Surgical treatment of neuroendocrine tumors of the lung

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Abstract

**Objective:** This report reviews the pattern of neuroendocrine (NE) differentiation, lymph-node involvement, extension of surgery, and survival in 125 NE lung tumor patients.

**Methods:** Standard diagnostic workup included CT scan, bronchoscopy, bronchial biopsy or Fine Needle Aspiration Biopsy, 111In-pentetreotide scan (OctreoScan) and mediastinoscopy in selected patients. NE differentiation was assessed based on the morphology and immunohistochemical reactivity for pan-neuroendocrine markers NSE, CGA, and Synaptophysin. For small cell carcinoma (SCC), only clinical stage I and II patients underwent surgery. Several different surgical procedures were utilized, from limited resections to lobectomy, pneumonectomy, and bronchoplastic procedures. Survival was assessed using Kaplan–Meyer method at 5 years.

**Results:** There were 79 typical carcinoid (TC), eight atypical carcinoid (AC), 18 large cell carcinoma (LCC) and 20 SCC patients. Mean age at diagnosis was 54.6 ± 15.2 (ranges from 16 to 77 years) for TC, 68.5 ± 9.1 (range 53–81) for AC, 68.7 ± 4.6 (range 58–77) for LCC, 64.6 ± 7.9 (range 48–82) for SCC. Male/female ratio was 1/1 for TC and AC, 2.6/1 for LCC and 9/1 for SCC. Lymph-node involvement was present in 14% of TC, 0% of AC, 31.5% of LCC, and 45% of SCC. Cancer specific survival was 96% for TC, 87.5% for AC, 37.5% for LCC, and 30% for SCC at 5 years from surgery. Presenting symptoms were invariably of respiratory-related. None had the carcinoid syndrome. History of tobacco abuse ranged from 46% for TC to 100% in SCC. Survival ranged from a minimum of 1 month for SCC to a maximum of 168 months with no evidence of disease for TC. Synchronous multicentric forms were found in 14% of TC. Twenty-one percent (4/19) of the patients with SCC treated by induction therapy and surgery, and in few cases by surgery and adjuvant chemotherapy are alive without the evidence of the disease for 5 years.

**Conclusions:** Due to the high percentage of lymph-node involvement and multicentric forms found in our series lobectomy with radical lymph-node dissection appears, in our opinion, the most appropriate surgical treatment in well-differentiated forms, while more limited resection appears sub-optimal. Also, due to the finding of recurrences many years after surgery, the follow-up must be accurate and protracted in this subgroup. Only Small Cell Lung Carcinoma patients in clinical stage I and II underwent surgery with good long-term results.

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1. Introduction

The wide spectrum of neuroendocrine (NE) differentiation of lung tumors comprises of neoplasm characterized by similar histochemical and immunohistochemical pattern but totally different clinical behavior. According to the last

Travis–WHO Classification (1999) [1] they range in fact from relatively indolent well-differentiated forms (carcinoids) to the highly aggressive, poorly differentiated forms (large cell and small cell). For this reason despite the common denomination of neuroendocrine tumors, a precise surgical and clinical strategy is required for each different histological subtype. Particularly the extension of surgical treatment in well-differentiated forms and the role of surgery in poorly differentiated forms have been a matter of debate in the last years.

The present report, reviewing the pattern of NE differentiation, lymph-node involvement, clinical and pathological staging, extension of surgery and their impact
on survival in a large number of NE lung tumor patients who underwent surgical treatment in our institution attempts to clarify the correct surgical strategy in this heterogeneous subgroup of lung tumors.

2. Patients and methods

We have analyzed the data of 125 patients affected with NE lung tumors, who underwent surgical treatment in a single institution at the Department of Surgical Sciences, Division of Thoracic Surgery, University of Perugia in Perugia and Terni, Italy from October 1983 to October 2003. In the same period, approximately 2000 patients were operated for lung cancer at the same institute.

