NEUROENDOCRINE TUMORS OF THE LUNG WITH SURGICAL RESECTION AND LYMPH NODE DISSECTION IN A TERTIARY THORACIC SURGERY CENTER

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Abstract

Context. Management of neuroendocrine tumors is highly dynamic, in both diagnosis and treatment.

Objective. Surgical resection with lymph node approach offers excellent 5-years survival.

Design. Between 2008 and 2011 we operated with radical intent 326 lung cancers.

Patients and Methods. Cases without lymph node approach were excluded. We found 38 neuroendocrine malignancies: 12 typical carcinoids, 3 atypical carcinoids, 4 large cell neuroendocrine carcinomas (LCNEC) and 10 small-cell lung cancers (SCLC). Limits of the study are: variable lymphadenectomy technique; absence of PET - CT and EBUS-TBNA (EndoBronchial UltraSound - TransBronchial Needle Aspiration) for staging; incomplete data for disease-free survival.

Results. We performed 13 pneumonectomies, 22 lobectomies and 3 non-anatomical resections. There were 5 bronchoplasties. The 5-year survival difference between NSCLC (non-small-cell lung cancer - 42.9%) and SCLC (40.53% - one of the best from the literature) is not statistically significant ($p=0.4780$). Five-years survival was 100% for typical and atypical carcinoids – the best published. We found lymph node metastasis in 2 typical carcinoids, in 2 atypical carcinoids and in 6 SCLCs.

Conclusions. For typical and atypical carcinoids, radical resection with lymphadenectomy offers 100% 5-years survival. Early-stage SCLC may benefit from radical resection; lymph node dissection is mandatory because of the well-known precocious lymphatic dissemination.

Key words: neuroendocrine lung tumors, radical resection, lymphadenectomy, lymph node dissection, carcinoid, small-cell lung cancer.

INTRODUCTION

Lung cancer is essentially classified in non-small cell lung cancer – NSCLC - and small-cell lung cancer – SCLC, based on pathology, management and

prognosis. NSCLC has as main classes: squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma and large cell carcinoma.

Neuroendocrine tumors of the lung are: typical carcinoid, atypical carcinoid, large cell neuroendocrine carcinoma (LCNEC) and small-cell lung cancer (SCLC). All are derived from Amine Precursor Uptake and Decarboxylation (APUD) cells, remnants of the neural crest, considered as malignant tumors by the 8th WHO classification of endocrine tumors (1). The management of neuroendocrine tumors is highly dynamic, in both diagnosis and treatment, as far as detailed biochemical and pathology specific markers and functional imaging are increasingly available.

The neuroendocrine differentiation is possible in all types of NSCLC, but inclusion in the neuroendocrine tumor category requires certain criteria to be met: clinical, imaging, biochemistry and pathology (including immunohistochemistry).

PATIENTS AND METHODS

The study is performed on cases operated between January 2008 and December 2011. We included pulmonary resections with radical intent with lymph node dissection for malignant primary lung tumor as evidenced by the histopathological report.

This communication is a subcomponent of the study – we selected the cases with neuroendocrine tumors and analyzed them in terms of lymphatic extension and postoperative survival.

For the postoperative staging of the tumors we used the 6th edition of the TNM (valid until January 1st, 2010) since most of the patients (241 out of 324, meaning ¾ of them) were operated before January 2010, so they were staged and treated according to the 6th edition of TNM.

For the statistical analysis of the group we

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studied numerous variables. Overall survival is defined as the time period between the surgical intervention and death. The data was systematized using the 2013 version of the Microsoft Excel program. Statistical analysis was done with the same application together with a few “add-ins” (WinStat, Xlstat) and with the online support provided by Vassar College Poughkeepsie, NY USA (www.vassarstats.net).

