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From the Desk of Director Research

Colorectal cancer is the third most common cancer in men and the second in women worldwide. Incidence rates vary in both sexes and are substantially higher in men than in women. Men have a higher probability of being diagnosed with cancer. The trend has also been observed in India.

Colorectal cancer is a pathology that originates from the epithelial cell lining of the gastrointestinal tract which undergoes sequential mutations in specific DNA sequences, thereby disrupting the normal mechanisms of proliferation and self renewal. There are several etiologic factors that may be involved in the development of colorectal cancer with an interplay of non-genetic, genetic and epigenetic factors. The non-genetic factors include the age, geographic variation, environmental influences, diet, use of drugs and lifestyle changes. Heritable genetic defects make a major contribution to the overall incidence of colorectal cancer. Studies have also highlighted the importance of hereditary factors in the risk of sporadic colorectal cancer. Epigenetic changes have also been observed in the development of colorectal cancer.

Colorectal cancer is usually diagnosed after a positive screening test or workup of a symptomatic patient. The therapeutic strategies for colorectal cancer include Surgery, Chemotherapy, Targeted Therapy and Radiotherapy. Surgery remains the primary modality for cure in patients with colorectal cancer. Adjuvant chemotherapy has been shown in a series of randomized trials, to prevent relapse in some patients, hence improving survival in defined risk groups. The prognosis of the patients with colorectal cancer is affected by many pathological, molecular and clinical features. There is a rapid need for developing strategies and guidelines for control of this disease, which focus on the treatment and screening aspects.

This issue of Cancer News profiles the complexities and advancements in the field of colorectal cancer, and includes regular articles, such as "Special Feature", "Guest Article", "Perspective", "Watch-Out", "Research & Development", "New Technologies", "Clinical Trials", "Globe Scan", "In Focus" and "Cancer Control".

We appreciate the contribution made by Dr Mohandas K Mallath, Senior Consultant, Department of Digestive Diseases, Tata Medical Center, Kolkata, for providing the "Guest Article" on "Targeted Therapy for Colorectal Cancer-What is New".

The understanding of Colorectal Cancer and its management is changing rapidly. The 12th Annual International Conference "RGCON-2013" being organized by the Institute from February 15th to 17th, 2013 has its main theme as "Changing Scenario in Colorectal Cancer". It would be a perfect forum to interact with the eminent international and national faculty.

Suggestions/comments from the readers are welcome.

Dr D C Doval

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Research & Analysis Team
Research Department

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SPECIAL FEATURE

WHAT WE NEED TO KNOW ABOUT COLORECTAL CANCER (CRC) IN 2013?

Epidemiology of CRC: Worldwide vs India

Worldwide, in both men and women, colorectal cancer (CRC) is the third most commonly diagnosed cancer and the third leading cause of cancer deaths (GLOBOCON 2008)¹. CRC accounts for 10 % of the total cancer burden worldwide with the age-standardised incidence rate of developed region being 10 fold more than that of India. Also there are higher incidence rates in the rest of Asia compared to India.

CRC in India ranks 6th among all cancers in both men and women with age-standardised incidence and mortality rates of 4.3 /100,000 & 3.2/100,000 population respectively. It accounts for the 4.7 % of total cancer burden in India with wide variation seen across different states in incidence rates with some states not even registering CRC in their top 10 cancers².

There is wide geographical variation in incidence across the world, much of which can be attributed to differences in diet, particularly the consumption of red and processed meat, fibre and alcohol, as well as bodyweight and physical activity.

Table: Colorectal Cancer: GLOBOCAN Data 2008

	Total Cancer Burden(%)	Age-Standardised incidence Rate (per 100,000 population)	Mortality Rate (per 100,000 population)
Worldwide	10	20.3	9.6
India	4.7	4.3	3.2
Asia	8.7	15.1	7.7
More developed regions	13.2	37.7	15.1
Less developed regions	7.5	12.1	6.8

A recent study from India³ found the incidence and survival rates of colorectal cancer are low in India compared to rising rates in East Asia, possibly due to the prevailing environmental factors and lifestyle, including reduced consumption of sugars, calories and fat-rich food; increased consumption of vegetables and fruits, and adequate physical activity with avoidance of overweight and obesity. These factors are responsible for the low risk of colorectal cancers. However, this low incidence rate was associated with a low 5-year relative

survival rate, suggesting severe deficiencies in early diagnosis and effective treatment in India.

Why CRC in India Occurs a Decade Earlier than the Western Population?

Similar to other cancer types, CRC is seen more often a decade earlier in India than in the western countries. There are at least four types of human colorectal carcinogenesis (adenoma-carcinoma sequence type, hereditary nonpolyposis colorectal cancer (HNPCC) type, *de novo* type, and colitic cancer type).

A recent Indian study found evidence of possible non-canonical pathway(s) driven early-onset colorectal cancer in India⁴. Comparative analysis of early and late-onset CRC from India with respect to common genetic aberrations, including Wnt, KRAS, and p53 (constituting the classical CRC progression sequence) in addition to MSI revealed the absence of Wnt and MSI in a significant proportion of early-onset as against late-onset CRC in India. In addition, KRAS mutation frequency was significantly lower in early-onset CRC indicating that a significant proportion of CRC in India may follow tumorigenesis pathways distinct from the classical CRC progression sequence, suggesting the possible existence of non-canonical tumorigenesis pathways in early-onset CRC in India.

Revised Vienna Classification for Colorectal Cancer Screening

Revised Vienna classification:⁵

- 1) No Neoplasia: (Negative for neoplasia)
- 2) Mucosal Low Grade Neoplasia: low-grade adenoma, low-grade dysplasia,
- 3) Mucosal High Grade Neoplasia: Mucosal high grade neoplasia, high-grade adenoma/dysplasia, non-invasive carcinoma (carcinoma *in situ*), suspicious for invasive carcinoma, Intramucosal carcinoma
- 4) Carcinoma: invading the submucosa or beyond

Effect of TNM Classification of Tumors of the Colon and Rectum (7th edition)

TNM 7 appears to be more subjective than TNM 5 due to the notes on N classification and the category N1c, promoting stage migration from II to III. National results should be reported with the version of TNM used in a given country⁵.

Clinical Biomarkers for Colorectal Cancer

Rapidly growing insight into the molecular biology of colorectal cancer has led to high hopes for the

identification of molecular markers to be used in optimized and tailored treatment regimens. Currently used markers in clinical practice include microsatellite instability (MSI) and guanylyl cyclase C (GCC) testing in the adjuvant setting, and KRAS mutation testing as used in the setting of epidermal growth factor receptor (EGFR)-targeted therapy for metastatic disease. Recently, mutations in the KRAS gene were shown to be strong negative predictors of response to EGFR inhibitors in metastatic disease. It has also been suggested that BRAF gene mutations may be predictive of EGFR inhibitor resistance⁶.

Novel Biomarker for Colorectal Cancer

- 1) Hypermethylation of the plasma septin-9 gene shows promise as a nonstool-based screening tool⁷.
- 2) Hypermethylation of the DYPD gene (encodes the enzyme dihydropyrimidine dehydrogenase) and variation of the uridine diphosphate-glucuronosyl-transferase 1A (UGT1A1) gene have predictive value for side effects and the efficacy of 5-fluoruracil and irinotecan, respectively⁷.
- 3) MicroRNA signatures: Aberrant microRNA (miRNA) expression might be of potential use as diagnostic and prognostic biomarker for cancers⁸.
- 4) Genomic signatures: Identification of a biomarker panel for colorectal cancer diagnosis & prognostic signatures for survival⁹.

Many markers also suffer from technical shortcomings resulting from the lack of quantitative techniques to capture the impact of the molecular alteration. The impact of markers obtained from microarray expression profiling needs to be further investigated in studies based on much larger cohorts, and cross-validation studies will be essential.

ACR Appropriateness Criteria Pretreatment Staging of Colorectal Cancer

Virtually all patients with colonic cancer will undergo some form of surgical therapy. Thus, the role of preoperative imaging is directed at determining the presence or absence of synchronous carcinomas or adenomas and local or distant metastases. In contrast, preoperative staging for rectal carcinoma has significant therapeutic implications and will direct the use of radiation therapy, surgical excision, or chemotherapy. CT of the chest, abdomen, and pelvis is recommended for the initial evaluation for the preoperative assessment of patients with colorectal carcinoma. Although the overall accuracy of CT varies directly with the stage of colorectal

carcinoma, CT can accurately assess the presence of metastatic disease. MRI, using endorectal coils, can accurately assess the depth of bowel wall penetration of rectal carcinomas. Phased-array coils provide additional information about lymph node involvement. Adding diffusion-weighted imaging to conventional MRI yields better diagnostic accuracy than conventional MRI alone. Transrectal ultrasound can distinguish layers within the rectal wall and provide accurate assessment of the depth of tumor penetration and perirectal spread, and PET and PET/CT have been shown to alter therapy in almost one-third of patients with advanced primary rectal cancer.

