

# Proceedings of the IASLC International Workshop on Advances in Pulmonary Neuroendocrine Tumors 2007

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**Abstract:** The International Association for the Study of Lung Cancer, (IASLC) International Congress on Advances in Pulmonary Neuroendocrine Tumors was a two-day meeting held at the Royal Brompton Hospital in London, United Kingdom on the thirteenth and fourteenth of December 2007. The meeting was led by 14 member international faculty—in the disciplines of pathology, surgery, medicine, oncology, endocrinology, nuclear medicine, diagnostic imaging, and biostatistics. The aims were twofold, as an educational meeting, and to develop the IASLC International Pulmonary Neuroendocrine Tumors Registry. The meeting highlighted the difference in presentation of the tumors, management options for early and advanced stage disease including the use of novel agents and approaches. The need, process, and approach to an International Registry of Pulmonary Neuroendocrine Tumors were emphasized. International collaboration to develop a retrospective registry, prospective data collection, virtual tissue bank, and collaborative clin-

ical trials were universally agreed as the best way to advance our understanding and treatment of these rare tumors.

**Key Words:** Neuroendocrine tumours, Typical carcinoid, Atypical carcinoid, Large cell neuroendocrine, Carcinoma.

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## TYPICAL AND ATYPICAL CARCINOID TUMORS—ANDREW NICHOLSON

Approximately 1 to 2% of lung tumors are typical and atypical carcinoids. They occur equally in both genders. Between the two tumors, typical carcinoids account for the majority with atypical carcinoids making up 11 to 24% of all pulmonary carcinoids. Typical carcinoids classically show organoid and/or trabecular architectures with mildly pleomorphic cells comprising nuclei with granular chromatin and indistinct nucleoli and moderate volumes of eosinophilic cytoplasm. Architecture may rarely be paraganglioid, clear cell, spindle cell, or melaninocytic. Mitoses are less than two per 2 mm<sup>2</sup> and there is no necrosis. The classic immunohistochemical markers for carcinoid tumors are chromogranin A, synaptophysin, and CD56 (most sensitive). Atypical carcinoids are distinguished from typical carcinoids by the presence of necrosis (typically small foci within islands of cells) and/or the presence of 2 to 10 mitoses per 2 mm<sup>2</sup>. Atypical carcinoids may also show greater architectural disorganization and increased pleomorphism, but these are not discriminatory criteria. Regional and distant metastases are more common in atypical carcinoids, but may rarely also be seen in typical variants.<sup>1</sup> Typical carcinoids arise sometimes on a background of diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH), especially when peripheral in location, and DIPNECH is regarded as preneoplastic in this context. Recently, cases of atypical carcinoids and large cell neuroendocrine carcinoma (unpublished data) have also been shown to arise in association with DIPNECH.<sup>2</sup> Given that TTF-1 positivity, spindle cell morphology, and association with DIPNECH are more commonly seen in peripheral carcinoids,<sup>3</sup> it may be that peripheral carcinoids are histogenetically different from central carcinoids although this requires further investigation.

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## LARGE CELL NEUROENDOCRINE CARCINOMA AND SMALL CELL CARCINOMA—WILLIAM D. TRAVIS

Large cell neuroendocrine carcinoma (LCNEC) and small cell lung carcinomas (SCLC) are the two high grade tumors in the neuroendocrine spectrum. LCNEC and SCLC comprise 3% and 15 to 20%, respectively, of all invasive lung cancers. There are no recognized preinvasive lesions for either tumor in contrast to diffuse idiopathic pulmonary neuroendocrine cell hyperplasia which is a rare preinvasive lesion for carcinoids. The diagnostic criteria for LCNEC include a neuroendocrine morphology with organoid nesting, trabecular and rosette-like patterns, increased mitoses (11 or more per high powered field or 2 mm<sup>2</sup>), features of nonsmall cell carcinoma and neuroendocrine differentiation by electron microscopy or immunohistochemistry. Approximately 80% of LCNEC are pure and 20% are combined LCNEC with other histologies such as adenocarcinoma or squamous carcinoma. Rossi et al.<sup>4</sup> found the following percentage of immunohistochemical expression in LCNEC for chromogranin A (65%), synaptophysin (53%), and CD56 (93%). The diagnostic criteria for LCNEC, large cell with neuroendocrine morphology, large cell carcinoma with neuroendocrine differentiation and large cell carcinoma (with no neuroendocrine features) are presented in Table 1. Neuroendocrine differentiation can be seen in 10 to 20% of nonsmall cell lung cancers (mostly adenocarcinoma), and the conflicting reports of the influence on survival and response to chemotherapy was highlighted.<sup>1</sup>

