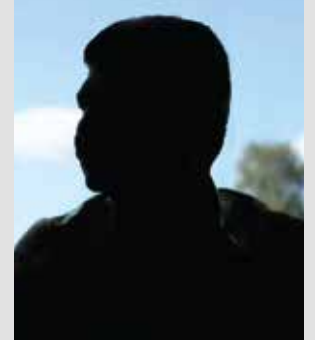


CASE STUDY

Genetic Testing of Somatic Tumors Indicates Optimal Chemotherapy Options

Quick Summary

- A 44-year-old male patient with colorectal cancer was referred to Strand Life Sciences for genetic analysis .
- A specific mutation, *KRAS*^{G12D}, was identified in the tumor tissue from the biopsy. Mutations in other genes like *NRAS*, *BRAF*, *PTEN*, *PIK3CA*, *SMAD4*, *APC* and *MET* were absent in the biopsy provided.
- Identification of the *KRAS*^{G12D} mutation indicated that the patient is likely to show an enhanced response to oxaliplatin.
- Absence of mutations in *NRAS*, *BRAF*, *PTEN*, *PIK3CA*, and other genes indicated that the patient is likely to show a standard response to fluorouracil therapy and a poor response to treatment with Panitumumab and Cetuximab.
- Genetic analysis indicated clear therapeutic options thereby saving time and treatment costs for the patient.



Introduction

Colorectal cancer is amongst the top ten cancers in women and men in India (Kaur, Tanvir; Sucharita,V. 2014). Although the incidence of colorectal cancer is low in India, when compared to incidence rates in Western and South-East Asian countries, the 5-year survival rates are also much lower in India. Comparisons of 5-year survival rates (1993-2001) show that the average survival rate across 4 cancer registries from India was 21.2% for rectal cancer, as against the average survival rate of 43.83% from other South-east Asian cities like Chiang Mai, Shanghai, Hong Kong, Singapore and Seoul (Pathy et al. 2012). Genetic mutations that have been identified in a study of Indian colorectal cancer patients include mutations in genes such as *KRAS*, *PIK3CA*, *BRAF*, *NRAS*, *TP53* and *APC* (Jauhri et al. 2017).



Patient Profile

Sushant Koparkar, a 44-year old man was referred to a prominent hospital in Pune. He complained of pain in the area surrounding the anus and occasional rectal bleeding. A tumor was detected 8 cm from the anal verge by colonoscopy.

The presence of the tumor (lump of cancer) was confirmed by a CT-scan. Histological examination of a tumor biopsy revealed that the tumor was an adenocarcinoma.

Figure 1. Colorectal Adenocarcinoma Detected by Colonoscopy

Representative Image: Colonoscopic Image of Colorectal Carcinoma

(Source: https://commons.wikimedia.org/wiki/File:Colorectal_cancer_eno_2.jpg?uselang=en-gb)

*Name changed to protect patient privacy

A sample of the tumor biopsy was sent to Strand for genetic analysis by a prominent pathologist. The Strand Tissue Specific Test for colon cancer was prescribed, in order to identify mutations in the tumor tissue.

Results

- The Strand Tissue Specific Test for colon cancer is designed to search for the presence or absence of genes that are frequently mutated, in most cancers.
- In Mr. Koparkar's case, many genes including *KRAS*, *NRAS*, *BRAF*, *MET*, *PIK3CA* were tested.

Drug Response

Therapy	Tested Marker(s)	Relevant Marker(s)	Likelihood of Response**
Oxaliplatin	<i>KRAS</i>	<i>KRAS</i> ^{G12D}	Enhanced
Fluorouracil	<i>SMAD4</i> , <i>APC</i>	None	Standard
Panitumumab	<i>NRAS</i> , <i>KRAS</i> , <i>BRAF</i> , <i>MET</i> , <i>PIK3CA</i> , <i>PTEN</i>	<i>KRAS</i> ^{G12D}	Poor
Cetuximab	<i>NRAS</i> , <i>KRAS</i> , <i>BRAF</i> , <i>MET</i> , <i>PIK3CA</i> , <i>PTEN</i>	<i>KRAS</i> ^{G12D}	Poor

