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Letter to the Editor

MET mutations are associated with aggressive and radioresistant brain metastatic non-small-cell lung cancer

The onset of brain lesions resulting from non-small-cell lung cancer (NSCLC) is associated with a poor prognosis, with only 5% of patients surviving beyond the first year after diagnosis.[1] Only a minority of carefully selected patients can be recommended for surgical resection of brain metastases.[2] Palliative brain radiotherapy (BRT) could be efficacious in improving symptoms and quality of life.[3]

However, growing evidence demonstrates that inappropriate execution of the MET-driven "invasive growth" program is implicated in the metastatic process and that MET overexpression promotes radiation-induced tumor invasiveness.[4,5]

Here, we assessed the MET molecular status in a relevant series of surgical samples from primary NSCLC, along with the corresponding brain metastases, in order to decipher the role of MET in predicting patients' outcomes and radiotherapy responsiveness.

A total of 68 NSCLC samples and their matched brain metastases were retrieved from consecutive cohorts from the archives of the pathology divisions of the University of Turin at the Città della Salute e della Scienza, Molinette Hospital of Turin and of San Luigi Hospital, Orbassano, Italy. The study received ethical approval from local institutional review boards. Each sample was independently reviewed by 2 dedicated pathologists (R.S. and P.C.), who confirmed all diagnoses according to the current World Health Organization classification.[6] We analyzed the entire coding sequence of *MET*, together with gene amplification by fluorescence in situ hybridization analysis, as already described.[7] Age, gender, and radiotherapy of primary tumor and brain metastases, histotypes, and survival were ascertained for each case. Descriptive statistics were produced for demographic, clinical, and laboratory characteristics of cases. Cox regression was used to determine the association of patients' characteristics with survival following diagnosis of brain metastases.

The cohort analyzed was characterized as follows. Of the 68 cases, 15 were female (22%) and 53 were male (78%); the mean age at diagnosis was 63.2 ± 9.1 years; the cumulative follow-up was 1438 patient-months, with a median overall survival of 12 months (interquartile range, 7–39). The adenocarcinoma histotype was represented in 54.4% of cases (37 patients); squamous cell carcinoma was detected in 20.5% of cases (14 patients), whereas neuroendocrine lineage occurred in 10.2% of cases (7 patients). The remaining 10 patients displayed undifferentiated carcinomas. All the studied patients underwent surgical removal of both the primary mass and the brain metastasis. Brain surgery followed the removal of the primary mass (from 1 to 15 mo); in one case the brain lesion was diagnosed and removed 1 month before the appearance of the primary lung tumor. Of all the patients, 73.5% (50 patients) underwent BRT after surgery.

In line with reported data (COSMIC database, http://cancer.sanger.ac.uk/cosmic), somatic *MET* mutations occurred in 4.41% (3) of primary lung tumors; 19.12% of those samples (13) harbored an increased *MET* gene copy number. We then investigated the MET molecular profile of metastatic brain lesions. Unexpectedly, 7.35% of patients (5) displayed activating *MET* mutations, while 22.39% of lesions (15 patients) were *MET* amplified. Two cases harbored mutations in both the primary and the metastatic lesion. Coexistence of *MET* mutation and amplification was not detected in any of the analyzed cases. Related clinical and molecular data are shown in detail in Table 1.

Notably, the mortality rate after BRT was significantly higher in tumors carrying *MET* somatic mutations compared with euploid *MET* wild-type lesions (hazard ratio, 4.39; 95% CI, 1.46–13.18; $P < .008$).

Overall, our findings have documented that the occurrence of *MET* mutations in brain metastasis from NSCLC neutralized the favorable effect of BRT, thus predicting a worse patients' outcome. Although preliminary, our findings are coherent with published data suggesting that MET targeting may impair radioresistance.[8] Moreover, for the first time, our results strongly indicate that MET activation by somatic mutations is associated with substantial radioresistance of highly invasive NSCLC. The above described *MET* mutations have 2 clinical implications: (i) a potential functional marker of highly aggressive lung tumors, easily detectable in the near future by the "liquid biopsy" approach[9]; (ii) a rationale for clinical trials with MET inhibitors in patients carrying advanced brain metastatic disease, directed to radiotherapy.

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Table 1. Clinico-pathological and molecular profile of the MET-mutated brain metastases

	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5
Gender	M	M	F	F	F
Age at diagnosis (y)	56	80	59	43	69
Histotype	U	LCNE	ADC	ADC	ADC
Brain metastatic site	Parietal lobe (r)	Frontal lobe	Parietal lobe (r)	Sella	Cerebellum
Number of brain lesions	1	1	1	1	1
MET mutational status					
Lung	T1010I	Wt	Wt	Wt	Wt
Brain	T1010I	E168D	E168D	E168D	T1010I
MET copy number					
Lung	2	2	2	2	2
Brain	2	2	2	2	2
EGFR exon 18–21	Wt	Wt	Wt	Wt	Wt
KRas exon 2	Wt	Wt	Wt	Wt	Wt
Overall survival (mo)	7	2	9	40	7
TtP (mo)	5	0	1	39	2
Survival from metastasis (mo)	2	2	1	1	4
Radiotherapy					
Lung	No	No	Yes	No	No
Brain	Yes	Yes	Yes	Yes	Yes
Type of radiotherapy	Stereotactic	Stereotactic	Stereotactic	Stereotactic	Stereotactic

Abbreviations: U, undifferentiated carcinoma; ADC, adenocarcinoma; LCNE, large-cell neuroendocrine carcinoma; TtP, time to progression; EGFR, epidermal growth factor receptor; Wt, wild type; KRas, Kirsten rat sarcoma viral oncogene homolog.
All the *MET* mutations were found clustered either in the juxtamembrane or in the extracellular semaphorin domain of the receptor. Both the T1010I and the E168D changes are already established somatic mutations, previously reported in both non-small- and small-cell lung cancers, displaying documented tumorigenic potential. None of the *MET*-mutated patients underwent chemotherapy after surgical removal of both primary and secondary lesions.

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