Up to two thirds of surgically resected SCLC are pure SCLC and the remaining are combined SCLC with other histologies such as adenocarcinoma, squamous carcinoma, or large cell carcinoma (Table 2). In addition to the three standard immunohistochemical markers, other highlighted markers were AE1/AE3, Ki-67, neuron specific enolase, Bombesin-like peptides PGP 9.5, and neuroendocrine-specific protein A and C. The difficulties of establishing a pathologic diagnosis because of crush artifacts were emphasized and

**TABLE 1.** Spectrum of Neuroendocrine Differentiation in Large Cell Carcinomas<sup>a</sup>

Diagnosis	Neuroendocrine Morphology	Neuroendocrine Features On Immunohistochemistry or Electron Microscopy
Large cell neuroendocrine carcinoma	Yes	Yes
Large cell carcinoma with neuroendocrine morphology	Yes	No
Large cell carcinoma with neuroendocrine differentiation	No	Yes
Large cell carcinoma with no neuroendocrine features	No	No

<sup>a</sup> From reference: Travis WD, Krug LM, Rusch V. Large cell neuroendocrine carcinoma. In D Raghavan, ML Brecher, DH Johnson, et al. (Eds.), *Textbook of Uncommon Cancer*. Chichester, West Sussex, England: John Wiley, 2006. Pp. 298–306.

**TABLE 2.** Histopathologic Differences Between SCLC and LCNEC/LCC<sup>a</sup>

Feature	SCLC	LCNEC/LCC
Cell size	Smaller (< 3 small resting lymphocytes)	Larger
N/C ratio	Higher	Lower
Nuclear chromatin	Finely granular, uniform	Coarsely granular, vesicular, less uniform
Nucleoli	Absent or faint	Often (not always) present, may be prominent or faint
Nuclear molding	Characteristic	Uncharacteristic
Fusiform shape	Common	Uncommon
Polygonal shape with ample pink cytoplasm	Uncharacteristic	Characteristic
Nuclear smear	Common	Uncommon
Basophilic staining of stroma and vessels	Occasional	Rare

<sup>a</sup> Travis WD, Linnoila RI, Tsokos MG, et al. Neuroendocrine tumors of the lung with proposed criteria for large-cell neuroendocrine carcinoma. An ultrastructural, immunohistochemical, and flow cytometric study of 35 cases. *Am J Surg Pathol* 1991;15:529–553.

sputum cytology suggested as a potential alternative. Similar survival is reported in patients with LCNEC and SCLC. Patients with SCLC and LCNEC are typically in the seventh decade of life. SCLC patients may be slightly older and there is a male predominance. The utility of mRNA gene expression profiling (Affymetrix U133A) in the classification of neuroendocrine tumors were presented. The differences in the management of SCLC (Surgery—controversial, Chemotherapy—primary approach, Radiation—effective locally) and LCNEC (Surgery—if resectable, Chemotherapy—Probably needed, Radiation—effective locally) were presented.

## CLINICAL PRESENTATION—JAMES R. JETT

The epidemiology of carcinoid tumors was presented as an annual rate in the SEER database (0.52 per 100,000 men, 0.89 per 100,000 women) and the Swedish registries (0.2 per 100,000 men, 1.3 per 100,000 women). The average age of presentation of patients with typical carcinoid tumors is 45 to 50 years, and 10 years older for patients with atypical carcinoid tumors. Typical carcinoid tumors are approximately four times more common than atypical. The uncertain relationship with smoking was emphasized. Approximately 75% of patients with carcinoid tumors present with central tumors, with symptoms of cough, hemoptysis, wheeze, recurrent pneumonia or chest pain in 52%. Ectopic hormone production resulting in carcinoid syndrome (1–5%), Cushing syndrome (1–2%), and acromegaly are rare. The utility of positron emission tomography (PET) was highlighted in a series of 16 patients with typical and atypical carcinoid tumors,<sup>5</sup> that reported PET positivity in 75% (not associated with any differences in tumor size).

## PARANEOPLASTIC SYNDROMES—PIERO FEROLLA

Paraneoplastic syndromes are by definition, disorders that may accompany benign or malignant tumors but are not

directly related to mass effects or invasion by the primary tumor or its metastases. They can be divided as hematological, neurologic, dermatologic, and hormonal.

The molecular mechanisms underlying paraneoplastic syndromes are incompletely understood. Genetic rearrangements are rare although cellular dedifferentiation or dysdifferentiation are more common in poorly differentiated neuroendocrine tumors, such as small cell and large cell neuroendocrine carcinomas. Other abnormalities may include alterations in transcriptional repression, changes in DNA methylation and other factors that govern cell differentiation.

