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### **329. Lung cancer staging and miscellaneous**

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**Interval change in prevalence and survival from lung cancer in the west of Ireland**

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Lung cancer is the most common cause of cancer-related death in Ireland with a five-year survival rate of 5%.

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**Aim:** To examine the demographics of lung cancer in the West of Ireland and interval changes in the prevalence and survival from late 1980s to 90s.

**Method:** A retrospective study of all lung cancer cases in the West of Ireland from the Irish national cancer registry and hospital records.

**Results:** Between 1998-2004, 989 patients were diagnosed with lung cancer in the West of Ireland; 627(63.4%) at Merlin Park Hospital compared to 333 between 1988-92. 407(71.6%) male and 161(28.4%) female compared to 85% and 15% in the previous study. 48.5% > 70 yrs of age and only 4.5% < 50 yrs. 59.5% were smokers, 25.5% had quit and 7.5% never smoked.

Squamous cell cancer was the commonest (30.6%) followed by poorly differentiated (20%), small cell (16%), large cell (15.5%), adeno Ca. (13.5%). Survival data were available for 337 patients: 232(69%) died within a year, 71(21%) survived one yr, 18(5.3%) survived 2 yrs, and only 16(4.7%) pts survived >2 yrs. This compares to only 1 patient surviving 2 yrs in the previous study.

Between 1994-2004, the annual % change and the European age standardised rate has increased for females (3.24%) and (3.44%) whereas in males these declined (-0.3%) and (-1.0%). The number of lung cancers in the West of Ireland was 29% less in females and 23% less in males than would have been expected based on the national rate.

**Conclusion:**

Our study indicates that there was a considerable increase in lung cancer cases in female between 1998-2004 and slight reduction in male cases. Despite the increase in survival compared to late 1980s, the 2 year survival is still poor due to late presentation.

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**Costs of initial bronchoscopic treatment (IBT) in resectable bronchial carcinoids (BC)**

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**Rationale:** We recently reported that IBT is 50% successful as a tissue sparing treatment alternative for surgical resection in 66 patients with BC. Median follow-up till October 2005 has been 59.5 months (range 4.5- 264). The excellent survival (only 2/5 total deaths attributed to BC) allows actual costs calculation of IBT strategy, which requires regular follow-up for a very long period of time in contrast to the gold standard of immediate surgical resection.

**Methods:** Actual costs in 34 patients after successful IBT have been compared to 32 patients who required completion surgery (CS group). Estimated costs if follow-up would have been performed according to the strict protocol i.e. half-yearly bronchoscopy and HRCT in the 1<sup>st</sup> two years and yearly thereafter have also been calculated.

**Results:** Actual total costs so far have been € 160,556 (IBT) and € 268,094 (CS), with average costs per patient of € 4,722 (IBT) and 8,378 (CS) respectively. Estimated costs would have been € 258,451 (IBT) and € 326,976 (CS) with per patient costs of € 7,602 (BT) and € 10,218 (CS) respectively.

**Conclusions:** Together with previously reported data on excellent outcome and better quality of life after IBT, current analysis shows that the costs of IBT strategy prove to be better than initially estimated. Data underscore the curative potential of IBT as a cost-effective treatment alternative for surgical resection.

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**Clinicopathological features of synchronously arisen multiple bronchioloalveolar carcinomas**

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**Aim:** To evaluate clinical and pathological features of synchronously arisen multiple bronchioloalveolar carcinomas (BACs).

**Methods:** Among 596 patients who underwent surgical resection for lung cancer in our hospital from July 2000 to May 2005, 19 (3.2%) had multiple BACs. Histologic diagnosis was made according to the Noguchi's classification. On high-resolution CT (HRCT), nodular lesions were classified into three patterns based on the extent of ground-glass opacity (GGO) within the nodule: pure GGO (almost 100% GGO), mixed GGO (GGO >50%) and solid nodule (GGO <50%).

**Results:** Nineteen patients comprised 11 females and 8 males, with the median age of 63 years. Thirteen patients (68%) had never smoked before, and sixteen were accidentally found to have nodules on chest X-ray or CT. Using HRCT, we detected a total of 80 nodules, composed 56 pure GGOs, 23 mixed GGOs, and 1 solid nodule. The mean size of nodules was 8.6 mm. Video-assisted thoracoscopic surgery (VATS) was performed in all patients. Surgical procedures were lobectomy with wedge resection in 9 patients, wedge resection in 6, lobectomy in 2, and segmentectomy with wedge resection in 2, respectively. Pathologically, a total of 142 lesions consisting of 91 BACs and 51 atypical adenomatous hyperplasias (AAHs) were found. Of 91 BACs, 46 were Noguchi's type A adenocarcinoma, 29 were type B, and 16 were type C, respectively. All patients are alive after the median follow-up of 22.6 months.