The limits of the study are: variations in the lymphadenectomy surgical technique (because of the presence in the study of several different surgeons); the routine absence of PET-CT studies; the permanent absence of EBUS-TBNA (EndoBronchial UltraSound–TransBronchial Needle Aspiration) for mediastinal staging; incomplete data for calculating the disease-free interval. The informed consent was obtained from every patient and attached to the patient records. The study has been approved by the ethical review committee.

Figure 1. Distribution and proportions of neuroendocrine carcinomas. Abbreviations: LCNEC = large cell neuroendocrine carcinoma; SCLC = small cell lung cancer.

Figure 2. Kaplan-Meier survival curves for NSCLC and SCLC after surgical resection with radical intent. Abbreviations: NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer.

RESULTS

Between 2008 and 2011 we operated with radical intent 326 cases of lung cancer of which 324 carcinomas and 2 sarcomas. Out of 324 lung carcinomas, 38 were neuroendocrine types (11.72%). There were 15 carcinoids (12 typical and 3 atypical), 3 LCNEC, 19 SCLC and 1 double carcinoma: LCNEC in right upper lobe and adenocarcinoma in the middle lobe (Fig. 1).

Five cases of SCLC were combined forms, all with squamous cell carcinoma and one with adenocarcinoma. Ten of the 15 carcinoids were confirmed by immunohistochemistry. All 4 LCNEC were also confirmed by immunohistochemistry using specific markers as shown in Table 1.

The gender distribution of the patients was: 9 female and 3 male for typical carcinoids; 2 female and 1 male for atypical carcinoids. SCLC was found in 1 female and 18 male. All patients with LCNEC were male.

We performed 13 pneumonectomies (4 right and 9 left), 22 lobectomies (of which 2 bilobectomies) and 3 non-anatomical resections (limited resections imposed by the altered cardiopulmonary status). There were 5 bronchoplastic procedures: 3 lobectomies with broncho-anastomosis and 2 bronchoplasties (in a right pneumonectomy and a lower bilobectomy). Six pneumonectomies were performed with intrapericardial approach of the pulmonary vessels. In 3 cases the invaded pericardium was resected and a pericardioplasty was performed. In 2 cases the postero-superior chest wall was resected because of the tumoral invasion;

Figure 3. Kaplan-Meier survival rate curves for the various histologies of resected lung cancer.

Table 1. Detailed immunohistochemistry performed after the histopathological diagnosis in 10 out of 15 cases of carcinoids, including the neuroendocrine markers

Number	Histological diagnosis	Sex	Age	Negative IHC stains	Positive IHC stains
1	Atypical carcinoid	f	48	TTF1 CD34	SYN CROMO TTF1 Ki67 - 10%
2	Atypical carcinoid	m	57	Ck7 TTF1	CROMO SYN Ki67 - 15%
3	Atypical carcinoid	f	50		TTF1 CROMO SYN Ck19 Ki67 - 10-15%
4	Typical carcinoid	m	56	TTF1	CROMO MNFI16 Ki67 - 5%
5	Typical carcinoid	f	59	-	- CROMO
6	Typical carcinoid	f	42	Ck7	SYN TTF1 Ki67 - 1-2%
7	Typical carcinoid	f	68	TTF1 CD117 Ck7 EGFR	CROMO SYN Ki67 - 2-3%
8	Typical carcinoid	f	40	-	- EMA Ck7 CROMO
9	Typical carcinoid	f	55		Leu7 SYN Ki67 - 1-3%
10	Typical carcinoid	f	51	-	-
11	Typical carcinoid	f	54	TTF1	SYN Ki67 - 3%
12	Typical carcinoid	m	54	-	-
13	Typical carcinoid	f	22	-	-
14	Typical carcinoid	f	57	TTF1	CROMO SYN Ki67 - 3%
15	Typical carcinoid	m	38		SYN TTF1 CROMO Ki67 < 3%

