

New Technology in Colorectal Cancer-a Boon or a Bane

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Abstract: Better patient care in today's world is almost synonymous with newer technology. Newer technology in the form of latest gadgets used for diagnostics, preoperative work up; per-operative care and post operative smooth recovery have become the part and parcel of our standard day to day quality care and any practitioner, nowadays, refusing to incorporate these gadgets in his day to day practice is labeled as orthodox and an outdated clinician.

We as service providers need to be technology friendly and at the same time try to use these gadgets for quality care and cure. We have to be the ones guiding the technology rather than being guided by the technology. But probably many a times that may not be true in day to day practice with most of us. With the result we have allowed the technology to be our bad master rather than utilizing its services as a good servant and probably in the name of better care many a times the new technology is used abusively rather than genuinely and the ultimate impact may not only be financial but even the physical; and the sole sufferer is the end user; that is the patient. I will in my article try to weigh the pros and cons of this theme and try to come out with a balanced conclusion for the worthy readers.

Keywords: New, Technology, Colorectal, Cancer, Polyps.

Patients don't care how much you know until they know how much you care.

William Osler

OLD APPROACH TO RECTAL CANCER

The most accepted and the conventional approach for the management of rectal cancer worldwide just a decade ago was:

- Surgical resection
- Pathology assessment and estimation of risk
- Treatment based upon classical TNM factors
- Postoperative concurrent chemo radiation [1]

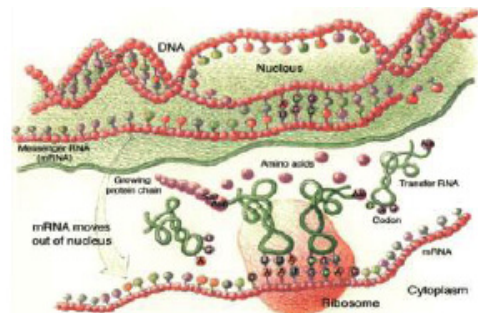
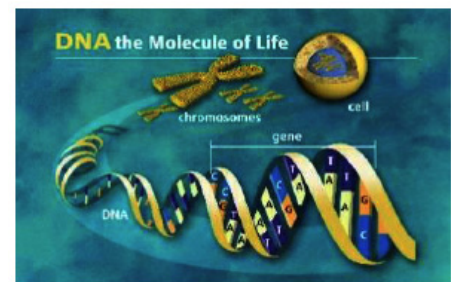
Recent Developments in Colo-Rectal Cancer (CRC)

- Optimal Preoperative Staging by MRI
- Selection of patients for Neo-adjuvant
- The concept of TME surgery
- Use of Staplers
- Sphincter saving surgery
- Concept of Neo-rectum
- PET Scan for recurrences
- Integration of knowledge in a multidisciplinary team approach

APPLES OF CRC



Cancer is a disease of abnormal DNA. Cancer is a somatic cell genetic disease. Any single step goes wrong, problems will come.



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Stool DNA Test (sDNA)

- Colon cells are shed continuously
- Polyps and cancer cells contain abnormal DNA
- Stool DNA tests look for abnormal DNA from cells