In the experience of the University of Perugia (Ferolla et al., submitted), when an accurate endocrinological evaluation is performed in the preoperative period in patients with bronchial carcinoid, up to 15% have either clinical or subclinical hypersecretion. A wide spectrum of hormones can be secreted from both well differentiated (carcinoid) and poorly differentiated lung neuroendocrine tumors (including ACTH, CRH, GHRH, ADH, serotonin, histamine, gastrin, calcitonin, tatykinins, CgA,  $\beta$ -HCG, NSE, bombesin, PTH, PTHrp, IGF1, IGF2, and others). The nonspecific serum neuroendocrine marker Chromogranin A is currently considered the most useful marker of well differentiated lung neuroendocrine tumors, although it is not associated with specific symptoms and an association with prognosis is not yet determined. A linear correlation has been demonstrated between nonspecific circulating neuroendocrine markers and the development of complications. For example, serotonin levels correlate with progression of heart valve and carcinoid heart disease,<sup>6</sup> and may be increased by cell lysis from the administration of chemotherapy.<sup>7</sup>

Thoracic neuroendocrine tumors (small cell lung carcinoma, bronchial carcinoid and thymic carcinoids/carcinomas in order of frequency) are the most common causes of ectopic ACTH production.<sup>8</sup> Unusual clinical presentations such as "cyclical" Cushing syndrome have been reported.<sup>9</sup> In a large series of patients with SCLC, 1.6% of the total were reported to have ectopic ACTH production.<sup>10</sup> One or more features of Cushing syndrome were observed in 57%, but the entire spectrum of the symptoms is rare. All patients present with hypokalemia and as type II diabetes develops, infections become the principal cause of morbidity and mortality.

Bronchial carcinoid tumors are the most frequent cause of ectopic acromegaly. The immunohistochemical demonstration of GHRH in the tumor cells and elevated plasma GHRH are crucial for the diagnosis as GH and IGF1 levels (both basal or after provocative tests) do not differentiate ectopic from ectopic secretion. Often tumor hypersecretion is multihormonal. Ectopic GH secretion without concomitant GHRH hypersecretion has been demonstrated only in a single case.<sup>11</sup>

Lung neuroendocrine tumors (mainly SCLC) are important causes of inappropriate ADH secretion (SIADH). Clinical features are indistinguishable from nonparaneoplastic causes and include hyponatremia with corresponding hypo-osmolality of serum and extracellular fluid. Compensatory mechanisms, such as decreased thirst, aldosterone suppression, and production of atrial natriuretic peptide, may mitigate the development of hyponatremia.

**TABLE 3.** Radiopharmaceuticals Available for Imaging

Radiopharmaceutical	Mechanism of Action
I-123 MIBG	Neuronal uptake I and II system
In-111 octreotide	Somatostatin receptor (SSR 2) binding and internalisation
F-18 FDG	GLUT 1 system
Ga-68 peptides (DOTATATE)	Somatostatin receptor (SSR 2) binding and internalisation
C-11-5-hydroxytryptophane	
C-11-L-DOPA	
C-11 methionine	

When single or multiple hormone hypersecretion is found in patients with neuroendocrine tumors, the association of multiple endocrine neoplasia type 1 (MEN1) should be borne in mind, as it is associated with significant mortality. The most appropriate timing and modality for imaging and hormonal follow-up for thoracic neuroendocrine tumors with MEN1 is still a matter of debate.

### NOVEL IMAGING TECHNIQUES—JAMSHED BOMANJI

The indications for imaging are usually to characterize the primary and screen for metastases. This can be achieved by conventional x-ray, CT, MRI, receptor scintigraphy (e.g., <sup>111</sup>In-Pentetreotide) and PET (<sup>68</sup>Ga DOTATATE, <sup>18</sup>F-FDG PET/CT). High resolution CT gives information such as size, position, density, calcification, edge configuration, and vascularity. MRI generally provides information similar to that of CT. There are a large number of radiopharmaceuticals available for imaging (Table 3). There is marked variation in affinity for <sup>111</sup>In-pentetreotide, <sup>123</sup>I-MIBG, and <sup>18</sup>F-FDG. For lung carcinoids, and in the author's opinion, the <sup>68</sup>Ga DOTATATE PET tracer should be the imaging modality of choice although it may not be widely available. Extensive experience is now being obtained using DOTA-DPhe1,Tyr3-octreotate (DOTATATE) (a SSR-2 analogue), radio-labeled to <sup>68</sup>Ga a positron emitter at the University College Hospital in London. <sup>68</sup>Ga DOTATATE typically shows uptake in well-differentiated neuroendocrine tumors, with reduced sensitivity in poorly differentiated tumors. It is best used to delineate primary tumor and secondary inflammatory reactions. In general, primary and well-differentiated neuroendocrine tumors show higher affinity for <sup>68</sup>Ga DOTATATE and metastatic and poorly differentiated tumors have a higher affinity for <sup>18</sup>F-FDG. <sup>68</sup>Ga DOTATATE is emerging as an important tracer for preoperative surgical planning and staging for recurrent disease possibly in combination with other imaging modalities.