ACR Appropriateness Criteria are evidence-based guidelines for specific clinical conditions that are reviewed every 2 years by a multidisciplinary expert panel and the guidelines rate the appropriateness of imaging and treatment procedures. In those instances in which evidence is lacking or not definitive, expert opinion may be used to recommend imaging or treatment¹⁰.

Novel Imaging Tools in CRC

MRI and CT scan along with the traditional enteroclysis examination have emerged at the forefront of intestinal imaging. Functional modalities, such as diffusion and perfusion imaging are also changing the way tumors and inflammatory bowel diseases are evaluated. CT colonography is now a valid alternative to optical colonoscopy.

- 1) CT colonography (see Fig) is highly sensitive for colorectal cancer, especially when both cathartic and tagging agents are combined in the bowel preparation¹¹.
- 2) Contrast-enhanced USG is being used for the assessment of inflammation and post-treatment changes.
- 3) Bio-imaging of colorectal cancer using near infrared-labeled EGF (EGF-NIR): EGF-NIR could provide an additional bio-imaging specific tool in the standardization of measurements of EGFR expression in CRC tissues¹².

Adjuvant Treatment of Colorectal Cancer^{13,14}

- 1) For stage I disease: No adjuvant therapy needed.
- 2) Stage II disease:
 - a) For low risk stage II disease, consider observation or enrolling in clinical trial or consider for capecitabine or 5 FU/LV in individual patients. FOLFOX is not considered based on the MOSAIC trial and the long-term sequel of oxaliplatin based therapy.
 - b) For high risk stage II disease (lymph nodes

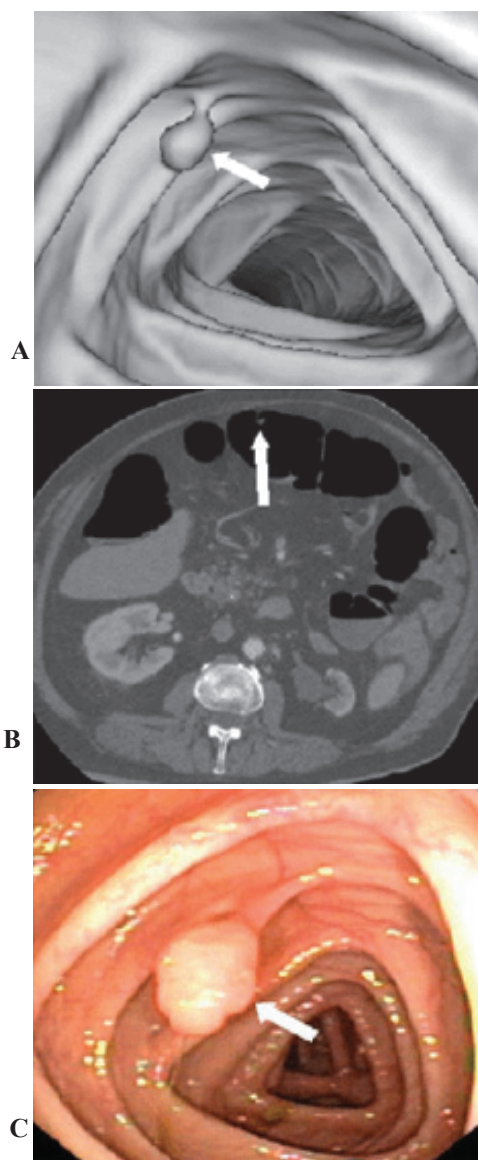


Fig: (A) The polyp in transverse colon was initially detected with CT colonoscopy (arrow) which was confirmed with axial image (B) & conventional colonoscopy (C). *Am J Gastroenterol.* 2004 Oct;99(10):1924-35

sampling <12, poorly differentiated tumour, vascular or lymphatic or perineural invasion, pT4 stage, clinical presentation with intestinal occlusion or perforation): Can be considered for adjuvant chemotherapy with 5FU/LV, Capecitabine, FOLFOX or CapeOx because of a small absolute benefit. However, recent analyses of the NSABP protocol C05-C08 demonstrated a 2%–3% benefit in the 5-year OS rate for the addition of oxaliplatin to FU-based adjuvant chemotherapy in stage II.

- 3) Stage III disease: Adjuvant chemotherapy should be offered to all eligible patients with stage III disease. FU and oxaliplatin combinations (FLOX, FOLFOX, XELOX) are superior to single-agent 5-FU in terms of DFS and OS.

Which agents should not be used in the Adjuvant Therapy?

- 1) Irinotecan: Three randomized phase III trial (PETACC 3, FNCLCC Accord02/FFCD9802, CALGB 89803) all failed with the addition of irinotecan to 5FU/LV.
- 2) Addition of targeted agents (cetuximab, bevacizumab) to FOLFOX: Two adjuvant trials with bevacizumab and one adjuvant trial with cetuximab have failed to show any benefit of adding these agents to standard chemotherapy. Although reasons for the negative results remain unknown, the divergent effects of bevacizumab and cetuximab in early versus advanced stage colon-cancer reinforce the notion that adjuvant and metastatic settings represent distinct diseases that require different treatments¹⁵.

Metastatic CRC Treatment

The most recent international, European and US guidelines recommend combination chemotherapy with the addition of a monoclonal antibody for the first-line treatment of mCRC¹⁶.

The addition of bevacizumab to fluorouracil (5-FU)/leucovorin, irinotecan plus bolus 5-FU/leucovorin, or irinotecan plus infusional 5-FU/leucovorin significantly improves the overall survival of patients with previously untreated metastatic colorectal cancer¹⁷. In addition, a significant increase in overall survival is seen when bevacizumab is added to oxaliplatin plus infusional 5-FU/leucovorin (FOLFOX) in patients with metastatic colorectal cancer who progressed on a non-bevacizumab-containing regimen. Although majority of the studies were performed prior to the identification of KRAS and BRAF as predictive biomarkers, subsequent analysis has shown the benefits of bevacizumab occur independent of the mutational status of these genes. In patients who have progressed on a bevacizumab-containing regimen, continuation of bevacizumab is significantly associated with an improved survival based on observational cohort studies.

A recent trial of first-line treatment with cetuximab in combination with FOLFIRI showed that such treatment reduced the risk of disease progression compared with FOLFIRI alone in patients with KRAS wild-type tumors. Another trial of first-line treatment in patients with wild-type KRAS mCRC showed that a combination of cetuximab and FOLFOX4 increased the likelihood of a response and was associated with a lower risk of disease progression than treatment with FOLFOX4 alone.

In Phase III PRIME trial, panitumumab in combination with FOLFOX4 significantly improved progression-free survival compared with FOLFOX4 alone in the first-line treatment of *KRAS* wild-type mCRC. Another phase III trial demonstrated that panitumumab in combination with FOLFIRI significantly improved progression-free survival compared with FOLFIRI alone in the second-line treatment of wild-type *KRAS* mCRC.

Second-line treatment depends on the first-line regimen used. For chemoresistant mCRC, cetuximab or panitumumab is recommended as monotherapy in patients with wild-type *KRAS* tumors.

Improvement in Survival after Colorectal Liver Metastasis (CLM) Resection

Hepatic metastases develop in approximately 50% of CRC cases, with 20%–25% of newly diagnosed metastatic colorectal cancer (mCRC) patients presenting with liver metastases at the time of primary diagnosis, and up to 50% of all CRC patients developing metastatic liver disease after resection of primary CRC¹⁸.

Patients who present with CLM can generally be divided into three groups: (1) those with resectable disease, (2) those whose metastases may become resectable, and (3) patients who are never going to become resectable.

Among those with liver-limited colorectal metastases, it has been reported that 10%–30% of patients have potentially resectable disease that can be treated with curative intent at the time of detection. Among those patients with successful resection of all evident metastatic disease, long-term survival appears to be improving, with 5-year survival reported to be over 50% in recent studies (range 16%–74%). Long-term survival of all patients with mCRC, both operable and inoperable, has been improving significantly over the last two decades. Increased use of liver resection has played some part in these improving outcomes, but wide variations in its use persist.

The management of patients with CLM should be determined by a multidisciplinary team. Preoperative chemotherapy has the potential to improve long-term survival after liver surgery for resectable disease.

