diagnoses and/or diagnoses from intraoperative frozen sections are often difficult for differentiating AC from TC, because small amounts of necrosis or few mitoses are sometimes unclear in those specimens. A randomized controlled trial is the best method to compare surgical efficacy. However, it may be impractical due to the rarity of carcinoid tumors. Moreover, AC has a poorer prognosis and a higher frequency of lymph node metastases than TC. Therefore, sublobar resection for TC might be the optimal surgical method because of lung preservation and lower mortality than lobectomy; however, limited resection for TC remains an area of controversy. Several reports[9] revealed that the clinical behavior, morphology, and prognosis of LCNEC were similar to those of SCLC, even though there might be several clinicopathological differences between SCLC and LCNEC in peripheral, small-sized, and high-grade neuroendocrine tumors.[10] Because it is difficult to diagnose patients with LCNEC pre-operatively, and most cases have been diagnosed postoperatively from surgically resected specimens, many reports on LCNEC have referred to surgical cases, of which the majority[9] revealed that patients with LCNEC had poor prognoses. Even patients with pathological stage I LCNEC have had poor prognoses, with five-year survival rates of 27-67%.[9] In patients with LCNEC who underwent radical surgery and complete resection, many recurrent tumors were observed as distant metastases.[10] Therefore, surgery alone is not sufficient to treat patients with LCNEC, and subsequent adjuvant therapy may be necessary.[10] Although there were high response rates with platinum-based and SCLC-based chemotherapies in patients with LCNEC, almost all patients had only partial responses.[9,10] Patients with LCNEC may not be able to expect complete responses with platinum-based and SCLC-based chemotherapies compared with patients with SCLC, even though these chemotherapies are as effective as adjuvant treatment. Therefore, patients with advanced-stage LCNEC had a poor prognosis because they could not always achieve a complete response. Although the indication for surgery is limited to stage I in patients with SCLC, surgery and adjuvant chemotherapy may achieve satisfactory results in terms of survival for patients with LCNEC with not only stage I but also stage II/III.[10] Therefore, surgical indications for patients with LCNEC may not be limited to clinical stage I cases, and surgery with adjuvant chemotherapy should be attempted for resectable LCNEC. **References:** 1. Arrigoni MG, Woolner LB, Bernatz PE. Atypical carcinoid tumors of the lung. *J Thorac Cardiovasc Surg*. 1972;64:413-21. 2. Travis WD, Colby TV, Corrin B, Shimosato Y, Brambilla E, editors. Histological Typing of Lung and Pleural Tumors. World Health Organization International Histological Classification of Tumors, XIII, 3rd ed. Berlin/Heidelberg: Springer-Verlag; 1999. 3. Rusch VW, Klimstra DS, Venkatraman ES. Molecular markers help characterize neuroendocrine lung tumors. *Ann Thorac Surg*. 1996;62:798-810. 4. Onuki N, Wistuba II, Travis WD, Virmani AK, Yashima K, Brambilla E, Hasleton P, Gazdar AF. Genetic changes in the spectrum of neuroendocrine lung tumors. *Cancer*. 1999;85:600-7. 5. Travis W.D, Brambilla E, Müller-Hermelink H.K, Harris C.C (Eds.): World Health Organization Classification of Tumors. Pathology and Genetics of Tumors of the Lung, Pleura, Thymus and Heart. IARC Press:Lyon 2004. 6. Iyoda A, Hiroshima K, Baba M, Saitoh Y, Ohwada H, Fujisawa T. Pulmonary large cell carcinomas with neuroendocrine features are high grade neuroendocrine tumors. *Ann Thorac Surg*. 2002;73:1049-54. 7. Fox M, Van Berkel V, Bousamra M II, Sloan S, Martin RC II. Surgical management of pulmonary carcinoid tumors: sublobar resection versus lobectomy. *Am J Surg*. 2013;205:200-8. 8. Daddi N, Ferolla P, Urbani M, Semeraro A, Avenia N, Ribacchi R, Puma F, Daddi G. Surgical treatment of neuroendocrine tumors of the lung. *Eur J Cardiothorac Surg*. 2004;26:813-7. 9. Iyoda A, Hiroshima K, Nakatani Y, Fujisawa T. Pulmonary large cell neuroendocrine carcinoma- its place in the spectrum of pulmonary carcinoma. *Ann Thorac Surg*. 2007;84:702-7. 10. Iyoda A, Makino T, Koezuka S, Otsuka H, Hata Y. Treatment options for patients with large cell neuroendocrine carcinoma of the lung. *Gen Thorac Cardiovasc Surg*. 2014;62:351-6. **Keywords:** carcinoid, Surgery, neuroendoctine

