2019台灣胸腔暨重症加護醫學會
2019 Taiwan Society of Pulmonary and Critical Care Medicine

Lung Adenocarcinoma with Neuroendocrine Differentiation: A Case Series Study

張皓鈞[1]、陳冠宇[1] 、張逸良[2]、施金元[1]

[1]Division of Pulmonology and Critical Care Medicine, Department of Internal Medicine, National Taiwan University Hospital

[2]Department of Pathology, National Taiwan University Hospital

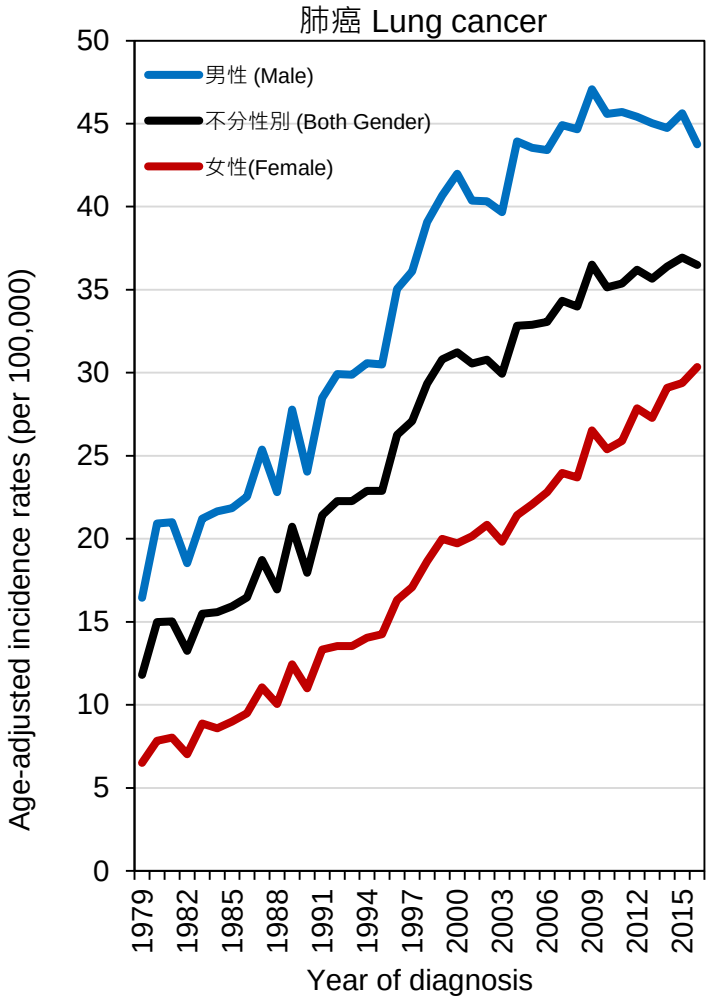
Introduction

- The importance of lung cancer has arose in Taiwan, due to its increasing incidence and relatively poor outcome

2016 年報

項　目	發生個案	
	男性	女性
個案數(人)	7,661	5,827
年齡中位數	68	65
粗率(每10萬人口)	65.37	49.30
年齡標準化率[2](每10萬人口)	37.62	26.85
年齡標準化率[3](每10萬人口)	43.23	29.89
性別比(年齡標準化率)	1.45	1

項　目	死亡個案	
	男性	女性
個案數(人)	5,961	3,411
年齡中位數	73	72
粗率(每10萬人口)	50.86	28.86
年齡標準化率[2](每10萬人口)	27.55	14.11
年齡標準化率[3](每10萬人口)	32.82	16.45
性別比(年齡標準化率)	2.00	1



