Next-generation sequencing in colorectal cancer patients: characterization and prognostic implications.

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Topic: *Basic Colon Cancer. Biomarkers and Translational Research.*

Background:

- The ESMO guideline for metastatic colorectal cancer (CRC) recommends testing the current validated biomarkers (MMR, KRAS, NRAS and BRAF) to guide precision medicine in CRC.
- Next-generation sequencing (NGS) may be a useful tool to identify new predictive and prognostic biomarkers.

Methods:

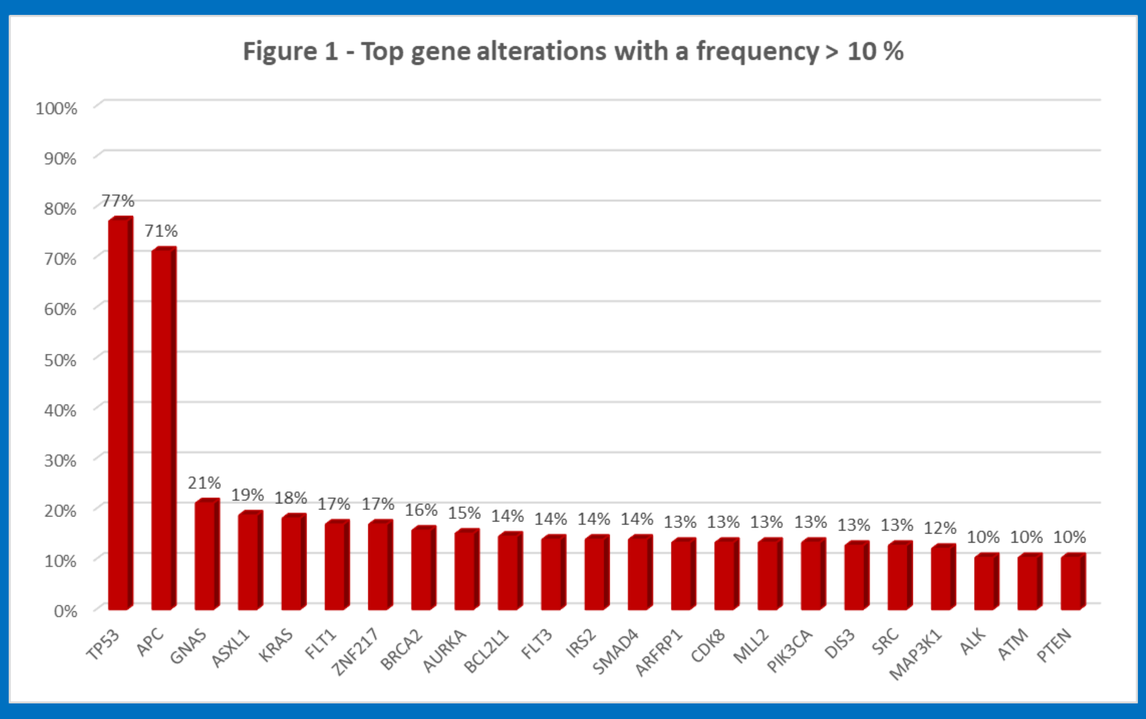
- Retrospective observational study in 250 patients treated at our institution, out of whom 166 were CRC patients.
- NGS was performed with Foundation One or Oncomine tests.

Results:

- The baseline clinical characteristics is shown in table 1 and the most frequent gene alterations identified in the NGS test is shown in figure 1.

Table 1 – Patients summary (n = 166)

Characteristic	% or median	Prognostic value
Age	61.8 years	N.S. (p>0.05)
Female	61.4 %	HR 1.5; p=0.044
KRAS-mut	13.3 %	HR 2.5; p<0.001
NRAS-mut	1.2 %	N.S. (p>0.05)
BRAF-mut	1.2 %	HR 7.1; p=0.008
HER2 positive	21.1 %	N.S. (p>0.05)
dMMR	0,7 %	N.S. (p>0.05)
OS	41.9 months	-
Deaths	69.7 %	-

