Staging and Molecular Alterations in Colorectal Carcinoma

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Pathologic staging based on tumor (T), regional lymph node status (N) and distant metastasis (M) classification is the best indicator of long term prognosis in patients with colorectal cancer (CRC). There are three well-recognized classification systems including Duke`s, Modified Astler-Coller and TNM (AJCC/UICC) as shown in Table-1.

Table-1

Stage	T	N	M	Dukes	MAC
0	Tis	N0	M0	-	-
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4	N0	M0	B	B3
IIIA	T1-T3	N1	M0	C	C1
IIIB	T3-T4	N1	M0	C	C2/C3
IIIC	Any T	N2	M0	C	C1/C2/C3
IV	Any T	Any N	M1	-	D

Tumor (T) stage:

The tumor stage is evaluated based on the depth of invasion in the colonic wall along with status of visceral peritoneum, adjacent organs and tumor deposits in pericolorectal soft tissue.

The incidence of lymph node metastasis with only mucosal invasion is very low to none supporting the classification of these tumors in Tis category.

The submucosal invasion is identified as stage T1. Incidence of regional lymph node metastasis is 10-15%. Lymphovascular invasion, presence of deep submucosal invasion (sm3), poorly differentiated histology, and tumor in lower third of rectum are associated with high likelihood of lymph node metastasis [1]. Adenocarcinoma arising from a polyp with invasion into the submucosa of the stalk of the polyp poses a significant challenge in further management. It is recommended to include in pathology report the differentiation of the tumor, status of lymphovascular invasion and distance of invasive component from the cauterized margin. Tumors with lymphovascular invasion, poorly differentiated histology and tumors with invasive component present less than 1mm from the cauterized margin need additional therapy, which is resection in most of the cases. Adenocarcinoma with submucosal invasion in a serrated polyp is likely to have higher incidence of lymph node metastasis as compared to adenocarcinoma arising in a pedunculated polyp, requiring more aggressive approach for the former. Interpretation of these features requires appropriate processing of the polypectomy specimens. The polypectomy specimens should be processed as shown in Figure-1.

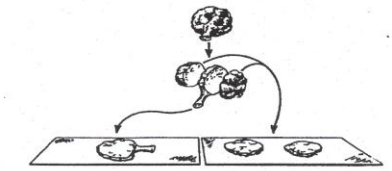

Figure 1. Diagrammatic illustration of method of processing polyps with stalks. After fixation, the polyp is trimmed on either side of the stalk and submitted in two blocks. Base of stalk is inked.

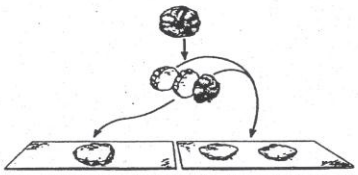

Figure 2. Polyps without stalks are trimmed after fixation on either side of the diathermy burn and submitted in two blocks. Base, if identified, is inked.

In fragmented specimens (piecemeal polypectomy) communication with gastroenterologist and surgeon is required for the appropriate orientation of the specimen and margin evaluation.

T3 tumors are the major bulk of the colon cancer resections. The T3 tumors include continuous extension of tumor beyond muscularis propria into the subserosal or non peritonealized fat. Depending upon the location of the tumor in different segments of colon and rectum the pericolorectal soft tissue may either represent subserosal or non peritonealized fat. The cecum, transverse colon and sigmoid colon are entirely intraperitoneal (serosal covering). The pericolonic soft

around all four surfaces of these colonic segments are subserosal. The ascending and descending colon are partly retroperitoneal. The posterior surface of ascending and descending colon is retroperitoneal and not covered by serosa. The posterior soft is non-peritonealized and represents a soft tissue margin. The other surfaces have serosal covering. The upper third of rectum is retroperitoneal posteriorly, middle third of rectum is retroperitoneal posteriorly and laterally and lower third of rectum is entirely retroperitoneal. It is essential to carefully examine the colorectal resection specimen and identify the radial soft tissue margins and serosal surface in ascending colon, descending colon and different parts rectum. The non continuous deposits in the pericolorectal soft tissue are addressed in subsequent paragraphs.

