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1684P Genetic Alterations as Independent Prognostic Factors to Predict the Type of Recurrence of Lung Cancer

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Background

Around 60% of lung cancers (LC) are radically treated with surgery or chemoradiation (CRT). Still 33-70% of patients develop recurrence with a median time to relapse 11-16.8 months and approximately 80% of recurrences [locally (LR) or distantly (DR)] occur within the first 2 years. Patients with LR usually have a better prognosis. Previous studies have focused mainly on the role of clinico-pathological characteristics for the risk of recurrence. The role of molecular mechanisms remains unclear. We aimed to analyze genomic features in LC patients with LR versus DR to predict the type and risk of recurrence.

Methods

191 patients were included (see Table 1.). Histological specimens from patients with LC recurrence (2015-2017) collected at the time of initial diagnosis were sent for whole exome sequencing (WES). Genomic data was analyzed for small genetic alterations, namely single nucleotide polymorphisms (SNPs) and insertion-deletion mutations (INDELs).

Table 1. Patients' and tumor characteristics.

Type of recurrence, N (%)	Local N=63 (33%)	Distant N=128 (67%)	Whole population N=191	p
Sex				
Female	16 (25.4)	36 (28.1)	52 (27.2)	0.73
Male	47 (74.6)	92 (71.9)	139 (72.8)	
Age				
>65	37 (65.1)	83 (66.4)	120 (62.8)	0.87
≤65	26 (34.9)	45 (33.6)	71 (37.2)	
Primary TNM status				
IA, IB	13 (20.63)	23 (18.9)	36 (18.9)	0.72
IIA, IIB	8 (12.7)	29 (22.6)	37 (19.4)	
IIIA	29 (46.03)	45 (35.16)	74 (38.8)	
IIIB, IIIC, IVA	13 (20.64)	31 (24.34)	44 (22.9)	
Histological type				
Adenocarcinoma	10 (15.87)	40 (31.25)	50 (26.3)	0.13
SCC	28 (44.49)	44 (34.38)	72 (37.7)	
Carcinoid	0	2 (1.57)	2 (1)	
Other NSCLC	8 (12.8)	11 (8.59)	19 (9.9)	
SCLC	12 (19.05)	23 (17.97)	35 (18.4)	
No malignancy histologically	0 (0)	3 (2.34)	3 (1.5)	
Not taken	5 (7.95)	5 (3.9)	10 (5.2)	
Type of primary treatment				
Surgery	12 (19.05)	55 (43.75)	67 (35.1)	**0.004**
CRT	31 (49.21)	50 (39.06)	81 (42.4)	
RT	16 (25.4)	17 (13.28)	33 (17.3)	
ChT	5 (6.35)	5 (3.91)	10 (5.2)	

Abbreviations: SCC, squamous cell carcinoma; NSCLC, non-small cell carcinoma; SCLC, small cell carcinoma; CRT, chemoradiotherapy; RT, radiotherapy; ChT, chemotherapy.

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Results

We identified significant INDEL mutations in 38 and 98 genes and SNP mutations in 63 and 179 genes in DR and LR groups, respectively. DMXL2 mutations and ABCC9 gene mutations caused by INDELs were only prominent in the DR group.
Enrichment analysis detected genes, like KNTC1, CLASP1, CLASP2 and CENPE, responsible of microtubule disturbance in the DR group (Fig 2a, 2b, Fig 3). In DR group mutated genes, like STIM1, ITPR3 and RYR3, were significantly enriched in cytosolic Ca2+ related Gene Ontology (GO) terms and pathways, whereas in LR group enrichment of terms related endoplasmic/sarcoplasmic reticulum Ca2+ was observed. Association between those gene alterations and recurrence in LC has not been published previously.