New Drugs Approved in 2012 for Colorectal Cancer^{19,20}

Ziv- Aflibercept & Regorafenib are the two new important drugs approved by FDA in 2012 for colorectal cancer treatment. Ziv- Aflibercept is a recombinant fusion protein consisting of VEGF-binding portions from the extracellular domains of human VEGF receptors 1

and 2 that are fused to the Fc portion of the human IgG1 immunoglobulin. It is approved for use in combination with FOLFIRI for the treatment of patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin containing regimen. Regorafenib is a multi-kinase inhibitor that is approved for patients with colorectal cancer when no adequate therapy exists.

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(Dr A Robert Louis, Consultant; Dr Sunil Kumar Gupta, Sr Consultant; Dept of Medical Oncology)

GUEST ARTICLE

TARGETED THERAPY FOR COLORECTAL CANCER-WHAT IS NEW

Summary

This review covers the advances in the use of targeting agents in the management of CRC. Among the large numbers of monoclonal antibodies (MAb) and tyrosine kinase inhibitors (TKI) that target a variety of molecular targets in patients with metastatic colorectal cancer (mCRC), Bevacizumab, Cetuximab, Panitumumab, Aflibercept and Regorafenib are currently approved. Combination of anti angiogenic drugs and growth factor inhibitors (Bevacizumab and EGFR inhibitors) has not improved the results. However, continuation of same or different anti angiogenic drugs after progression of mCRC has improved survival. Of interest is the emerging role of Aspirin in a select group of CRC patients given the fact that all the targeted drugs are prohibitively expensive for routine use in India. The recent results of the Cancer Genome Atlas project indicate that CRC in future will be subdivided into different subtypes based on molecular alterations and thereby opening the way to more targeted approaches. The discovery of targets in various pathways and targeted therapies will continue at frenetic pace. Further refinement driven by predictive and prognostic markers can be expected in the next few years.

Introduction

The incidence of CRC is low in most parts of India with an age adjusted rates below 5 per 100,000.

Unfortunately the 5-year survival for patients with CRC is far below those in most developed countries. Our war on mCRC began with cytotoxic drugs like Irinotecan, Oxaliplatin and Capecitabine that constitute the first line of attack. These drugs are not selective and damage normal cells and tumor cells. Unravelling of the carcinogenesis pathways has resulted in the development of less toxic targeted therapies. Targeted therapy uses drugs that target specific molecular targets in the pathways involved in the development and progression of cancer. Five targeted therapy drugs have been approved by the US Food and Drug Administration. These are: Bevacizumab, Cetuximab, Panitumumab, Aflibercept and Regorafenib. Two of these (Bevacizumab and Cetuximab) are already approved in India and the third, (Panitumumab) is due for approval by mid-2013. This overview summarizes the advances in the use of targeted treatments in the treatment of mCRC.

Angiogenesis Inhibitors in Colorectal Cancer

Angiogenesis is an integral part of carcinogenesis (1). The process of angiogenesis is abnormal and inefficient resulting in tissue hypoxia and abnormal perfusion which further contributes towards angiogenesis. Angiogenesis is tightly regulated by several growth factors acting on several receptors, such as the VEGFs and their receptors (VEGFRs). The VEGF family is made up of five members, including various VEGF-A to VEGF-E and a placental growth factor PlGF (1). Bevacizumab is the first anti-angiogenic drug to receive approval for first- and second-line treatment of mCRC (2, 3). Extensive evaluation and use of Bevacizumab provide high level evidence for anti-VEGF strategies in the treatment of CRC (2-4). Clinical experience of Bevacizumab indicates that: (1) Bevacizumab provides modest response rates as a single agent and much better activity when combined

Table 1. List of Targeted Therapy Drugs Approved for Metastatic Colorectal Cancer

Class of Drugs	Mechanism	Target	Approved Drug
Monoclonal antibodies	Receptor tyrosine kinase inhibitor	ErbB: HER1/EGFR	Cetuximab
Monoclonal antibodies	Receptor tyrosine kinase inhibitor	ErbB: HER1/EGFR	Panitumumab
Monoclonal antibodies	Angiogenesis inhibitor	VEGF	Bevacizumab
Small molecule (nibs)	Receptor tyrosine kinase inhibitor	VEGFR-TIE2	Regorafenib
Monoclonal antibodies	fusion protein antagonist	VEGF-A, VEGF-B	Aflibercept

with conventional chemotherapy. (2) Bevacizumab has good activity when combined with all the standard chemotherapy combinations, but is ineffective when combined with anti-EGFR agents. (3) Continuing use of Bevacizumab after progression offers survival benefits. (4) Its use in adjuvant setting has not improved survival. It appears that the effects of VEGF-A blockade by Bevacizumab are time bound, with tumor progression developing in most patients. The mechanisms include intrinsic and adaptive resistance, mediated by factors beyond VEGF and new approaches are needed. Efforts to validate predictive biomarkers and best combination treatments to offer for mCRC patients are ongoing and much more basic and clinical research is required.

Newer Anti-angiogenic Drugs

Several targeted agents (Vatalanib, Cediranib, Brivanib, Axitinib, Sunitinib, Regorafenib, Aflibercept AMG-706, etc), with anti-angiogenic properties have been investigated in mCRC. Among these Aflibercept and Regorafenib, received approval as the new-targeted agents for the treatment of mCRC. These two drugs reinforce the concept of continuing anti-angiogenesis therapy after tumor progression.

Regorafenib is an oral multi-kinase inhibitor that targets angiogenic, stromal and oncogenic receptor tyrosine kinase (5). Regorafenib was tested in an international phase 3 trial at 114 centres in 16 countries in patients (5). 1052 patients with mCRC who had progressed during or within 3 months after the last standard therapy were screened and 760 patients were randomised to receive Regorafenib (n=505) or placebo (n=255). 753 patients initiated treatment (Regorafenib n=500; placebo n=253; population for safety analyses). Median overall survival was 6.4 months in the Regorafenib group versus 5.0 months in the placebo group (hazard ratio 0.77; 95% CI 0.64-0.94; one-sided $p=0.0052$). Treatment-related adverse events occurred in 465 (93%) patients assigned Regorafenib and in 154 (61%) of those assigned placebo. Common adverse events of grade three or higher related to Regorafenib were hand-foot skin reaction (83 patients, 17%), fatigue (48, 10%), diarrhoea (36, 7%), hypertension (36, 7%), and rash or desquamation (29, 6%). Regorafenib is thus the first small-molecule multikinase TKI showing survival benefits in mCRC which has progressed after all standard therapies. This study provides evidence for a continuing role of targeted treatment after disease progression, with

Regorafenib and has been approved for use as new line of therapy in this treatment-refractory mCRC.

Aflibercept is a recombinant fusion protein that is comprised of vascular endothelial growth factor (VEGF) binding portions from the extracellular domains of human VEGF receptors 1 and 2, fused to the Fc portion of the human IgG1 immunoglobulin (6). Structurally this molecule is very different from Bevacizumab, but functionally they are anti-angiogenic. Aflibercept serves as an angiogenic factor trap that blocks the binding of VEGF-A, VEGF-B, and placental growth factor. In a recent Phase III trial (VELOUR) is evaluating Aflibercept as a second line treatment for mCRC in combination with FOLFIRI (6). In total, 1226 patients with mCRC received FOLFIRI and either Aflibercept (4 mg/kg) or a placebo every 2 weeks after failure of one Oxaliplatin-based therapy. PFS was 6.90 months versus 4.67 months (hazard ratio [HR] 0.758, $P=0.00007$) and objective response rate (ORR) 19.8% versus 11.1% ($P=0.0001$). Median OS was 13.50 months for Aflibercept arm and 12.06 months for placebo arm (HR 0.817, $P=0.0032$). Aflibercept was approved for use in second line settings on the basis of significant improvement in OS, progression-free survival (PFS), and RR. Treatment discontinuation for adverse events occurred in 26.6% and 12.1% in Aflibercept arm and placebo arm, respectively and was consistent with anti-VEGF therapy.