### SURGERY FOR TYPICAL AND ATYPICAL CARCINOIDS—VALERIE W. RUSCH

Surgical series from 1985 to 2006 report the postsurgery 5 year survival ranging from 92 to 100% for patients with typical carcinoid tumors and 69 to 78% for patients with atypical carcinoid tumors. The factors influencing prognosis

include histologic subtype, nodal metastasis (especially for atypical carcinoid tumors), ability to achieve complete resection and age. Data from 378 patients in the MSKCC neuroendocrine database from 1992 to 2007 were presented, illustrating similarities and differences in patient demographics, stage and the excellent survival in patients with typical carcinoid tumors, and intermediate survival in patients with atypical carcinoid tumors. Postsurgical recurrence rates ranged between approximately 5 to 30%, with recurrence in distal sites approximately four- to five-fold more common than local recurrence.

### **SURGERY FOR LARGE CELL NEUROENDOCRINE CARCINOMA—HISAO ASAMURA**

From 1981 to 2006, the National Cancer Centre in Tokyo operated on 159 patients with large cell neuroendocrine carcinoma. The median age of the cohort was 67 years, with 89% men. Complete resection was achieved in 92%, with the percentages in pathologic stage I to IV as 53, 18, 28, and 2%, respectively. In total, 46 patients experienced distant recurrence and 21 patients had local recurrences. The overall 5-year survival was 46%. Patients with resected LCNEC had a poorer survival compared with other NSCLCs with pathologic stage I and the overall survival was similar to that of small cell lung cancer.

### **INFLUENCE OF CELL TYPE AND STAGE ON POST SURGICAL SURVIVAL—ERIC LIM**

Malignant potential of neuroendocrine tumors are governed by stage (extent of disease) and grade (reflected by cell type). If prognosis is determined predominantly by disease extent then complete resection alone may suffice, nevertheless, if prognosis is determined predominantly by cell type, then complete resection alone may be inadequate. Data from the 177 patients in the Brompton Hospital cohort were presented, and Cox regression used to ascertain the joint influence of cell type and stage on survival. Although both increasing stage and cell type were predictors of poorer prognosis, on joint analysis, cell type had a stronger influence on adverse survival. However, the two were not mutually exclusive. As with most other surgical series from individual centers, the numbers of events in general are small, nodal involvement is relatively rare, therefore a clear answer can only be obtained by the development and analysis of an international registry.

### **PRIMARY CHEMOTHERAPY—BRITT SKOGSEID**

Data from 61 patients treated for advanced bronchial carcinoid tumors at Uppsala University were presented. The overall 5 and 10 year survival from diagnosis was 70 and 48%, respectively. From the start of treatment, however, the overall 5-year survival was 39%. For well differentiated neuroendocrine tumors of the lung, there are no accepted treatment regimens. At Uppsala University, the first line treatment is Temozolomide and the second line is Streptozotocin and doxorubicin or 5-fluorouracil (FU). Alternative regimens include cisplatin and etoposide (1st line for poorly differentiated tumors as assessed on Ki-67 index), biotherapy

( $\alpha$ -interferon, somatostatin analogues), embolization, and radiofrequency ablation. Temozolomide is an oral alkylating agent that methylates guanine resulting in incorrect pairing during DNA replication. Resistance to temozolomide is associated with high methyl guanine DNA methyltransferase (MGMT) levels. Temozolomide was administered to 36 patients with advanced foregut tumors as third to fifth line therapy, with 14% partial response and 53% with stable disease.<sup>12</sup> A prospective trial is required to establish the efficacy of this as first line treatment. Results from Mirty et al.<sup>13</sup> suggested that cisplatin and etoposide was more efficacious in patients with poorly differentiated tumors. There have been only few responders to streptozotocin and doxorubicin or 5-fluorouracil with stable disease in approximately 25%.