國民健康署年報
台灣癌症登記中心

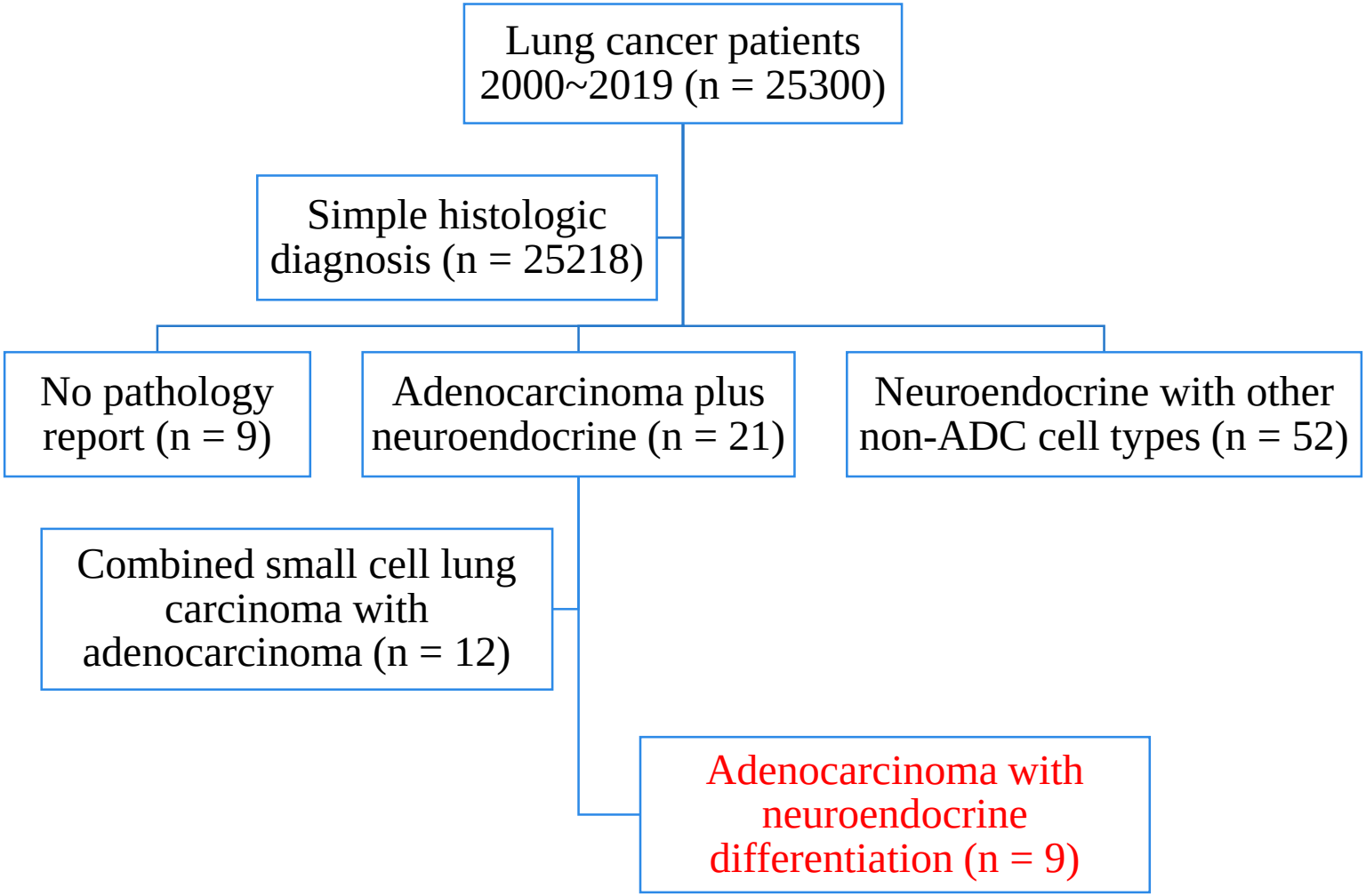
Introduction

- Pulmonary neuroendocrine (NE) malignancy includes two distinct categories
  - A series of neoplasms with NE light-microscopic appearance: low-grade typical carcinoid, intermediate grade atypical carcinoid, and high-grade large cell neuroendocrine carcinoma (LCNEC) & small cell lung carcinoma (SCLC)
  - Combined neuroendocrine tumor: combined SCLC or combined LCNEC
- NE differentiation can also be detected in 10~20% of NSCLC by IHC studies
- Among NSCLC, adenocarcinoma (ADC) is the most common type in Taiwan
- We are interested in adenocarcinoma with neuroendocrine differentiation's (NED) clinical features

* LCNEC: Large Cell Neuroendocrine Carcinoma, SCLC: Small Cell Lung Carcinoma, TC: Typical Carcinoid, AC: Atypical Carcinoid, NSCLC: Non-Small Cell Lung Cancer, IHC: Immunohistochemistry

J Thorac Oncol. 2015;10:1243-1260.
J Thorac Oncol. 2011;6:244-285.

