4.1 MODULATION OF NEURON-RESTRICTIVE SILENCING FACTOR EXPRESSION IN LUNG CANCER

T.A.S. Baikhali, C Eccleston, J Chen, TM Elson
Liverpool University, Liverpool, United Kingdom

Small cell lung cancer (SCLC) is characterised by the expression of neuronal genes not seen in non-SCLC (NSCLC) or normal lung. The full-length neuron-restrictive silencer factor (NRSF) is a transcriptional repressor of neuronal genes in non-neuronal cells. We previously identified a splice variant of NRSF that encodes a truncated sNRSF isoform expressed only in SCLC, and aimed to determine its function and downstream targets. We have shown that the expression of several NRSF-regulated genes correlated with that of sNRSF in lung cancer and used reporter constructs based on NRSF-regulated promoters, such as arginine vasopressin (AVP), as readout for sNRSF function. Mutation of an NRSF binding site reduced expression was pro

of NRSF splicing in SCLC. Lung cancer cells with modulated sNRSF expression will now be used to identify novel target genes regulated by sNRSF in lung cancer by microarray and proteomic analysis. Identification of biological relevant genes will help us to understand the role of sNRSF and may ultimately provide new opportunities for developing detection or treatment strategies.

4.2 STABILITY AND HETEROGENEITY OF EXPRESSION PROFILES IN LUNG CANCER SPECIMENS HARVESTED FOLLOWING SURGICAL RESECTION

FH Blackhall, M Pintilie, DA Wigle, J Jurisica, MS Tsao
Canada, Ontario Cancer Institute, Princess Margaret Hospital and University of Toronto, Toronto

One of the major concerns in microarray profiling studies of clinical samples is the effect of tissue sampling and RNA extraction on the resultant data. We analysed gene expression in lung cancer specimens that were serially harvested from the tumour and snap-frozen at several intervals up to 120 minutes after surgical resection. Global gene expression was profiled on 1.7K cDNA microarrays, and selected stress and hypoxia-activated genes were evaluated using realtime RT-PCR. Remarkably, similar gene expression profiles were obtained for the majority of samples regardless of the time that had elapsed between resection and freezing. Realtime RT-PCR studies showed significant heterogeneity in the expression levels of stress and hypoxia-activated genes in samples obtained from different areas of a tumour specimen at one time point after resection. The variations between multiple samplings were significantly greater than those of elapsed time between sampling/freezing.

Overall, samples snap-frozen within 30-60 minutes of surgical resection are acceptable for gene expression studies; thus, making sampling and snap-freezing tumour samples in a routine surgical pathology laboratory setting feasible. However, sampling and pooling from multiple sites of each tumour may be necessary for expression profiling studies to overcome the molecular heterogeneity present in tumour specimens.
4.5 PET-BASED MAPPING OF LYMPH NODE SPREAD IN NON-SMALL CELL LUNG CANCER (NSCLC)

DB Landau, S Ahmad, M O’Doherty, T Treasure, Guys & St Thomas’ NHS Trust, London, United Kingdom

Introduction: Numerous studies have shown that PET is more accurate than CT at identifying thoracic lymph nodes in NSCLC. The aim of this study is to investigate the pattern of mediastinal nodal involvement in NSCLC in relation to primary tumour location using PET scanning.

Method: Patients were selected from a database of 1400 patients who had PET scans for suspected lung cancer between 2000 and 2002. Tumour position and site of any lymph node metastases were noted. Nodes were considered positive if the Standardised Uptake Value (SUV) was significantly raised relative to the surrounding region.

Results: 288 patients out of 513 were node positive on PET. Of 242 upper zone (UZ), 126 midzone (MZ) and 145 lower zone(LZ) tumours, 46%, 40% and 45% respectively were ipsilateral hilar node positive (IHIN+), 8%, 5% and 20% respectively were subcarinal node (SCN) positive and 7%, 4% and 2% respectively were tracheobronchial node (TBIN+) positive. In IHIN+ patients 14%, 6% and 23% respectively of UZ, MZ and LZ tumours showed increased activity in the SCN, 11%, 6% and 5% in the TBN and 17%, 7% and 14% in the contralateral hilar nodes (CHN). In IHIN negative patients the corresponding figures were 18%, 27% and 70% for SCN, 14%, 18% and 0% for TBN and 21%, 18% and 10% for CHN.

Conclusions: IHIN involvement is similar regardless of primary tumour location. SCN involvement is more common with LZ tumours. TBN involvement is more common with UZ tumours. The CHN are more commonly involved than other nodal areas more frequently sampled in routine clinical practice. The clinical implication of this finding is that some patients are significantly undertreated. The TBN and SCN groups may represent 2nd station nodes of distinct lymphatic pathways from IH.

4.6 RESPIRATORY MOTION MODELLING FOR OPTIMISATION OF NON-SMALL CELL LUNG CANCER (NSCLC) RADIOTHERAPY

S Ahmad 1, DB Landau 1, JM Blackall 1, M Miquel 2, DJ Hawkes 2

1 Guy’s & St. Thomas’ NHS Trust, London, United Kingdom, 2 King’s College London, London, United Kingdom

Introduction: Despite recent improvements in NSCLC treatment, respiratory motion significantly impacts on radiotherapy planning. We are developing a system to model respiratory motion by investigating complex 3D lung motion and deformation in 10 healthy volunteers and patients with lung cancer, to create subject-specific models using a novel MR and CT based imaging and non-rigid registration method.