Among NE tumors, 79 were typical carcinoid (TC), 8 atypical carcinoid (AC), 18 large cell carcinoma (LCC) and 20 small cell carcinoma (SCC). Retrospective analysis of the clinico-pathologic data, surgical procedures, and outcome were performed. Data were collected using NET software (Ibis Informatica and Arreté, Milan, Italy).

Standard diagnostic workup included CT scan, bronchoscopy, bronchial biopsy and video-assisted multiple biopsy (VATS) or Fine Needle Aspiration biopsy (FNAB), and from 1996 ¹¹¹In-pentetreotide scan (OctreoScan). Mediastinoscopy was performed in selected cases (all SCC patients, CT scan finding of mediastinal node enlargement for the other NE subtypes).

NE differentiation was assessed on the basis of morphology and immunohistochemical reactivity for pan-neuroendocrine markers Neuron Specific Enolase (NSE), Chromogranin A (CGA), Synaptophysin (SYN) [2]. In each case, the presence of necrosis, number of mitoses, and Ki-67 index were evaluated. Multiple forms and tumourlets were carefully researched by performing serial sections of the pulmonary parenchyma specimens in 14% of TC (four multicentric carcinoids and seven cases with multiple tumorlets). Lymph-node involvement was present in 14% of TC, 0% of AC, 31.5% of LCC, and 45% of SCC.

Twenty-five percent (5/20) of the patients with SCC treated by the induction therapy and surgery are alive without the evidence of disease at 5 years.

3. Results

3.1. Surgical procedures

Primary surgical resection consisted of the following procedures: one palliative endobronchial laser treatment alone, two enucleations, one wedge resection, four typical segmental resections, three bronchoplastic procedures, nine sleeve lobectomies, 50 lobectomies, six bilobectomies, and four pneumonectomy for TC; seven lobectomies and one pneumonectomy while one patient did not undergo surgical treatment due to low performance status for AC. Surgical treatment for LCC consisted of 14 lobectomies, three bilobectomies and one pneumonectomy. Finally, five wedge resections, six lobectomies, two bilobectomies, seven pneumonectomies were performed for SCC.

Lobectomy was the most common procedure in all subtypes except SCC (62.5% in TC, 87.5% in AC; 71.4% in LCC, and 30% in SCC). Endobronchial laser treatment was performed usually in preparation for surgery.

3.2. Survival

Cancer specific survival data assessed using Kaplan–Meyer method is displayed in Fig. 1. In well-differentiated forms the overall survival at 5 years was, respectively, 96% (mean survival 63 ± 49.2 months) for TC and 87.5% (mean survival 50 ± 42.4 months) for AC. A slight decrease was noted around 10 years from surgery in both groups (Fig. 1). In poorly differentiated forms, the overall survival at 5 year was, respectively, 37.5% (mean survival 23 ± 19.4 months) for LCC and 30% (mean survival 29 ± 27.2 months) for SCC.

4. Discussion

The classification of NE lung tumors has been revised in 1999 by the World Health Organization (WHO) from Travis...
and co-workers [1]. Despite the common NE differentiation, several differences characterize the four histological subtypes (Table 1).

Due to the totally different features and outcome between well-differentiated and poorly differentiated forms, it is therefore more appropriate to analyze some of the results separately.

4.1. Well-differentiated neuroendocrine tumors (carcinoids)

No sex prevalence has been found in this subgroup. In our series, the male/female ratio was near to one (0.95/1) in agreement with other reported series. Only in another large series of 2931 patients [5], a female prevalence was described for patients under 50 years of age. The ratio of TC to AC is similar to those reported in the literature; although in some series, the prevalence of AC reached a higher percentage [6]. Probably this disparity occurring in series published before 1999 is due to the slightly different criteria (particularly in the number of mitoses) of the former WHO classification. It should be considered that many retrospective reviews of surgical pathology series report a greater incidence of diagnostic error in separating the subgroup AC from LCC.