Materials and Methods



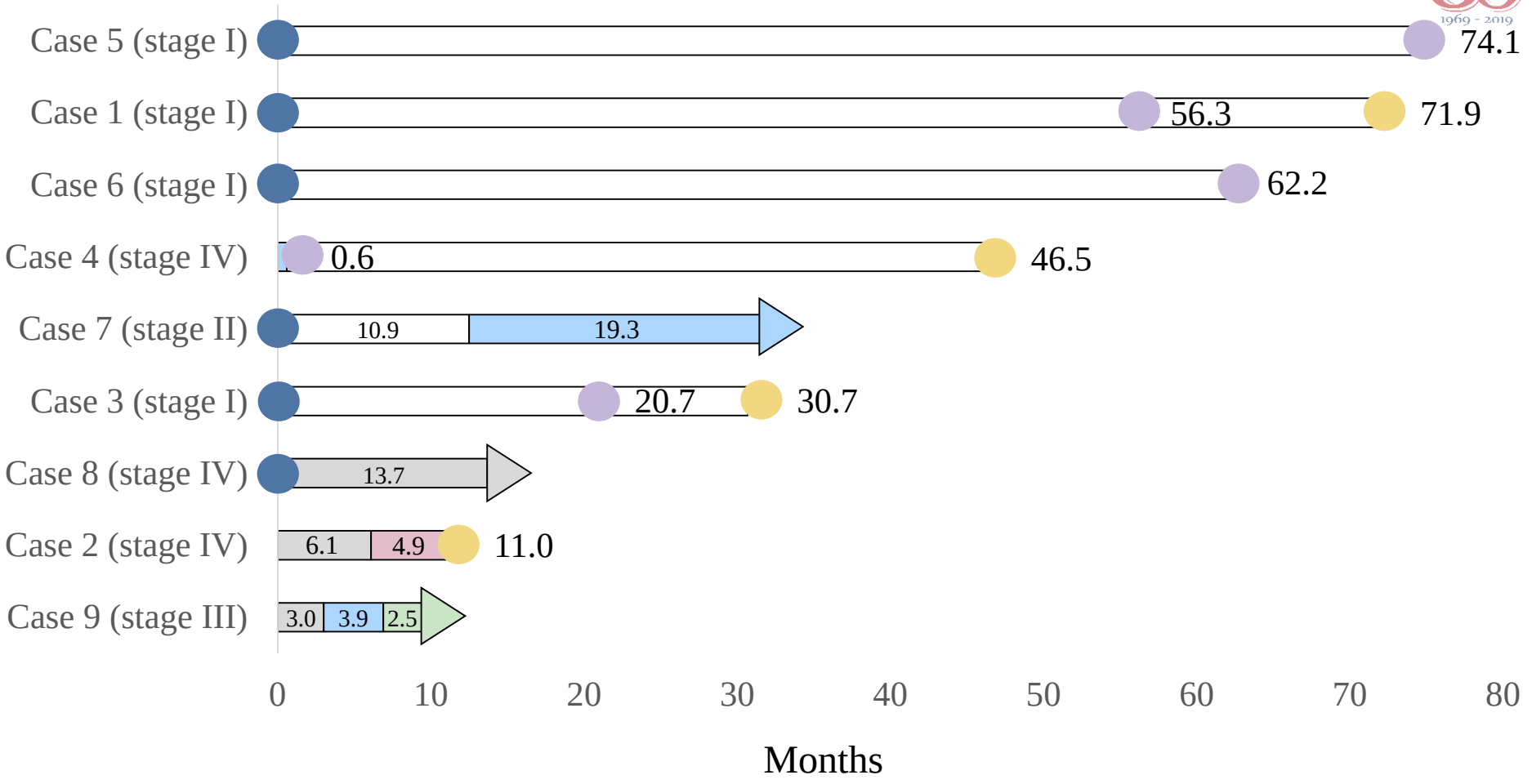
Results

- Age: 47~89 (mean: 69.3), male : female = 7 : 2
- TTF-1 (+): 8, synaptophysin (+): 9, chromogranin (+): 4
- Four had tested for *EGFR*
  - Wild type: 3, exon 19 deletion: 1
- Stage I (n = 4) → operation (2 lobectomy and 2 wedge resection) without recurrence
- Stage II (n = 1) → lobectomy and recurred 11 months later
- Stage III (n = 1) → lobectomy + adjuvant platinum doublet, PD after 4 months
- Stage IV (n = 3)
  - Platinum doublet, PD in 6 months
  - Empirical Iressa and then loss follow-up
  - Bi-lobectomy + adjuvant platinum doublet, no PD for 13 months

*TTF-1: Thyroid Transcription Factor-1, EGFR: Epidermal Growth Factor Receptor, PD: Progressive Disease

Case No.	1	2	4	5	6	7	8	3	9
Age (years)	84	72	89	71	65	61	47	74	59
Gender	M	M	M	M	M	M	M	F	F
Smoking	Y	Y	Y	Y	Y	N	Y	N	N
Diagnostic year	2005	2011	2013	2013	2014	2017	2018	2013	2019
TTF-1	+	+	-	+	+	+	+	+	+
