treatment failure. Adjuvant chemotherapy improves survival, but the absolute gain is modest and generally limited to stage II-IIIA. High-risk pts may be identified by gene expression profiles and considered for adjuvant chemotherapy.

Methods: Of a consecutive series of 174 pts who underwent curative pulmonary resection between 2000 and 2004, we selected 66 stage I-IIIA SqCLC pts (64 pts stage I and II and 2 pts stage IIIA): 33 pts who developed distant metastases and 33 who were free of distant relapse after a median follow-up of 37 months (range, 24-64 months). Snap frozen primary tumor specimens were obtained at the time of surgery. Sections were taken from blocks of tumor tissue for RNA extraction, and gene expression of 29 genes was assessed by RT-PCR using low density arrays. Expression values were dichotomized using the median as a cut-off value.

Results: The univariate analysis identified 10 genes with significant prognostic value: CSF1, EGFR, CA IX, PH4, KIAA0974, ANLN, VEGFC, NTRK1, FN1, INR1. In the multivariate Cox model, CSF1 [HR=3.5, p=0.005], EGFR [HR=2.7, p=0.02], CA IX [HR=0.2, p<0.0001] and tumor size >4 cm [HR=2,7, p=0.02] emerged as significant predictors of survival. A risk score based on the expression of CSF1, EGFR and CA IX was 70% accurate in predicting death risk. This model also performed well in predicting development of distant metastases, with 64% sensitivity and 73% specificity. A strong correlation was observed between some of these genes. For example, high levels of PH4 were related to low or no expression of CA IX ($\varrho = -0.33$; p=0.007).

Conclusions: Overexpression of CSF1 and EGFR, and downregulation of CA IX was associated with particularly poor prognosis in SqCLC. Simultaneous assessment of the expression of these genes defines the group of SqCLC pts who might derive the highest benefit from adjuvant chemotherapy.

P2-101 BSTB: Prognostic Factors Posters, Tue, Sept 4

Preliminary assessments using nonlinear regression analysis of semilog survival curve plots to detect and characterize prognostically distinct subgroups in non-small cell lung cancer patients treated with epidermal growth factor receptor tyrosine kinase inhibitors.

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Background: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are effective vs non-small cell lung cancer (NSCLC). Several known factors influence therapy efficacy.

Hypothesis: We hypothesized: 1) patient survival curves follow first order kinetics. 2) Dichotomous (present vs absent) prognostic factors give inflection points on plots of log % cell survival vs time. 3) Nonlinear regression analysis of log-linear survival plots might permit identification and characterization of prognostically distinct subgroups, and this could: a) aid in identification of prognostic factors b) facilitate assessment of whether a therapy was having an impact on a distinct subpopulation or on the whole group.

Methods: Since much is already known about impact of EGFR TKIs in distinct NSCLC subgroups, we used published survival curves for EGFR TKI-treated patients to conduct preliminary assessments of this proposed methodology. We manually measured curve height from 215 published survival or progression-free survival curves, replotted data as semilog plots, and performed compartmental nonlinear regression

analyses using WinNonlin version 5.0.1 to assess number, size and half-life of identifiable distinct subgroups.

Results: Patterns identified were 1, 2, and 3 compartment curves, with 2 compartment curves being most common. Some 1 compartment curves were convex, and some of these had a terminal plateau after the convexity, suggesting that they actually had a second compartment that had not been recognized by the analytical program due to the convexity. Of 199 curves assessed in detail, 16 were 1 compartment without convexity, 11 were 1 compartment with convexity, 98 were 2 compartment without convexity, 69 were 2 compartment with convexity in the first portion, and 5 were 3 compartment. Analyses continue to assess whether we can identify specific treatment parameters or population factors that correlate with curve characteristics.

