The importance of molecular testing in colorectal cancer diagnosis, treatment and prognosis

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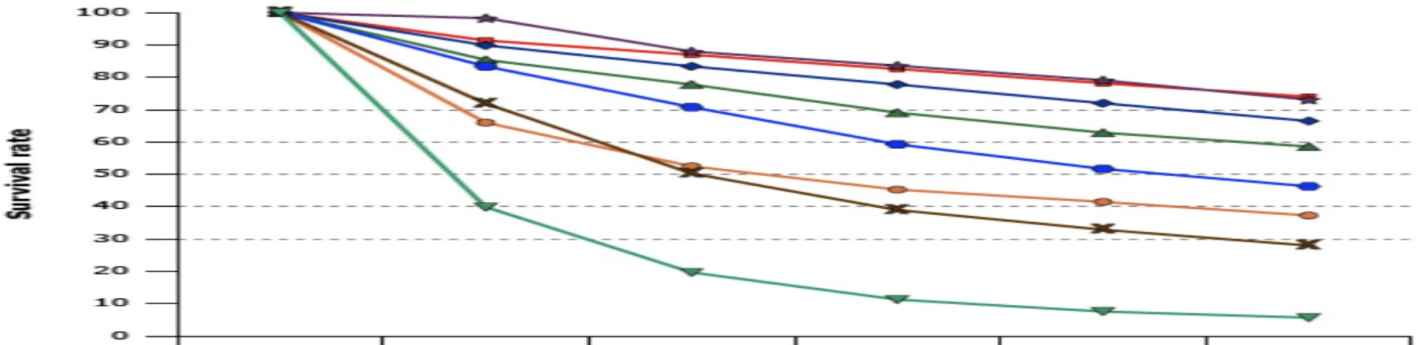
- ✓**Colorectal cancer is the third most commonly diagnosed cancer in males and the second in females.**
- ✓**Colorectal cancer is a leading cause of cancer-related death in many countries.**
- ✓**The most important indicator of outcome following resection of colon cancer is the pathologic stage at presentation.**
- ✓**Approximately 20 to 25 percent of patients with colorectal cancer have metastatic stage.**
- ✓**The majority of patients with metastatic colorectal cancer cannot be cured.**

Observed survival rates for 28,491 cases with adenocarcinoma of the colon



	0	1	2	3	4	5
I	100.0	91.4	87.0	82.6	78.2	74.0
IIA	100.0	89.9	83.4	77.8	72.0	66.5
IIB	100.0	85.4	77.8	69.1	62.9	58.6
IIC	100.0	66.0	52.5	45.3	41.5	37.3
IIIA	100.0	98.3	88.0	83.6	79.1	73.1
IIIB	100.0	83.4	70.8	59.3	51.7	46.3
IIIC	100.0	71.9	50.3	39.0	32.9	28.0
IV	100.0	39.9	19.7	11.3	7.6	5.7

Years from diagnosis

Data from the SEER 1973 to 2005 Public Use File diagnosed in years 1998 to 2000. Stage I includes 7417; Stage IIA, 9956; Stage IIB, 997; Stage IIC, 725; Stage IIIA, 868; Stage IIIB, 1492; Stage IIIC, 2000; and Stage IV, 5036.

SEER: Surveillance, Epidemiology, and End Results.

What are the diagnostic tools for colorectal cancer in our clinics

- ✓History & physical examination
- ✓FOB, new generation
- ✓Colonoscopy
- ✓Imaging (CT Scan, MRI, PET Scan)
- ✓CEA, Biochemistry tests
- ✓Pathology report & IHC
- ✓Especial tests such as KRAS, NRAS, BRAF, MSI

Therapeutic options in colorectal cancer

- ✓ **Surgery (local excision or wide resection)**
- ✓ **Chemotherapy (adjuvant or systemic setting)**
  - **Stage II- III**
- ✓ **Targeted therapy in metastatic colorectal cancer**
  - **Bevacizumab, Cetuximab, Panitumumab, Aflibercept, Ramucirumab, Regorfenib**
- ✓ **Immunotherapy**
  - **Pembrolizumab, Nivolumab, Ipilumumab**

- ✓**Colorectal cancer represents an ideal model for the study of the molecular pathogenesis of cancer due to (the accessibility of tissue for biopsy and the clear progression from normal colonic epithelium to invasive cancer via an intermediate precursor, the adenomatous polyp).**
- ✓**A multistep process of specific genetic changes is thought to drive the transformation from normal colonic epithelium to an invasive cancer.**
- ✓**Single specific germline mutation underlie the common inherited syndromes (eg, adenomatous polyposis coli, lynch syndrome).**
- ✓**Others, such as mutations of TP 53 suppressor gene, generally occur late in the process.**
- ✓**The concept of microsatellite instability (MSI) provides an additional layer of complexity to this model (The MSI- high phenotype ia associated with Lynch syndrome and is also observed in approximately 10-15% of sporadic colorectal cancer).**

- ✓**The available data suggest that most colorectal neoplasias begin with inactivation (through a germline or sporadic mutation) of the APC gene, whether or not MSI is present.**
- ✓**However , the genetic events may thereafter diverge, depending upon the mechanism underlying genetic instability(ie, chromosomal instability, germline mutation in DNA mismatch repair enzymes, CpG island hypermethylation phenotype).**
- ✓**This has led to the molecular classification of colorectal cancer into three carcinogenic pathways.**

Oncogenes

- ✓**Oncogenes are homologs of normal cellular genes that participate in cell growth and cell cycle regulation.**
- ✓**A mutational change in an oncogene leads to constitutive activation of the gene, which then results in uncontrolled cellular proliferation.**
- ✓**Among the oncogenes implicated in sporadic colorectal cancer are RAS, MYC, SRC and HER2.**
- ✓**RAS mutations are found in up to 50 percent of sporadic colorectal cancer.**
- ✓**The RAS family exist as three cellular variants, HRAS, NRAS, and KRAS.**

Tumor suppressor genes

- ✓From a therapeutic standpoint, it is hoped that p53 may prove to be a highly selective and effective target for intervention.
- ✓BRCA1 and BRCA2 are tumor suppressor genes known to function in homologous recombination.
- ✓Although the data regarding the risk of colorectal cancer in BRCA carriers have been inconsistent, prospective study of BRCA1 mutation carriers suggested an increased risk of colorectal cancer in women age 30-49.

Fecal immunochemical testing (FIT)

- ✓**The effectiveness for cancer prevention or early detection is an important factor when selecting a colorectal cancer screening test.**
- ✓**Among patients performing fecal immunochemical testing (FIT) every two years, the rate of detection of clinically important colorectal steadily declined in the Left colon over 12 years, but remained relatively unchanged in the right colon.**
- ✓**These results are consistent with a lower sensitivity of FIT for proximal colon lesions.**

Impact of molecular subtype on colorectal cancer risk

- ✓**Aspirin and other NSAID inhibit colorectal carcinogenesis.**
- ✓**There are limited data on their colorectal risk reduction by molecular subtype.**
- ✓**In a population based case control study, regular use of aspirin and NSAID was associated with an approximately 30 percent reduction in colorectal cancer.**
- ✓**Specifically, aspirin or NSAID use was associated with a lower risk of MSI stable, BRAF wild type, and KRAS wild type colorectal cancer,**
- ✓**But not associated with risk reduction for high MSI, BRAF mutated, or KRAS mutated colorectal cancer.**