Synaptophysin	+	+	+	+	+	+	+	+	+
Chromogranin	+	-	-	-	-	+	-	+	+
EGFR	NA	NA	Wild type	Wild type	NA	NA	Wild type	NA	Exon 19 deletion
ALK	NA	NA	NA	NA	-	+	-	NA	-
PD-L1	NA	NA	NA	NA	NA	NA	0%	NA	0%
Cancer stage	I	IV	IV	I	I	II	IV	I	III
First line treatment	OP	C/T	TKI	OP	OP	OP	OP + C/T	OP	OP + C/T
Death	Y	Y	Y	N	N	N	N	Y	N
*Overall survival	71.8 months	11.0 months	46.7 months	77.6 months	65.9 months	32.1 months	17.3 months	30.7 months	7.3 months

*Follow-up until 2019/11/30
**OP: Operation, C/T: Chemotherapy


Case 5 (stage I)
74.1
Case 1 (stage I)
56.3
71.9
Case 6 (stage I)
62.2
Case 4 (stage IV)
0.6
46.5
Case 7 (stage II)
10.9
19.3
Case 3 (stage I)
20.7
30.7
Case 8 (stage IV)
13.7
Case 2 (stage IV)
6.1
4.9
11.0
Case 9 (stage III)
3.0
3.9
2.5
0
10
20
30
40
50
60
70
80
Months
Operation
Mortality
Last follow-up
Platinum doublet chemotherapy
Non-platinum doublet chemotherapy
Platinum doublet chemotherapy and immunotherapy
TKI