Method: Models were constructed using a voxel-based image registration technique to coregister MR images acquired throughout the breathing cycle. A high-quality reference image, acquired at exhale, was aligned to each of a sequence of scans at positions between exhale and inhale. Two different image acquisition techniques were used: 1. free breathing and 2. at various breath-hold positions between exhale and inhale. Positions of all points on the surface of the lung were plotted against diaphragm position, chosen to represent position in the respiratory cycle. Studies were made of different models to analyse inhale and exhale trajectories of breathing.

Results: Maximum displacement of 16mm, at maximal inhale was observed when comparing inhale to exhale data. Comparison of two breathing cycles showed 19mm displacement, at mid-cycle position. Disproportionately large displacements of up to 27mm were seen when comparing free breathing to breath-hold models. Diaphragm-adjacent lung was most mobile (42mm displacement) especially in the superior-inferior direction. However, up to 10mm lateral movement also occurred at the lung apex.

Conclusions: Our results suggest that inter-cycle variation may be greater than intra-cycle variation and that breath-hold models do not accurately represent lung motion when the subject is breathing freely, as they would be during radiotherapy treatment. We believe that modelling technology has the potential to be used for optimisation of radiation delivery and to further develop 4D radiotherapy planning.

4.7 THE TIMING OF THORACIC IRRADIATION IN LIMITED DISEASE SMALL CELL LUNG CANCER

L. E. James 1, A. Hackshaw 1, S. G. Spiro 1, R. M. Rudd 1, P. Clarke 1, C. Trask 1, N. H. Gower 1, P. G. Harper 1, R. S. Souhami 1, 1 United Kingdom, University College, London, 2 United Kingdom, St Bartholomew’s Hospital, London, 3 United Kingdom, Southend Hospital, Essex, 4 United Kingdom, Guy’s Hospital, London

Uncertainty about the optimal timing of thoracic irradiation (TI) led us to undertake a randomised trial comparing survival in patients given ‘early’ TI (with the 2nd cycle of chemotherapy) with those given ‘late’ TI (with the 6th cycle of chemotherapy). Our trial aimed to replicate that of an NCIC study (JC0 1993;Vol 11:2:336) in which early TI increased 3-year survival by 10%. Between January 1993 and January 2002, 325 patients were randomised to receive either early TI or late TI. All patients received chemotherapy, which was given every 21 days for 6 courses and consisted of cyclophosphamide, doxorubicin and vincristine, alternating with cisplatin and etoposide. Thoracic radiotherapy dose was 40Gy in 15 fractions over 3 weeks. Prophylactic cranial radiotherapy, 25Gy in 10 fractions over 2 weeks, was given to responding patients with a negative, post treatment, brain scan.

Survival at 3 years was similar between the two arms; 10% in those who received early TI and 20% in those who received late TI (hazard ratio 1.18, 95% CI 0.93-1.51, p=0.18). This is in contrast to the NCIC trial. We therefore looked at other trials on the topic:

Trial Number of patients Difference in median survival (early - late) % who completed all chemotherapy courses

Murray 1993 308 +5.2 (p=0.01) 87 84
Jeremic 1997 103 +8.0 (p=0.05) Similar in 2 arms
Takada 2002 228 +7.5 (p=0.10) 86 86
Perry 1987 270 -1.5 (p=0.08) Lower in early arm
Week 1997 206 +1.5 (p=0.41)
Current trial 325 -2.6 (p=0.18) 69 80

Three trials showed that early TI was better and 3 trials showed no difference (or early TI slightly worse). The difference in results seem to be associated with chemotherapy uptake. Early TI may only be better if the assigned chemotherapy regimen is maintained and not reduced.

4.8 GEFITINIB (‘IRESSA’; ZD1839) IN PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC): THE ROYAL MARSDEN EXPERIENCE

NR Maisey, MParton, C Harper-Wynne, K Sumpter, S Ashley, TEisen, MOBrien

Royal Marsden Hospital, London, United Kingdom

Background: Gefitinib, an inhibitor of the intracellular tyrosine kinase domain, has demonstrated useful activity in advanced pre-treated NSCLC (IDEAL I / II). The clinical efficacy of gefitinib was assessed as part of an Expanded Access Programme.

Methods: Patients (pts) were treated with gefitinib 250mg/day. Endpoints included overall survival (OS) and time to treatment failure (TTF). Objective and symptom responses (OR, SR) were assessed at 1 month intervals.

Results: 141 pts were assessed: median age 65 (35-88); male/female, 81/60; performance status (PS) 0/1/2/3, 1/45/39/16%; advanced disease 90%. Pts (n=12) with bronchoalveolar adenocarcinoma (BAC) had significantly lower OS / TTF (9 and 5 weeks respectively). Pts (n=12) with squamous cell carcinoma (SCC) had significantly higher OS / TTF (20 and 8 weeks respectively). OS / TTF 20 weeks (95% CI 13-28) / 8 weeks (95% CI 7-10) respectively.

Conclusions: There were no significant differences between histology subtypes and no differences in response or symptom control between OR and SR. There was no significant difference in response between patients with or without CNS metastases.

Trial Number of patients Difference in median survival (early - late) % who completed all chemotherapy courses

Murray 1993 308 +5.2 (p=0.01) 87 84
Jeremic 1997 103 +8.0 (p=0.05) Similar in 2 arms
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