical resection, and due to the extension of the disease, may involve virtually other lobes. The long-term data from these patients are the object of another ongoing study.

A high standard pathology practice is required to diagnose MNEP, with routine detailed examination of the non-tumorous parenchyma away from the TC[31,32]. 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 as in the background of DIPNECH-related MNEP[11,14]. Histological and immunohistochemical studies are required for the diagnosis of MNEP, When widespread pulmonary neuroendocrine cells proliferation is confirmed in the non-neoplastic parenchyma of patients with a pulmonary TC, a high-resolution CT may be useful[2].

The concomitant presence of MNEP indicates a close clinical follow-up, although the modality of choice and timing of examinations have not been standardized yet[4,14]. In fact, while most patients with MNEP remain stable over many years, a subset of patients can also experience disease progression. In the case of progressive disease,

multidisciplinary management should be considered, and the role of PRRT, long-acting somatostatin analogues, everolimus, capecitabine-temozolomide, steroids, and redo-surgery requires further studies[14,18,27]. However, an individualized approach is often undertaken. Eventually, in selected patients with radiological and clinical evolution of DIPNECH with severe airflow obstruction, lung transplantation may be indicated[16,27].

Although this study is the first to analyze a limited cohort of patients from high-volume centers with two *ad hoc* models of statistical analyses, some limitations should be noted. This is a retrospective series, cases were operated upon in two centers in a long period of time, the modality and timing of follow-up were not standardized.

Conclusion

The association with MNEP seems to represent a clinically and prognostic relevant factor in TC. Based upon the present study results, we recommend a specific and careful pre-operative workup, a systematic pathological evaluation of the surgical specimen, including non-tumorous lung parenchyma, and a long-term postoperative follow-up in these cohorts of patients. Furthermore, the significant involvement of inhalant exposure, along with active/passive smoking history and GERD, should always be evaluated in the clinical history of these patients. Multidisciplinary clinical management is crucial, and clinical trials are needed to establish the best medical options in progressive patients.

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Table 1: Standardized differences of baseline covariates in unmatched and matched sample

Covariate	**TC (N=36)** N (%) or Mean+/-STD Median(range)	**MNEP+TC (N=36)** N (%) or Mean+/-STD Median(range)	**Standardized difference (Matched sample)**	**Standardized difference (Unmatched sample)**	**Standardized difference (IPTW)**
Age Category			0.114	0.317	0.008
<=65	23(63.9)	21(58.3)			
>65	13(36.1)	15(41.7)			
Stage					
I/II	29(80.6)	30(83.3)	0.072	0.302	0.054
III/IV	2(5.6)	2(5.6)	0.000	0.010	0.001
X	5(13.8)	4(11.1)	0.084	0.364	0.059
Smoking			0.000	0.281	0.031
No	9(25.0)	11(25.0)			
Yes	27(75.0)	27(75.0)			
Location			0.063	0.544	0.008
Central	9(25.0)	10(27.8)			
Peripheral	27(75.0)	26(72.2)			
Gender			0.171	0.193	0.200
Female	20(55.6)	23(63.9)			
Male	16(44.4)	13(36.1)			
Side			0.114	0.225	0.001
Left	15(41.7)	13(36.1)			
Right	21(58.3)	23(63.9)			
Primary Tumor Diameter	16.5+/-6.8 15(6-35)	17.4+/-11.0 16.5(6-71)	0.103	0.454	0.040
Centre			0.056	0.158	0.029
Toronto	17(47.2)	18(50.0)			
Perugia	19(52.8)	18(50.0)			
Follow-up time (years)	8.32+/-4.4 7.6(1.9-20.2)	8.26+/-4.7 6.9(2.1-17.7)	0.014	0.415	0.121

Table 2: Overall survival

Analysis Method	**Sample size**	**Sample size MNEP+TC/TC**	**Events/ censored**	**Hazard ratio (95% CI)**	**p-value**
1:1 PS matched analysis	72	36/36	16/56	2.78 (0.84-9.3)	0.095
Adjusting the effect of MNEP+TC vs TC in the Cox regression model using PS	225	40/185	28/197	2.77 (1.15-6.66)	**0.023**
IPTW as weight in Cox regression model	225	40/185	28/197	2.43 (1.08-5.47)	**0.031**
Multivariable analysis- with group (MNEP+TC vs. TC) and age	234	41/193	28/206	4.23 (1.95-9.19)	**<0.001**
Unadjusted analysis					
Univariable analysis (MNEP+TC vs. TC)	234	41/193	28/206	4.78 (2.23-10.2)	**<0.001**

Table 3: Progression

Analysis Method	Sample size	Sample size MNEP+TC/TC	Events/ censored	Hazard ratio (95% CI)	p-value
1:1 PS (Robust GEE SE) ATT	72	36/36	8/64	-*	<0.001
IPTW as weight in Cox regression (Robust GEE SE) ATT	225	40/185	15/210	9.45 (3.10-28.8)	<0.001
Unadjusted analysis					
Univariable analysis (MNEP+TC vs. TC)	234	41/193	15/219	7.34 (2.62-20.5)	<0.001

*In the matched dataset, all 8 events were in MNEP+TC group, and therefore hazard ratio cannot be calculated.