MS 07.05
ESTS Registration for Neuroendocrine Tumors

P.L. Filosso,[1] F. Guerrera,[1] P. Lyberis,[1] E.L.N.S. Committee[2]
[1]Sugical Sciences, University of Torino Italy, Torino/IT, [2]University Torino, Torino/IT

Lung Neuroendocrine Tumors (NETs) are rare neoplasms derived from the neuroendocrine cells of the bronchopulmonary epithelium. They represent about 25% of all the neuroendocrine tumors, and no more than 2%-3% of all the primary tumors of the lung. Their incidence has recently increased by approximately 6% per year, probably due to the improved awareness as well as for the diffusion of lung cancer screening programs worldwide. NETs' incidence now ranges from 0.2 to 2 per 100,000 individuals per year in the United States. Their rarity, along with the lack of randomized clinical trials, make lung NETs' global management still questioned, especially in case of advanced diseases, and only few clinical recommendations currently exist. In 2012, during the Annual Meeting in Essen (Germany), the European Society for Thoracic Surgeons (ESTS) created a new Working Group (WG) specifically dedicated to the Lung NETs. The Steering Committees was composed by the following Thoracic Surgeons: Pier Luigi Filosso (Torino, Italy-Chair), Pascal Alexandre Thomas (Marseille, France), Mariano Garcia-Yuste (Valladolid, Spain), Eric Lim (London, UK), Federico Venuta (Rome, Italy), Alessandro Brunelli and Konstantinos Papagiannopoulos (Leeds, UK), Hisao Asamura (Tokyo, Japan). The aim of this WG was to create a group of physicians expert on Lung NETs in order to improve scientific knowledge on such rare neoplasms, and disseminate it among the scientific community. A specific database was rapidly designed, to retrospectively collect data of patients operated for lung NETs, and it was sent to all the ESTS Members who expressed their interest to this project. Moreover, a survey concerning lung NETs'clinical management was prepared and its results were recently published (Future Oncol. 2016;12:1985-1999). Up to now, 2040 operated NETs patients have been collected amongst 17 high-volume International Thoracic Surgery Institution worldwide. This retrospective database was used for several studies about lung NETs clinical behavior and outcome. In particular, the outcome and prognostic factors of two aggressive lung NETs: atypical carcinoids (ACs) and large-cell neuroendocrine carcinomas (LCNCs) were the object of the first publication (Eur.J.Cardiothorac Surg. 2015;48:55-64). For ACs, age ($P<0.001$), tumor size ($P=.015$) and sub-lobar resections ($P=0.005$) were independent negative prognostic factors; for LCNCs, only pTNM stage III tumors ($P=0.016$) negatively affected outcome in the multivariate analysis. Local recurrences and distant metastases were statistically more frequent in LCNCs ($P=0.02$), as expected. A prognostic model of survival for typical carcinoids (TCs) was the matter of the second publication (Eur.J.Cardiothorac Surg. 2015;48:441-447): an analysis of 1109 TC patients was performed. A prediction model for mortality, evaluating age, gender, previous malignancies, peripheral tumor location, TNM stage and ECOG PS was elaborated, and the final model showed a good discrimination ability with a C-statistic equal to 0.836 (bootstrap optimism-corrected 0.806). Moreover, this model has been recently validated by *Cattoni and Coll*. The treatment of biologically aggressive/advanced lung NETs was recently investigated in a paper published by the Journal of Thoracic Disease (J.Thorac. Dis. 2015;7:S163-S171). Surgery, whenever feasible, remains the mainstay of treatment, and chemo/radiotherapy should be reserved to progressive diseases. In case of resected N1-N2 carcinoids, a "watch and see" policy and a close clinical/radiological follow-up is also recommended. Surgery alone is not sufficient to treat high-grade NETs (e.g.: LCNC): adjuvant CT is suggested even in early stages. Platinum-Etoposide regimen demonstrated to be the most effective; Irinotecan and other biological drugs are also regarded to be very promising. The management of advanced lung NETs should be tailored by multidisciplinary teams including Medical and Radiation Oncologists, Surgeons,