**Conclusions:** Multiple GGO on HRCT strongly suggests multiple and synchronously arisen BACs. Pathological examination revealed more BAC or AAH

lesions than CT detection. VATS is useful for both diagnosis and treatment of multiple BACs.

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**Narrow band imaging with high resolution bronchovideocopy: a new approach to be visualize angiogenesis in squamous cell carcinoma of the lung**

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**Introduction:** We investigated the ability of a high resolution bronchovideocopy system with narrow band imaging (NBI) to detect blood vessels structure in the squamous cell carcinoma (SCC) of bronchi including carcinoma in situ (CIS) and micro invasive carcinoma in addition to the bronchial dysplasia.

**Methods:** Seventy nine patients with abnormal sputum cytology and lung cancer patients were entered. White light examination by high resolution bronchovideocopy was first performed. Observations were repeated with NBI light to examine microvascular networks in the bronchial mucosa. Spectral features on the RGB (Red/Green/Blue) sequential videoscope system were changed from the conventional RGB broadband filter to the new NBI filter. The wavelength ranges of the NBI filter were 400-430 nm(Blue), 400-430 nm(Green), and 520-560 nm(Red).

**Results:** The microvessels, vascular networks and dotted vessels in squamous dysplasia and several dotted vessels and tortuous vessels of various sizes and various grades in SCC were clearly observed in NBI with high resolution bronchovideocopy. Capillary blood vessels and tumor vessels mean diameters of CIS, micro invasive carcinoma and invasive carcinoma were 63.7±8.2 μm, 136.5±29.9 μm and 259.4±29.6 μm, respectively. The results indicate a statistically significant increase with mean vessels diameters in the three groups (p<0.029).

**Conclusion:** NBI with high resolution bronchovideocopy was useful in the detection of the several dotted vessels and tortuous vessels of various sizes and various grades in SCC. This may enable detect the onset of angiogenesis during multi-step carcinogenesis of the lung.

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**Endobronchial ultrasound and PET positive nodes in bronchial carcinoma**

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In bronchial carcinoma when positron emission tomography with 18-fluorodeoxyglucose (FDG-PET) shows increased emission in the mediastinal lymph nodes, confirmation by tissue biopsy is necessary. In this particular situation we have evaluated the use of real time lymph node aspiration under endobronchial ultrasound control.

Consecutive patients referred for staging and/or diagnosis of PET positive mediastinal nodes in the setting of suspected or confirmed bronchial carcinoma were included. The results of lymph node aspiration, performed under local anaesthesia in outpatients, were collected and if non-diagnostic surgical exploration was performed.

20 patients were studied between December 2004 and September 2005. The average number of ultrasound guided needle aspirations per patient was 4.8±1.2. Cytological or histological confirmation of malignancy was obtained by needle biopsy in 12 patients. The 8 negative cases were confirmed by surgical biopsy. In this preliminary series the sensitivity, specificity and negative predictive value of ultrasound guided aspiration of PET positive nodes was 100%.

Endobronchial ultrasound with needle aspiration should be considered a primary method of investigation of PET positive mediastinal lymph nodes.

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**EBUS-TBNA for mediastinal restaging**

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**Study objective:** Protocols using induction chemotherapy for advanced lung cancer are more frequently used with the hope that surgery can be performed after the cancer is downstaged. The current restaging modalities either have a low diagnostic accuracy (computed tomography) or can be technically difficult (Re-, mediastinoscopy). Endobronchial ultrasound guided TBNA is an excellent tool for mediastinal lymph node staging and may have a role in restaging also.

**Methods and patients:** Patients with NSCLC and proven ipsilateral or subcarinal lymph node metastases (N2 disease, 3A disease stage) who had been treated with

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induction chemotherapy and showing at least stable disease or partial response on CT imaging underwent mediastinal restaging by EBUS-TBNA. This was followed by surgical resection of the tumour with lymph node dissection.