Advances in EGFR Inhibitors in the Treatment of Colorectal Cancer

The epidermal growth factor receptor (EGFR) is a member of the ErbB family of closely related tyrosine kinase receptors: EGFR (ErbB-1/HER-1), ErbB-2 (HER-2/neu), ErbB-3 (HER-3), and ErbB-4 (HER-4). These receptors are transmembrane glycoproteins with an intracellular domain with tyrosine kinase activity for downstream signalling of proteins involved in tumor cell proliferation, invasion, migration, and inhibition of apoptosis. Cetuximab and Panitumumab are two monoclonal antibodies that block the ligand binding site of the EGFR, thus inhibiting the downstream intracellular signalling. Cetuximab is a chimeric human mouse antibody, while Panitumumab is a fully humanized monoclonal anti-EGFR antibody. Common side effects of these antibodies include acneiform rash, diarrhoea, and hypomagnesaemia and hypersensitivity reactions that can be particularly severe with the chimeric antibody. The early studies had

failed to demonstrate a correlation between the intensity of EGFR expression and the response to treatment and Cetuximab was used in all CRC. Later studies had revealed that the absence of KRAS activating mutation within tumor cells was an important predictive marker of response to Cetuximab and/or Panitumumab given as monotherapy or in combination with chemotherapy (7). Analyses from several large trials show that patients with tumors bearing the KRAS mutation do not respond to either Cetuximab- or Panitumumab-based therapy. Nevertheless, the presence of a wild type of KRAS in tumors does not guarantee a good response to EGFR inhibitors in all. More recent studies suggest that, together with KRAS mutations, the evaluation of EGFR gene copy number (GCN), and other downstream pathway targets, such as BRAF, NRAS, PIK3CA mutations or loss of PTEN expression, results in reduced benefit from anti-EGFR mAbs (8). These findings are now being tested under the acronym of quadruple negative mCRC.

Aspirin and Colorectal Cancer

In a well designed retrospective study, Alabama researchers collected data from 964 patients with CRC who were grouped based on the presence or absence of a mutation within the PIK3CA gene (9). 17% of patients carried a mutated PIK3CA gene. The use of aspirin after diagnosis in patients with the gene mutation was associated with a 46% reduction in overall mortality and an 82% reduction in CRC-specific mortality. In contrast, aspirin use in patients without the mutation did not affect either overall or colorectal-specific mortality (9). Thus, at least one in every six patients with locally advanced CRC may benefit from this therapy. While this evidence is not good enough to change practise we are accumulating more information and aspirin may well become one of the oldest drugs to be used in 21st-century as a targeted agent.

Conclusions

It is clear from past experience in colon cancer and other tumors that there is a need to identify clinically meaningful predictive markers of response to targeted therapy. Beyond the obvious clinical benefit for patients, it is likely that the identification of predictive markers can also reduce the costs of cancer treatment. Many questions remain unanswered regarding the appropriate use of Bevacizumab or EGFR inhibitors in patients with metastatic colorectal cancer. Although studies of combinations of targeted agents have been disappointing

so far, it is likely that with our better understanding of tumor biology, more efficacious combinations of targeted therapy will emerge in the future (10-12).

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(Dr Mohandas K Mallath, Senior Consultant, Department of Digestive Diseases, Tata Medical Center, Kolkata)

PERSPECTIVE

TUMOR BUDDING IN COLORECTAL CARCINOMA: A NEW PROGNOSTIC FACTOR

Introduction

“Tumor Budding” is defined as an isolated single cancer cell or a cluster of detached cells composed of up to five undifferentiated cancer cells in the stroma ahead of the invasive front of colorectal carcinoma (CRC). Dedifferentiation and dissociation of cancer cells has been reported to be the first event of invasion and metastasis in experimental studies. Tumor budding is the morphologic expression of this event.

The correlation of tumor budding with clinical outcome in colorectal cancer was first reported by Jass and colleagues. Prognostic value of tumor budding has since been recognized by many investigators. Besides, being a prognostic indicator, its potential for therapeutic decision making in T2 and T3 (stage II) CRC is being investigated.

A campaign for objective assessment of this potentially useful marker has been initiated. Investigators are also actively involved in defining the biological and molecular attributes of tumor buds.

CRC is the third most commonly diagnosed type of cancer in men and women worldwide. It arises from two

main pathways of chromosomal instability and abnormal mismatch repair induced by methylation phenotype. Despite this apparently limited origin, the tumors are biologically heterogeneous with different outcomes even in early stages (stages I and II) CRC. There is, therefore, a compelling need for biomarkers helpful of selecting patients with aggressive disease that might benefit from adjuvant and targeted therapy.

Morphology & Biology of Tumor Budding

As the name implies the “Tumor Budding” refers to tiny sprouts or detached tumor cells lying singly or in small aggregates, usually no bigger than 5 cells (the Japanese workers often use the limit of four tumor cells) ahead of the advancing edge of the tumor. These are observed mostly in well and moderately differentiated CRC and not in poorly differentiated CRC where larger aggregates are observed and represent the tumor cell aggregates bereft of any architectural organization. Being in the vanguard, these tumor cells are expected to assist the tumor in invasion through the stroma and cause lymphatic and vascular invasion. It has been stated by many workers that tumor budding is linked to epithelial mesenchymal transformation and characterized by formation of pseudopods, loss of membranous E Cadherin, strong nuclear and cytoplasmic expression of B catenin and overexpression of Cmet. The pseudopod formation results in many pseudopod being sectioned away from the main cell mass and these appear as anucleate pink

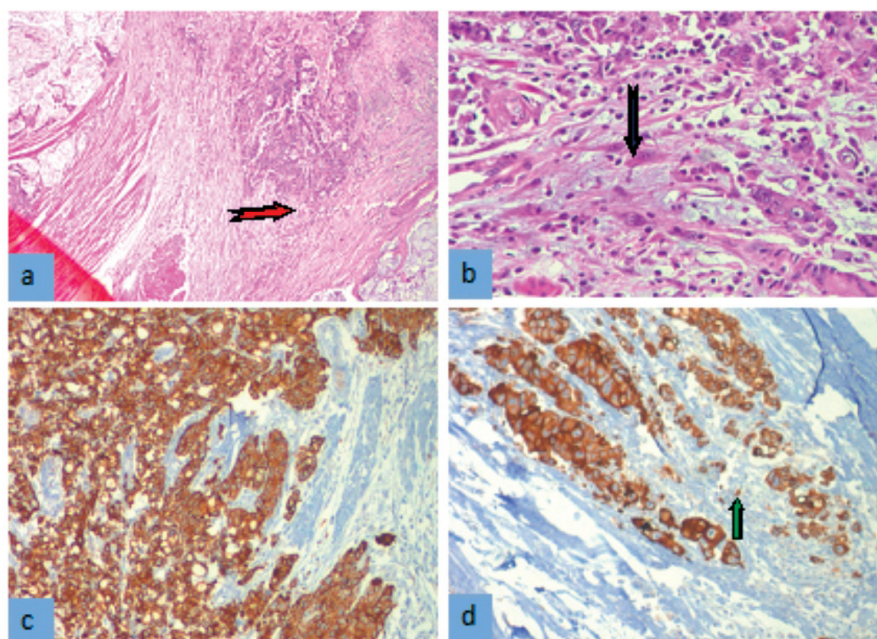


Fig1. a) Tumor budding at the advancing edge- Red arrows. b) The blue arrow highlights the spindle cell transformation (EMT). c) CK immunohistochemistry highlight minimal / no budding at the advancing edge .d) high grade Tumor budding and pseudoglobule (green arrow) highlighted by cytokeratin staining.

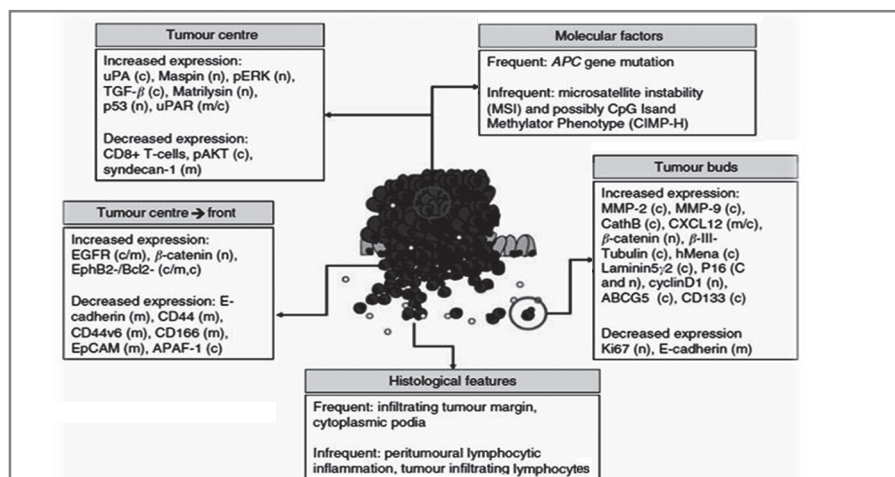


Fig2. The molecular and histological changes in tumor buds.