Pathologists, Pulmonologists, Endocrinologists, Interventional Radiologists; patients' prognosis is mainly dependent on tumor grade and its anatomical extent. Large-cell neuroendocrine carcinoma (LCNC) is a rare tumor characterized by an aggressive biological behavior and poor prognosis; its optimal treatment is still under debate. Some recent reports indicate that adjuvant chemotherapy (CT) may have a beneficial effect on survival. Data from 400 patients with resected LCNC were analyzed. The 3- and 5-year survival rates were 54.1% and 45%, respectively. With the multivariable model, increasing age, ECOG $\geq$2 and advanced TNM stage were indicators of poor prognosis. Weak evidence of a higher overall survival in patients receiving adjuvant CT (adjusted hazard ratio 0.73; 95% confidence interval: 0.56-0.96, P $=$0.022) was also observed (Eur.J.Cardio-Thorac.Surg. 2017;52:339-345). In Stage I TCs (SITCs) non-anatomical resections (wedge) are sometimes advocated because of their indolent behavior. An analysis on effect of surgical procedure on SITC patients' survival was therefore done (Eur.J.Cardiothorac.Surg. 2017 *submitted paper*). Eight-hundred seventy-six SITC patients (569 females,65%) were included in this study; the 5-year OS rate was 94.3% (95%CI:92.2 −95.9). At univariable analysis, wedge resection resulted to be associated with a poor prognosis (5-year OS 82%,95%CI:0.71-0.89,P<.001) compared to other anatomical resections. At multivariable score-adjusted analysis, wedge resection confirmed to be an independent predictor of poor prognosis (HR2.17,95%CI: 1.19-3.96,P=.012). Since 2106, a lung NETs *prospective* database is active through the official ESTS European Database, and up to now, more than 150 new cases have been collected. Through this new platform, very easy to be used, we are confident to collect, in few years, more data especially on possible tumor recurrences and their treatment, as well as on the role of emerging biological drugs used in the adjuvant setting in advanced diseases. An active participation of Medical/Radiation Oncologists to this scientific project would be also desirable. The active role of the most important Scientific Societies could strongly support the success of this scientific project. **Keywords:** Surgery, registry, Lung neuroendocrine tumors

MS 07.06
Which Chemotherapy or Targeted Therapy is Better for Treatment of LCNEC Patients: SCLC-based versus Non-SCLC-based Regimens?