T4 category includes gross or microscopic extension into the adjacent organs including other segments of colon, perforated tumors and extension of the tumors at the outer serosal surface or radial soft tissue margin. Presence of tumor cells and not the inflammatory or desmoplastic response at these sites are considered as stage T4. Greene et al [2]showed influence of T stage independent of N stage on long term survival in CRC. In a large cohort of patients with N1 disease the patients with T1-T2 stages had better prognosis than T3-T4. In addition, the T4 patients did worse than T3, although the difference did not reach the statistical significance due to smaller sample size. Quah et al [3] showed stage T4 is an independent worse prognostic factor in patients with stage II disease. In addition, T4 tumors with gross or microscopic extension to other bowel segments or other

viscera have worse outcome than tumors with serosal or radial margin involvement [4,5].

Role of adjuvant chemotherapy in Stage II (T3/T4N0) CRC tumors is a major challenge in clinical management of colon cancer patients. The data are conflicting and role of adjuvant chemotherapy is still controversial [6]. The high risk factors for recurrence and poor outcome in these patients include stage T4, perforation, poorly differentiated histology, peritumoral lymphovascular invasion and inadequate number of lymph nodes sampled. Although, direct evidence in support for these high risk factors for initiating adjuvant chemotherapy in stage II CRC is lacking, the indirect evidence of benefits of adjuvant chemotherapy is available from stage III patients.

The rectal carcinoma is treated by the preoperative chemoradiation followed by surgery in majority of centers. More than one study have shown that complete pathologic response, defined by absence of residual tumor cells is a strong predictor of long term survival. It is recommended to submit the majority of grossly identifiable tumor or entire scar area of treated tumor for microscopic examination to appropriately identify the patients with complete pathology response.

The CAP has classified tumor regression (response) in four grades as shown in table-2.

Table-2

Description	Tumor Regression Grade
No viable cancer cells	0 (Complete response)
Single cells or small groups of cancer cells	1 (Moderate Response)
Residual cancer outgrown by fibrosis	2 (Minimal response)
Minimal or no tumor kill; extensive residual cancer	3 (Poor response)

Regional Lymph Node (N) stage:

The pathology N stage includes regional lymph nodes and/or soft tissue deposits in pericolorectal soft tissue, discontinuous from the primary tumor.

Examination of as many lymph nodes as possible is pivotal in the management of CRC patients as higher number of regional lymph nodes examined and more number of negative lymph nodes increase the confidence that the patients does not have a micrometastasis. In a series of 36,000 patients of stage II CRC the National Cancer Database Study (NCDB) [7,8] study showed 5 year survival ranged from 64% with one to two lymph nodes examined to 86% if more than 25 lymph nodes were examined. Although, there is no absolute number of minimum lymph nodes examined, the NCDB recommends that at least 13 regional lymph nodes should be retrieved and declared pathologically negative before the patient is treated as stage II. The AJCC [9] recommendation is to examine at least 12-14 lymph nodes in colorectal resection specimens in patients who did not have preoperative neoadjuvant therapy.

Different N stages are attributed as per the number of lymph nodes involved as number of positive lymph nodes has clear impact on long term outcome in these patients. Metastiasis in 3 nodes or less is N1 and more than 3 nodes is N2. Patients with N2 disease demonstrate significantly poor outcome as compared to the patients with N1 disease regardless of T stage [2].

Soft tissue deposit in pericolorectal soft tissue regardless of their size are a poor prognostic factor for disease free survival [10]. In majority of cases the step sections of the soft tissue deposit demonstrate vascular invasion, peirneural invasion or residual lymph node. AJCC recommends that soft tissue deposit with smooth contour is identified as a positive lymph node and a soft tissue deposit with irregular contour is identified as a large vessel invasion. There is also a suggestion of giving a separate category to the soft tissue deposit in T1 and T2 tumors with negative nodes and to consider the soft tissue deposit with T stage in T3/T4 tumors.

