PIK3CA mutation in metastatic colorectal cancer (mCRC): association with clinico-pathological features and outcome

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BACKGROUND

- ✓ Mutations in *PIK3CA*, an EGFR downstream effector, and the subsequent activation of AKT pathway plays an important role in colorectal carcinogenesis.
- ✓ Considering the frequent co-occurrence of *PIK3CA* and *RAS* mutations, conflicting data exist about its impact on prognosis of mCRC patients and its predictive role to anti-EGFR therapy.
- ✓ However, PI3K inhibitors have been developed and are currently under investigation in mCRC.

METHODS

- ✓ Data from mCRC patients treated at Azienda Ospedaliero-Universitaria Pisana from 1 Jan 2005 to 31 Dec 2017, whose tumours had been analysed per clinical practice by MALDI-TOF MassArray were retrieved.
- ✓ Association between *PIK3CA* mutation and clinico-pathological features was analysed by $\chi 2$ test.
- ✓ Overall survival curves were estimated with Kaplan-Meier method and compared by log-rank test.

RESULTS

- ✓ Tumours from 90 (17%) out of 542 patients included in this analysis were *PIK3CA* mutated (Figure 1).
- ✓ Among 53 patients for whom *PIK3CA* status was available on both primary tumours and metastasis, the concordance was 92.4%.
- ✓ Compared to *PIK3CA* wild-type tumours, mutated ones were more often *RAS* mutated, MSI high, and right-sided (Table 1).

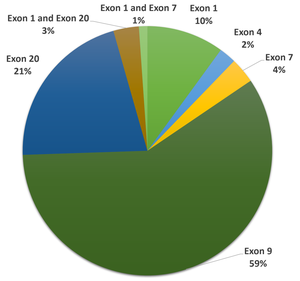

Figure 1 – *PIK3CA* mutations

Characteristics	*PIK3CA* wild-type	*PIK3CA* mutated	P
Sex			
Female	197 (43.59%)	46 (51.11%)	0.232
Male	255 (56.41%)	44 (48.89%)	
Age			
<70 years	261 (57.74%)	53 (58.89%)	0.933
≥70 years	191 (42.26%)	37 (41.11%)	
Primary tumor location			
Left	203 (44.91%)	36 (40%)	
Rectum	105 (23.23%)	8 (8.89%)	**0.0004**
Right	144 (31.86%)	46 (51.11)	
Histotype			
Mucinous	98 (26.20%)	25 (34.25%)	0.2061
Non mucinous	276 (73.80%)	48 (65.75%)	
Primary tumor resected			
No	56 (12.39%)	16 (17.78%)	0.2281
Yes	396 (87.61%)	74 (82.22%)	
Time to metastases			
Metachronous	140 (30.97%)	22 (24.44%)	0.2672
Synchronous	312 (69.03%)	68 (75.56%)	
No. of metastatic sites			
1	290 (64.16%)	51 (56.67%)	0.2208
>1	162 (35.84%)	39 (43.33%)	
RAS status			
Mutated	237 (52.43%)	62 (68.89%)	**0.006**
Wild-type	215 (47.57%))	28 (31.11%)	

Characteristics	*PIK3CA* wild-type	*PIK3CA* mutated	P
BRAF status			
Mutated	44 (9.82%)	10 (11.24%)	0.8318
Wild-type	404 (90.18%)	79 (88.76%)	
MSI status			
High	16 (5.16%)	9 (15.79%)	**0.0083**
Stable	294 (94.84%)	48 (84.21%)	
Lymph nodal metastases			
No	355 (78.54%)	66 (73.33%)	0.3449
Yes	97 (21.46%)	24 (26.67%)	
Liver metastases			
No	151 (33.41%)	31 (34.44%)	0.9457
Yes	301 (66.59%)	59 (65.56%)	
Lung metastases			
No	344 (76.11%)	62 (68.89%)	0.1905
Yes	108 (23.89%)	28 (31.11%)	
Peritoneal metastases			
No	365 (80.75%)	74 (82.22%)	0.8591
Yes	87 (19.25%)	16 (17.78%)	
Ovarian metastases			
No	441 (97.57%)	85 (94.44%)	0.2088
Yes	11 (2.43%)	5 (5.56%)	
Local recurrence			
No	421 (93.14%)	88 (97.78%)	0.1503
Yes	31 (6.86%)	2 (2.22%)	

Table 1 - Patients' characteristics according to the absence of presence of a *PIK3CA* mutation.

- ✓ *PIK3CA* mutations were not associated with OS (36.4 vs 35.9 mos, HR 1.17, 95%CI 0.85-1.62, p=0.3), with no difference among those affecting exon 9 and 20 (36.4 vs 27.5 mos, HR 0.77, 95%CI 0.39-1.54, p = 0.44).
- ✓ In ***RAS/BRAF* wild-type** (N 188) and in ***RAS* mutated** (N 299) subgroup, no difference in terms of OS was found between *PIK3CA* mutated and wild-type patients (38.1 vs 44.4 mos, HR 1.22, 95%CI 0.60-2.48, p=0.55 and 27.5 vs 34.4 mos, HR 1.26, 95%CI 0.85-1.86, p=0.22, respectively), though *PIK3CA* mutated had shorter OS.
- ✓ In ***BRAF* mutated** subgroup (N 54), *PIK3CA* mutated patients had longer OS compared to *PIK3CA* wild-type (not reached vs 14.4 mos, HR 0.37, 95%CI 0.16-0.85, p=0.09) – Figure 2.
- ✓ Among 39 chemorefractory *RAS/BRAF* wild-type patients evaluable for response to an anti-EGFR agent, only 2 were exon 9 *PIK3CA* mutated and achieved stable disease.

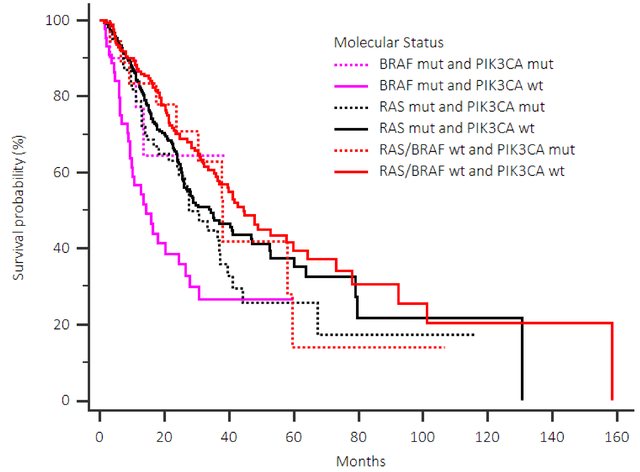

Figure 2 – Overall survival according to molecular status.

CONCLUSIONS

- ✓ *PIK3CA* mutated tumours displayed specific clinico-pathological features and a strong concordance was found between primary tumour and paired metastases.
- ✓ Interestingly, a different impact on prognosis of *PIK3CA* mutation in *RAS/BRAF* wild-type, *RAS* mutated or *BRAF* mutated mCRC patients was observed and deserves validation.

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