Fig 1a

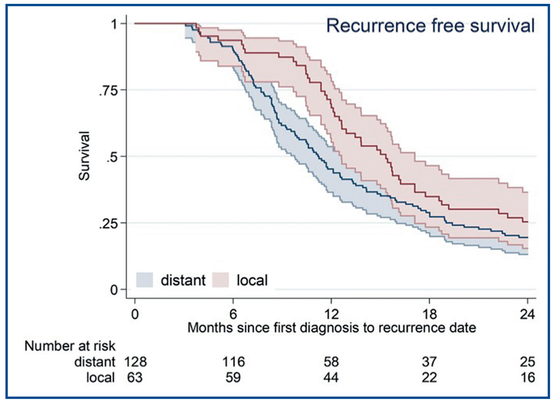

Fig 1b

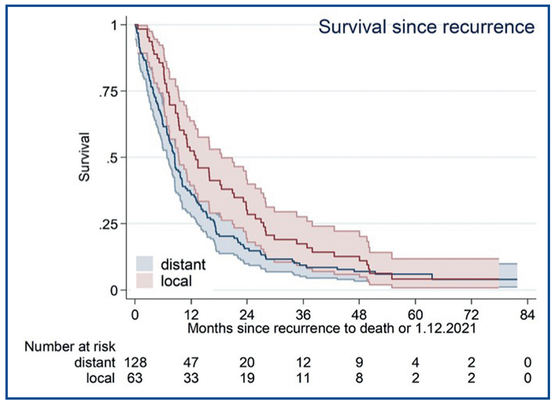

Fig 1. RFS from initial diagnosis to recurrence [mRFS 15.4 vs 11.2 m (p=0.20)] (Fig 1a); OS from recurrence to death [mOS 12.9 vs 8.5 m (p=0.007)] (Fig 1b).

Fig 2a

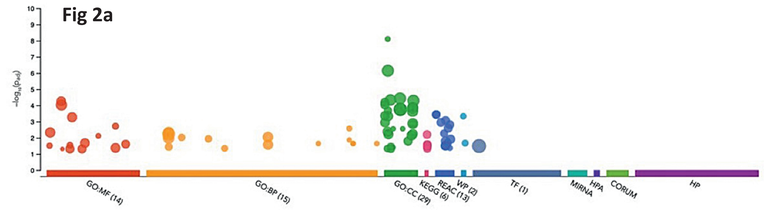

Fig 2b

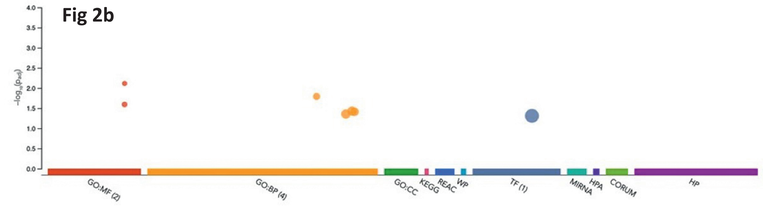

Fig 2. Gene enrichment results for the DR (Fig 2a) and LR (Fig 2b) group integrating SNPs and INDELs generated by the g:Profiler. Genes are enriched in multiple GO terms, such as molecular function, biological process, cellular compartment, KEGG, and Reactome pathways. The local recurrence group exhibits much fewer enrichments with only a few belonging to GO molecular function or biological process group.

Fig 3

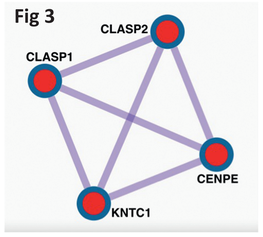

Fig 3. Detection of physical protein-protein interactions in the DR group examining SNPs and INDELs combined.

Conclusion

The addition of genomic markers to clinico-pathological characteristics may predict the type of recurrence and prognosis for patients with LC. Collectively our findings indicate distinct genomic signatures in the LR and DR cohorts, with microtubule disturbance and calcium regulation playing a crucial role in invasiveness in DR of LC. Found genetic alterations warrant further analysis to improve patients' management.

REFERENCES:
Goldstraw P et al. The IASLC Lung Cancer Staging Project: Proposals for the Revision of the TNM Classification for Lung Cancer. JTO, 2016.; Aupérin A et al. Meta-analysis of concomitant versus sequential chemoradiotherapy in locally advanced non-small-cell lung cancer. JCO, 2010. ; Antonia SJ et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. NEJM, 2017.; Spigel DR et al. Five-year survival outcomes with durvalumab after chemoradiotherapy in unresectable stage III NSCLC: An Update from the PACIFIC trial. JCO, 2021.; Sugimura H et al. Survival after recurrent NSCLC after complete pulmonary resection. Annals of Thoracic Surgery, 2007.; Planchard D et al. Metastatic NSCLC: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology, 2018.; Dziedzic DA et al. Risk Factors for Local and Distant Recurrence After Surgical Treatment in Patients with NSCLC. Clinical Lung Cancer, 2016.
Ann Valter declares no conflict of interest with this work.