The clinical significance of isolated tumor cells identified by Hematoxylin and Eosin sections, cytokeratin immunohistochemistry or by molecular markers is unclear. These cases are still considered N0 with annotation i+ (N0(i+)). Similarly clinical significance of sentinel lymph node in patient outcome is still under evaluation and is not encouraged in a regular clinical setting [11].

Distant Metastasis:

Approximately 50% of patients with CRC develop distant metastasis. Commonest sites of metastasis are liver and lung. Other sites including but not limited to are other segments of intestine, peritoneum, and omentum. Recently it has been suggested to classify the M1 stage in to two categories with one having single distant metastatic site and other having more than one distant metastatic sites. Due to new chemotherapy regimens with targeted therapy and surgical resections the disease free survival of patients of CRC with distant metastasis has markedly improved in last decade [12]. These newer developments has brought focus on identifying the parameters to better characterize the patients with metastatic CRC in terms of improving the outcome and identifying a more effective therapy. Most recently two studies have shown that pathologic response in the liver metastases is an independent prognostic factor for overall and disease free survival in hepatic colorectal metastasis [13].

Molecular alterations in CRC

Colorectal cancer results from mutational activation of oncogenes and inactivation of tumor suppressor genes. Somatic mutations of more than one gene is required for malignant transformation and accumulation of multiple genetic events rather than sequence of mutational changes lead to colon cancer development. In spite of extensive studies only few molecular alterations have shown to be of clinical significance.

A. Mismatch repair genes and colon cancer:

DNA mismatch repair (MMR) genes correct the replication errors. Due to defective correction of the replication errors in microsatellites (short nucleotide repeats), the length of microsatelltes in tumor cells is different as compared to normal DNA, which is defined as microsatellite instability (MSI). MSI-high tumor is defined when more than third of six NCI recommended markers show allelic shift. MSI-low tumor is defined when less than one-third NCI recommended markers show allelic shift. MSI-stable tumor is defined when none of the markers show allelic shift. The DNA mismatch repair genes most commonly involved in MSI are hMSH2/hMSH6 and hMLH1/hPMS2.

MSI-high colon carcinoma comprises of 15-20% of all colon cancer. They are divided in to the two groups based on hereditary predisposition.

First group includes colon cancer arising in patients with Lynch (HNPCC) syndrome. These patients and affected family members have germ line mutation in the MMR genes. The most commonly affected genes are hMSH2 and hMLH1. These patients are also likely to develop endometrial adenocarcinoma, ovarian carcinoma, sebaceous tumors of skin, keratoacanthoma, urothelial carcinoma, pancreaticobiliary adenocarcinoma, gastric adenocarcinoma and glioblastoma. Recently, revised Bethesda guidelines have been published for MSI testing to detect patients with HNPCC [14].

Second group of MSI-high colon cancer is sporadic colon cancer without a strong familial predisposition. These tumors generally show methylation of CpG island of

hMLH1 promoter region, silencing the effecter hMLH1. These patients or their family members are not at high risk of developing other HNPCC related tumors.

Certain histologic features have been associated more frequently with MSI-high colon carcinoma. These histologic features include increase in tumor infiltrating lymphocytes, variegated histology, and histologic types including mucinous, signet ring cell, poor differentiation or medullary carcinoma. Additional features include peritumoral nodular lymphoid aggregates (Crohn's like reaction) and pushing tumor border. Original Bethesda guidelines included right sided colon cancer with undifferentiated histology under 45 years old patients or signet ring cell histology under 45 years old patients as two of the seven criteria for evaluation of tumors for MSI. The revised Bethesda guidelines for testing of tumors for MSI include histologic features as one of the five criteria. According to these guidelines colorectal cancer with MSI-H histology diagnosed in a patient who is less than 60 years of age should be tested for MSI by immunohistochemistry or molecular assay.