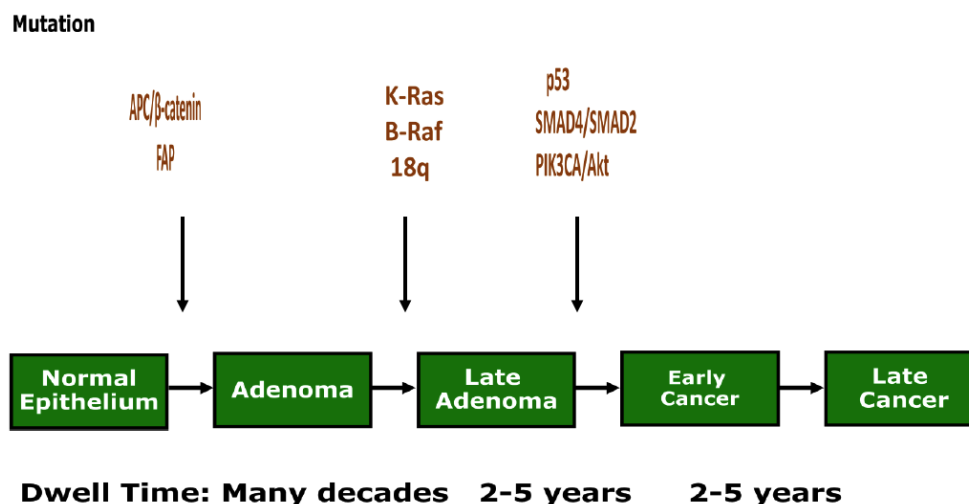
Limitations

Miss rates

Not covered by insurers

Recently FDA has approved this test so can be used freely to detect carcinoma at early stages, however lack of availability of these tests at most places may be the biggest limiting factor.

Genetic Model of Colorectal Cancer



MOLECULAR BIOLOGY

Concepts of molecular biology gave an insight in the prognosis of various types of colorectal cancers like

- P53 Protein Mutant Expressed cancers are radio-resistant.
- KRAS, DCC and P53 positive tumors show poor prognosis.
- MSI or Low Cox2 Expression & P21 Marker positive tumors show good prognosis.

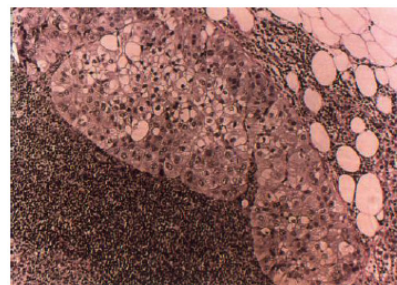
Clinically it has facilitated the clinician to prognosticate the different types of cancers more elaborately and as treating surgeons we can offer better explanations to things which used to be a mystery in the past.

Techniques Used in Molecular Pathology

- DNA level
- Comparative genomic hybridisation (CGH)
- Fluorescence in situ hybridisation (FISH)
- RNA level
- Gene expression-transcription
- cDNA and oligonucleotide arrays
- Serial analysis of gene expression (SAGE)
- Protein level
- Gene expression: translation-proteomics and mass spectrometry
- Tissue arrays; functional genomics
- Other techniques used in molecular pathology

- Microdissection
- Knockout and transgenic organisms
- Quantitative and real-time PCR

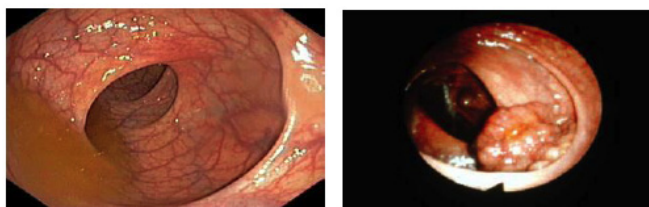
All these techniques allow a clinician to go into more and more complex details of tumorigenesis at molecular level in order to offer more individualized and scientific treatments.



Colonoscopy: Colonoscopy continues to be a gold standard. It allows a visual surveillance of whole colon, therapeutic manipulation of small polyps and a tissue diagnostic advantage of the visualized lesion.

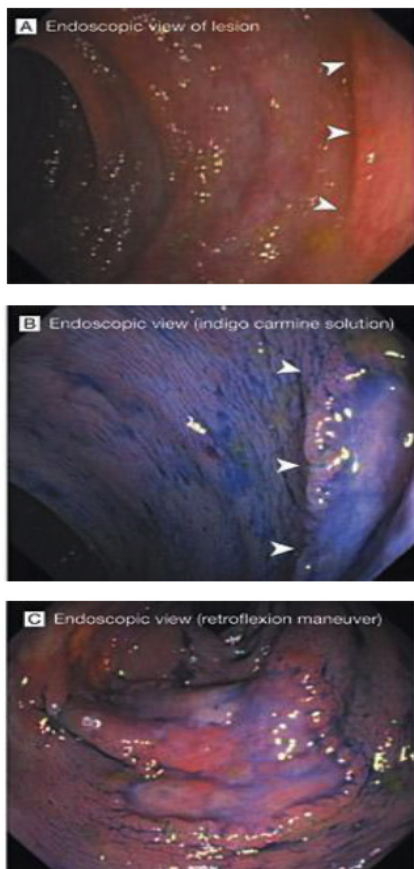
Limitations

- This is an invasive investigation.
- Whole colon may not be negotiated in all patients.
- An obstructive lesion does not allow a colonoscope to progress; hence any synchronous lesion may be missed.
- A flat lesion may be missed.