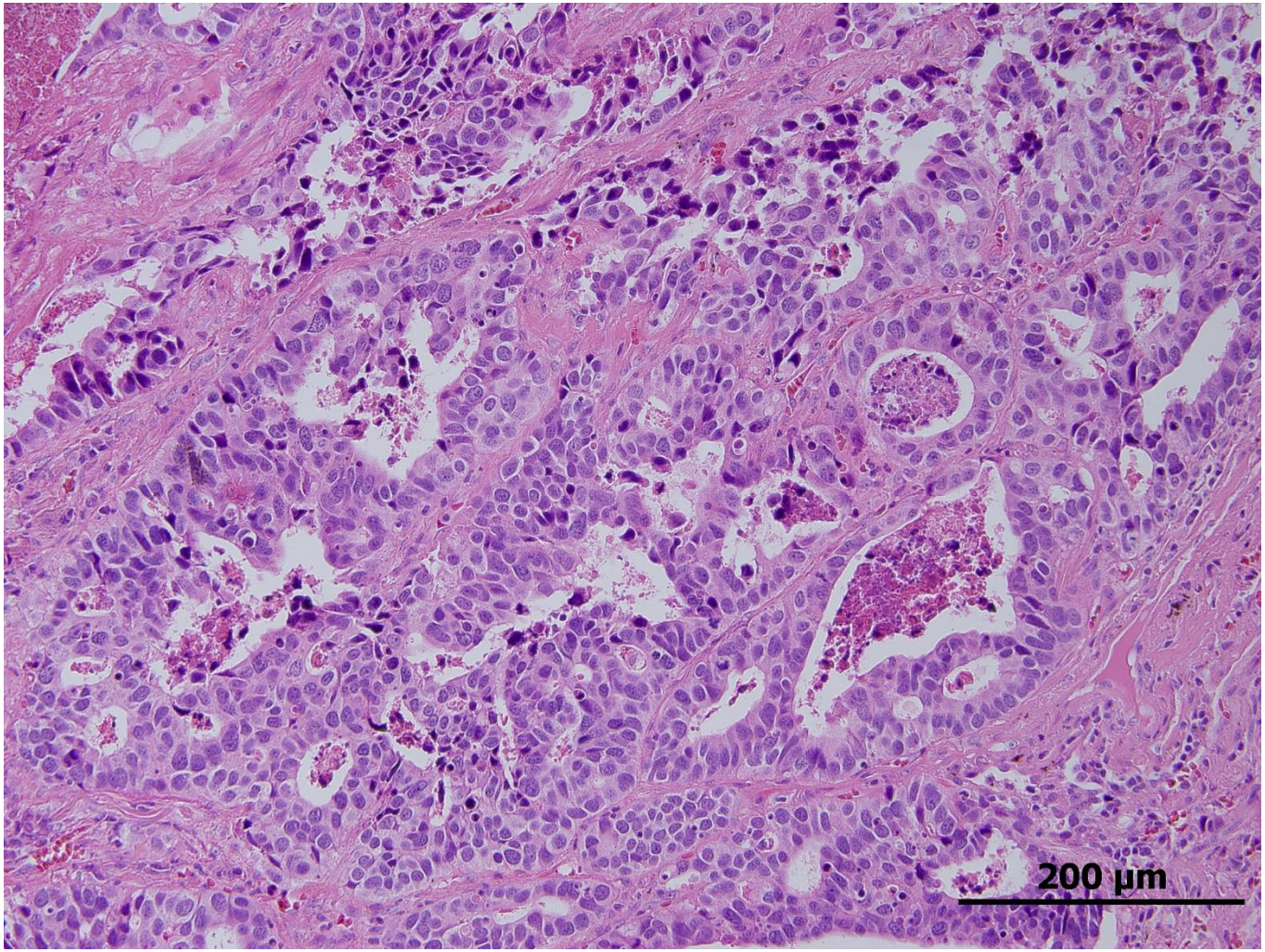
Results

- ADC with NED is adenocarcinoma with neuroendocrine markers (usually with one of the 3 markers: synaptophysin, chromogranin A, or CD56)

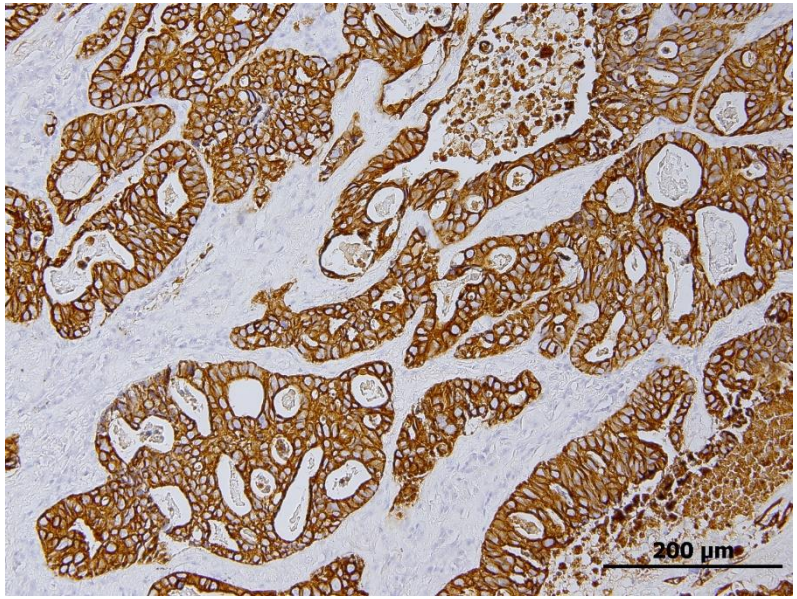
- In this case series study, we demonstrated a high positive rate of synaptophysin (9/9) in ADC with NED, while about half were chromogranin positive (4/9)

