Table S3. Clinical characteristics of patients with panel-consensus LCNEC meeting all WHO 2015 criteria (N=108)

Clinical characteristic	Total cohort	Chemotherapy clusters			NSCLC-t versus	
	Total	NSCLC-t	NSCLC-pt	SCLC-t	NSCLC-pt	SCLC-t
	N (%)	*N (%)*	*N (%)*	*N (%)*	*P-value*	*P-value*
Patients	108 (100)	51 (47)	16 (15)	41 (38)	-	-
Age (median, IQR)	65 (55-71)	65 (55-69)	68 (57-74)	63 (54-71)	0.62[i]	0.82[i]
Gender (males)	61 (57)	28 (55)	8 (50)	25 (61)		
Number of organs with metastases					1.00†*	**0.04†**
1	48 (45)	22 (43)	10 (62)	16 (39)		
2	41 (38)	23 (45)	5 (31)	13 (32)		
3	9 (8)	1 (2)	0 (0)	8 (19)		
>3	10 (9)	5 (10)	1 (6)	4 (10)		
Organ metastases at diagnosis						
Bone	31 (29)	12 (24)	5 (31)	14 (34)	0.53	0.26
Liver	62 (57)	28 (55)	10 (63)	24 (59)	0.59	0.72
Brain	15 (14)	8 (16)	0 (0)	7 (17)	0.18	0.86
Adrenal gland	14 (13)	8 (16)	0 (0)	6 (15)	0.18	0.88
Lung	13 (12)	7 (14)	2 (13)	4 (10)	1.00	0.75*
Pleura	2 (2)	1 (2)	0 (0)	1 (2)	1.00*	1.00*
Lymph node	23 (21)	11 (22)	4 (25)	8 (20)	0.74	0.81
Non-clustered subtype of CT					-	-
Gemcitabine	38 (35)	38 (75)	-	-		
Paclitaxel	7 (7)	7 (14)	-	-		
Docetaxel	5 (5)	5 (10)	-	-		
Vinorelbine	1 (1)	1 (2)	-	-		
Etoposide	41 (38)	-	-	41 (100)		
Pemetrexed	16 (15)	-	16 (100)	-		
Cycles of chemotherapy					0.30‡	0.20‡
1	14 (13)	4 (8)	2 (14)	8 (20)		
2	12 (11)	5 (10)	3 (19)	4 (10)		
3	12 (11)	5 (10)	2 (13)	5 (12)		
4	63 (49)	26 (51)	9 (56)	19 (46)		
>4	15 (14)	10 (20)	0 (0)	5 (12)		
Data lacking	1 (1)	1 (2)	0 (0)	0 (0)		
Additional chemotherapy						
Second line	25 (23)	11 (22)	3 (19)	11 (27)	1.00*	0.56
Third line	5 (5)	3 (6)	0 (0)	2 (5)	1.00*	1.00*

Abbreviations: IQR, interquartile range; N, Number; CT, chemotherapy; NSCLC-t, cluster of gemcitabine, paclitaxel, docetaxel and vinorelbine chemotherapy; NSCLC-pt, cluster of pemetrexed chemotherapy; SCLC-t; cluster of etoposide chemotherapy; WHO, World Health Organization.

[i] Tested with Mann Whitney U test

† Compared ≤2 organ metastases with >2 organ metastases.

‡ Compared ≤2 cycles versus ≥3 cycles of chemotherapy, excluding unknown cases.

* Tested with Fisher Exact test

Table S4. Clinical characteristics of patients diagnosed with LCNEC in the routine practice (N=164)