Abbreviations: CD117 = SCFR = mast/stem cell growth factor receptor = proto-oncogene c-Kit = tyrosine-protein kinase Kit; CD34 = hematopoietic progenitor cell antigen; Ck19 = cytokeratin 19; Ck7 = cytokeratin 7; CROMO = chromogranin; EGFR = epidermal growth factor receptor; EMA = epithelial membrane antigen; Ki67 = nuclear antigen used as a cellular marker for proliferation; Leu7 = CD57 = membrane glycoprotein with cell adhesion functions; MNFI16 = anti-cytokeratin antibody; SYN = synaptophysin; TTF1 = thyroid transcription factor.

in one case chest wall reconstruction was necessary. In other 4 cases the chest invasion was limited to the parietal pleura, which was resected. Other associated resections were: esophageal muscular external wall, phrenic nerve, sympathetic nerve.

All pulmonary resections included excision of the lymphatic stations, intrapulmonary and/or mediastinal. Cases without lymph node approach were

excluded from the study (as we explain in Discussion).

Postsurgical tumor stages are presented in Table 2, together with N status and lymph node station involved in every patient. Skip metastases were not found in neuroendocrine tumors.

Overall survival correlates positively with carcinoid tumors ($p=0.0006$) and with typical carcinoids ($p<0.0001$). There is no statistically significant

Table 2. Lymph node involvement in each case of neuroendocrine carcinoma and pathological stage according to it (the edition 6th of TNM was used for staging since most patients were staged and treated according to it)

No.	Histological type	Gender	Age	Type of surgical resection	Pathological stage	Lymph node status	Lymphatic stations involved
1	LCNEC	m	56	LLL	IA	N0	
2	LCNEC	m	70	WR LLL	IB	N0	
3	LCNEC	m	56	RUL	IB	N0	
4	SCLC	m	68	LEFT PN	IIB	N0	
5	SCLC	m	78	LEFT PN	IIB	N0	
6	SCLC	m	57	LEFT PN	IIIA	N2	5, 6
7	SCLC	f	47	RLL	IB	N0	
8	SCLC	m	69	RIGHT PN	IIB	N0	
9	SCLC	m	64	LEFT PN	IIIA	N2	5, 10
10	SCLC	m	48	LEFT PN	IV	N2	3a, 7, 8, 9, 10
11	SCLC	m	54	RLL	IB	N0	
12	SCLC	m	55	RUL	IIB	N0	
13	SCLC	m	56	RUL	IIB	N0	
14	SCLC	m	63	2 WR: RLL, RUL	IIIA	N0	
15	SCLC	m	65	WR LUL RIGHT PN	IIIA	N2	5
16	SCLC combined	m	68	bronchoplastic resection	IIB	N0	
17	SCLC combined	m	47	LEFT PN	IIIA	N2	5, 10
18	SCLC combined	m	71	RUL	IB	N0	
19	SCLC combined	m	56	LUL	IIB	N0	
20	SCLC combined	m	63	RUL	IIB	N1	peribronchial
21	SCLC intermediate type	m	61	LUL	IA	N0	
22	SCLC intermediate type	m	68	RUL	IIB	N0	
23	Atypical carcinoid	f	48	LEFT PN	IB	N0	
24	Atypical carcinoid	m	57	RLL	IIIA	N2	7, 11i
25	Atypical carcinoid	f	50	LEFT PN	IIIA	N2	9, 10
26	Typical carcinoid	m	56	LLL	IIB	N1	peribronchial
27	Typical carcinoid	f	59	RUL with broncho-anastomosis	IB	N0	
28	Typical carcinoid	f	42	INF BILOB	IB	N0	
29	Typical carcinoid	f	68	RLL	IB	N0	
30	Typical carcinoid	f	40	LUL with broncho-anastomosis	IB	N0	
31	Typical carcinoid	f	55	RIGHT PN	IIB	N1	10
32	Typical carcinoid	f	51	LEFT PN	IIB	N0	
33	Typical carcinoid	f	54	RIGHT PN INF BILOB	IB	N0	
34	Typical carcinoid	m	54	bronchoplastic resection	IB	N0	
35	Typical carcinoid	f	22	LLL	IB	N0	
36	Typical carcinoid	f	57	RUL	IA	N0	
37	Typical carcinoid	m	38	LUL with broncho-anastomosis	IA	N0	
38	Double carcinoma: LCNEC+adenocarcinoma	m	64	RUL	IIB	N0	