Techniques to Improve Detection in the Flat Polyp

Various modalities to increase the pickup rate used as an adjunct to normal colonoscopy are:



Narrow-band imaging: refers to an imaging technique for endoscopic diagnostic medical tests, where light of specific blue and green wave lengths is used to enhance the detail of certain aspects of the surface of the mucosa. A special filter is electronically activated by a switch in the endoscope leading to the use of ambient light of wavelengths of 440 to 460 nm (blue) and 540 to 560 nm (green). Because the peak light absorption of hemoglobin occurs at these wavelengths, blood vessels will appear very dark, allowing for their improved visibility and in the improved identification of other surface structures.

In gastrointestinal endoscopy, narrow band imaging has found use in the identification of Barrett's esophagus [2], in the identification of pit patterns to classify colorectal polyps and tumors [3], and in the identification of atypical dysplastic cells in the colon of patients with ulcerative colitis [4]. Also, in cystoscopy, narrow band imaging is useful in differentiating between benign and malignant cells [5].

Chromo-Endoscopy

Stains used in chromo-endoscopy have three major mechanisms. Absorptive stains have an affinity for particular mucosal elements, and include Lugol's iodine, methylene blue and gentian violet. Lugol's iodine specifically stains non-keratinized squamous epithelium, and is useful for identifying squamous tissue, squamous dysplasia and carcinomas. Methylene blue stains absorptive epithelium and is useful for identifying abnormality in the small intestine and colon. Barrett's esophagus involves change in the mucosa of the esophagus into a tissue that includes glands (intestinal metaplasia), and as a result, can be identified with methylene blue staining [6]. Also, methylene blue has been used to identify dysplasia in patients with ulcerative colitis [7].

Contrast stains are not absorbed but rather provide contrast by permeating between irregularities in the mucosa to highlight irregularities. The primary contrast stain is indigo carmine, administered at varying concentrations between 0.1% and 0.8%. The chief utility of indigo carmine is in the identification of dysplastic cells in individuals with chronic ulcerative colitis.

Reactive stains undergo an observable change due to a chemical process related to the function of the gastrointestinal tract. Congo red is used as a test for achlorhydria in the stomach, as it changes color from

red to black at a pH less than 3. Should acid not be present in the stomach, it would remain red [8].

The most common applications for chromoendoscopy are: identification of squamous cell carcinomas or dysplasia of the esophagus, identification of Barrett's esophagus and dysplasia, identification of early gastric cancer, characterization of colonic polyps and colorectal cancer, and in screening for dysplasia in individuals with ulcerative colitis [7].

The dyes used for chromoendoscopy are typically considered to be safe. Some dyes such as indigo carmine may discolour the feces temporarily. Lugol's iodine when applied to the esophagus can lead to discomfort, inflammation (of the esophagus or stomach) or rarely allergy. Sodium thiosulfate has been used to avert this [7].

A similar technique to narrow-band imaging using blue and green filters has been used in endoscopes manufactured by Fujinon, termed Fuji Intelligent Chromoendoscopy (FICE), and has been referred to as virtual chromoendoscopy [9]. Other techniques that can enhance detail of mucosa include confocal microscopy, magnification endoscopy and optical coherence tomography.

Endocytoscopy: The endocytoscope is an ultra-high magnification (450-1125 times) catheter-type endoscope that can be passed through the working channel of a colonoscope and used, in combination with chromo agents, to provide in-vivo histologic images. In a study of 75 lesions detected during routine colonoscopy, endocytoscopic images correlated closely with histopathologic images. With endocytoscopy it was possible to distinguish between neoplastic and non-neoplastic lesions and adenomas and invasive cancers [10].