There is a slight but not statistically significant predominance of central forms, associated with respiratory signs and symptoms (the most frequent hemoptysis, wheezing, cough, dyspnea and localized recurrent pneumonia). Our series confirms the high frequency of associated multiple bronchietases in TC, a well-known consequence of the long-term bronchial obstruction typical of central forms. It is still a matter of debate whether the occurrence of multicentric forms and tumorlets might in some way be related to chronic lung damage and hypoxia, conditions known to elicit NE cells hyperplasia [7,8].

The high frequency of lymph-node involvement and multicentric forms found in our series emphasizes the need for radical oncologic surgery based on adequate pulmonary resection (segmental and other limited procedures must be avoided) associated with radical node dissection. Thorough evaluation of the lymph-nodes and research of multicentric forms in the same lobe should always be performed, furthermore in the 2002 AJCC staging [3], multiple forms situated in the same lobe were classified as T4. For these reasons we propose lobectomy with lymph-node dissection as a standard procedure, also in well-differentiated forms, considered in the past low-malignancy lesions, and therefore, treated sometimes with enucleation or endoscopic procedures. Bronchoscopic resection alone, not allowing lymph node staging and identification of multicentric forms, appears therefore, sub-optimal, often being not curative and lacking some of the prognostic information essential for therapeutic decisions. For this purpose it should be emphasized that the presence of synchronous carcinoid or tumorlets must be carefully researched performing serial section of the pulmonary parenchyma.

4.2. Poorly differentiated neuroendocrine carcinomas

All the patients affected by poorly differentiated forms in our series were heavy smokers with a long history of tobacco abuse. In all the other reported series, a strict correlation with smoke was found, being SCC

<table>
<thead>
<tr>
<th>NE subtype</th>
<th>Typical carcinoid (TC)</th>
<th>Atypical carcinoid (AC)</th>
<th>Large-cell carcinoma (LCC)</th>
<th>Small-cell carcinoma (SCC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>79</td>
<td>8</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>Male/female ratio</td>
<td>39/40</td>
<td>4/4</td>
<td>13/5</td>
<td>18/2</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.6 ± 15.2 (16–77)</td>
<td>68.5 ± 9.1 (53–81)</td>
<td>68.7 ± 4.6 (58–77)</td>
<td>64.6 ± 7.9 (48–82)</td>
</tr>
<tr>
<td>Lymph-node metastases</td>
<td>10/79 (14%)</td>
<td>0/8 (0%)</td>
<td>6/19 (31.5%)</td>
<td>9/20 (45%)</td>
</tr>
<tr>
<td>Mean diameter (mm)</td>
<td>23.1 ± 11.3 (5–55)</td>
<td>25.6 ± 11.4 (14–45)</td>
<td>31.6 ± 15.6 (9–75)</td>
<td>30 ± 16.6 (5–63)</td>
</tr>
<tr>
<td>Right(R)/left(L)</td>
<td>37R/42L</td>
<td>2R/6L</td>
<td>10R/8L</td>
<td>8R/12L</td>
</tr>
<tr>
<td>% of smokers</td>
<td>53</td>
<td>62</td>
<td>94.4</td>
<td>100</td>
</tr>
<tr>
<td>Location</td>
<td>38P/41C</td>
<td>5P/3C</td>
<td>20P</td>
<td>13P/7C</td>
</tr>
</tbody>
</table>

C, central; P, peripheral.
diagnosed in 98.9% of smokers and only in 1.1% of non-smokers.

The mean age of the patients at the time of diagnosis was 68.7 ± 4.6 (range 47–84) in our series for LCC and 64.6 ± 7.9 (48–82) for SCC while is estimated around 60 years (ranging from 32 to 79 years) as a mean value in a meta-analysis of the other reported series.

A male predominance is evident. The male/female ratio was 9/1 in our series for SCC and 2.6/1 for LCC in accordance with other reported series. However, some longitudinal observational trials reported a constantly diminishing male/female ratio probably due to the increasing number of smokers in the female population [9].