Abbreviations: INF BILOB = inferior bilobectomy; LCNEC = large cell neuroendocrine carcinoma; LLL = left lower lobectomy; LUL = left upper lobectomy; PN = pneumonectomy; RLL = right lower lobectomy; RUL = right upper lobectomy; SCLC = small cell lung cancer; WR = wedge resection; Lymphatic stations: 3a = prevascular, 5 = subaortic, 6 = paraaortic, 7 = subcarinal, 8 = paraesophageal, 9 = pulmonary ligament, 10 = hilar, 11i = interlobar inferior.

correlation between survival and SCLC, atypical carcinoid or LCNEC, although survival was better for atypical carcinoids and worse for SCLC and LCNEC.

For all the patients in our study the calculated

5-year survival rate was 43.38%. The 5-year survival rate for resected NSCLC was 42.9%. For resected SCLC the value is 40.53%. The survival differences between NSCLC and SCLC are not statistically significant

($p=0.4780$), the two survival rates are similar (Fig. 2).

Figure 3 presents Kaplan-Meier survival curves for the various histological types of resected lung cancer. Survival rate for the 3 patients with resected LCNEC is difficult to calculate; the only interpretable value is a 66% survival rate at 2 years. Mean survival rate is 24.66 months and the median is 28 months. Two patients died after 18 and 28 months respectively, the third was still alive after 23 months. The double carcinoma (LCNEC and adenocarcinoma) was excluded from the LCNEC group; he was still alive at 33 months from surgery.

All patients with carcinoid tumors were alive at the end of the study. Calculated 5-years survival rate was 100% for both typical and atypical carcinoids. Mean survival was 62 months for typical and 60 months for atypical carcinoids.

For carcinoid tumors and for LCNEC, uni- and multivariate analysis showed no correlations with TNM descriptors. For SCLC, uni- and multivariate analysis showed that patients with SCLC have more advanced stages at presentation.

DISCUSSION

Neuroendocrine tumors of the lung have been classified over the time into different types: typical carcinoid, atypical carcinoid, large cell neuroendocrine carcinoma (LCNEC), small-cell lung cancer (SCLC), intermediate cell type neuroendocrine carcinoma (2-7). In the last WHO classifications of lung tumors (2015), neuroendocrine tumors are grouped together in one category, despite their different clinical behaviour, therapeutic management and survival rates (7-8).

Tumourlets are multiple tumoral entities smaller than 0.5 cm, difficult to detect on CT or PET-CT, with the same Kultchitsky cell origin as all neuroendocrine tumors, in which the hyperplastic cells could be in any stage of the malignity spectrum (9).

Diffuse idiopathic neuroendocrine cell hyperplasia (DIPNCH) appears secondary to inflammation or hypoxia and is considered to be a precursor of the tumourlets and also a preneoplastic state for some carcinoid tumors (2, 8, 9). Neuroendocrine differentiation is described on electron microscopy, immunohistochemistry and other molecular studies (10).

For carcinoid tumors we performed bronchoplasties and bronchoanastomoses, with or without pulmonary resections, (as in our previous series published in 2009 (11)) and classical lung resections – but only cases with lymphadenectomy

were included in the study. Initially, lymphadenectomy was not performed as routine in carcinoid tumors, so those cases without lymph node dissection (or at least lymph node sampling) were excluded.