Although, above histologic features suggest a possibility of MSI-high tumors there are certain limitations of definitely diagnosing MSI-high colon carcinoma on the basis of histology. In a study of 323 patients, Alexander et al [15] showed mucinous and signet ring cell histology had very high specificity but low sensitivity in identifying the MSI-high tumors. Smyrk et al [16] in a study of 138 tumors concluded that quantitation of tumor infiltrating lymphocytes (TIL) can be a simple single histologic criteria to select the cases for MSI testing. Shia et al[7] studied utility of

histologic features in predicting MSI in Lynch (HNPCC) syndrome and sporadic colon cancer. They also found TIL counts to be of greater sensitivity and specificity of all the histologic parameters in predicting MSI status in both Lynch syndrome/Lynch syndrome like and sporadic cases. They did not find significant difference in odds ratio for MSI-high for any morphologic features between the Lynch syndrome group and sporadic group. In summary, a pathologist can raise a possibility of MSI-high tumors but the MSI status should be confirmed by either immunohistochemistry or molecular MSI assay. Even when IHC or molecular tests are to be performed to confirm the MSI-high status, the clinician may still prefer to discuss the issue with patient before requesting these tests as these tests can be considered `genetic tests`.

Lindor et al [17] demonstrated a high sensitivity (92.3%) and very high specificity (100%) of immunohistochemistry for detection of defects in hMLH-1 and hMSH-2. The predictive value of normal IHC for an MSS/MSI-low phenotype was 96.7% and predictive value of abnormal IHC was 100% for MSI-high phenotype. The choice of the molecular versus immunohistochemistry primarily depends upon the acceptability of missing a small number of cases if only IHC is performed.

Clinical significance of sporadic MSI-high colon cancer has been a recent focus. Gryfe et al [18] in a large study showed a survival advantage of MSI high tumors independent of standard prognostic factors including stage. In addition, they also showed less likelihood of metastasis to regional lymph nodes. Samowitz et al [19] also observed better prognosis in stage III MSI high colon cancer. MSI-high

tumors are shown to be resistant at least in vitro to 5-FU and other commonly used chemotherapeutic agents like cisplatin, doxorubicin, paclitaxel (Taxol) and etoposide in some studies but not in others.

There is not enough evidence to recommend routine testing for MSI in CRC patients, as concluded by the ASCO 2006 recommendations [20]. A national Phase III cooperative oncology group clinical trial is addressing MSI and 1q LOH in adjuvant setting in stage II colon cancer to assign patients to observation or chemotherapy.

B. Loss of Heterozygosity (LOH) of chromosome 18q:

The long arm of chromosome 18 contains several genes which are important in CRC cancer pathogenesis and progression. These genes include tumor suppressor genes, DCC (deleted in colon cancer), SMAD-4 (DPC-4), and SMAD-22. 18q LOH and absence of DCC protein have been reported for many years to be associated with poor prognosis. The LOH determined by using 2-10 microsatellite markers with polymorphic markers in area of DCC gene (18q21) is used most commonly. The LOH is defined in different studies as loss of one loci or loss of all tested loci. This variability in defining LOH is a limiting factor in assessment of 18q LOH as a prognostic marker in CRC. More than one studies have shown that LOH of 18q is associated with significantly worse prognosis in univariate and multivariate analysis in stage II CRC patients. Small number and retrospective nature of these studies makes it premature to use 18q LOH as marker for clinical use [20]. A national Phase III cooperative oncology group clinical

trial is addressing MSI and 1q LOH in adjuvant setting in stage II colon cancer to assign patients to observation or chemotherapy.

Loss of DCC by immunohistochemistry has shown to be associated with poor survival outcome. Two of the three positive studies showed loss of DCC to be an independent prognostic factor in multivariate analysis and one study found loss of DCC predicts response to fluorouracil based therapy. Lack of standardization of immunohistochemistry and large prospective trials are lacking to recommend this marker for clinical use.

C. Epigenetic alterations (Promoter CpG island methylation, CIMP):

Aberrant hypermethylation of promoter CpG rich island, leading to transcriptional inactivation of effector region is a third and relatively a new pathway in pathogenesis of CRC. Although, numbers and types of epigenetic markers influence the molecular subtyping, three major types of CRC are identified based on methylation profile [21] as shown in table-3.