Ultrasound in Rectal Cancer Diagnosis: Staging of Rectal Cancer by ERUS [11]

uT0 Confined to mucosa

uT1 To but not through submucosa

uT2 Into but not through muscularis propria

uT3 Through bowel wall into perirectal fat

uT4 Involving adjacent structures

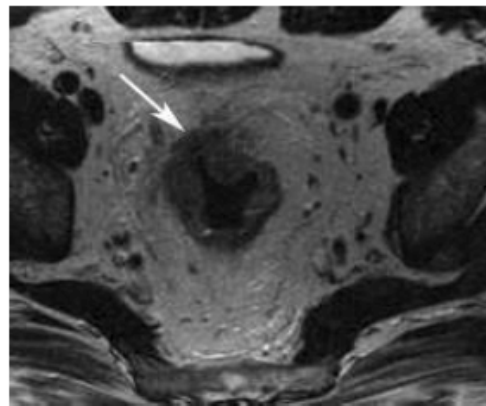
uN0 No definable lymph nodes by ultrasound

uN1 Ultrasonographically apparent lymph nodes



Spiral CT

The introduction of spiral CT scanner has revolutionized the concept of pre-operative staging in CRC. This investigation gives a broader overview of the T, N and M Stage. The treating surgeon can very easily select the tumors suitable for neo-adjuvant treatment before subjecting them to surgery, thus, decreasing the rates of inoperability and increasing the overall survival.



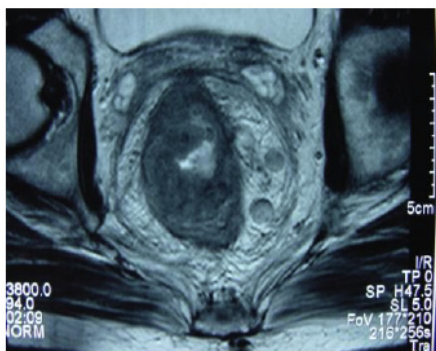
MRI

- High Resolution Thin Slice (<1mm)
- Depth of extramural spread accurately identified
- CRM –Better delineated (greatest advance)

- Traditional
 - Proximal
 - Distal
- Detects “Extramural Venous Invasion (EMVI)”
- Detects nodes as mixed signal intensity with irregular border.

An operating surgeon will always benefit better by a pelvic MRI to assess the T stage in a better way.

INVOLVEMENT OF PUBORECTAL SPHINCTER



EXTRAMURAL VEIN INVASION



INVOLVEMENT OF PUBORECTAL SPHINCTER



Virtual Colonoscopy

This is a novel technique where overlapping trans-axial helical CT images are reconstructed following a standard bowel preparation and air insufflations.

- 2-D multi-planar reformations and 3-D endoluminal images are viewed
- Sensitivity for detection of lesions >10 mm in size (75-94%)
- Successful in 90% of patients with occlusive colon cancer [12,13]

Rationale

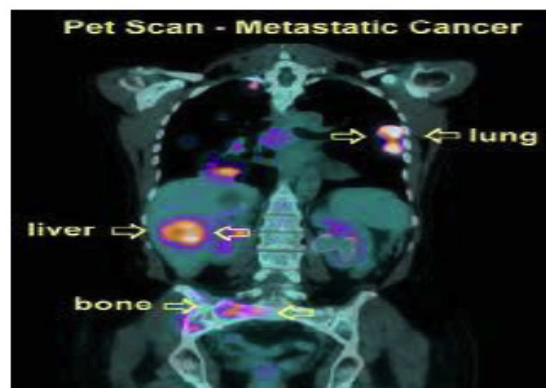
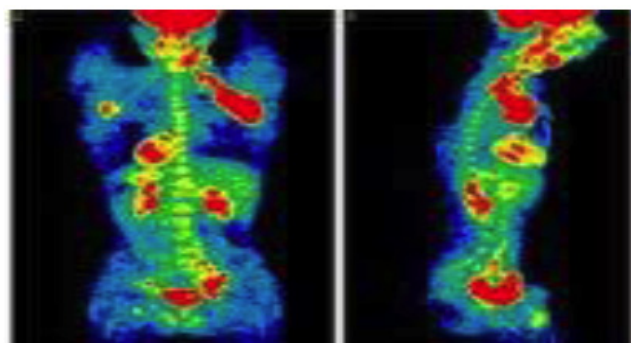
- Allows detailed evaluation of the entire colon.
- A number of studies have demonstrated a high level of sensitivity for cancer and large polyps.
- Minimally invasive (rectal tube for air insufflations).
- No sedation required.