Conclusions: When log % survival is plotted vs time, most survival curves have one or more inflection points suggesting distinct subpopulations that differ by one or more dichotomous prognostic factors. These early analyses suggest that it is feasible to use compartmental nonlinear regression analysis to assess survival curves, although more complex modeling will be needed to optimally characterize curves with convex early portions. We plan to now use this methodology prospectively to link tumor and patient characteristics to prognostic subgroups. We will test the hypotheses that: 1) dichotomous variables account for curve inflection points. 2) The further to the right along the survival curve, the more homogeneous the remaining population for a phenotype conferring good prognosis. 3) Curve convexities are due to specific treatment practices (eg, discontinuing therapy after a set time period) or else are due to identifiable epigenetic events triggered early in therapy that lead to a maximum attainable survival time. 4) Assessment of therapies with respect to changes they induce in relative subgroup sizes and half-lives will help elucidate whether a treatment is affecting one patient subpopulation to a greater extent than another, and whether it is shifting patients from a poor prognosis group to a good prognosis group. Support: NCI Cancer Center Support Grant 5-P30 CA16672 to UTMDACC.

P2-102 BSTB: Prognostic Factors Posters, Tue, Sept 4

Prognostic value of pretreatment serum Cyfra 21-1 and CRP in non-small cell lung cancer patients treated by surgery

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Background: Pathologic stage of disease is the most important prognostic factor in non-small cell lung cancer (NSCLC) patients treated by surgery. Nevertheless there is a great discrepancy in survival time observed within the groups with the same pathologic stage of disease. The aim of the present study was to assess the prognostic role of pretreatment serum level of cytokeratin marker - Cyfra 21-1 and an acute phase protein - CRP in NSCLC patients (pts) treated by surgery.

Methods: 39 pts, 30 men, 9 women, median age 62 (42-78) years, treated by surgery entered this study. Pathologic stage of disease was: Ia-IIb in 32 pts, IIIa in 4 pts, IIIb in 2 pts and IV in 1 pt (single homolateral lung metastasis). Sera for Cyfra 21-1 (Elecsys Roche) and CRP (Roche/Hitachi) were obtained before surgery.

Results: After 2 years of follow up 30 pts were still alive (pathologic stage Ia-IIb in 27, IIIa - in 2, and IIIb in 1). 9 pts were dead (pathologic stage Ia-IIb in 5, IIIa in 2, IIIb in 1 and IV in 1). Pretreatment serum CRP exceeded 10 mg/l in 7/9 pts who died and 14/30 pts who were

alive. Median serum CRP values were 23.5 (0.2-122.6) mg/l and 3.72 (0.1-82.8) mg/l respectively (p=0.029). No correlation between CRP and pathologic stage of disease was found. Pretreatment Cyfra 21-1 exceeded 3.3 ng/ml in 6/9 pts who died and 7/30 pts who were alive. Median Cyfra 21-1 concentrations were 5.29 (2.5-14.5) ng/ml and 1.92 (0.7-6.2) respectively (p=0.0003). This difference was also significant if only stage I and II pts were taken into analysis.

Conclusion: Cyfra 21-1 and CRP are prognostic indicators in NSCLC patients treated by surgery and their influence on survival is probably partly independent from pathologic stage of disease.

P2-103   BSTB: Prognostic Factors Posters, Tue, Sept 4

Cytological Status of Pre- and Post-Operative Pleural Lavage and Lymph Node Recurrence in Patients with Early Stage Non-Small Cell Lung Cancer

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Background: Intraoperative pleural lavage cytology (PLC) in patients with early stage of non-small cell lung cancer (NSCLCs) has been considered as possible aids to assess prognosis of lung cancers and was reported to be useful in detecting sub-clinical pleural dissemination, local and systemic recurrence. Many studies revealed that only pre-operative PLC is necessary. We conduct a prospective study to explore any possible association of pre- and post-operative PCL and lymph node recurrence and the potential usefulness of post-operative PCL.