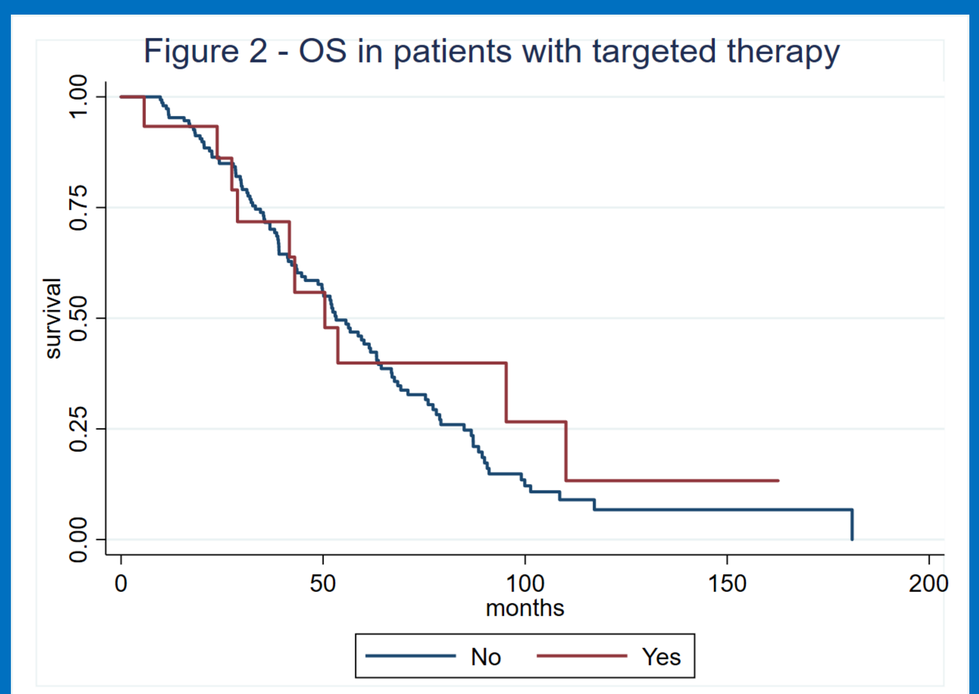


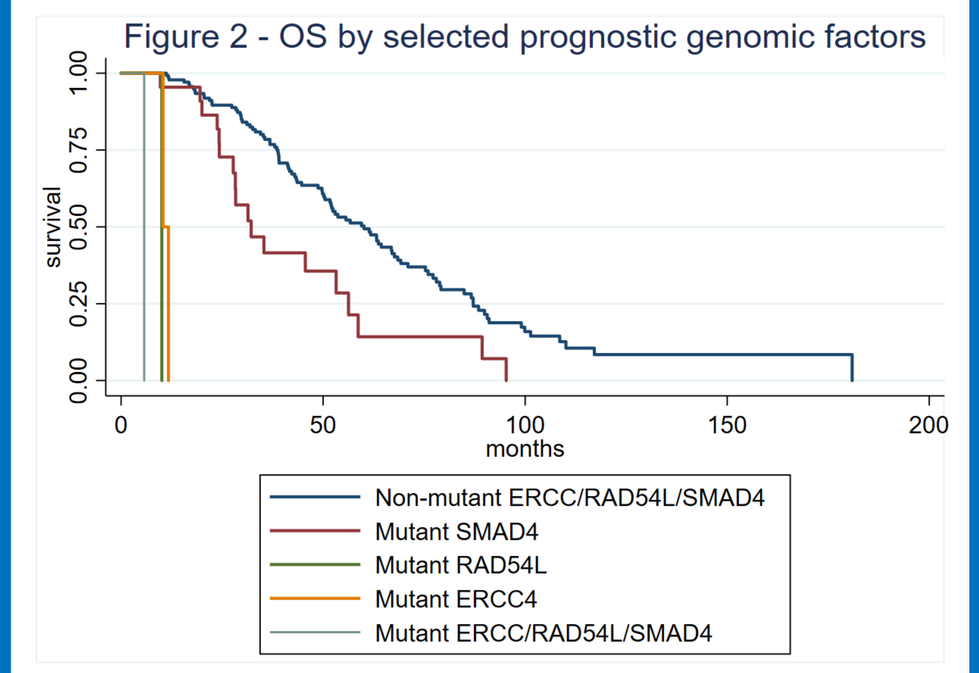
Results (cont.):

- A potentially targetable gene was identified in 38 CRC patients (22.8%), and molecular guided therapy was administered in 39.5% of them, without significant benefit in OS. (HR 0.63; 95%CI 0.28-1.45) (figure 2).
- The univariate analysis identified 36 genes as significant prognostic biomarkers (p<0.05):

  BCL6, BRAF, CCND2, CIC, CTNNA1, DOT1L, ERCC4, ERG, EZH2, FANCL, FBXW7, GNA13, GSK3B, HNF1A, JAK2, KEL, KRAS, MAPK1, MEN1, MERTK, MET, MLH1, MTOR, NOTCH3, P2RY8, PTCH1, PTPN11, RAD54L, RICTOR, SMAD4, SRC, STAG2, TNFAIP3, TSC1, TSC2 and WHSC1.

- The genomic signature combining three independent prognostic factors (ERCC4, RAD54L and SMAD4), was able to predict the survival outcomes of our CRC patient cohort (p<0.001) in the multivariate analysis.





CONCLUSIONS:

- **Although without available targeted therapy, TP53 and APC genomic alterations occur in more than 70% of CRC patients.**
- **The NGS guided genomic signature including ERCC4, RAD54L and SMAD4; provided a useful prognostic information in our CRC patients cohort.**
- **In addition, NGS is an available tool to identify new potential targets for the treatment of CRC patients.**