Limitations

- Bowel Prep
- Steep learning curve
- Colonoscopy for biopsy and therapeutic reason

PET Scan

This investigation is still not used as a primary tool of evaluation in colorectal malignancy. However, this is considered to be an investigation of choice on follow-up to rule out a recurrence or a metastatic disease.



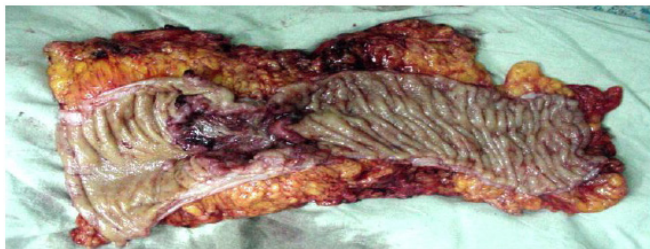
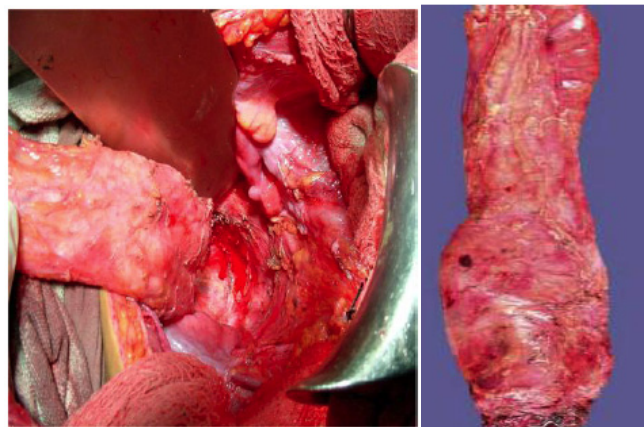
CEA in Colorectal Cancer

- Recommended for monitoring of recurrence at 2-3 months intervals for >2 years after diagnosis of Stage II or III tumors
- CEA first detected resectable recurrences more frequently than any other tests and is the most cost effective approach.
- Poorly differentiated tumors may not form CEA [14].

A rising CEA alone is not sufficient evidence to prompt a change in treatment. Disease progression should be confirmed with radiographic testing (e.g., CT scan) or a biopsy before changing treatment.

Total Mesorectal Excision (TME)

This surgical technique is now-a-days a gold standard for all rectal cancers. The said technique was described and popularized by William Heald in eighties. As per this concept we don't only take care of the proximal and distal resection margins but also include all the surrounding lymphatics in the mesovascular envelope. This concept of taking care of the circumferential resection margin (CRM) has globally significantly decreased the local recurrence rate in rectal cancers [15].



In present day world anybody not performing TME for rectal cancer will mean an inadequate and incomplete surgery. For the better outcome in your

patients it would be always wise for any surgeon to learn the craft from experts rather than practicing incomplete surgery and making the patient more prone to recurrences.

Laparoscopic Surgery

Now-a-days the laparoscopic technique has become a part n parcel of all surgeries. Even though, the learning curve is tedious but still most of the advanced centers in the world are practicing this technique. The famous RCTS like Barcelona, COST, COLOR and MRC Trials have quite extensively checked the safety, morbidity and mortality profile of the laparoscopic technique and it has been proved beyond doubt that laparoscopy if not better but is at least equivalent to open surgery in colon cancer but the results still are not as good as open in rectal surgery which definitely are expected to improve as soon as the learning curve is negotiated [16].