None of the patients with carcinoids had paraneoplastic syndromes with clinical manifestations; we did not perform plasmatic and urinary marker dosing of hormones related with any possible paraneoplastic syndrome. In the literature, carcinoid syndrome is cited in less than 1% at presentation and Cushing's syndrome in 1-6% (12). Table 1 presents the patients with carcinoid tumors and the detailed immunohistochemistry performed on their tumors (in 10 out of all 15 carcinoids, typical and atypical).

Regarding carcinoid tumors, the typical carcinoid is usually endobronchial, being defined by <2 mitotic figures per 2 mm^2 and no necrosis. It presents metastases in 1-20% of cases (2, 7, 12-14). The surgical resection has an absolute indication and the survival rate is 90-95% at 5 years (13).

We found lymph node metastases in 2 cases (Table 2) – 16.66%. In one case the peribronchial lymph nodes were found with metastases after left lower lobectomy with interlobar, hilar and subcarinal lymphadenectomy. The other case was a right central tumor with hilar metastatic adenopathy, diagnosed as squamous-cell carcinoma (bronchoscopic biopsy), which imposed right pneumonectomy with intrapericardial approach of the pulmonary vessels and lymphadenectomy (superior and inferior paratracheal, subcarinal, paraesophageal and hilar stations). Immunohistochemistry showed it was actually a typical carcinoid.

One hundred percent survival rate at 5 years is better than values found in literature. Our study confirms that typical carcinoids are tumors with low-grade malignancy but their cure asks for radical resection. Together with pulmonary resection, lymphadenectomy (hilar and mediastinal) is mandatory for complete excision of the typical carcinoid, this being associated with good survival in patients with a typical carcinoid even if there is N2 node involvement.

The atypical carcinoid is more aggressive, usually presenting as a lung carcinoma. At diagnosis there are lymph node metastases in 30-50% of cases (2, 7, 9, 12-14). The radical treatment is surgical resection with intrapulmonary and mediastinal lymph node dissection – this is strongly recommended with any suspicion of atypical carcinoid (12). The rate of survival at 5 years is 42-75% (14).

We found lymphatic metastases in 2 out

of 3 cases – 66.66%, more than in the literature, in mediastinal, hilar and intrapulmonary stations (Table 2). Interestingly, the case without lymphatic metastases presented with hematogenous metastases, in both ovaries. Resection of the pelvic tumors showed metastases from atypical carcinoid of lung origin; after chemotherapy, the primary tumor was resected by left pneumonectomy and mediastinal and hilar lymphadenectomy.

Although lymphatic metastases were more frequent than in the literature, the 5-years survival (100%) was much better than the published values. This reinforces the idea of radical resection (lobectomy with resection of invaded structures and lymphadenectomy - mediastinal, hilar and intrapulmonary) for atypical carcinoid.

Regarding large-cell neuroendocrine carcinoma (LCNEC) – it is a rare but very aggressive form of lung cancer. It is usually found as a pulmonary nodule (T1 or T2 tumor), but only 10% of the patients are alive after 2 years (14). It is found in approx. 3% of all lung cancers. The diagnosis of LCNEC implies the neuroendocrine morphology (organoid pattern) and expression of at least one neuroendocrine marker (such as chromogranin CROMO, synaptophysin SYN and neural cell adhesion molecule NCAM (15)).

In our study there were only 3 cases of LCNEC – 0.92% of 326 lung cancers, probably due to the difficult pathological diagnosis. There were one T1 and two T2 tumors – small tumors, like those described in the literature, with no lymphatic metastases.

Regarding small-cell lung cancer (SCLC) – this represents about 20% of all pulmonary carcinomas. It is usually a central tumor with large metastatic adenopathies in the mediastinum, similar to primary tumors of mediastinum (16). The overall 2-year survival rate is less than 5% in SCLC (17).

Any tumor with at least 10% of small cells should be classified as combined SCLC (2), (8). At immunohistochemistry, SCLC expresses neuron-specific enolase (NSE), creatine kinase, synaptophysin, chromogranin, serotonin (occasionally), often epidermal growth factor (EGF), cytokeratins 8 and 18, and Leu-7.