The large cell NE carcinoma is the rarest type of tumor among lung NE neoplasms but recent reports have underlined how retrospective analyses using the correct criteria of the WHO–Travis Classification (1999) identified a significant percentage of misdiagnosed LCC, particularly in the AC group. Together with necrosis, in fact the number of mitoses in 10 high-power fields is the main criterion for separating LCC and SCC from AC. Due to the sometimes-irregular distribution of mitoses in the tissue, the use of more reliable criteria, only in part described by the WHO classification (in the last classification it has only been specified that mitoses should be counted in the areas of highest mitotic activity) like Ki67 index and other markers are advocated to reduce the percentage of misdiagnosis.

4.3. Conclusive remarks

Due to the high percentage of lymph-node involvement and multicentric forms found in this series, lobectomy with radical lymph-node dissection appears, in our opinion, the most appropriate surgical treatment in well-differentiated forms, while more limited resection appears sub-optimal. Also in this subgroup, due to the finding of recurrences many years after surgery, the follow-up must be accurate and protracted. Only SCLC patients in clinical stage I and II underwent surgery, with good long-term results.

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References


Appendix A. Conference discussion

Dr L. Molins (Barcelona, Spain): In Spain we have a neuroendocrine lung tumor group. My question is about lymph node metastasis in carcinoid tumors. This is a retrospective study from 1983, so, which was the policy: sampling or resection of the nodes? And, this 14% of lymph node metastasis, did it influence survival? Our results did not.

Dr N. Daddi: In our retrospective review only enucleation and wedge resection procedures for well-differentiated neuroendocrine tumours were performed without any lymphnode sampling. The percentage of lymphnode metastatic involvement in typical carcinoid is referred mainly to the 69/79 patients undergoing standard or bronchoplastic resections. In all cases radical node dissection or mediastinal node sampling through mediastinoscopy were performed. The latter procedure was indicated when planning a sleeve resection in order to avoid extensive mediastinal dissection and ischemic damage to the airways.

Regarding lymphnode involvement in the survival analysis we might say that it did not affect our review. In our follow-up we noticed that five patients, who died because of the recurrence of typical carcinoid, only one had lymphnode involvement (N2) with major surgical resection (right pneumonectomy). Two patients underwent standard resections (lobectomy) with N0 and two patients received minor surgical procedures (enucleation and laser disobliteration) with Nx.

Atypical carcinoids were not affected by the N disease, since three patients died of recurrence and all of them were N0.

Dr F. Rea (Padova, Italy): I’m quite surprised. You have 14% of lymph nodes positive in typical carcinoid, and we can see that all the worldwide literature has around 2, 3%, and you have no lymph nodes in atypical carcinoid. Do you have some comment?

Dr N. Daddi: According to the data available from the literature, lymphnode involvement in typical carcinoids is quite variable ranging from 2 to 3% as you mentioned to over 10%.
As to the absence of metastatic lymphnodes in atypical carcinoids, the few cases observed compared to the large number of typical carcinoids might be an explanation.

Dr P.L. Filosso (Torino, Italy): My first question is about the pattern of recurrences: did you experience high recurrence rate in atypical carcinoid or in large cell neuroendocrine carcinoma, rather than typical carcinoid? The second question is: what is your policy about the follow-up of these patients? Did you routinely use octreoscan or not? And, finally, which kind of adjuvant therapy did you perform?

Dr N. Daddi: First of all: regarding your last question about the adjuvant therapy, I can’t be more specific since at present several protocols are being studied by our oncologists. Concerning the follow-up: we are now recalling all our patients and we are starting to check them with the OctreoScan and several neuroendocrine blood markers.

About your first question: we observed a higher recurrence rate in patients with large cell tumours (10/18 pts, 55.5%), all of them died within 24 months. One of the eight patients alive, at this moment, has a recurrence, after 24 months.

Concerning the typical carcinoid we discovered distant metastases in five patients (5/79 pts, 6.3%); three of them before 10 years, and two after 10 years. All of them died of the disease, conversely atypical carcinoid tumors had higher recurrence rates (3/8 pts, 37.5%), within the first 10 years, and two out of three died. The remaining one died shortly thereafter 10 years.