KRAS, *NRAS* AND *BRAF* MUTATION PROFILING IN A SERIES OF 90 METASTASIC COLORECTAL CANCER SPANISH PATIENTS. AN ESTIMATION OF COST SAVINGS.

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BACKGROUND

Metastasic colorectal cancer (mCRC) patients harbouring a mutation in codon 12 or 13 of the *KRAS* do not benefit from therapy with antibodies targeting Epidermal Growth Factor Receptor (*EGFR*). Recently, several studies have shown that an extended study of the RAS family genes (KRAS exons 3 and 4; and *NRAS* exons 2, 3 and 4) could help to detect those patients that although having a wild-type KRAS exon 2 will not respond to anti-EGFR treatment. The aim of this study was to assess the *KRAS*, *NRAS* and *BRAF* mutational profiling in a series of spanish patients with mCRC and to extrapolate these results to the economic implications of a better triage.

DESIGN

Ninety mCRC were included in a prospective study from December 2013 to August 2014. DNA was extracted from formalin-fixed paraffin embedded sections. Mutations in exon 2 (codons 12 and 13) of *KRAS* and *BRAF* V600E mutation were analized with KRAS-BRAFStripAssay® (Viennalab). Further mutations in *KRAS* exons 3 and 4 and exons 2, 3 and 4 of *NRAS* were tested when no mutation in *KRAS* exon 2 was found. The extended study was performed as well in those cases with a G13D mutation (a proposed predictive marker of response to anti-EGFR) and independently of the *BRAF* status (Figure 1). *KRAS* exons 3 and 4 (codons 59, 61, 117 and 146) were analized using RAS extension Pyro® Kit (Qiagen). *NRAS* mutations in exons 2 (codons 12 and 13), 3 (codon 59 and 61) and 4 (codons 117 and 147) were analized using the Therascreen® NRAS Pyro® kit and RAS extension Pyro® Kit (Qiagen).

In our Hospital the median cost per month of a treatment with anti-EGFR is 2.000€ and the median progression-free survival of mCRC patients is 8 months.

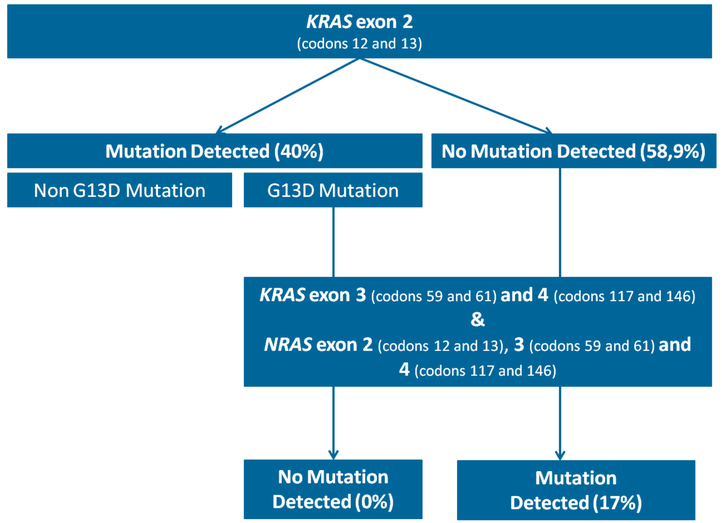

Figure 1. The extended RAS study algorithm in our institution. Results are shown in brackets (% patients).

	Mutation (% patients)
KRAS	
Exon 3	A59T (11,1%)
	Q61H (22,2%)
Exon 4	A146T (33,4%)
NRAS	
Exon 2	G12D (11,1%)
	G13R (11,1%)
Exon 3	Q61E (11,1%)
Exon 4	-

Figure 2. Detailed results of the nine patients with *KRAS* exon 2 native and a mutation detected in the RAS extended study.

RESULTS

Thirty-six (40%) cases had a mutation in *KRAS* exon 2. Fifty-three (58,9%) were native and were tested with the extended study together with 5 cases that carried a G13D mutation. None of the G13D cases had another mutation. Nine (17%) of the fifty-three *KRAS* exon 2 native cases had a mutation in another exon of *KRAS* or *NRAS* (Figure 2 and 3). Eight (8,9%) cases had V600E mutation in *BRAF*, no other mutation was identified. In 1 (1,1%) case a valid result was not achieved.

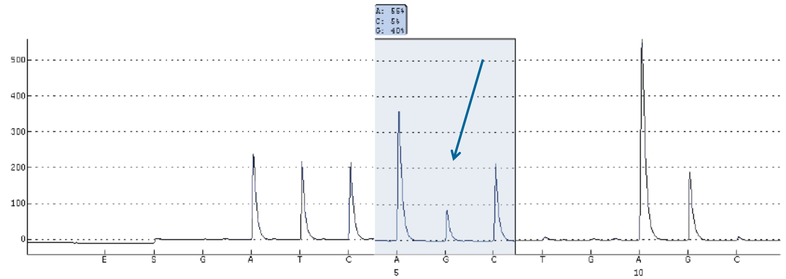

Figure 3. Pyrogram of a *KRAS* A146T mutation (arrow indicates a G to A change).

CONCLUSIONS

• In this series the implementation of the RAS extended study allows the identification of a further 17% of the KRAS exon 2 native patients that will not respond to anti-EGFR therapy; supposing a saving of 144.000€.

• The global percentage of patients with a mutation in a RAS family gene rises to 57%.

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