Predictive and prognostic value of cell-free DNA in plasma and pleural lavage among surgically treated adenocarcinomas (ADCL) of the lung

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Background

- In resectable adenocarcinoma (ADCL) lung cancer patients, cell-free DNA (cfDNA) in plasma was found to predict the presence of minimal residual disease[1]
- Although pleural recurrences occur in 20-40% cases (either isolation or in combination with distant location), this site has never been evaluated to discover a possible novel route of early malignant cell spread before spreading distantly[2]
- This study was aimed to evaluate if cfDNA in pleural lavage serve as an early biomarker to predict the promotion of pleural spread and prognosis in resectable ADCL

Methods

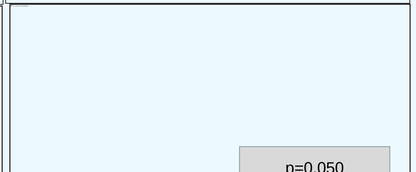
- Consecutively resected ADCL within a period of 24 months were evaluated for cfDNA levels in preoperative plasma (Pre-P), intraoperative pleural lavage (IP-L) and postoperative (at 1 month) plasma sample (Post-P).
- CfDNA was isolated from the stored pleural lavage and plasma using QIAamp DNA Blood Mini Kit (QIAGEN).
- DNA extracted plasma and pleural lavage DNA were measured quantitatively by qPCR in a TaqMan probe detection approach using the human β-actin gene as the amplifying target.

Results

- All of the study patients (n=23) were negative for malignant cells in IP-L cytology.
- The median cfDNA levels in Pre-P, IP-L and Post-P were 83.1ng/ml, 153.5ng/ml and 88.0ng/ml respectively.
- A positive correlation was demonstrated between Pre-P and IP-L levels (correlation coefficient r= 0.478, p=0.007).

Fig.1 Overall survival (OS) of all patients

Fig.2 Comparison of cfDNA in pleural lavage (IP-L) with OS



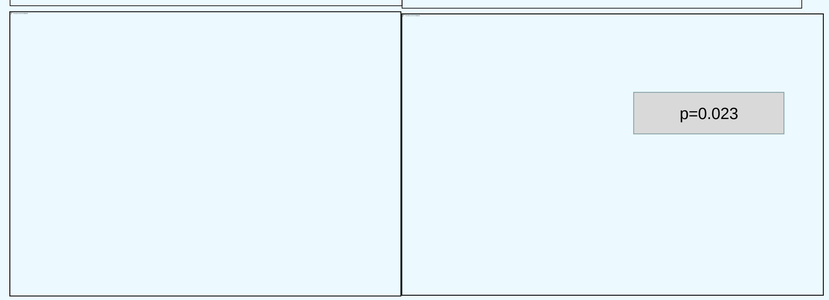
- A significant overall survival (OS) and disease-free survival (DFS) was recorded for patients with cfDNA level cut-offs at 125ng/ml, 175ng/ml and 100ng/ml respectively for Pre-P, IP-L and Post-P.
- The area under the curve (AUC) for IP-L with DFS was found to be at a significant range (AUC=0.901, Standard error rate=0.050).
- Tumors with stage >T2 produced significantly more cfDNA levels in IP-L (p=0.033).

- The median OS was 23.7 months, figure 1.
- Patients with raised cfDNA in Pre-P (>125ng/ml) and IP-L (>175ng/ml) had a significantly poorer 2-year OS, p=0.026 and p=0.037 respectively (figure 2).
- The hazards (OS) were also higher for those with raised cfDNA in IP-L (HR=6.821, 95%CI=0.989-12.796, p=0.050).

- The median DFS was 16.9 months (figure 3.)
- A raised IP-L (>175ng/ml) correlated significantly with poorer DFS at 2-years (p=0.003) and a significant increase in hazards of DFS (HR=11.455, 95% CI=1.395-24.434, p=0.023), (figure 4.).
- Multivariate analysis suggested higher IP-L as a poor prognostic factor for both OS and DFS.

Fig.3 Disease free survival (DFS) of all patients

Fig.4 Comparison of cfDNA in pleural lavage (IP-L) with DFS



Conclusion

- Among patients with operable ADCL, cfDNA in pleural lavage can be a reliable biomarker for both recurrence and overall survival
- Our findings suggest that IP-L cfDNA levels could possibly be a better indicator than plasma cfDNA levels for early detection of minimal residual disease that might benefit from therapeutic intervention.
- Further studies with larger number of patients in this direction are necessary to establish our results.

References

1. Abbosh C, Birkbak NJ, Wilson GA, Jamal-Hanjani M, Constantin T, Salari R, et al. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. Nature. 2017 Apr 26;545(7655):446-451.
2. Circulating Cell-Free DNA in Plasma/Serum of Lung Cancer Patients as a Potential Screening and Prognostic Tool. Clin Chem