Table-3

CIMP+MSI High CRC (type 1)	**CIMP+MSI stable CRC (type 2)**	**CIMP- MSI stable CRC (type 3)**
Site: Proximal (Right sided)	Site: Proximal (Right sided)	Site: Distal (left sided)
Precursor: Hyperplastic polyp/Serrated adenoma	Precursor: Villous adenoma	Precursor: Tubular adenoma
Frequent BRAF mutation and MLH-1 mutation	Frequent K-ras mutation	Frequent p53 mutation
Rare MSI and p53 mutation	Rare MSI, BRAF and	Infrequent MSI, K-

	p53 mutation	ras and BRAF mutation
? better survival	? Poor survival	?intermediate survival
Sporadic or HNPCC MSI high CRC		

At present the focus is on applying the promoter methylation profiling in pathogenesis of colon cancer with proposed two different pathways. One “serrated pathway” with CIMP+MSI high colon cancer with precursor lesion being hyperplastic polyp/serrated adenoma and second is the classical adenoma-carcinoma pathway with CIMP+/- MSI stable colon cancer [22]. More studies are needed to better define the role of methylation in determining its clinical application to determine the outcome and deciding a mode of therapy.

D. Molecular alterations and chemotherapy and targeted therapy

1. Markers for single-agent fluoropyrimidines

Because 5-fluorouracil has been in use for decades, the most extensive evaluation of potential markers for sensitivity and resistance to chemotherapy in patients with colorectal adenocarcinoma is available for this drug. Thymidylate synthase (TS) is the target of 5-FU, and dihydropyrimidine dehydrogenase (DPD) and thymidine phosphorylase (TP) participate in its catabolism. As a result, these enzymes have been studied extensively at the DNA, RNA, and protein levels, and high levels of expression by immunohistochemistry and mRNA associated with poor outcome [23,24]. Recently, additional enzymes important in 5-FU effects have been identified, including mRNA expression of TNFRSF1B, SLC35F5, and orotate phosphoribosyltransferase [25,26].

Expression of TS has been evaluated by quantitative reverse transcriptase polymerase chain reaction amplification for identification of mRNA, and immunohistochemistry with a variety of different antibodies has been studied. The resulting literature is a quagmire of results in the advanced-disease and adjuvant setting with various chemotherapy regimens, variable methodologies, and, not surprisingly, conflicting results. On the whole, elevated TS expression may be associated with poor response and reduced survival after 5-FU based regimens [27], but many studies have not found the marker to identify responders or survivors [28,28,30], and the level of evidence does not favor clinical utilization of the assay (11). A clinical trial in the Eastern Cooperative Oncology Group (protocol E4203) is currently addressing in prospective fashion the potential utility of immunohistochemical expression of TS as an indication for non-fluoropyrimidine-based therapy. Dihydropyrimidine dehydrogenase (DPD) catabolizes 5-FU, and deficiency in the activity of the gene product predisposes to the development of toxicities [31,32]. The frequency of deficiency is very low, and routine testing is not done at present. Capecitabine is an oral fluoropyrimidine. Because it has been in use for far shorter time than 5-FU, the pharmacogenetics and pharmacogenomics are less well-studied. Initial publications suggest that the characteristics of enzymes involved in the metabolism of fluoropyrimidines may have similar potential as markers as for 5-FU [33].

2. Markers for oxaliplatin

High expression of the excision repair cross-complementing 1 (ERCC1) gene whose product removes oxaliplatin adducts from DNA has been associated with

poor outcome after oxaliplatin [27] . Increment in the ratio of soluble FAS to FAS ligand/CD95 by enzyme linked immunosorbent assay in blood after treatment with oxaliplatin and 5-FU combination chemotherapy has been reported as a marker of chemosensitivity and decreased ratio as a predictor of chemoresistance in advanced colorectal cancer patients [34]. It seems likely that the finding is a generic effect, rather than specific to the agents used. Favorable germline genotypes from polymorphisms in XPD-751, ERCC1-188, GSTP1-105, and TS-3'-untranslated region were also associated with survival in this setting [35].

3. Markers for irinotecan

Irinotecan is a topoisomerase I inhibitor that is converted to SN-38, the active moiety, by carboxylesterases. This camptothecin derivative has been widely used in combination with 5- FU/leucovorin, oxaliplatin, and bevacizumab [36]. Polymorphism in the UGT1A1 gene is associated with increased toxicity, prompting a warning label on the package insert for the drug [37]. Genotyping of patients before initiation of therapy is likely to become common practice.