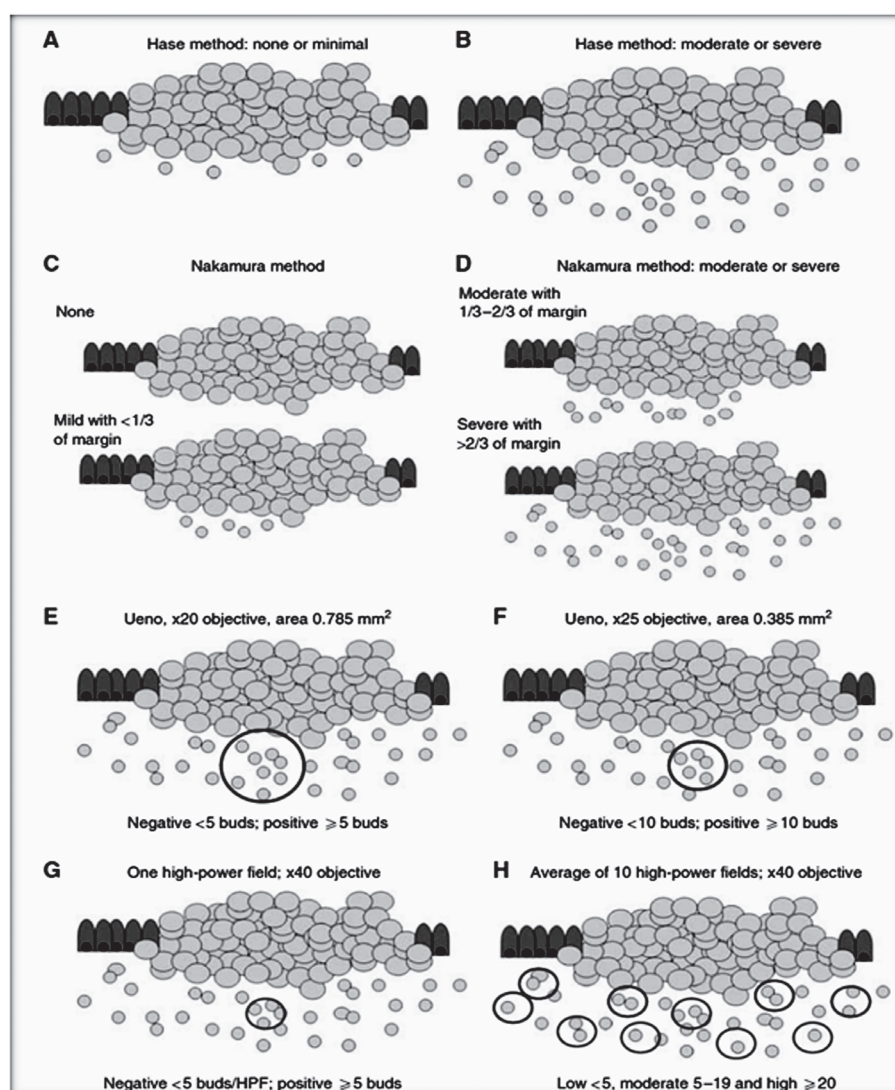


Fig 3. Various Methods of Enumerating Tumor Buds

globules in the bud on H&E preparation. These are better highlighted by cyokeratin staining (Fig 1d). High expression of metalloproteinases and uroplasinogen activator has also been reported. This, coupled with loss of E cadherin expression, promotes tumor cell migration.

A variety of other molecular changes has also been identified and are shown in Fig 2.

The next question that begs an answer is how many of these tumor buds are significant and how shall these be enumerated? Many workers have tried to address this

issue and three of the proposed methods for enumeration are shown in Fig 3. To be relevant in clinical practice for prognostication and therapeutic decision making, it is necessary that reproducible method with threshold cut off be clearly defined. The densest area (hot spot) for budding is chosen and examined for tumor budding and reported by the selected method. Ueno method is considered most appropriate because of being objective, has well standardized size of the field and provides cut off to describe negative, mild, moderate and high budding.

Prognostic Implications of “Tumor Budding”

Overall, there are published data on more than 500 patients with early invasive colorectal carcinoma for whom tumor budding was related to nodal status as assessed by histopathological examination of surgical resection specimens, either from lymphadenectomies concurrent with tumor resection or from completion resections. In all these studies, the groups of patients with high-degree tumor budding were observed to have rates of lymph node involvement around 30%, whereas the rate was much lower in groups with little tumor budding. Importantly, in these studies, depth of invasion, tumor grade and lymphatic permeation were also assessed, and by multivariate analysis tumor budding was observed to be an independent factor. Likewise, tumor budding has also been associated with blood vessel invasion.

Multiple studies have shown that patients with high tumor budding (BUD high) have two to three-fold relative risk of succumbing to their disease or developing metachronous metastases. Furthermore, multivariate regressions were performed in some of these studies and tumor budding was found to add prognostic information to the TNM criteria.

Today, it is widely accepted that tumor budding is an important predictor for recurrence and poor prognosis in advanced colorectal cancers

Conclusion

In summary, tumor budding seems to be a competent prognostic factor in CRC. Its definite implementation will depend on a selected, internationally accepted scoring system. Personal preference is for Ueno method which takes average of 10 HPF and has a scoring in numerical values. Furthermore, tumor buds can be helpful in separating the early stage CRC requiring adjuvant therapy and can also be the target for new therapeutic approaches.

(Dr Anurag Mehta, Director Laboratory and Blood Bank Services, RGCI & RC)

WATCH-OUT

European Patent for Colorectal Cancer Drug

This is an innovative Russian drug candidate to treat various gastrointestinal tract cancers, particularly colorectal neoplasm, one of the most widespread cancers known today. MetaMax, a Russian biotech start-up specializing in cancer medicine development, has obtained Eurasian patent #017179 for its “pharmaceutical composition to treat hyper-proliferative diseases and its application”. The patent confirms MetaMax’s exclusive rights for its MM-D37K drug candidate in all the Eurasian Patent Convention member-states (including the former Soviet Union states of Azerbaijan, Armenia, Belarus, Kazakhstan, Kyrgyzstan, Russia, Tajikistan and Turkmenistan) and in the Republic of Moldova. MM-D37K is a special case of a technological platform based on chimeric peptide sequences. As part of this platform development “MetaMax” is conducting further R & D to find new peptide sequences using the methods of molecular modeling and preclinical PoC. This new intellectual property is also planned to be actively protected in order to expand the product portfolio for the treatment of pancreatic cancer, bladder cancer, kidney cancer and glioblastoma.

(<http://marchmonthnews.com>, Dec 12, 2012)

Novel Anti-Cancer Isoquinolinamine Compounds

Rexahn Pharmaceuticals, Inc. a clinical stage pharmaceutical have been granted European patent No. 2099765 to Rexahn, entitled “5, 6, or 7-Substituted-3-arylisoquinolinamine derivatives as antitumor agents.” This patent covers several new isoquinolinamine compounds and their pharmaceutical composition and method for producing an anti-tumor effect. Studies show that isoquinolinamine compounds have potent anti-tumor properties in several cancer cell lines, such as breast, prostate, colon, ovary, kidney, pancreas, glioblastoma and melanoma. This class of isoquinolinamine compounds significantly inhibited the growth of paclitaxel (Taxol) resistant HCT-15 human colorectal cancer cells and tumor growth in an in vivo model of nude mice injected with paclitaxel-resistant HCT-15 human colorectal cancer cells. Rexahn has been awarded patents for isoquinolinamine compounds in the United States, Mexico, China and now Europe.

(www.pharmabiz.com, Jan 04, 2013)

RESEARCH & DEVELOPMENT

Anti-EGFR Therapy in Metastatic Colorectal Cancer

Only patients with wild-type (WT) KRAS tumors benefit from anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (Mabs) in metastatic colorectal cancer (mCRC). However, the impact of low-frequency KRAS mutations (<10%) on the response to anti-EGFR Mabs has yet to be evaluated. In a recent retrospective study, patients were categorized as WT or low-frequency mutation when KRAS mutation was <10% (KRAS low MT). A total of 168 patients treated by anti-EGFR Mabs for mCRC were analyzed. According to pyrosequencing, 138 tumors remained KRAS WT, while 30 tumors were KRAS low MT. In the KRAS low MT and KRAS WT groups, the response rates were 6.7% and 37.0%, respectively, while stabilization amounted to 23.3% versus 32.6% and progression to 70% versus 29% ($P < 0.01$). Progression-free survival was 2.7 ± 0.5 months for KRAS low MT and was 6.0 ± 0.3 months for KRAS WT ($P < 0.01$). These results appear to validate consideration of low-frequency KRAS mutation tumors as positive, and justify a large-scale prospective study.