Adjustment for PS as a covariate in the model analysis and multivariable analysis is not performed for the outcome of PFR as limited number of events (N=15) does not allow for either adjustment of covariates or PS under the rule of thumb of 10 events per variable.

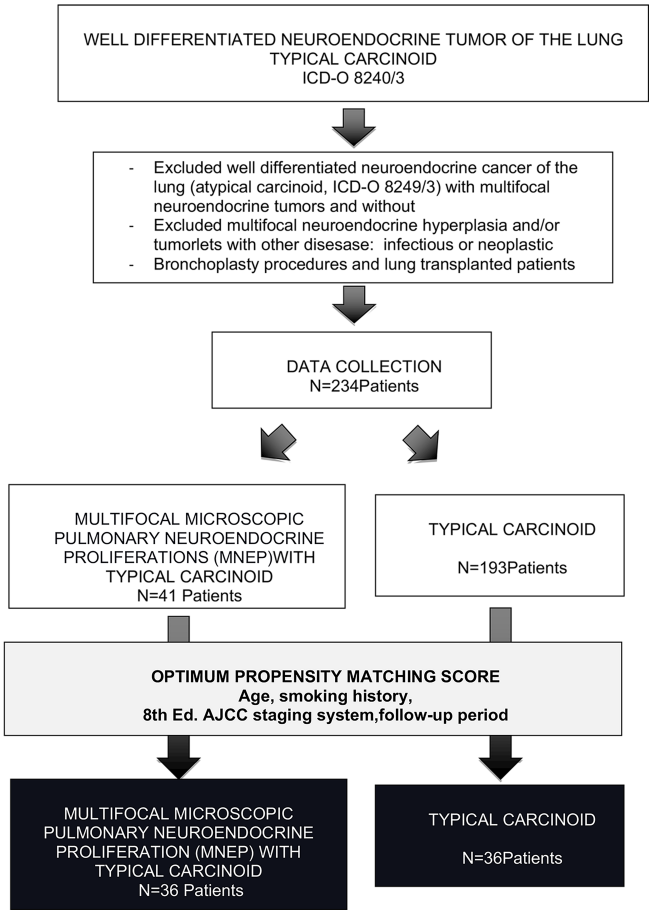
Figure Legends

Figure 1. Flow chart of the patient's selection.

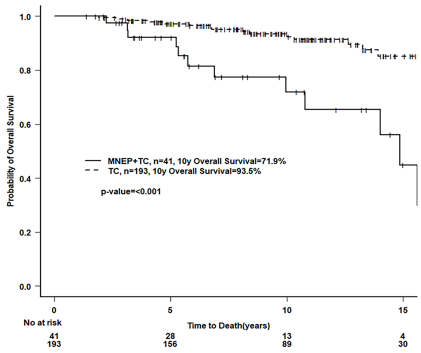
Figure 2. The Overall Survival (A), Progression Free Rate (B) along with Probability of Progression (C) curves for MNEP+TC (dashed line) and TC (continuous line) in the unmatched population.

Figure 3. The Forest Plot displays the estimated results pooled by two groups (MNEP+TC vs TC).

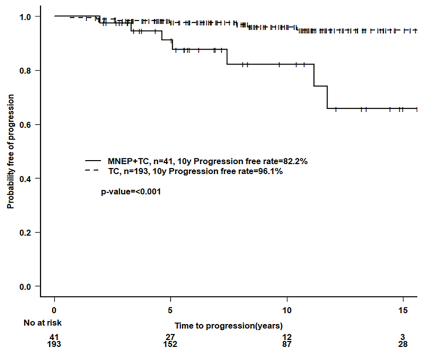
Figure 4. The Overall Survival (A) and Progression Free Rate (B) curves for MNEP+TC (dashed line) and TC (continuous line) in the matched population.