However, at present most of the literature is in agreement that laparoscopic surgery is associated with:

Less post-operative pain

Better cosmesis

Early return of bowel function

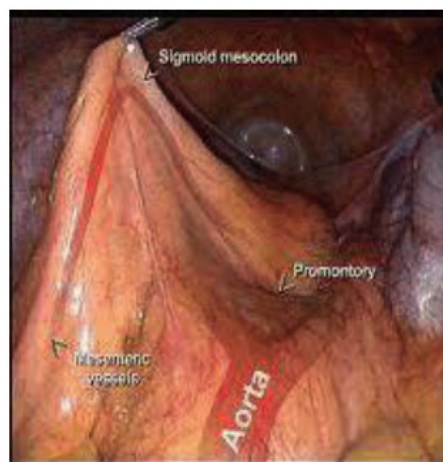
Shorter hospital stay

And that too without sacrificing oncological clearance

In Twelve trials on laparoscopic surgery which included more than 3346 patients

No difference was found in recurrence rate

And no difference in Cancer related mortality when compared to open surgery.

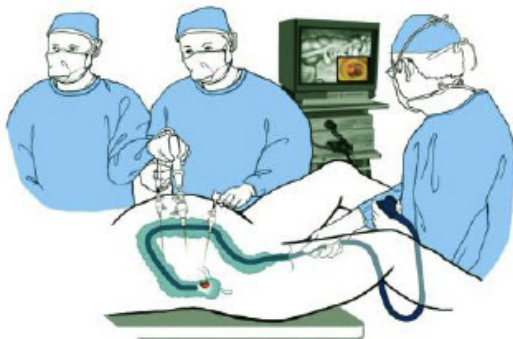


However, Technical Complexity and long Learning curve can compromise oncologic Outcomes”..... [17]

Besides, the operating surgeon after mastering the craft properly has the advantage of a magnified vision, can reach the deeper confines of pelvis more comfortably and can see and preserve nerves more comfortably.

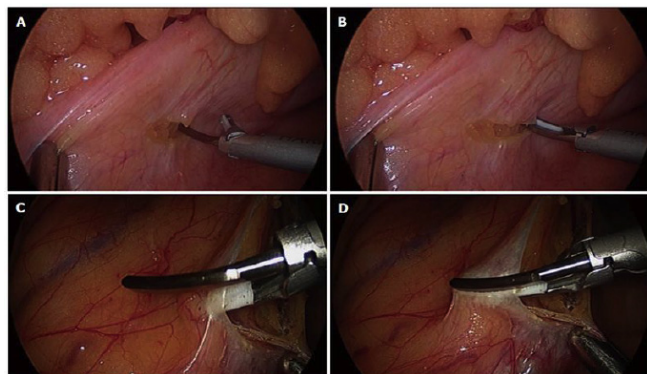
Combined CO2 Colonoscopy & Laparoscopy

This technique has the advantage of localizing the lesion per rectum as well as per abdomen and is very helpful in lesions where it is quite difficult to localize the lesion laparoscopically because of lack of tactile sensation. Even though this technique still has not picked up much but this definitely is a technique with a significant advantage for impalpable lesions.



Energy Sources

This is a big leap to improve hemostasis, have better vision and cut and explore in difficult areas laparoscopically. Energy sources like cauteries, harmonic scalples, ligasure, Mseal are the necessary part of the armamentarium in the surgical theatres to make big procedures possible without any significant blood loss.



The learning curve of the operating surgeon has been greatly facilitated by these wonderful gadgets

which always provide us a bloodless field and thus, facilitate a hassle-free magnified vision and grossly decrease the conversion rates.

Robotic Rectal Surgery

The Da Vinci Surgical system was developed to overcome shortcomings of laparoscopy. It has the advantage of:

- Three dimensional imaging
- Stable camera and operating platform
- Articulating instruments with 7 degree of freedom
- Motion scaling and tremor free movements
- Ergonomic Comfort



Oncologic Outcomes

- Negative distal and circumferential margins 99.3%
- Mean number of harvested lymph nodes 14.1
- Complete pathologic response 19.3%
- No Port site recurrence
- Disease free Survival at 3 years 76.6%
- Three year overall Survival rate 77% [18]

The evolution of Robotic Surgery is limited due to small numbers of high volume centers. The Robotic Technology will radically change general surgery and the fractionated subspecialties.