The standard therapy for early SCLC was considered to be combined chemotherapy with early, concurrent thoracic radiotherapy. Resection is indicated in selected cases: stage I SCLC (SCLC presented as solitary pulmonary nodule (18)), mixed-histology tumors, as adjuvant to chemotherapy with good response, resectable tumors non-responding to

chemotherapy, emergency cases (palliative surgery for hemoptysis, tumoral abscess, non-controllable pain) (19-21). Recently, a growing body of literature suggests that early-stage SCLC may be more amenable to local control following resection, with surgery being an important component of the multimodal therapy (22). Radical resection of SCLC was performed in different studies and the 5-year survival rates were: 42%, with 50% after lobectomy *versus* 20% after limited resection (23); 38% for stages I and II and 16% for stages III and IV (24); 31% for SCLC, with better survival rates for elective surgery than for the incidental surgery (for comparison, 5-year survival rate for resected NSCLC was 45% in the same study) (25). The role of induction chemotherapy before radical resection is that of earlier treatment of distant micrometastases and reduction of the primary tumor (22). Postoperatively, all patients should receive chemotherapy; patients with mediastinal involvement should receive concurrent chemo-radiotherapy (22).

LCNEC and SCLC stratified by stage have the same survival rate (4, 26).

Beginning with the 7th edition of TNM staging, applied from January 2010, the carcinoid tumors and the SCLC are also included, based on IASCL database survival analysis, on T, N and M categories and on TNM stages (27, 28). This is also valid in the 8th edition of TNM staging, applied from January 2017 (7, 8, 29).

In our study, SCLC represents 16% of all carcinomas. 18 of 19 patients with SCLC presented as resectable lung tumors without preoperative pathological diagnosis. They were surgically approached as NSCLC. We found lymph node metastases in 31.57% of patients with SCLC; by comparison, lymph node metastases in NSCLC patients were found in 44.01% of cases. Statistical analysis showed that SCLC spreads through lymphatic metastases more frequently only in N1 stations ($p=0.0127$), maybe because SCLC was resected in earlier stages as compared to NSCLC. But we compared the number of cases resected in stage pI and we found that 21.05% of SCLC (4 out of 19) were resected in pathological stage I (IA or IB), and 38.73% of NSCLC (110 out of 284) were resected in pathological stage I (IA or IB). Also by comparison, in pathological stage IV there were resected 5.26% of SCLC (one case) and 2.81% of NSCLC (8 cases).

For our resected SCLC (all stages grouped together) the 5-year survival rate is 40.53% - it is one of the best survival rates in literature. The survival difference between NSCLC and SCLC is

not statistically significant ($p=0.4780$) in our study, the two survival rates being similar. In our opinion, this confirms the fact that early stage SCLC benefits from radical resection and overall survival is similar to resected NSCLC.

In conclusion, neuroendocrine tumors of the lung are: typical carcinoid, atypical carcinoid, large cell neuroendocrine carcinoma (LCNEC), small-cell lung cancer (SCLC). Starting with 2010, TNM staging has also included both carcinoids and SCLC, so now every lung carcinoma is TNM staged. For typical and atypical carcinoids, radical resection is mandatory for a 100% 5-year survival rate, like the one we obtained. Because lymph node metastases are present even in typical carcinoids, lymphadenectomy/ lymph node dissection (mediastinal, hilar and intrapulmonary) is strongly indicated for radical excision.

Small-cell lung cancer or microcellular carcinoma may benefit from radical resection, especially in early stages; 5-year survival rate is similar to resected non-small cell lung cancer in our study. The survival rate of 40.53% is one of the best in the literature. Lymphadenectomy is mandatory because of the well-known early lymphatic dissemination.

Conflict of interest

The authors declare that they have no conflict of interest.

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