4. Markers for bevacizumab

This monoclonal antibody against vascular endothelial growth factor (VEGF) in combination with 5-FU/leucovorin or irinotecan and 5-FU/leucovorin improves survival of patients with advanced colorectal cancer [38]. Despite extensive efforts, predictive markers have not been identified.

5. Markers for antibodies to EGFR

Although demonstration of EGFR in a tumor would seem logically to be required for effective targeted therapy with agents targeting the gene product, several studies have shown no relationship of immunohistochemical expression in single-agent therapy with cetuximab and combination therapy of cetuximab with irinotecan in patients with advanced disease [39], or with single-agent panitumumab [40]. In single-agent therapy with cetuximab, low expression of EGFR, cyclo-oxygenase 2 and interleukin-8 mRNA was associated with improved overall survival and high expression of vascular endothelial growth factor mRNA with resistance in patients with advanced refractory disease [41]. Germline polymorphism of the cyclin D gene and gene expression levels of VEGF have been reported to be associated with efficacy of cetuximab [27]. Recent data have suggested that ras gene mutation indicates absence of improved survival with both single-agent cetuximab and panitumumab.

6. Markers in combination therapy regimens

Use of combination chemotherapy is standard practice but poses challenges for the use of markers because of the various mechanisms of action of cytotoxic and targeted agents. Studies have begun to address these situations. Germline polymorphisms of TS, XRCC1 and UGT1A1 were evaluated in patients with advanced colorectal cancer treated with 5-FU and irinotecan or 5- FU and oxaliplatin [42]. With the latter regimen, patients with TS 5' single nucleotide polymorphism and/or favorable XRCC1 genotypes had better time to progression. With the combination of capecitabine and irinotecan, patients whose tumor had TP expression by immunohistochemistry had improved overall survival whereas TS

and DPD were not predictive [43]. High expression of ERCC1 and TS mRNA in patients with advanced colorectal cancer treated with 5-FU and oxaliplatin has been associated with poorer survival [44]. In rectal cancer patients treated with chemoradiation with a 5-FU regimen, high intratumoral TS after therapy was reported to be predictive of unfavorable outcome [45].

Conclusion:

In spite of extensive effort in finding biomarkers for prediction of outcome in CRC, the staging based on clinical staging and examination of pathology specimens is the best predictor of long term survival and appropriate in-depth examination of surgical pathology specimens is more important than any known biomarkers in assessing the prognosis. Validation of molecular markers requires large prospective studies and assessment of cost benefit ratio for patients with CRC.

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Serrated adenocarcinoma: The clinicopathological features and its histogenesis

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Recently, sessile serrated adenoma / polyp (SSA/SSP) is recommended to be distinguished from traditional serrated adenoma and hyperplastic polyp, however, the significance of SSA/SSP in carcinogenetic pathway still remaing unclear. On the other hand, a new concept of 'serrated adenocarcinoma' was proposed by Mäkinen, which included carcinomas with or without a serrated adenoma component. In addition to the characteristic clinicopathohlogical fearures, it was also supported to be a subtype of colorectal carcinoma by molecular events.

We have experienced 16 lesions (13 cases) of serrated adenocarcinoma of the colorectum. Clinicopathologically, female and right-sided location were predominant in 'serrated carcinoma'. Its histological characteristics are as follows; 1) serrated structure of carcinomatous glands, 2) infiltrative growth, 3) high incidence of mucinous carcinoma (or presence of mucin pools), 4) tendency of de-differentiation at the invasive front, 5) rare necrotic foci. Immunohistochemically, almost all lesions revealed pure gastric-phenotype.

Its clinical background (especially in sex ratio and lesion location) is different from that of carcinoma arising from traditional serrated adenoma, however, it is similar to that of SSA/SSP. Therefore, the precursors or early lesions of serrated adenocarinoma may be SSA/SSP, and they probably grow into advanced carcinoma very fast.

In addition, diagnostic criteria will be discussed for several cases of serrated lesions.