

c-MET (SP44) IHC in Metastatic Lung Adenocarcinoma: Prevalence, Correlates, and Cytology-Histology Concordance

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INTRODUCTION

The FDA recently approved the c-MET SP44 immunohistochemistry (IHC) assay as a companion diagnostic for MET-targeted therapy in lung cancer. Previous studies have shown c-MET overexpression in 25–55% of lung adenocarcinomas, with a potential association with poor overall survival. Since c-MET IHC is routinely performed on both cytologic and surgical biopsy specimens at initial diagnosis, understanding its reliability across different specimen types is clinically important.

AIM

In this single-center, retrospective study, we examined the prevalence, clinicopathologic and molecular features of c-MET expression in stage IV lung adenocarcinoma, as well as the concordance of c-MET SP44 staining between cytologic specimens and matched tissue biopsies.

METHODS

26 pleural, 1 peritoneal, and 3 pericardial samples, with matched surgical pathology specimens from 30 patients with stage IV lung adenocarcinoma, were stained for c-MET. Staining intensity was evaluated using the Koeppen scoring criteria (Koeppen et al., 2014), with a 3+ score defined as strong membranous or cytoplasmic staining in ≥50% of tumor cells. At the patient level, c-MET positivity was defined as a 3+ score in either the cytology or matched surgical pathology specimen. Concordance between cytology and surgical pathology specimens was assessed using linear-weighted Cohen's kappa, weighted observed agreement, and binary concordance (c-MET positive vs negative). Clinicopathologic and molecular variables were extracted and compared according to c-MET status using Fisher's exact test and the chi-square test for trend as appropriate.