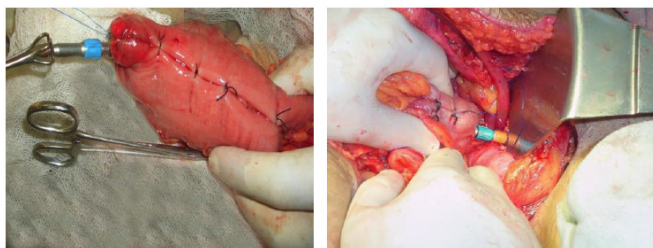
In a developing country like India cost factor becomes the biggest limitation for propagation of this technology.

In many centres a Hybrid technology comprising of a blend of laparoscopy and robotic surgery is practiced to take advantage of both technologies and decrease the time and cost factor.

Reservoir [15]

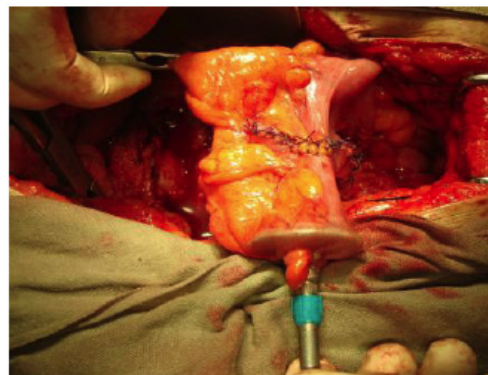
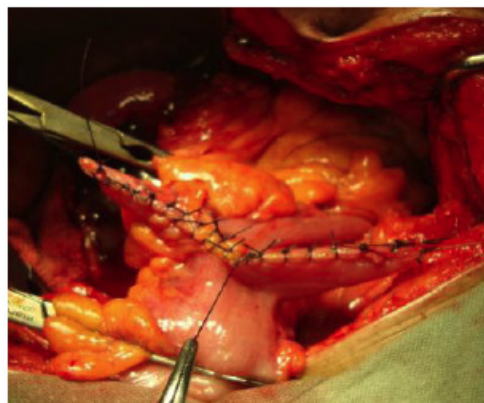
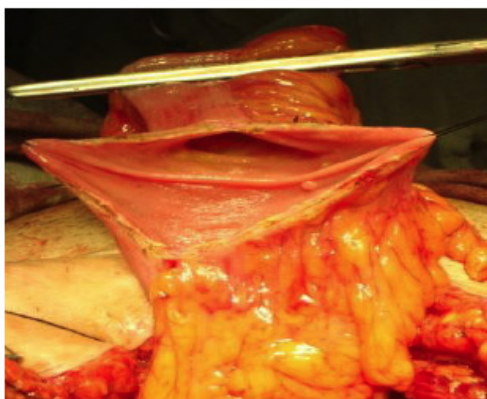
The importance of constructing a reservoir was felt after the identification of anterior resection syndromes which developed in some patients following low or ultra low resection due to loss of reservoir. In order to overcome this problem Lazorthes introduced the concept of a neo-rectum by constructing a J Pouch. Then other types of pouches were also tried like

- S Pouch
- W Pouch
- Coloplasty
- End to Side anastomosis



COLOPLASTY [19]

After completion of TME CDH/CEEA used for circular anastomosis, a vertical incision in colon is closed transversely by linear staplers/sutures. The outcome is creation of a physiological neo reservoir known by the name of Coloplasty. The pouch will help greatly in reducing the symptoms of anterior resection syndrome but leak rates from anastomosis may be more as compared to J Pouch as it involves an end to end anastomosis in comparison to end to side anastomosis used in J Pouch.