(Ann Oncol, Jan 4, 2013)

Clinical Outcome in Primary Colorectal Cancer

A new study from England has compared four different tracer kinetic models for the analysis of dynamic contrast material-enhanced computed tomographic (CT) data for predicting 5-year overall survival in primary colorectal cancer. Archival dynamic contrast-enhanced CT data from 46 colorectal cancer patients were analyzed. Following receiver operating characteristic analysis, parameters of the different kinetic models and tumor stage were compared. Blood flow was lower with the distributed parameter model than with the conventional compartmental and adiabatic tissue homogeneity models ($P < .0001$). Mean transit time was longer with the distributed parameter model than with the conventional compartmental and adiabatic tissue homogeneity models ($P < .0001$). Blood volume, permeability-surface area product, and $v(e)$ were higher with the conventional compartmental model than with the adiabatic tissue homogeneity, distributed parameter, or generalized kinetic models ($P < .0001$). Parameter values differed significantly between models. Of the models investigated, the

distributed parameter model was the best predictor of 5-year overall survival.

(Radiology, Jan 7, 2013)

Robotic Anterior Resection of Rectal Cancer

With advanced stereoscopic vision, lack of tremor, and the ability to rotate the instruments surgeons find that robotic systems are ideal laparoscopic tools. Study from China evaluated the role of robotic anterior resection in rectal cancer. Between Nov 2010 and Dec 2011, a total of 22 patients were operated with Da Vinci with robotic system. Data regarding the outcome and pathology reports were prospectively collected in a dedicated database. Mean operative time was (220 ± 46) minutes (range, 152-286 minutes); the median number of lymph nodes harvested was (14.6 ± 6.5) (range, 8-32), and the circumferential margin was negative in all cases. The distal margin was (2.6 ± 1.2) cm (range, 1.0-5.5 cm). The mean length of hospital stay was (7.8 ± 2.6) days (range, 7.0-13.0 days). Macroscopic grading of the specimen was complete in 19 cases and nearly complete in three patients. Thus, robotic anterior resection for rectal surgery is safe and feasible in experienced hands. This technique may facilitate minimally invasive radical rectal surgery.

(Chin Med J (Engl), Jan 2013)

Sleep Duration and Incidence of Colorectal Cancer

Researchers from USA have prospectively examined the association between sleep duration and risk of colorectal cancer (CRC). In the Women's Health Initiative Observational Study, 75828 postmenopausal women reported habitual sleep duration at baseline 1993-1998. Cox proportional hazards regression model was used to estimate the hazard ratio (HR) of CRC and its associated 95% confidence interval (CI). About 851 incident cases of CRC through 2010 were ascertained, with an average 11.3 years of follow-up. Compared with 7 h of sleep, the HRs were 1.36 (95% CI 1.06-1.74) and 1.47 (95% CI 1.10-1.96) for short (~5 h) and long (~9 h) sleep duration, respectively, after adjusting for age, ethnicity, fatigue, hormone replacement therapy (HRT), physical activity, and waist to hip ratio. The association was modified by the use of HRT (P -interaction=0.03). Both extreme short and long sleep durations were associated with a moderate increase in the risk of CRC in postmenopausal women. Sleep duration may be a novel, independent, and potentially modifiable risk factor for CRC.

(Br J Cancer, Jan 3, 2013)

NEW TECHNOLOGIES

Breath Test to Screen Colorectal Cancer

Researchers at the University Aldo Moro of Bari, Italy, have developed a relatively simple breath analysis test that could be used for colorectal cancer screening. The study has demonstrated a different metabolite profile of colon cancer patients compared to healthy subjects. The study comprised of 37 breath samples collected from colon cancer patients prior to surgery and 41 healthy controls that were found to be disease-free after undergoing a colon cancer screening. All the samples were analyzed using gas chromatography linked to mass spectrometry. The initial analysis identified that out of total 58 volatile organic compounds (VOCs), 15 could differentiate between cancer-positive and cancer-negative individuals. The statistical analysis showed that the VOC profile had an 85% predictive accuracy, an 86% sensitivity, and a specificity of 83%. The scientists conclude that technique of breath sampling is very easy and non-invasive, though the method is in early phase of development, and its findings support the value of breath testing as a screening tool.

(Science Daily, Dec 5, 2012)

Molecular Signature for Colorectal Cancer

A team of scientists at Everist Genomics, Ann Arbor, Michigan, have generated the first 5-gene prognostic signature (OncoDefender-CRC) capable of accurately predicting the risk of recurrence of cancer in patients with lymph node-negative invasive colorectal carcinoma. The formalin-fixed paraffin embedded tissues obtained at surgery were retrieved from 74 patients with colorectal cancer (CRC) for training sets and 215 patients with stage II colon cancer for an external validation (EV) set. Using reverse transcriptase-polymerase chain reaction, the molecular signature correctly classified 62 of 92 recurrent patients and 87 of 172 nonrecurrent patients in EV set. The high-risk patients had a greater probability of 36-month recurrence (42%) than low-risk patients (26%) independent of T-classification, the number of lymph nodes examined, histologic grade, anatomic location, age and sex etc. The 5-gene molecular assay surpassed current National Comprehensive Cancer Network Guidelines (hazard ratio 0.897). The test ruled out the need to retrieve ≥ 12 lymph nodes for accurate prognostication. It identifies patients who are more likely

to develop recurrent disease after the curative surgery and hence are most likely to benefit from adjuvant treatment.

(Cancer, Nov 1, 2012)

New Drug for Advanced Colorectal Cancer

The US Food and Drug Administration has approved a new drug, Stivarga (regorafenib), to treat patients with colorectal cancer that has progressed after prior treatment and metastasized to other parts of the body. Stivarga, pill is a multi-kinase inhibitor that blocks several enzymes which promote cancer growth. The safety and effectiveness of the drug were evaluated in a single clinical study comprising of 760 patients. The study results show that the severely ill patients treated with Stivarga and best supportive care (BSC) live on an average 1.5 months longer than those treated with placebo plus BSC. The patients also experienced a longer progression-free survival for a median of two months compared to a median of 1.7 months in patients receiving placebo plus BSC. The most common side effects of the drug reported in patients included weakness, loss of appetite, hand-foot syndrome, diarrhea, mucositis, weight loss, high blood pressure, and altered voice volume or quality etc.

(U.S. Food and Drug Administration, Sep 27, 2012)

Novel Prognostic Biomarker for Colorectal Cancer

Researchers at Tokyo Medical and Dental University have identified a novel prognostic marker for the distant metastasis of colorectal cancer (CRC) using integrated expression and copy number analysis. The expression of mRNA in CRC tissue was profiled in 115 patients with an Affymetrix Gene Chip and the copy number profiles were generated for 122 patients using an Affymetrix 250K Sty Array. The genes which showed upregulated expression as well as copy number gains in patients with CRC metastasis were extracted as candidate biomarkers. The expression of candidate gene mRNA was validated using quantitative reverse transcription polymerase chain reaction assays. The expression of protein encoded by the candidate gene was further assessed using immunohistochemical staining of tissue from 269 patients. Following the analyses, it was observed that gene NUCKS1 was significantly higher in CRC tissue as compared to normal tissue. The over-expression of NUCKS1 protein was found to be associated with significantly worse overall survival and relapse-free survival. The findings indicate that NUCKS1 is an independent risk factor for CRC recurrence and may be used as a prognostic marker.

(Int J Cancer, Oct 15, 2012)

CLINICAL TRIALS

Aflibercept to FOLFIRI in Metastatic Colorectal Cancer

A phase III randomized trial was conducted at the University Hospital Gasthuisberg, Belgium, to study the effect of adding the novel antiangiogenic agent aflibercept to FOLFIRI in patients with metastatic colorectal cancer (mCRC) previously treated with oxaliplatin and bevacizumab. Patients were randomly distributed into two groups. One group received aflibercept (n=612) 4 mg/kg intravenously and other (n=614) received placebo every 2 weeks in combination with FOLFIRI. Treatment was continued until disease progression or unacceptable toxicity. The primary end point was overall survival. Results showed that aflibercept and FOLFIRI significantly improved overall survival relative to placebo plus FOLFIRI with median survival times of 13.50 versus 12.06 months, respectively. Aflibercept also significantly improved progression-free survival (PFS), with median PFS times of 6.90 versus 4.67 months, respectively. Overall study showed that aflibercept in combination with FOLFIRI conferred a statistically significant survival benefit over FOLFIRI combined with placebo in patients with mCRC.