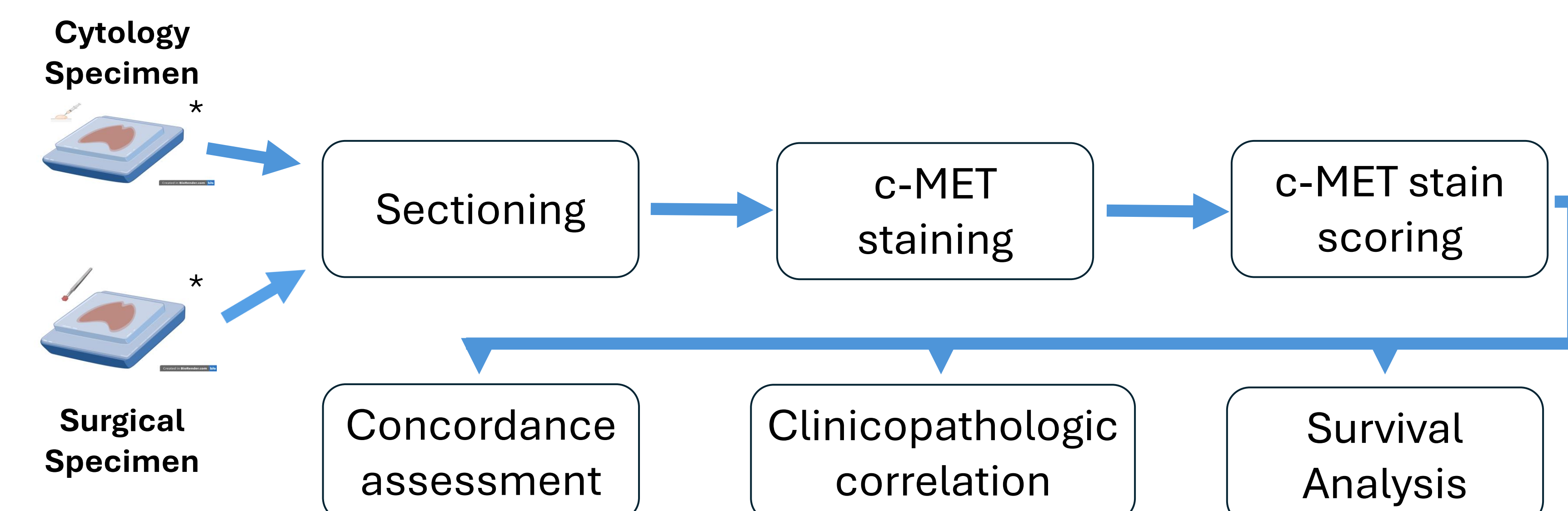


Figure 1: Study workflow

* Images generated using Biorender

c-MET Concordance

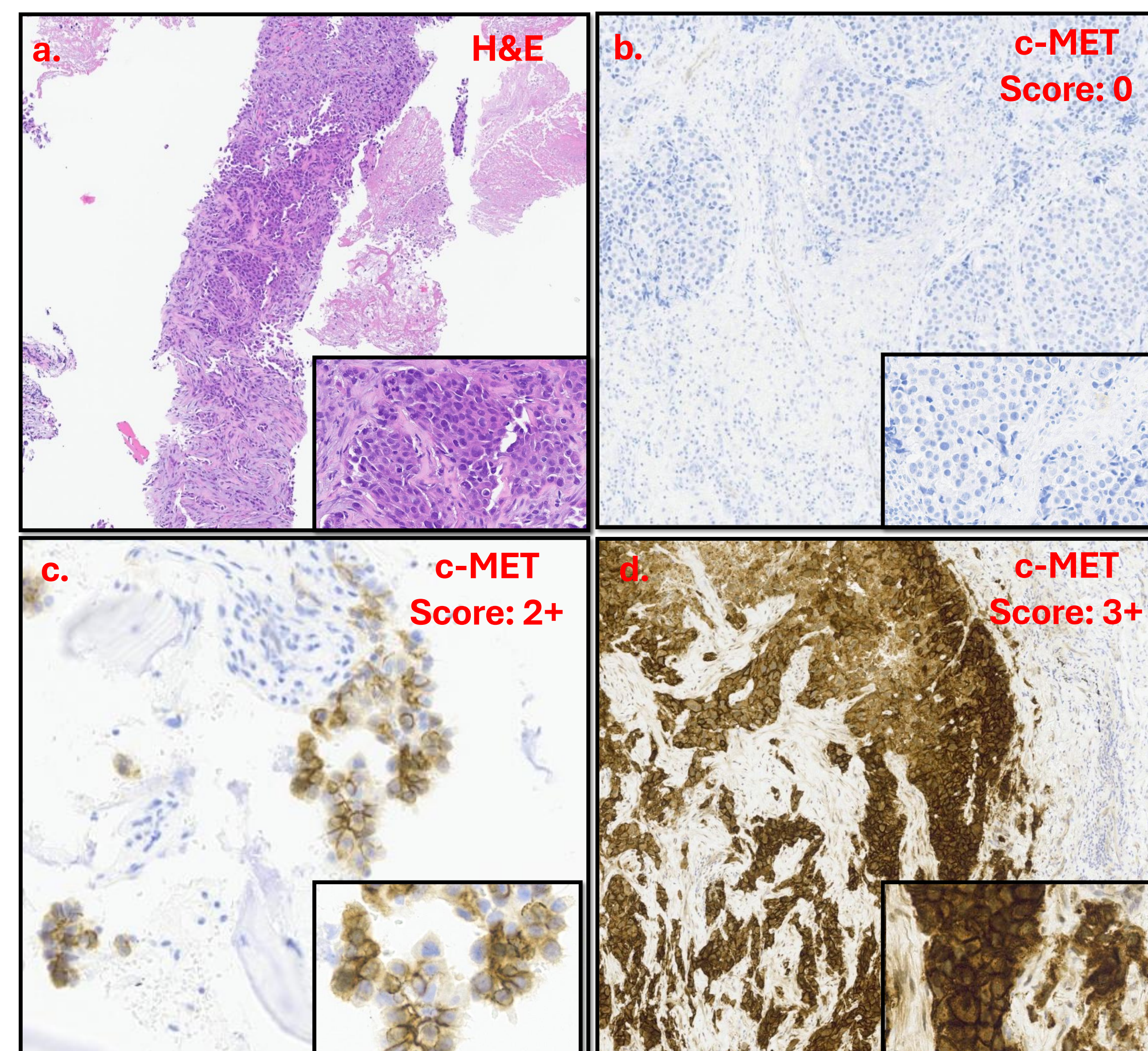


Figure 2: Observed c-MET staining intensities. (a) Solid type adenocarcinoma within a lung core biopsy. (b-d) c-MET staining of adenocarcinoma within pleura (b), bone (c) and lung (d).

Table 1: c-MET staining intensities (n=27)

c-MET Score	Cytology Specimens	Surgical Specimens
0	7	4
1+	0	0
2+	4	8
3+	16	15

Table 2: Weighted Concordance (n=24)

Weighted Observed Agreement	78.5%
Linear Weighted Cohen's k	0.336, p = 0.041*

Table 3: Binary Concordance (n = 24)

Positively concordant pairs	11
Negatively concordant pairs	5
Total binary concordance	16 (66.7%)

c-MET staining and scoring was successfully performed on 27 cytology specimens and 27 surgical pathology specimens, including 24 matched pairs. There was strong concordance between c-MET staining in cytologic and surgical specimens with a weighted observed agreement of 78.5% and a Cohen's kappa of 0.336 ($p = 0.041$). Concordance of c-MET positivity (3+) and negativity (0, 1+, or 2+) was 66.7%.