WELL DIFFERENTIATED NEUROENDOCRINE TUMOR OF THE LUNG
TYPICAL CARCINOID
ICD-O 8240/3
- Excluded well differentiated neuroendocrine cancer of the lung (atypical carcinoid, ICD-O 8249/3) with multifocal neuroendocrine tumors and without
- Excluded multifocal neuroendocrine hyperplasia and/or tumorlets with other disesase: infectious or neoplastic
- Bronchoplasty procedures and lung transplanted patients
DATA COLLECTION
N=234Patients
MULTIFOCAL MICROSCOPIC PULMONARY NEUROENDOCRINE PROLIFERATIONS (MNEP)WITH TYPICAL CARCINOID
N=41 Patients
TYPICAL CARCINOID
N=193Patients
OPTIMUM PROPENSITY MATCHING SCORE
Age, smoking history,
8th Ed. AJCC staging system,follow-up period
MULTIFOCAL MICROSCOPIC PULMONARY NEUROENDOCRINE PROLIFERATION (MNEP) WITH TYPICAL CARCINOID
N=36 Patients
TYPICAL CARCINOID
N=36Patients

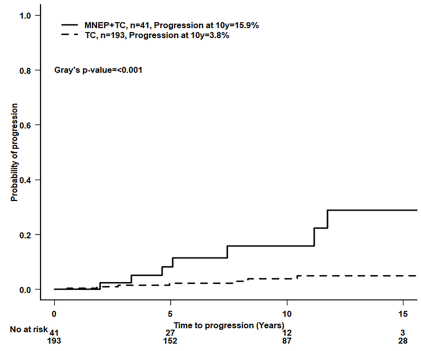
A

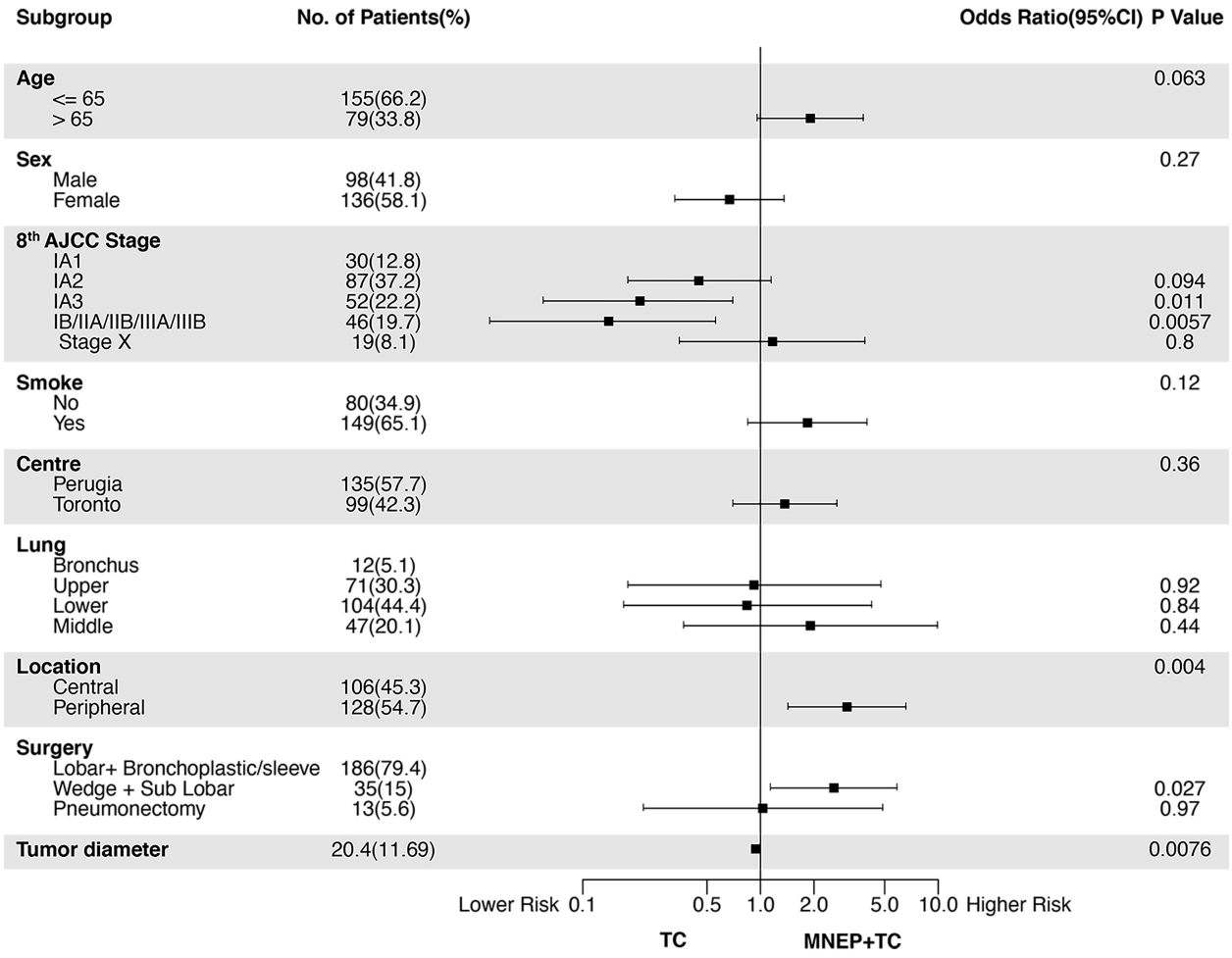

Probability of Overall Survival
1.0
0.8
0.6
0.4
0.2
0.0
MNEP+TC, n=41, 10y Overall Survival=71.9%
TC, n=193, 10y Overall Survival=93.5%
p-value=<0.001
0
5
10
15
No at risk
Time to Death(years)
41
193
28
156
13
89
4
30