Methods: From December 2004 to December 2006, PLC was performed before and after any manipulation or resection of the lung in 24 consecutive patients, who had no macroscopic pleural effusion, dissemination, or diffuse adhesion, and who subsequently underwent curative resection for NSCLCs. The operations were performed by only one surgeon and the results of PLC with reference to clinicopathologic characteristics were evaluated and reported by only one pathologist. Tumor recurrence (local and systemic) was analyzed.

PLC consisted of cytological analysis of 50 mL of saline irrigated over the lung surface immediately after thoracotomy and after complete curative resection with radical mediastinal lymph node dissection.

Results: Nine (38%) of 24 patients had positive cytological findings. Positive cytological findings were observed more frequently in patients with adenocarcinoma, pleural involvement of the tumor and male gender.

Five (55%) of 9 patients had positive cytology in pre-operative PLC, 3 (33%) in post-operative and 1 (11%) in both pre- and post-operative PLC. Exact McNemar significance probability test showed no association between pre- and post-operative cytological status (p= 0.727).

The risk of lymph nodes recurrence after 3 month of curative surgery in patients with negative and positive pre-operative PLC was 5.6% and 33.33% respectively (risk ratio = 6, 95%CI = 2 to 8, p = 0.143). In patients with both negative pre- and post-operative cytology, negative pre-operative but positive post-operative, positive pre-operative but negative post-operative, and positive both pre-and post-operative were 6.7%, 0%, 20.0% and 100% respectively (p=0.123).

Conclusions: No relationship between cytological status of pleural lavage fluid pre-operatively and post-operatively was detected. The study showed that if malignant cells were found in pre-operative PLC, the risk of lymph node recurrence in 3 months increased by 6 times, and maximum risk occurred when the malignant cells was found in both pre- and post-operative PLC. However, the increased risk was not statistically significant because of the lack of statistical power due to small study size. If sample size were increased it may reveal that PLC may also be required at the time of curative resection for non-small cell lung cancer in order to estimate the risk of lymph node recurrence.

P2-104   BSTB: Prognostic Factors Posters, Tue, Sept 4

Role of ERCC1, XRCC3, Aurora A and TGFBR1 single nucleotide polymorphisms (SNP) and CHFR and 14-3-3 sigma methylation in a customized cisplatin (cis) trial based on ERCC1 mRNA levels in stage IV non-small-cell lung cancer (NSCLC) patients (p)

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Background: The primary aim of this trial was response. In both the control arm and in the genotypic arm with low tumor ERCC1 mRNA levels, p received docetaxel(doc)/cis; in the genotypic arm with high tumor ERCC1 mRNA levels, p received doc/gemcitabine. Response was significantly higher in the genotypic arms. We examined 324 p for genetic markers that could influence response, including ERCC1 118 C/T, ERCC1 C8092A, XRCC3 241 (Thr to Met), Aurora A 91 T>A, Aurora A 169G>A, a SNP within intron 7 of the TGFBR1 gene (Int7G24A), and an in-frame germline deletion (TGFBR1*6A). Methylation of 14-3-3 sigma and CHFR were also analyzed.

Methods: DNA from peripheral lymphocytes was used for genotyping (Taqman assay) and methylation-specific PCR was used for 14-3-3 sigma and CHFR in pretreatment serum DNA.

Results: There were no differences in clinical characteristics among the different SNP types, except that p with Aurora A 91 AA had higher tumor ERCC1 mRNA levels (P=0.005). No relationship was found between ERCC1 SNPs and tumor ERCC1 mRNA levels. A strong correlation was found between the Int7G24A and XRCC3 241 SNPs (P=0.03). The Int7G24A GA type had a higher odds ratio (OR) of response (OR 2.32) than the AA type (OR 3.15) (P=0.02). XRCC3 241 MetMet had a lower probability of response (OR 0.23) (P=0.04). No other differences in response were observed according to any of the other SNPs or methylation. In the multivariate model, the best response was observed in p with performance status (PS) 0, low ERCC1 levels, and XRCC3 241 SNP (Table).