RESULTS

Clinicopathologic and Molecular Features

Table 4: PD-L1 by c-MET status

PD-L1 level	c-MET+ (n = 20)	c-MET- (n = 10)	
<1% (n,%)	3 (15%)	5 (50%)	
1% - 50% (n,%)	8 (40%)	4 (40%)	
≥50% (n,%)	9 (45%)	1 (10%)	p = 0.019*

c-MET positivity was observed in 66.7% of patient samples. PD-L1 expression demonstrated a significant ordinal trend with c-MET positivity ($p = 0.019$). No association was observed with other clinicopathologic variables including metastatic and nodal stage.

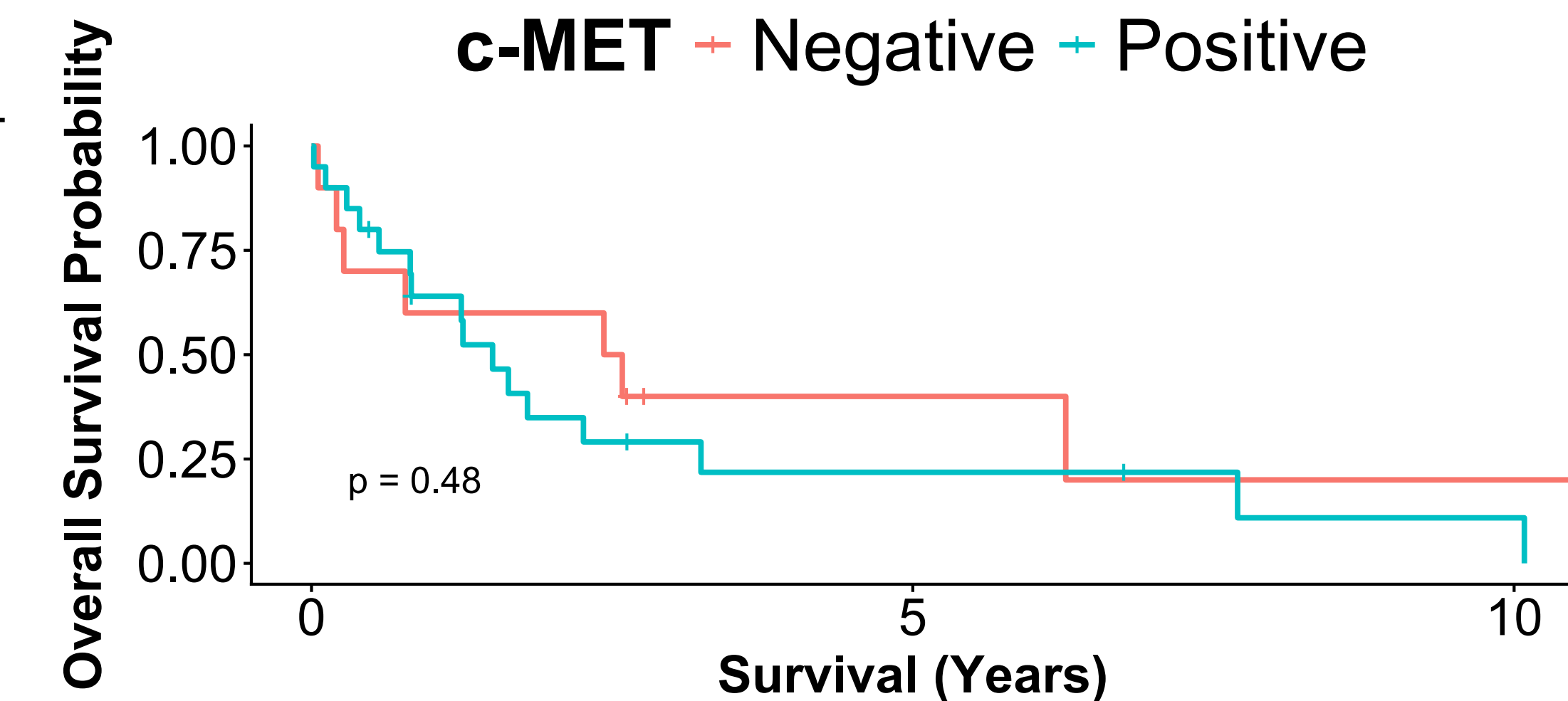


Figure 3: Overall survival stratified by c-MET status. c-MET positivity was not associated with overall survival (Log rank $p = 0.48$; HR 1.38, 95% CI 0.56–3.39; $p = 0.49$).