Clinical characteristic	Total cohort	Chemotherapy clusters			NSCLC-t vs.	
	Total	NSCLC-t	NSCLC-pt	SCLC-t	NSCLC-pt	SCLC-t
	N (%)	N (%)	N (%)	N (%)	P-value	P-value
Patients	164 (100)	72 (44)	22 (13)	70 (43)	-	-
Overall survival (95% CI)	7.6 [6.9-8.3]	7.8 [6.5-9.2]	7.9 [5.3-10.4]	6.8 [5.7-7.9]	0.74	0.17
Progression free survival (95% CI)	5.0 [4.6-5.5]	5.3 [4.5-6.2]	4.6 [3.7-5.5]	4.8 [4.2-5.3]	0.96ⱡ	0.41ⱡ
Age (Median, IQR)	63 (56-70)	64 (56-70)	69 (58-74)	63 (53-69)	0.81[i]	0.31[i]
Gender (males)	86 (52)	35 (49)	10 (46)	41 (59)	0.80	0.23
Number of organs with metastases					1.00†*	**0.008†***
1	71 (43)	33 (46)	14 (64)	24 (34)		
2	59 (36)	30 (42)	5 (23)	24 (34)		
3	20 (12)	4 (5)	2 (9)	14 (20)		
>3	14 (9)	5 (7)	1 (4)	8 (12)		
Organ metastases at diagnosis						
Bone	49 (30)	20 (28)	3 (14)	26 (37)	0.18	0.23
Liver	83 (51)	34 (47)	8 (36)	41 (59)	0.37*	0.18
Brain	34 (21)	12 (17)	5 (23)	15 (21)	0.76*	0.48
Adrenal gland	32 (20)	14 (20)	5 (23)	13 (19)	0.77*	0.90
Lung	25 (15)	12 (17)	1 (5)	12 (17)	0.29*	0.94
Pleura	3 (2)	2 (3)	0 (0)	1 (1)	1.00*	1.00*
Lymph node	28 (17)	13 (18)	8 (36)	7 (10)	0.09	0.17
Non-clustered subtype of CT					-	-
Gemcitabine	57 (35)	57 (79)	-	-		
Paclitaxel	9 (6)	9 (13)	-	-		
Docetaxel	5 (3)	5 (7)	-	-		
Vinorelbine	1 (1)	1 (1)	-	-		
Etoposide	70 (42)	-	-	70 (100)		
Pemetrexed	22 (13)	-	22 (100)	-		
Cycles of chemotherapy					0.35‡*	0.16‡
1	20 (12)	6 (8)	2 (9)	12 (17)		
2	15 (9)	5 (7)	4 (18)	6 (9)		
3	19 (12)	11 (16)	2 (9)	6 (9)		
4	83 (51)	36 (50)	14 (64)	33 (47)		
>4	24 (15)	11 (15)	0 (0)	13 (19)		
Data lacking	3 (2)	3 (4)	0 (0)	0 (0)		
Additional chemotherapy						
Second line	44 (27)	18 (25)	5 (23)	21 (30)	0.83	0.51
Third line	6 (4)	3 (4)	1 (5)	2 (3)	1.00	1.00*

Abbreviations: IQR, interquartile range; N, Number; CT, chemotherapy; CI, 95% confidence interval; ; NSCLC-t, clustered platinum gemcitabine, paclitaxel, docetaxel or vinorelbine chemotherapy; NSCLC-pt, NSCLC platinum-pemetrexed chemotherapy; SCLC-t, SCLC platinum-etoposide chemotherapy.

ⱡ N=154 patients; [i] Tested with Mann Whitney U test; † Compared ≤2 organ metastases with >2 organ metastases; ‡ Compared ≤2 cycles versus ≥3 cycles of chemotherapy, excluding unknown cases; * Tested with Fisher Exact test

Table S5. Comparison of characteristics of patients with complete and with lacking chemotherapy data diagnosed with LCNEC in the routine pathology practice (N=225).

Clinical characteristic	Total cohort	Chemotherapy information		
	Total	Complete	unavailable	versus
	N (%)	*N (%)*	*N (%)*	*P-value*
Patients	225 (100)	164 (73)	61 (27)	-
OS (95% CI)	7.9 [7.1-8.7]	7.6 [6.9-8.3]	9.2 [7.7-10.6]	0.16
Age (Median, IQR)	63 (56-70)	63 (56-70)	62 (56-69)	0.50[i]
Gender (males)	130 (58)	86 (52)	44 (72)	**0.01**
Number of organs with metastases				0.68
1	102 (47)	75 (48)	27 (47)	
2	75 (35)	52 (33)	23 (40)	
3	25 (12)	19 (12)	6 (10)	
>3	13 (6)	11 (7)	2 (3)	

Abbreviations: 95% CI, 95% confidence interval; IQR, interquartile range; N, Number; LCNEC, large cell neuroendocrine carcinoma.

[i] Tested with Mann Whitney U test