S. Thongprasert *Oncology Unit, Bangkok Hospital Chiang Mai, Chiang Mai/TH*

Staging of large cell neuroendocrine carcinoma (LCNEC) was classified based on non-small cell type (TNM stage). The treatment of early stage (I, II) was mainly surgery; the use of neo-adjuvant and adjuvant chemotherapy are in consideration but there's not a standard approach; for stage III which limited to the thoracic area, the role of concurrent chemotherapy and radiotherapy is one of the options. Whether the regimen of chemotherapy should be similar to small cell lung cancer (SCLC) or the regimen of non-small cell lung cancer (NSCLC) is not clear. Most of the data are in favor of SCLC regimen which is Cisplatin plus etoposide; however the data came from retrospective and small numbers of patients, thus there's an unmet need to improve the treatment of LCNEC. Large Cell Neuroendocrine Carcinoma and Small Cell Lung Cancer are both consider high grade neuroendocrine carcinoma of the lung. Small cell is the most frequent type of lung neuroendocrine tumor, occurs around 15% of lung cancer while Large Cell neuroendocrine carcinoma was only about 3% of lung cancer. According to WHO classification in 2004 LCNEC was classified as a variant of large-cell carcinoma; however in 2015 WHO classification LCNEC was classified into a group of neuroendocrine tumor which includes SCLC, typical carcinoid, atypical carcinoid and LCNEC. According to genomic analysis, LCNEC was separated into two groups. Some have genomic characteristic of SCLC and some have genomic characteristic of NSCLC. The new modalities such as anti-angiogenesis and in the case of EGFR mutation the treatment with EGFR inhibitor should be considered. The role of met inhibitors in LCNEC should be explored. Thus there is a long way to go in order to improve the outcome of this rare lung cancer type. **Keywords:** large cell neuroendocrine carcinoma, chemotherapy regimen

MS 08.02
Current Role of RT in MPM

A. Wrona *Medical University of Gdansk, Gdańsk/PL*

Local therapy as the primary treatment modality of early malignant pleural mesothelioma (MPM) remains highly controversial due to lack of clear benefit in comparative clinical trials. In specialized experienced centers, the initial approach is usually surgical resection —extrapleural pneumonectomy (EPP) or pleurectomy/decortication (P/D). No consensus exists with regard to the optimal use of radiotherapy (RT) in MPM. At the present time, there is no evidence to support the use of radical RT as a single modality in MPM, because of the inability to deliver a therapeutic high dose of radiation (e.g. 60Gy in 30 fractions) to the entire pleura without overdosing the surrounding organs at risk. However, RT has been used in the management of MPM in three indications: as prophylaxis to reduce the incidence of recurrence and pain at sites of diagnostic or therapeutic instrument insertion, as part of multimodal definitive treatment (following induction chemotherapy and surgical resection) to improve locoregional control in early-stage disease and for palliation of symptoms (mainly chest wall pain) in patients with advanced disease. During thoracoscopy, thoracocentesis or needle biopsy in patients with MPM, the seeding of tumor cells along the needle tract may occur, leading to painful metastases at the intervention sites in 20-50% of cases.[1] Prophylactic radiotherapy to chest wall sites of invasive procedures has previously been recommended. However, recent randomized studies (e.g. SMART trial) have shown that prophylactic RT should not be routinely used to prevent procedure tract metastases (PTMs) in MPM, as it confers no benefits in terms of chest pain control, analgesia use, survival, QoL and the data on the potential effect on PTMs' incidence reduction are discrepant.[1] Instead patients should undergo careful clinical follow-up allowing the immediate detection and treatment of PTMs. Surgical resection alone in early MPM is associated with high local recurrence rates (69% after P/D and 38% after EPP).[2] Therefore, to reduce local failure rate conventional RT has been used as a component of potentially curative trimodality treatment. Adjuvant RT was first used in patients after EPP and was delivered with anterior posterior photon fields matched with electron boost fields. A similar hemithoracic RT technique was explored after P/D, but additional block for central part of the lungs was required. The population based studies data on the potential role of adjuvant RT in improving overall survival (OS) are conflicting.[3] However, a subsequent analysis utilizing the National Cancer Database (NCDB) revealed the improvement of the 2-year rate of OS from 20% to 34% in patients with MPM receiving conventional RT after surgery.[3] Without significant improvement in local control and overall survival after P/D, conventional RT has been shown to decrease local recurrence after EPP to 13% and result in a median survival of 17 months.[3] The benefit in local control was strongly dose-dependent and obtained with a median dose of $\geq$54Gy [3]. Subsequently, the IMRT technique was implemented to improve adjuvant RT outcomes after P/D (IMPRINT approach). This novel method offers better coverage of the extensive, irregularly shaped target, safer dose escalation in the target volume and optimal sparing of OARs, but results in more heterogenous dose distribution, with a larger volume of normal tissue receiving low-dose radiation than in conventional techniques. IMRT was shown to be associated with a lower incidence of local recurrence (14% vs 42%),