### **ADJUVANT CHEMOTHERAPY—ERIC BAUDIN**

The principles of adjuvant chemotherapy are to treat patients with high risk of recurrence or death after complete surgery to increase the disease-free and overall survival. At present, there is little information to clearly define the risk of recurrence and risk/benefit ratio of adjuvant therapy. As the survival of typical carcinoids is excellent, and with concurrent chemo-radiotherapy being standard of care for small cell lung carcinoma, the main focus of adjuvant chemotherapy is on atypical carcinoid tumors and large cell neuroendocrine carcinomas.

Large cell neuroendocrine carcinomas are heterogeneous tumors with a 5-year survival that is mainly dependant on stage. Adverse markers of prognosis are mitoses more than 37 per 10 high powered fields, a positive neuroendocrine marker and the presence of metastatic disease.<sup>14</sup> Of patients who develop recurrences, 91% occur within the first 2 years with 25 to 35% local recurrence and 50 to 56% distant metastasis. Studies published from 1993 to 2006 have reported partial or complete response to cisplatin based combinations range from 41 to 78% in patients with stage III to IV disease. A number of studies have reported 100% 5-year survival with adjuvant and induction chemotherapy.<sup>15,16</sup> Small-cell based chemotherapy has been reported to achieve better results compared with nonsmall cell based regimens.<sup>17</sup> There has also been a report of octreotide therapy to reduce recurrence.<sup>18</sup> Cisplatin and etoposide regimens have been associated with excellent survival in stage I disease, but the best regimen is still to be established. This strategy may not be sufficient in stage II–III disease and combination radiotherapy should be considered. Clearly a prospective randomized trial is required.

In general, the 5-year survival of patients with atypical carcinoid tumors range are better in patients without lymph node involvement compared with those with reported N1 disease. Significant difference in the outcome of this two subgroups of patients has been observed recently.<sup>19</sup> One study reported the 5-year survival of patients with atypical carcinoid with N2 disease to be 22%.<sup>20</sup> Local and metastatic recurrences occurs in 23%, respectively.<sup>21</sup> There have been too few reports to objectively assess the efficacy of adjuvant chemotherapy, the target subset who would benefit and the agent of choice. Atypical carcinoids with N2 disease are

candidates for adjuvant therapy. The prognostic classification for patients with atypical carcinoids and N1 disease needs to be further evaluated.

### MANAGEMENT OF ADVANCED DISEASE—MARTYN CAPLIN

The SEER database has reported 13,715 cases of carcinoid tumors over the period 1973–1999, of which 25% were of bronchopulmonary origin.<sup>22</sup> The survival of pulmonary carcinoid tumors is dependant on histologic grade with 10-year survival decreasing from 70 to 30 to 5% for low, intermediate, and high grades, respectively.<sup>23</sup> It is the practice of the author to perform a biochemical profile for patients with suspected neuroendocrine tumors. This includes measurement of chromogranin A, urinary 5HIAA, peptide screen, ACTH, and GHRH. In addition, one needs to consider hereditary conditions such as MEN-1. Chromogranin A is elevated in 58% and is related to tumor burden in gastrointestinal carcinoids.<sup>24</sup> Image utilizing CT and/or MRI is used for staging, however, the most sensitive modality for metastatic disease is somatostatin receptor scintigraphy. Histologic diagnosis is required in metastatic disease. The prognostic indicators for carcinoid tumors include size, degree of differentiation, proliferative index (Ki67)/mitotic index, presence of necrosis, cosecretion of peptides and metastases, especially to the liver and bones. In patients with neuroendocrine tumors, surgery should be the main treatment option if feasible. Symptomatic patients with residual disease should be considered for a trial of somatostatin analogue therapy. Asymptomatic patients with residual disease may be considered for an observation protocol or treatment utilizing somatostatin analogue therapy or consideration of new agents such as SOM230 and RAD001, however, this should be in the context of a clinical trial. In patients who progress, there are a number of other therapeutic options and these include: chemotherapy<sup>25</sup> (e.g., etoposide/cisplatin regimen; or streptozotocin-based regimen or temozolomide regimen); biotherapy (interferon or somatostatin) may be considered for small volume diffuse disease in low grade tumor; radionuclide therapy (<sup>131</sup>I MIBG, <sup>90</sup>Y DOTA octreotide, or <sup>177</sup>Lu octreotate) may be considered in patients who have positive nuclear medicine imaging and patients may be considered for trials of new agents (RAD001 an mTOR inhibitor, Bevacizumab a vascular endothelial cell growth factor receptor inhibitor and Sunitinib a multiple receptor tyrosin kinase inhibitor). In patients with predominant hepatic disease chemo-embolization,<sup>26,27</sup> ablation therapy,<sup>28</sup> and surgery<sup>29</sup> can be considered. The evidence base for the management of advanced bronchial neuroendocrine tumor is extremely limited and, therefore, patients should be seen in specialist NET units and should be encouraged to participate in clinical trials.