(J Clin Oncol, Oct 2012)

FOLFIRI & Bevacizumab for Colorectal Cancer

As first-line chemotherapy, FOLFIRI has shown its efficacy in combination with bevacizumab. To evaluate the efficacy and safety of FOLFIRI and bevacizumab as second-line chemotherapy in patients with metastatic colorectal cancer, a phase II trial was conducted in National Cancer Center Hospital, Japan. Total 25 patients were enrolled with median age of 62 and previously treated (except with irinotecan and bevacizumab). Patients received FOLFIRI with bevacizumab at a dose of 10 mg/kg intravenously on day 1 administered every 2 weeks until disease progression. The primary endpoint was the response rate. Overall response rate was 32% with 8 patients showing partial responses, 15 with stable disease, and 2 with disease progression. Median progression-free survival was 11.6 months. Median overall survival was 21.4 months. The grade 3/4 adverse events with treatment were neutropenia, leukopenia and diarrhea.

The results were considered promising as the combination is an active and well-tolerated treatment as second-line chemotherapy treatment.

(Int J Clin Oncol, Dec 2012)

TAS-102 for Pretreated Colorectal Cancer

Researchers at National Cancer Center Hospital, Japan, have performed a double-blind, randomised, placebo-controlled phase 2 trial to investigate the efficacy and safety of TAS-102, a novel oral nucleoside antitumor agent in pretreated metastatic colorectal cancer. Total 169 patients were recruited in the study, more than 20 years of age, had confirmed colorectal adenocarcinoma, and intolerant to fluoropyrimidine, irinotecan, and oxaliplatin based chemotherapy. Of the 169 patients, 112 were assigned to TAS-102 and 57 to placebo who made up the intention-to-treat population. Randomisation was done with minimisation methods, with performance status as the allocation factor. The primary endpoint was overall survival. Results showed that median overall survival was 9.0 months in the TAS-102 group and 6.6 months in the placebo group. Adverse effects in 50% patients given TAS-102 was grade 3 or 4 neutropenia, 28% had leucopenia and 19% anaemia. Through this study, it was found that TAS-102 has promising efficacy and a manageable safety profile in patients with metastatic colorectal cancer who are refractory or intolerant to standard chemotherapies.

(Lancet Oncol, Oct 2012)

Vaccine for Colorectal Cancer

A phase I/II clinical trial was done at Leden University Medical Centre, Netherland to find the safety and efficacy of combination of Interferon-alpha (IFN- α) with p53 synthetic long peptides (p53-SLP) vaccine. Study recruited total eleven patients of colorectal cancer, already treated for the metastatic disease. Safety and p53 specific immune responses were determined before and after vaccination. Toxicity of this combination vaccine was limited to grade I or 2 with predominantly small swellings at the vaccination site. After vaccination, it was found that all the patients harbored p53 specific T cells that could be detected in blood samples of the patients and these cells induced significantly more IFN- α . Results of the current study revealed that p53-SLP vaccination combined with IFN- α is safe and displays a broader p53 specific immunoglobulin G response.

(Int J Cancer, Sep 5, 2012)

GLOBE SCAN

Colorectal Cancer Gene Database

The CRC gene database, which gathers all genetic association studies on colorectal cancer, allows for researchers to accurately interpret the risk factors of the disease and provides insight into the direction of further colorectal cancer research. While diet and lifestyle may affect colorectal cancer incidence, so may genetic factors, however, it is important to determine which genetic factors are most heavily associated with colorectal cancer incidence. In order to determine the genetic factors associated with colorectal cancer, the researchers, gathered data from previously published guidelines for assessing cumulative evidence on genetic association studies, and performed meta-analyses on all the data, compiling all genetic association studies published in the field. The researchers found that 16 independent gene variants had the most highly credible links to colorectal cancer, with 23 variants. The analysis thus provides a resource for mining available data and puts into context the sample sizes required for the identification of true associations.

(Canada: Journal of the National Can Inst, Sep 27, 2012)

Obesity and Colorectal Cancer

Current research indicates that there is a moderate but consistently reported association between general obesity (as determined by BMI) and colorectal cancer incidence and mortality. The relative risk associated with obesity is higher for cancer of the colon than for cancer of the rectum and it is higher in men than in women. By contrast, abdominal adiposity (as determined by waist circumference or waist-to-hip ratio) is similarly strongly associated with colon cancer in men and women, suggesting that abdominal adiposity is a more important risk factor for colon cancer than general adiposity, at least in women. Putative mechanisms that may account for the link between adiposity and colorectal cancer risk include hyperinsulinemia, insulin resistance, inflammation, altered immune response, oxidative stress, as well as disturbances in insulin-like growth factors, adipokines, and sex steroids. Understanding the link between obesity and colorectal cancer may pave the way for targeted prevention of colorectal cancer morbidity and mortality.

(Germany: Front Biosci, Jan 13, 2013)

Diet and Colorectal Cancer

Multiple factors have been described among the causes of non-hereditary colorectal cancer. In Western countries, the most common risk factors include upper-middle socioeconomic status and dietary regimens rich in proteins and animal fats. High consumption of red meats, smoked foods, cold cuts, or canned foods is believed to contribute to carcinogenesis as they directly affect epithelial turnover and cause metabolism of biliary acids. Dietary fibers have protective effects in that they capture the fats and biliary acids, thereby inhibiting their activity. Tobacco smoking acts both locally and systemically on the colorectal mucosa through the production of carcinogenic agents. Finally, the action of alcohol, in association with nicotine addiction, also increases the risk of developing colorectal tumors. Knowledge of dietary and environmental factors is of paramount importance in implementing preventive strategies for colorectal cancer.

(Italy: Front Biosci, Jan 2013)

Decrease in Colorectal Cancer

Use of colonoscopy for colorectal cancer screening could explain a significant decrease in the cancer's incidence over the past decade, according to a new study. A team from Stanford University School of Medicine scrutinized data collected from more than 2 million patients over the past 20 years, and found a drop in colorectal cancer incidence correlated with Medicare's extension of colonoscopy coverage in 2001. Colorectal cancer is the second-leading cause of cancer-related deaths in the United States, according to the Federal Centers for Disease Control and Prevention. The American Cancer Society and other groups recommend colorectal cancer screening for people at average risk beginning at age 50. The authors looked for trends in colorectal cancer surgery, which reflect cancer incidence. They also specifically looked for differences in rates of cancer in the lower versus the upper colon, as colonoscopy is hoped to have a benefit in preventing cancers in both areas due to its extended reach. The results of the study suggest that increased use of colonoscopy may explain the decrease in incidence of upper colon cancer - through the identification, and removal, of precancerous polyps - in the last decade. Hence, the availability of a screening technique that effectively detects and removes precancerous lesions makes colorectal cancer a uniquely preventable cancer.

(USA: Gastroenterology, Oct 23, 2012)

IN FOCUS

CURRENT STATUS OF ROBOTIC COLORECTAL SURGERY

Introduction

Worldwide, more than 1 million individuals will develop colorectal cancer (CRC) annually, with a disease-specific mortality rate of nearly 33%. In the developed world, CRC is the third most common cancer in men and the second in women. Although the highest incidence rates are found in Western countries, CRC has been gradually increasing in other parts of the world over the past 20-30 years.

On the other hand, substantial progress has been made in CRC management in recent decades with minimal invasive surgery rapidly gaining acceptance among colorectal surgeons worldwide. Several prospective randomized trials have demonstrated that there are no differences in oncologic outcomes between laparoscopic and open surgery approaches for treating CRC. However, laparoscopic resection of rectal cancer is technically demanding and has a steep learning curve. There are several technical drawbacks to conventional laparoscopic surgery, including limited motion of instruments in a narrow pelvic cavity, relative loss of dexterity, inadequate visual field associated with unstable camera view, and assistant's traction which is not under the surgeon's control. Therefore, the emergence of the robotic surgical system which has several advantages, such as superior three-dimensional vision, seven degrees of freedom of movement truly mimicking the movements made by surgeon's hands, lack of tremor, and far superior ergonomics compared to conventional laparoscopy, was extremely fortunate.

Since the first robotic-assisted radical prostatectomy was successfully performed by Binder and Kramer in Germany in 2001, robotic surgery has dramatically changed the surgical management of clinically localized prostate cancer. In the short period, robotic-assisted radical prostatectomy has become standard of care. Robotic surgery was naturally introduced to the field of general surgery, particularly rectal cancer resection, because its technological advantages can be maximized when the operation is performed in the narrow pelvis.