J Thorac Oncol. 2015;10:1243-1260.
J Thorac Oncol. 2011;6:244-285.

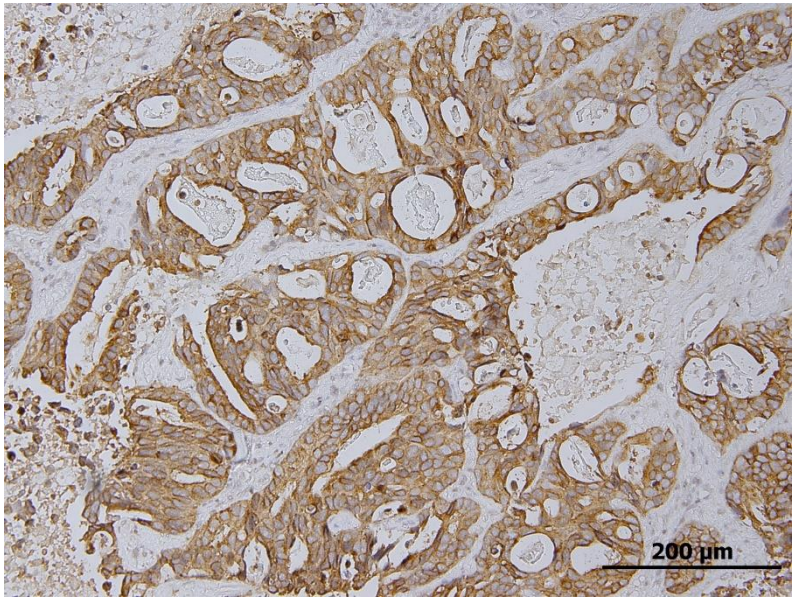
Case 1, HE Stain, Cribriform Pattern

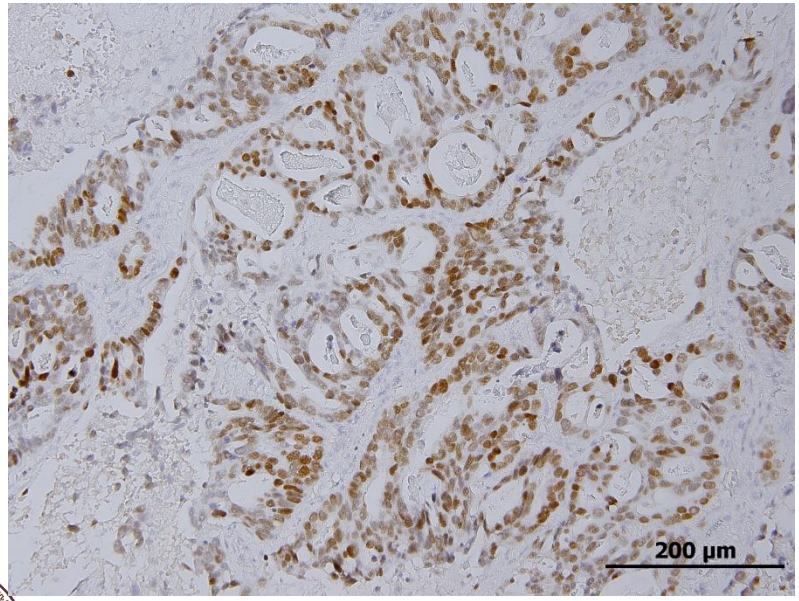


CK7 (+)