New Methods in Cancer Treatment

The newer drugs and other modalities being tried at present to improve the overall survival and QOL are:

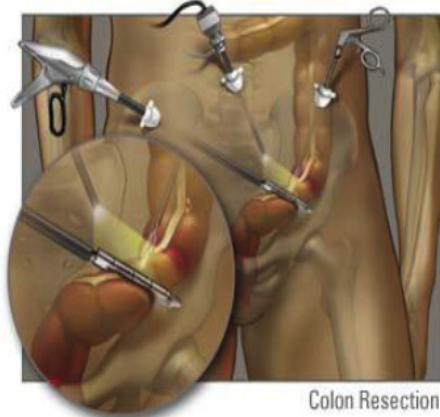
- Vascular Endothelial Growth Factor (VEGF) inhibitor like Avastin, Erbitux and Vectibix.
- Immunotherapy: recognize cancer cell as foreign cell, attack the cancer cell
- Interferon-alfa, interleukin-2
- DNA vaccines
- Hormonal therapy
- Radiation: new imaging system precisely positioning and aiming target cells, different radiation dosage and therapy.
- Chemotherapy (including hormonal therapy): new drug development, more specific and less toxic (find the specific pathways and blocking it specifically).

New Technology

It has proved to be a big boon in colorectal cancers because of:

- Better investigative tools
- Better Staging

- Down staging
- Better Surgery
- Better Drugs
- Logical follow up
- Better survival
- Better QOL



Challenge

- PICK up nodes < 5mm (33% of all nodes)
- Pick up micro-mets.
- Use of CH/RT as a safe practice
- Overloaded Govt Sector
- Costly corporate sector
- Screening Programmes
- Breaking Bonds

“What will give me the greatest chance of cure or longer life, and at what price?”

- Wendy Schlessel Harpham, M.D.

The Most Important Challenge in Cancer Management is Early Detection

Axiom: Early detection of cancer leads to cure

Operating Room of Future

- WOK: Wall of Knowledge (multiple flat screens)
- Input:
 - OPTICS, XRAYs, MEDICAL RECORD
 - Consultations (Pathology, other specialists)
- Teaching input from remote site
- Bluetooth technologies (phone, data, images)



Future Biomarkers

- CEA and/or survivin-positive DTCs may be a promising biomarker for prognosis assessment in CRC [20].
- Ang-2, Tie-2 and VEGFR-2 involved in the development, invasion, metastasis, and prognosis of colorectal cancer, and play important roles in the angiogenesis of the tumors [21].

Other Future Initiatives

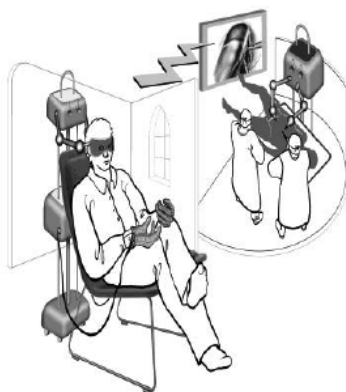
Telepresence Robotics

Expert surgeon can enter the remote OR and assist the team there

Robots will make complex decisions

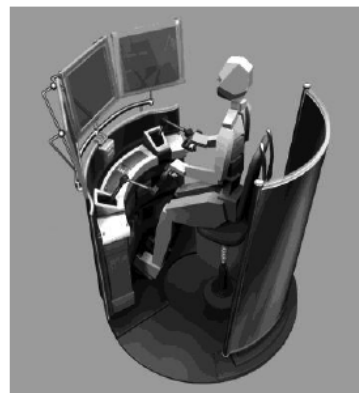
New Technology is definitely going to be more and more precise in the coming years. The diagnosis will be more accurate, the treatment will be more targeted and more patient friendly, the machines and the robots will do most of the job precisely and efficiently; overall survival and QOL will definitely be better but the big question remains at what cost? In most of the developing world this type of advanced technology may not be accessible to most of the population because of the cost factor till the time the existing Governments don't take real progressive steps in health care and medical insurance does not come into play in a big way, the boon of new technology may be simply a bane for the developing world.

Telepresence



Expert surgeon can “enter” the remote OR

Assist the team there



Robotics

Robots will make

complex decisions

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