Application in Clinical Practice

The first robotic-assisted colectomies were reported in 2002 by Weber et al, who performed successful

robotic-assisted laparoscopic sigmoidectomies and right hemicolectomies for diverticulitis. Since then, a wide range of colorectal operations have been performed, including right and left hemicolectomies, sigmoid resections, rectopexies with/without resection, anterior resections, abdominoperineal resections, and total colectomies. At present, application of the robotic surgical system for total mesorectal excision (TME) seems to have the greatest potential benefit, as it is expected to prove its ability when the operation is performed within a confined pelvis.

The majority of recent studies have been focusing on robotic TME for rectal cancer. Other procedures like right hemicolectomy or sigmoid resection are relatively straightforward procedures for the colorectal surgeon, and can be effectively and safely performed using conventional laparoscopy. Furthermore, after considering the higher medical cost and longer operating time, it is less attractive to implement robotic colorectal surgery except for TME in rectal cancer. Some authors suggest alternative roles for the robot in the field of colon surgery, such as intracorporeal anastomosis, easier taking down of the splenic flexure, natural orifice specimen extraction, or as a training tool.

Safety and Feasibility

In general, longer operating time is widely considered to be one of the disadvantages of robotic surgery, along with higher cost and lack of tactile sense, compared with conventional laparoscopic procedure. The robotic surgical system is still complex and bulky, and therefore a large operating room is needed and it takes significantly longer to prepare the device. The most frequent causes of conversions include difficulty in pelvic dissection, which can cause bleeding from the lateral pelvic wall, rectal perforation, and unintended injury to an adjacent organ. The most important technological advantage of the robotic surgical system is its ability to perform a fine dissection in a narrow pelvic cavity due to a stable, three-dimensional image and a freely articulating EndoWrist (Intuitive Surgical, Sunnyvale, USA). Similar outcomes of postoperative recovery between robotic and laparoscopic colorectal surgery were reported in most of the available publications comparing postoperative course in their case matched analysis, and showed no differences in first flatus passage, time to resume diet and postoperative hospital stay. Robotic colorectal surgery seems to be equivalent to laparoscopic surgery in terms of overall operative complications. To the best of our

knowledge, there is no report of postoperative mortality from robot-related complications. As most studies are based on data from highly experienced laparoscopic colorectal surgeons, there is a definitive difference in the surgeon's expertise between the two operative techniques. We hypothesize that this difference may attenuate the benefits of robotic surgery, resulting in similar clinical outcomes rather than superior results due to its technological advantages. In view of the results achieved so far, robotic colorectal surgery can be performed safely and feasibly by the skillful laparoscopic surgeon.

Oncologic Outcomes

There is increasing evidence that the number of harvested lymph nodes has an important impact on survival. A pooled analysis including more than 60,000 patients demonstrated that the number of harvested lymph nodes is associated with survival in colon cancer. Therefore, it is one of the most important outcomes to be evaluated in any surgical treatment proposed for colorectal cancer. Also, other parameters, such as distal resection margin length or circumferential resection margin (CRM) involvement rate, which can be an index of surgical quality, were no different between the two groups in rectal cancer surgery. The widespread acceptance of TME surgery as the gold standard operative procedure for patients with rectal cancer promises to be one of the most important factors in reducing local recurrence. Nevertheless, the CRM may still be positive if the tumor extends up to or through the mesorectal fascia. Also, as more sphincter-saving surgeries are performed even in very low rectal cancer, the risk of CRM involvement may be increasing, regardless of perfect TME performance. We believe that macroscopic evaluation of TME completeness should be an additional parameter in cases with CRM involvement in order to ensure the oncologic safety of the procedure.

Evidence of the oncologic outcomes of robotic rectal cancer surgery is also limited. In multicenter study of robotic TME by Pigazzi et al., the 3-year overall survival rate was 97% in 143 consecutive patients with rectal cancer undergoing robotic surgery and no isolated local recurrences were found during the mean follow-up period of 17.4 months. In that study, the absence of a control group, relatively short follow-up period, and extensive use of neoadjuvant chemo radiation could have been barriers to reaching definitive conclusions. Nevertheless, their excellent results suggest that robotic surgical system is likely to improve local disease control.

Prospective controlled trials should be conducted to verify whether robotic surgery for rectal cancer could improve local disease control and disease-free survival, as well as reduce postoperative morbidity. Only prospective clinical trials with long-term follow-up can clearly determine whether the technological advantages of the robotic surgical system can translate into favorable surgical or oncologic outcomes. Currently, an international, multicenter, randomized controlled trial of robotic-assisted versus laparoscopic resection for rectal cancer (ROLARR) is proposed.

Bladder and Sexual Function

Bladder and sexual dysfunction are well-known complications and are closely related to avulsion or direct injury to pelvic autonomic nerves following rectal resection. As normal bladder and sexual function is controlled by sympathetic input from the superior hypogastric plexus and parasympathetic input from the pelvic splanchnic nerves, inadvertent damage to these nerves will result in postoperative bladder and sexual dysfunction, the severity of which will depend on the extent of the injury and the relative components of the autonomic supply affected. Hypogastric nerve injury results in the failure of complete bladder filling and loss of ejaculation in men, whereas injury to the sacral parasympathetic nerves results in poor depressor contraction and erectile dysfunction. Before the introduction of TME, the incidence of postoperative bladder and sexual dysfunction was high, with reported rates of 10–30% and 40–60%. Even with incorporation of autonomic nerve-preserving techniques in TME, bladder and sexual dysfunction is reported to be in the range of 0–12% and 10–35% of patients, respectively.

There are two contrary hypotheses about the impact of laparoscopic TME with pelvic autonomic nerve preservation on postoperative bladder and sexual function: one is that the magnified view of the pelvis afforded by the laparoscope may facilitate identification of the autonomic nerves and thus prevent inadvertent injury, while the other is that several technical pitfalls of laparoscopic surgery may predispose to nerve injury. However, Jayne et al, showed that laparoscopic rectal resection did not adversely affect bladder function, but there was a trend towards worse male sexual function from the CLASICC trial's patients. They also found that conversion to open surgery was independent predictor of postoperative male sexual dysfunction. Whether accurate pelvic dissection by robot with three-dimensional

vision can improve bladder and sexual function compared with laparoscopic surgery is not clear. Several studies have reported low conversion rates of robotic resection for rectal cancer and we can expect this to translate into better preservation of bladder and sexual function. However, to the best of our knowledge, there is no high level of evidence evaluating bladder and sexual function after robotic TME.

Summary

Current evidence establishes the safety and feasibility of robotic colorectal surgery. Robotic surgery achieves equivalent clinical short-term outcomes except for longer operating times and lower conversion rates compared with laparoscopic surgery. Limited preliminary studies appear to report short- or mid-term oncologic outcomes with comparable or better results as compared to laparoscopic surgery.

(Dr Selvakumar, Clinical Associate; Dr Shivendra Singh, Senior Consultant & Chief, GI Oncosurgery)

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CANCER CONTROL

Aggressive Form of Colorectal Cancer and Family History

Researchers have reported that when people with a family history of colorectal cancer (CRC) develop the disease, their tumors often carry a molecular sign that the cancer could be life-threatening and may require aggressive treatment. In the current study it was found that many CRC patients with a family history of the disease, the long interspersed nucleotide element 1 (LINE-1) in their tumor cells was hypomethylated compared to individuals without a family history which is usually hypermethylated. Because this type of colorectal cancer can become dangerous, testing colorectal cancer patients for tumor LINE-1 hypomethylation may offer a valuable way of identifying those in greatest need of aggressive treatment. Such testing could also help identify patients whose relatives may be at increased risk for the aggressive form of the disease. Further study is needed to determine how this type of testing can be used in a clinical setting.

(J Natl Cancer Inst, Nov 21, 2012)

Chronic Constipation and Colorectal Cancer

Patients with chronic constipation may be at increased risk of developing colorectal cancer and benign neoplasms, according to a study presented at the American College of Gastroenterology's 77th Annual Scientific Meeting. The study, investigated the prevalence and incidence of colorectal cancer (CRC) and benign neoplasms in 28,854 patients with chronic constipation (CC) and 86,562 controls without CC that were identified from a large retrospective database (Jan '99-Sep '11). Researchers found that both CRC and benign neoplasms are more prevalent in chronic constipation patients compared to a control population free from chronic constipation. The risk of developing CRC was 1.78 times higher for chronic constipation (CC) patients and the risk of developing benign neoplasms was 2.70 times higher. This study demonstrates an association, not causation, between chronic constipation and both colorectal cancer and benign neoplasms. Prospective studies would advance the understanding of prevention and management of these disorders.

(Science Daily, Oct 22, 2012)



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