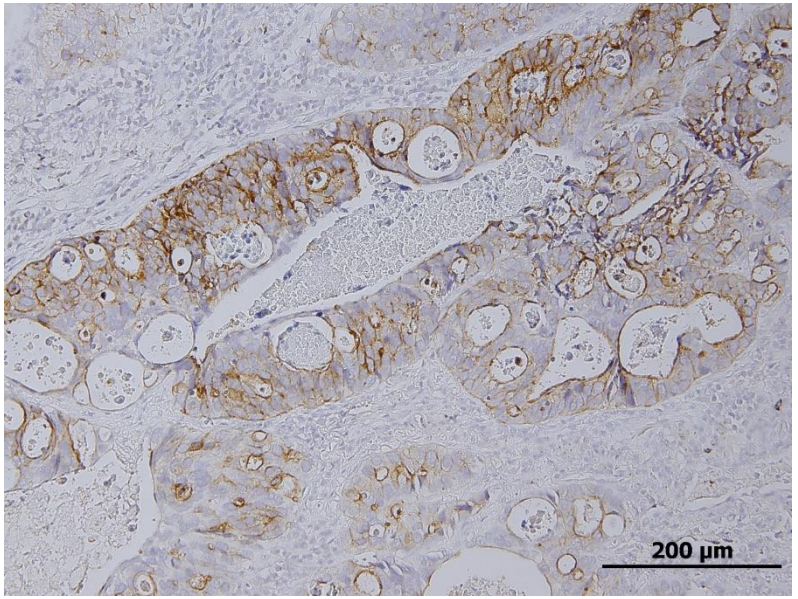


Synaptophysin (+)





TTF-1 (+)



Chromogranin (+)

Discussion

- ADC with NED is seen more often in male and smokers
  - Our study suggested the same result: male (7/9), smoker (6/9)
- ADC with NED seldom has driver mutations
  - Our data showed one with *EGFR* mutation and another with *ALK*
- ADC with NED shows high positive rate of synaptophysin than chromogranin
  - We found compatible results: synaptophysin (9/9), chromogranin (4/9)

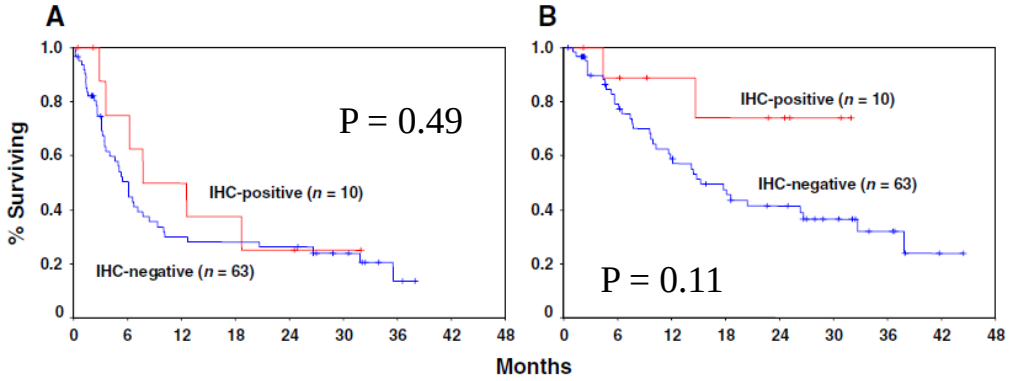
*ALK: Anaplastic Lymphoma Kinase

Zhongguo Fei Ai Za Zhi. 2019;22:507-511.
Histopathology. 2005;46:195-201.