### RADIONUCLIDE THERAPY—DIK KWEKKEBOOM

For patients with inoperable neuroendocrine tumors, a number of therapeutic options exist including somatostatin analogues,  $\alpha$ -interferon, radiofrequency ablation, (chemo) embolization, chemotherapy, and peptide receptor radionuclide therapy (PRRT). Radiolabeled somatostatin analogues

**TABLE 4.** Radiolabelled Somatostatin Analogues for Peptide Receptor Therapy

[ <sup>111</sup> In-DTPA <sup>0</sup> ]octreotide
[ <sup>90</sup> Y-DOTA <sup>0</sup> ,Tyr <sup>3</sup> ]octreotide
[ <sup>90</sup> Y-DOTA <sup>0</sup> ]lanreotide
[ <sup>177</sup> Lu-DOTA <sup>0</sup> ,Tyr <sup>3</sup> ]octreotate
[ <sup>177</sup> Lu-DOTA <sup>0</sup> ,Tyr <sup>3</sup> ]octreotide
[ <sup>90</sup> Y-DOTA <sup>0</sup> ,Tyr <sup>3</sup> ]octreotate

that can potentially be used for PRRT are listed in Table 4. At Erasmus University, [<sup>177</sup>Lu-DOTA<sup>0</sup>,Tyr<sup>3</sup>]octreotate has been used in patients with inoperable neuroendocrine tumors that have proven uptake on Octreoscan, without prior therapy with other radiolabeled somatostatin analogues.<sup>30</sup> In practice, amino acids are infused, followed by intravenous granisetron and intravenous <sup>177</sup>Lu-octreotate. This usually requires an overnight stay. The maximum dose is based on bone marrow and renal toxicity and is calculated individually (usually between 600 and 800 mCi). Side effects include temporary hair loss (62%), nausea (25%), vomiting (10%), and pain (10%). Hormonal crisis are experienced in 1%, and may be due to tumor lysis, discontinuation of somatostatin analogue therapy, amino acids, or emotional stress. In the experience at Erasmus University, all patients recovered with supportive care (fluids, octreotide, corticosteroids, and correction of acidosis and hypokalemia). In a series of 504 patients, there was a 1% incidence of serious therapy-related complications comprising of two patients who developed serious liver toxicity and three who developed myelodysplastic syndrome. For patients with bronchial carcinoids, 6/9 experienced remission, with no differences between typical and atypical subtypes, with an overall median survival of 31 months.<sup>31</sup> In general, there is further need for further validation and standardization of treatment. Randomized trials will be required to compare efficacy. In general PRRT is associated with high tumor response rate, limited side effects, good quality of life, and relatively long progression free survival.

### CURRENT AND NOVEL BIOMARKERS—ELISABETH BRAMBILLA

The sensitivity and specificity of immunohistochemical neuroendocrine tumor marker are listed in Table 5.<sup>32</sup> Typical and atypical carcinoid tumors tend to have positive neuroendocrine markers, with the following cytokeratin profile - AE1-AE3 positive, KL1 positive, CK1,5,10,14 negative. In addition, the tumors tend to be TTF-1 negative with a Ki-67

**TABLE 5.** Discriminative Value of Neuroendocrine Markers

Marker	Sensitivity (%)	Specificity (%)
NSE	82	68
Leu7	39	97
Chromogranin	85	97
Synaptophysin	80	97
NCAM (CD56)	95	97
34 $\beta$ E12 negative	95	95

range between 3 and 15%, of which typical carcinoid tumors tend to be 0 to 5% and atypical carcinoid tumors between 5 and 15%. Large cell neuroendocrine carcinoma expresses tyrosine kinase receptors (c-kit 62%, SCF 47%, PDGF-R $\alpha$  60%, PDGF-R $\beta$  82%, and Met 47%). In LCNEC and SCLC, TTF-1 is expressed at variable levels but not amplified. The p53 pathway is the central point of in the pathogenesis of these tumors. Native p53 expression and p53 mutations increase from no expression in typical carcinoids to high expression in LCNEC and SCLC. As the tumor grade increases, there are corresponding increases in the loss of Rb gene expression (mutually exclusive to P16/CyclinD1 alterations) with increased expression E2F1 expression and P14 losses. SKP2 and cyclin E are expressed in LCNEC and SCLC and both increase with the grade of tumor. On the whole, there is an apparent spectrum of low grade (typical carcinoid) to intermediate grade (atypical carcinoid) to high grade tumors (LCNEC and SCLC), but stem cell of origin and absence of mixed carcinoid and high grade tumors suggesting 2 different histogenesis patterns of these tumors with typical and atypical carcinoids in one group and LCNEC/SCLC in another.