- A specific mutation, *KRAS*^{G12D}, was identified in the colorectal cancer biopsy. Growth of cancers resulting from this mutation can be controlled by treatment with oxaliplatin. In fact, the response to oxaliplatin treatment is enhanced in tumors bearing this mutation (Lin et al. 2014; Lin et al. 2013).
- Mutations in *SMAD4* and *APC* were not identified in this biopsy. Since these genes are wild-type (unmutated), the patient is likely to respond to another chemotherapeutic drug: Fluorouracil. However, the sensitivity of the cancer towards this growth inhibitory drug is not likely to be lesser or greater than that seen in other colorectal cancer patients. Essentially, fluorouracil is not the most optimal choice for treating this patient, unless there are no other options.
- Genetic variants were not detected in other genes like *BRAF*, *NRAS*, *MET*, *PTEN* and *PIK3CA*, indicating that the cancer is unlikely to respond to targeted drugs like Panitumumab and Cetuximab. Wild-type *KRAS* is the target molecule of these drugs and their efficacy in tumors bearing the *KRAS*^{G12D} mutation is highly reduced (Amado et al. 2008; Kumar et al. 2014).

Conclusions

- A specific *KRAS* mutation, *KRAS*^{G12D}, was identified in the colorectal cancer biopsy provided.
- Identification of this mutation helped to identify chemotherapeutic drugs that are likely to have maximum effect in controlling cancer cell proliferation.
- The absence of the wild-type *KRAS* gene in the tumor tissue also helped to rule out the use of targeted therapies like Panitumumab and Cetuximab.
- A clear therapeutic roadmap for this patient was established, based on the genetic analysis of the tumor.

Strand Tissue Specific Test for Colon Cancer

The Strand Tissue Specific Test for Colon Cancer covers genes that are frequently mutated in colorectal cancer – *KRAS*, *NRAS*, *BRAF*, *PTEN*, *SMAD4*, *APC*, *MET*, *PIK3CA*

References

- Amado, R.G. et al., 2008. Wild-Type KRAS Is Required for Panitumumab Efficacy in Patients With Metastatic Colorectal Cancer. *Journal of Clinical Oncology*, 26(10), pp.1626–1634. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18316791> [Accessed May 24, 2017].
- Jauhri, M. et al., 2017. Prevalence and coexistence of KRAS, BRAF, PIK3CA, NRAS, TP53, and APC mutations in Indian colorectal cancer patients: Next-generation sequencing–based cohort study. *Tumor Biology*, 39(2), p.101042831769226. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/28222664> [Accessed April 6, 2017].
- Kaur, Tanvir; Sucharita, V.I. subcommittee on C.C., 2014. Consensus Document For Management of Colorectal Cancer. Available at: <http://www.icmr.nic.in/guide/cancer/Colorectal/Colorectal Cancer.pdf> [Accessed May 23, 2017].
- Kumar, S.S. et al., 2014. KRAS G13D Mutation and Sensitivity to Cetuximab or Panitumumab in a Colorectal Cancer Cell Line Model. *Gastrointestinal cancer research : GCR*, 7(1), pp.23–6. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24558511> [Accessed May 24, 2017].
- Lin, Y.-L. et al., 2014. Oxaliplatin-Based Chemotherapy Is More Beneficial in KRAS Mutant than in KRAS Wild-Type Metastatic Colorectal Cancer Patients. *Z. Zuo, ed. PLoS ONE*, 9(2), p.e86789. Available at: <http://dx.plos.org/10.1371/journal.pone.0086789> [Accessed May 24, 2017].
- Lin, Y.-L. et al., 2013. Oxaliplatin-based Chemotherapy Might Provide Longer Progression-Free Survival in KRAS Mutant Metastatic Colorectal Cancer. *Translational oncology*, 6(3), pp.363–9. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23730417> [Accessed May 24, 2017].
- Pathy, S. et al., 2012. The Incidence and Survival Rates of Colorectal Cancer in India Remain Low Compared With Rising Rates in East Asia. *Diseases of the Colon & Rectum*, 55(8), pp.900–906. Available at: <http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00003453-201208000-00011> [Accessed May 23, 2017].