Immunohistochemical detection of neuroendocrine differentiation in non-small-cell lung cancer and its clinical implications

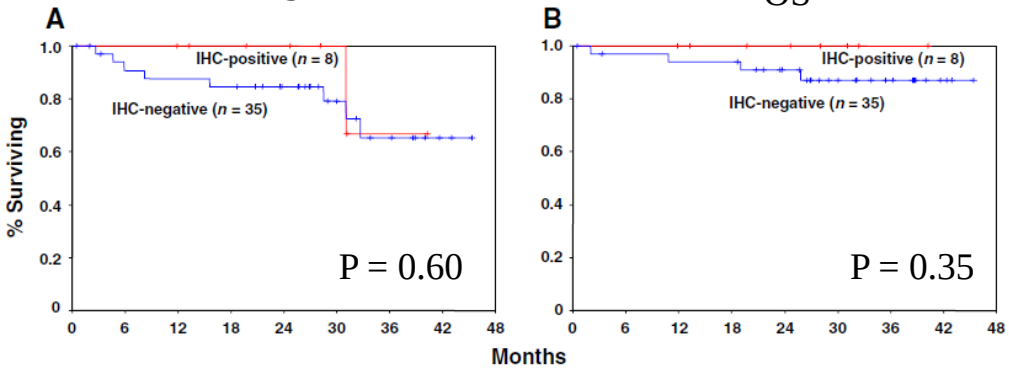
Yoshihiko Segawa · Saburo Takata · Masanori Fujii · Isao Oze · Yoshiro Fujiwara · Yuka Kato · Atsuko Ogino · Eisaku Komori · Shigeki Sawada · Motohiro Yamashita · Rieko Nishimura · Norihiro Teramoto · Shigemitsu Takashima

Patients undergoing non-surgical resection



PFS

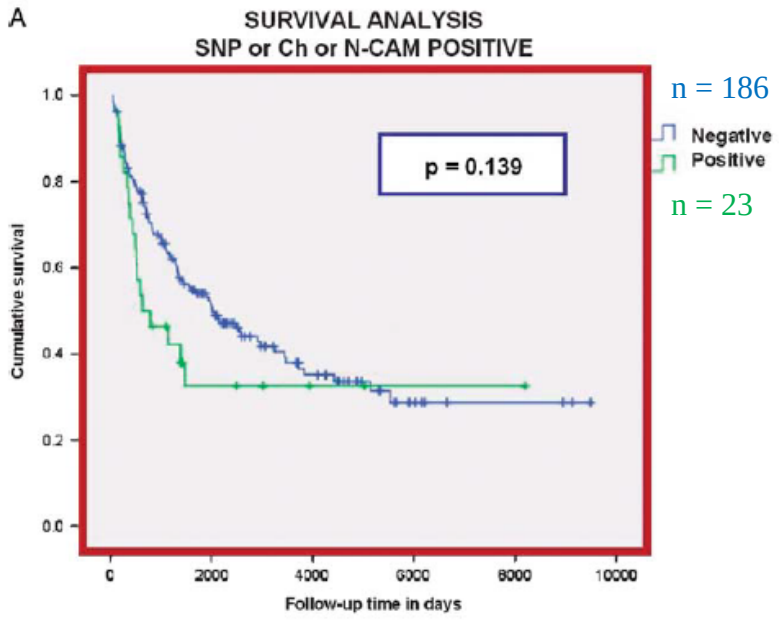
OS



Patients undergoing surgical resection

Nonsmall Cell Lung Carcinoma With Neuroendocrine Differentiation—An Entity of No Clinical or Prognostic Significance

Diana N. Ionescu, MD, Diana Treaba, MD,† Cyril B. Gilks, MD,* Samuel Leung, BSc,* Daniel Renouf, MD,‡ Janessa Laskin, MD,‡ Richard Wood-Baker, MD,§ and Allen M. Gown, MD†*



OS of ADC with / without NED

*PFS: Progression Free Survival, OS: Overall Survival

J Cancer Res Clin Oncol. 2009;135:1055-9.
Am J Surg Pathol. 2007;31:26-32.

Conclusion

- According to the 2015 WHO lung cancer classification and the 2011 IASLC/ATS/ERS lung ADC classification, NSCLC have NED is not formally recognized as a class of tumors
- Until now, there is no conclusion about its significance on prognosis
- Further studies with more cases are needed

* WHO: World Health Organization, IASLC: International Association for the Study of Lung Cancer, ATS: American Thoracic Society, ERS: European Respiratory Society

J Thorac Oncol. 2015;10:1243-1260.
J Thorac Oncol. 2011;6:244-285.

Thank you for your attentions