### BIOLOGIC THERAPY—BRITT SKOGSEID

Currently,  $\alpha$ -interferon and somatostatin analogues are the two main forms of bio-therapy. The indications for use in patients with carcinoid tumors are endocrine symptoms and those in which chemotherapy is contraindicated. The principle mechanism for the action of  $\alpha$ -interferon is not yet elucidated and a number of possible mechanisms have been proposed (Table 6). In a meta-analysis involving 414 patients with neuroendocrine tumors, clinical response was observed in 32 to 53%, biochemical response in 39 to 49%, and tumor response in 12 to 20%. There is also evidence supporting improved survival in patients on continuous interferon therapy compared with those that have stopped or received other treatments. Specifically for bronchial carcinoid tumors, however, Granberg et al.<sup>33</sup> reported that none of the 27 patients demonstrated any tumor response to combination of  $\alpha$ -interferon and somatostatin. Octreotide, however, remains an important treatment modality for the management of carcinoid crises. Other emerging treatment options include sorafenib and sunitinib. More work is required to evaluate biologic agents in these rare diseases.

**TABLE 6.** Possible Mechanisms for the Action of  $\alpha$ -Interferon

Stopping of the cell cycle from G0 to G1 phase
Induction of differentiation
Cytotoxicity
Increase MHC class I expression on tumor cells
Inhibition of growth factors or their receptor expression
Immune stimulation
Production of cytokines
Stromal changes
Anti-angiogenesis

### HISTORY AND BACKGROUND TO THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER NEUROENDOCRINE TUMORS REGISTRY—WILLIAM TRAVIS

The IASLC pathology panel met in 1995 to validate the current pathologic classification of pulmonary neuroendocrine tumors, and over subsequent decades, discussion were underway with Elisabeth Brambilla (Grenoble), Valerie Rusch (MSKCC) and Bruce Johnson (Dana Farber). Initiatives for a registry were proposed at the neuroendocrine symposium at the World Conference of Lung Cancer in Barcelona in 2005 and several funding proposals were made to the IASLC. In 2006 Peter Goldstraw (Brompton Hospital) the chair of the IASLC staging committee was interested to explore the TNM system in carcinoid tumors. Although data from a large number of neuroendocrine tumors were received in the IASLC staging project, there were a number of important limitation, T factor details were limited, and subgroups for detailed evaluation (e.g., multiple nodules, atelectasis, pleural invasion) were lacking. It was also not possible to differentiate between typical and atypical carcinoid tumors. The establishment of an international registry is critical to develop collaborations that allow for combining data on rare neuroendocrine tumors, to encourage participation of existing (Japan, Spain) registries, and the development of new national registries. The aim would be to establish an international consensus and a worldwide uniform approach for diagnosis, and develop a tissue network for study of molecular changes with hope of identifying molecular therapeutic targets.

### THE IASLC NEUROENDOCRINE TUMORS REGISTRY—PETER GOLDSTRAW

The IASLC Lung Cancer Staging Project collected data on over 100,000 cases of lung cancer treated by all modalities of care, between 1990 and 2000, from 46 Institutions in over 19 countries across the globe.<sup>34</sup> After an initial sift, 81,015 cases were suitable for inclusion within their database. Of these 67,725 cases were of NSCLC and analysis of these has informed the revisions proposed for the forthcoming, 7th edition of TNM for lung cancer.<sup>35–38</sup>

Within the database there were 13,290 cases of SCLC. Analysis of these cases confirmed that the TNM classification was appropriate for SCLC, including those cases being treated by nonsurgical modalities.<sup>39</sup> The database did not specifically request data on carcinoid tumors as these have previously been excluded from the TNM staging system.<sup>40,41</sup>

However, data was submitted on 518 carcinoid tumors and analysis of these has suggested that TNM should be applied to carcinoid tumors in the forthcoming, 7th edition of TNM.<sup>42</sup> The delineation of “atypical” and “typical” cases were not reliable in this data and further cases will be accumulated prospectively to confirm this suggestion. Large cell neuroendocrine carcinoma (LCNEC) was only classified as a distinct entity within the WHO classification in 1999.<sup>43</sup> Therefore, there are very few such cases within the database.