**Results:** 83 Patients (54 male, 29 female, mean age 55,6 y.) had either a partial response ( $n=44$ ) or stable disease ( $n=39$ ) based on sequential CT scans of the thorax. Overall 143 nodes in N2 position were punctured, in 129 (90%) lymphocells were seen in the smears. The sensitivity, specificity and diagnostic accuracy of EBUS-TBNA per patient in restaging mediastinal LN were 70, 100 and 75%, respectively. EBUS-TBNA was performed in an ambulatory setting. No complications occurred.

**Conclusions:** EBUS-TBNA is an accurate, safe and minimally invasive diagnostic technique for the restaging of mediastinal lymph nodes after induction therapy in NSCLC. It's routine use for this purpose should be considered.

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**Accuracy of re-mediastinoscopy and fusion PET-CT in the assessment of lymph node (LN) downstaging after induction chemotherapy for N2 non-small cell lung cancer (NSCLC)**

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**Background:** Surgery is a rewarding treatment in patients with stage IIIA(N2) NSCLC when mediastinal LN downstaging is achieved after induction chemotherapy. Restaging of the mediastinum is an important, but difficult and controversial issue.

**Methods:** Prospective comparison of re-mediastinoscopy and fusion PET-CT for restaging purposes in 30 patients with potentially resectable mediastinoscopy proven N2 NSCLC (period 04/2002 till 04/2005). After 3 to 4 courses of cisplatin-based induction chemotherapy, the tumour was reassessed by video mediastinoscopy and PET-CT (interval between both max. one week). All non-progressive patients underwent thoracotomy, with intended complete resection and systematic LN dissection.

**Results:** At initial mediastinoscopy an average of 3.8 LN stations were biopsied. One third of the patients had multilevel N2 disease, half had positive subcarinal LNs. PET-CT detected residual mediastinal LN disease after induction with a sensitivity of 77%, a specificity of 92% and an accuracy of 83%. This was significantly better than re-mediastinoscopy (sensitivity 29%, accuracy 60%). Effectiveness of re-mediastinoscopy was hampered by adhesions and fibrosis, impeding adequate exploration.

**Conclusion:** Fusion PET-CT to assess mediastinal LN downstaging after induction chemotherapy for NSCLC is very promising. In our experience, re-mediastinoscopy is disappointing in patients who had a thorough initial mediastinoscopy. The good positive predictive value of PET-CT for persisting mediastinal LN metastasis makes it an attractive tool to evaluate the indication for surgery in this setting.

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**Effect of vascular endothelial growth factor antisense oligonucleotides and low molecular weight heparin on pulmonary thromboembolism in mice with Lewis lung cancer**

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**Objective** To investigate the effect of vascular endothelial growth factor (VEGF) antisense oligonucleotides(ASODN) or/and low molecular weight heparin (LMWH) – fragmin on coagulation and pulmonary thromboembolism(PTE) in mice with Lewis lung cancer.

**Methods** 48 C57BL mice were randomized into six groups: tumor control group, VEGF-ASODN group, VEGF-MSODN group, LMWH group, combined group and healthy control group. After the former five groups were injected with tumor cells, sodium chloride, VEGF-ASODN, VEGF-MSODN, LMWH, VEGF-ASODN plus LMWH, and sodium chloride were given respectively (once every two days, 15 times altogether). Coagulation initiator tissue factor (TF) were detected by ELASA method; thrombosis and embolism were detected by tissue HE staining method; TF protein level in tumor tissue by Western blot assay.

**Results** The mean concentration of plasma TF in LMWH group, combined group and healthy control group were  $20.00 \pm 1.26$ ,  $23.50 \pm 5.62$ ,  $9.40 \pm 2.92$  which were lower than that of tumor control group ( $27.08 \pm 5.40$ ) ( $P < 0.05$ ), but the concentration of plasma TF in ASODN group was  $34.13 \pm 9.63$  which was higher than that of tumor control group ( $P < 0.05$ ). PTE was relatively common, the rates of PTE in tumor control group, ASODN group, MSODN group, LMWH group, combined group, and healthy control group were 37.5%, 50.0%, 37.5%, 25.0%, 25.0% and 0%, respectively. TF protein expression in tumor tissue was higher in ASODN group.

**Conclusions** There existed hypercoagulation tendency in mice with Lewis lung cancer. VEGF-ASODN may exacerbate coagulation so as that the risk to PTE increased, but LMWH may reduce hypercoagulation.