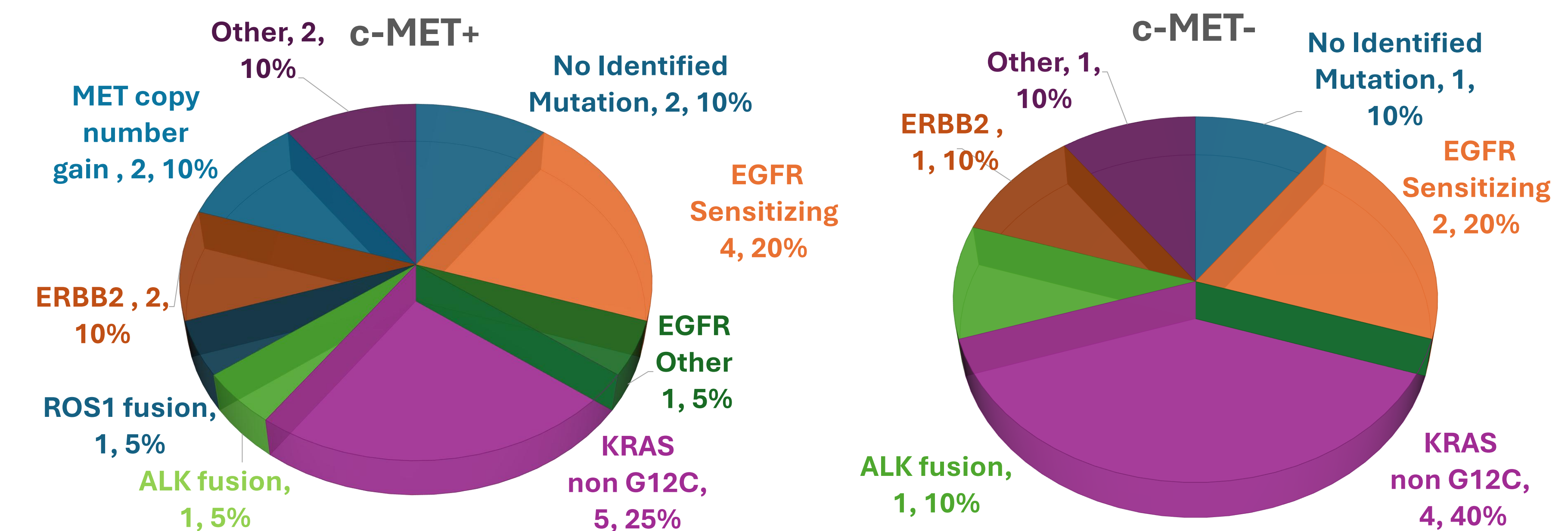


Figure 4: Molecular alterations by c-MET status. The proportion of molecular drivers is broadly comparable between groups.

CONCLUSION

- c-MET (SP44) immunostaining showed modest agreement between cytologic cell block and matched biopsy specimens, supporting the feasibility of assessing c-MET on cytology specimens in stage IV lung adenocarcinoma. Until more robust data become available, dual testing of surgical and cytologic specimens may be necessary to comprehensively evaluate patient eligibility and prevent false negatives.
- In this cohort, c-MET positivity was associated with increasing PD-L1 expression but not with nodal status, metastatic stage, or overall survival. Larger datasets are needed to further clarify the true relationship between c-MET status, clinicopathologic variables and patient survival while adjusting for tumor stage, a major confounder in survival analysis.

References:
Koeppen H, Yu W, Zha J, Pandita A, Penuel E, Rangell L, Raja R, Mohan S, Patel R, Desai R, Fu L, Do A, Parab V, Xia X, Januario T, Louie SG, Filvaroff E, Shames DS, Wistuba I, Lipkind M, Huang J, Lazarov M, Ramakrishnan V, Amler L, Phan SC, Patel P, Peterson A, Yauch RL. Biomarker analyses from a placebo-controlled phase II study evaluating erlotinib+onartuzumab in advanced non-small cell lung cancer: MET expression levels are predictive of patient benefit. Clin Cancer Res. 2014 Sep 1;20(17):4488-98. doi: 10.1158/1078-0432.CCR-13-1836. Epub 2014 Mar 31. PMID: 24687921; PMCID: PMC4504679.