The IASLC Lung Cancer Staging Project, therefore, seeks to register additional neuroendocrine tumors. As funds are limited it is necessary to be selective and discussion

within the forum suggested that the following subgroups should be prioritized:

- a. Atypical carcinoid tumors.
- b. Typical carcinoid tumors with nodal metastases.
- c. LCNEC cases treated by all modalities of care, including multimodality treatment.

The IASLC hope that the neuroendocrine registry can be used to facilitate collaborative research, create virtual tissue bank arrangements, and establish clinical study groups.

### OVERVIEW OF THE REGISTRY TO DATE—ERIC LIM

Over the course of the last three World Conferences on Lung Cancer, Professor William Travis has been leading the development of an international registry of pulmonary neuroendocrine tumors, and recently with the support of Professor Peter Goldstraw, the IASLC has limited funding for support of the development of such a registry. A satellite meeting was in at the World Conference of Lung Cancer in Korea 2007, to obtain further international involvement, publicity for the initiative and to establish resources for the project. From the submissions of the participants in this conference (in London) alone, we can see the number cases available for study. This includes the two less common subgroups—carcinoid tumors with nodal metastases and medically treated patients. In addition, we now know that many centers perform node sampling/dissection and bank tissue samples. With limited resources, the international community need to decide on the subset of tumors in which data should be collected for the retrospective and prospective registries, the data fields and time frame in which this should be achieved.

### DATA COLLECTION AND SUBMISSION—JOHN CROWLEY

CRAB stands for Cancer Research And Biostatistics, and is a not-for-profit organization based in Seattle, USA. Statistic projects run by CRAB include cancer clinical trials for the US Southwest Oncology Group and with industry partners. CRAB is also the statistics center of the IASLC Staging Project and the Myeloma Institute for Research and Therapy at the University of Arkansas for Medical Sciences. The data fields associated with the IASLC International Pulmonary Neuroendocrine Tumors Project are likely to be based on the existing model used for submission of the IASLC Staging Project.

(The rest of this presentation was based on a PDF of the existing UICC lung cancer staging data fields.)

### SUMMARY OF THE DISCUSSION BY SURGEONS AND ONCOLOGISTS—VALERIE RUSCH AND JAMES JETT

The surgeons and oncologists in the breakout session to determine the scope and direction of the IASLC International Pulmonary Neuroendocrine Tumors Project brought up a number of questions. This includes the need to determine the

outcome of typical carcinoids with lymph node metastases, the outcome of atypical carcinoid, LCNEC, and very early SCLC (solitary pulmonary nodule) to determine if they represent a different population compared with the larger SCLC population. There was interest in determining the incidence of neuroendocrine tumors by subtype with time, differences in the outcome of central and peripheral tumors, impact of multiple tumor/tumorlets and if patients with recurrent disease have a different tumor characteristics. There was interest in quantifying the incidence and types of associated paraneoplastic syndromes. The group believed that there was a lack of studies on imaging characteristics, optimal staging pathways and characterization of the molecular features. The group raised the awareness on the need to further evaluate the role of serum markers in the diagnosis, staging, and clinical management. It was generally agreed that more work is required to determine the treatment options for patients with advanced disease. There were suggestions to conduct a Phase II trial of Temozolamide as first line treatment for patients with metastatic bronchial carcinoid tumors, and a trial of adjuvant therapy for completely resected LCNEC was of interest to the participants.

### SUMMARY OF THE DISCUSSION BY PATHOLOGISTS—WILLIAM TRAVIS AND ANDREW NICHOLSON

Issues raised in the breakout sessions by pathologists were divided into retrospective and prospective issues and included the following. Retrospectively, pathologists could help focus on key rare subsets to study and central pathologic review could be organized for entities such as typical carcinoids with nodal and/or distant metastases, atypical carcinoids, (LCNEC), and resected small cell carcinomas. Retrospectively, pathologic review should only be done for cases with adequate clinical data. Prospectively, there is a need for pathology review for problematic diagnoses such as LCNEC in any therapeutic trials to ensure accurate patient selection. This could be done regionally with specific leaders/reference centers in each region. Prospectively, large cell carcinoma with neuroendocrine morphology needs further study in relationship to LCNEC. Prospectively, due to limited resources in the process of development of an international registry, only selective biomarker data would be submitted. Retrospectively and prospectively, studies involving tumor microarray are to be encouraged, but should be done locally (not globally). The final logistics for pathologic review needs to be defined further once there is a clearer idea on the final number of cases involved.

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