B

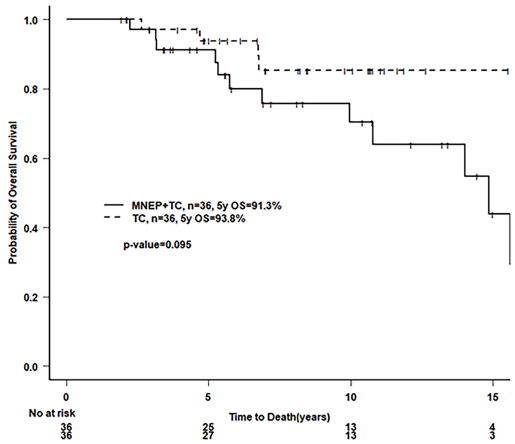

Probability free of progression
1.0
0.8
0.6
0.4
0.2
0.0
MNEP+TC, n=41, 10y Progression free rate=82.2%
TC, n=193, 10y Progression free rate=96.1%
p-value=<0.001
0
5
10
15
No at risk
Time to progression(years)
41
193
27
152
12
87
3
28

C

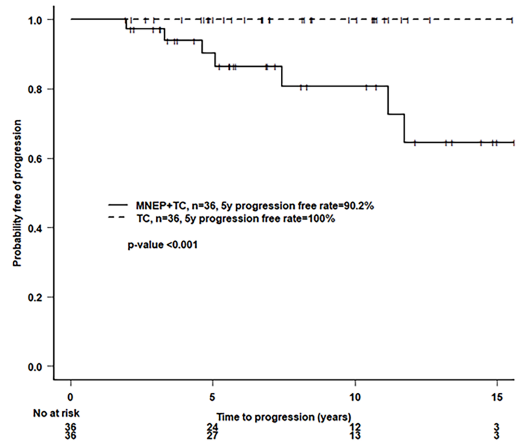

Probability of progression
1.0
0.8
0.6
0.4
0.2
0.0
MNEP+TC, n=41, Progression at 10y=15.9%
TC, n=193, Progression at 10y=3.8%
Gray's p-value=<0.001
0
5
10
15
No at risk
Time to progression (Years)
41
193
27
152
12
87
3
28


Subgroup
No. of Patients(%)
Odds Ratio(95%CI)
P Value
Age
0.063
<= 65
155(66.2)
> 65
79(33.8)
Sex
0.27
Male
98(41.8)
Female
136(58.1)
8th AJCC Stage
IA1
30(12.8)
IA2
87(37.2)
0.094
IA3
52(22.2)
0.011
IB/IIA/IIB/IIIA/IIIB
46(19.7)
0.0057
Stage X
19(8.1)
0.8
Smoke
0.12
No
80(34.9)
Yes
149(65.1)
Centre
0.36
Perugia
135(57.7)
Toronto
99(42.3)
Lung
Bronchus
12(5.1)
Upper
71(30.3)
0.92
Lower
104(44.4)
0.84
Middle
47(20.1)
0.44
Location
0.004
Central
106(45.3)
Peripheral
128(54.7)
Surgery
Lobar+ Bronchoplastic/sleeve
186(79.4)
Wedge + Sub Lobar
35(15)
0.027
Pneumonectomy
13(5.6)
0.97
Tumor diameter
20.4(11.69)
0.0076
Lower Risk
0.1
0.5
1.0
2.0
5.0
10.0
Higher Risk
TC
MNEP+TC

A


Probability of Overall Survival
1.0
0.8
0.6
0.4
0.2
0.0
MNEP+TC, n=36, 5y OS=91.3%
TC, n=36, 5y OS=93.8%
p-value=0.095
0
5
10
15
Time to Death(years)
No at risk
36
36
25
27
13
13
4
3

B


Probability free of progression
1.0
0.8
0.6
0.4
0.2
0.0
MNEP+TC, n=36, 5y progression free rate=90.2%
TC, n=36, 5y progression free rate=100%
p-value <0.001
0
5
10
15
Time to progression (years)
No at risk
36
36
24
27
12
13
3
3