Cancers of the Colon and Rectum: Identical or Fraternal Twins?
Theodore S. Hong1, Jeffrey W. Clark2, and Kevin M. Haigis3

Summary: Colorectal cancer represents a major cause of cancer morbidity and mortality, with approximately 1.2 million cases and 600,000 deaths worldwide each year. Because of the anatomic continuity of the colon into the rectum, cancers affecting these organs have historically been considered equivalent. In this Prospective, we discuss the clinical and experimental data suggesting that colon cancer and rectal cancer are highly related, but distinct, diseases. Reconsidering the relationship between these cancers has implications for the development of new therapeutic paradigms. Cancer Discovery; 2(2): 117–21. © 2012 AACR.

INTRODUCTION
Colorectal cancer represents a major cause of cancer morbidity and mortality, with approximately 1.2 million cases and 600,000 deaths worldwide each year (1). The colon and rectum are related anatomically, and therefore colon cancers and rectal cancers are typically considered to be essentially the same disease. Yet, they differ clinically in one very important aspect: rectal cancer has a substantially greater rate of local recurrence (2–4). Because of this increased risk, patients with locally advanced rectal cancer receive a combination of radiation and chemotherapy before surgery, with postoperative chemotherapy to follow. In contrast, patients with colon cancer proceed directly to surgery and are given chemotherapy only if lymph nodes are involved or if they have other high-risk pathologic features.

This difference in the treatment paradigm has led to some confusion regarding the development of future strategies for colon cancer and rectal cancer. Are the distinct clinical responses of colon cancers and rectal cancers attributable to inherent biological differences or simply to medical treatment issues? The prevailing philosophy is that rectal cancer is colon cancer with a local control problem. As a result, the therapeutic paradigm is focused primarily on improving the local control rate through surgical and radiation-based strategies. Moreover, the paradigm to control metastatic relapse continues to be directly extrapolated from colon cancer studies, which specifically exclude rectal cancer because of the confounding impact of chemoradiation. Here, we discuss the clinical similarities and differences between colon cancer and rectal cancer and the scientific data suggesting similarities and differences.

ANATOMIC INFLUENCES ON LOCAL RECURRENCE
The surgical accessibility of cancers of the colon and rectum plays a major role in their distinct clinical management. Although the colon and rectum represent 2 separate regions of a contiguous organ—the large intestine—the anatomic distinction between the colon and rectum relates to their intraperitoneal versus retroperitoneal locations within this organ. The colon begins in the right lower quadrant of the peritoneal cavity at the ileocecal valve, travels superiorly to the hepatic flexure in the right upper quadrant, comes across anteriorly from right to left to the splenic flexure, and proceeds inferiorly to the left lower quadrant. At the left lower quadrant, the colon swings medially and exits the peritoneal cavity into the pelvis.

In contrast to the abdomen, where there is ample room for a surgeon to obtain widely negative margins, the pelvic inlet is quite narrow. The rectum itself is in the posterior pelvis and surrounded by perirectal fat, which is enveloped by an avascular fascial plane known as the mesorectal fascia. This mesorectal envelope houses the regional lymph nodes of the rectum. The mesorectum is tightly bounded by the sacrum and associated sacral nerves posteriorly, the iliac vessels and branches of the sacral nerves laterally, and the genitourinary structures anteriorly. In men, the upper rectum borders the bladder anteriorly, and the middle and lower rectum lies adjacent to the seminal vesicles and the prostate. In women, the upper rectum is bounded by the uterus and the middle and lower rectum are bounded by the posterior vagina. As the rectum descends inferiorly/distally towards the anal canal, the pelvis tapers narrowly. Because the pelvic space harboring the rectum is significantly narrower than the abdomen, and the lower pelvis is narrower than the upper pelvis, the possibility of a clean resection becomes more challenging as the surgeon attempts a rectal, compared with a colonic, resection. As a result, there is a greater likelihood of local recurrence.

MANAGEMENT OF LOCALLY ADVANCED RECTAL CANCER versus COLON CANCER
When a patient is suspected of having locally advanced colon cancer (T3–T4a or node-positive, excluding T4b), surgery...
is the first treatment if the metastatic survey is negative (Fig. 1, Table 1). In this setting, surgery is associated with excellent local control, with local failure rates between 3% and 5% (2). If the lymph nodes are involved (stage III disease), a patient will have approximately 60% risk of distant, metastatic relapse, which can be decreased by approximately 20% (relative risk reduction of one third) with addition of a fluoropyrimidine-based adjuvant systemic chemotherapy (5). In some cases of high-risk features, such as T4 cancers, clinical evidence of perforation at surgery, poorly differentiated histology, lymphovascular invasion, or insufficient node sampling (<12 nodes), some clinicians will offer adjuvant therapy because these high-risk features may be associated with a risk of recurrence similar to that of stage III disease.

Locally advanced rectal cancer is associated with a substantially greater risk of a local recurrence. In the Swedish Rectal Study, one of the first randomized trials evaluating the use of preoperative radiation therapy in rectal cancer, patients with stage II disease who had surgery alone had a local relapse risk of 22%, and patients with stage III disease had a local relapse risk of 46% (3). The suspected reasons for this high rate of relapse were the anatomic restraint on surgical resection (discussed previously in this article) and the technical nature of the operation. Historically, the surgeon would bluntly mobilize the rectum itself by hand, leading to a high frequency of positive margins and retained nodal tissue. The likelihood of local recurrence and subsequent death caused by rectal cancer is markedly greater in the setting of a positive margin (4).

For this reason, modern surgical techniques require the surgeon to perform a total mesorectal excision, whereby the surgeon sharply excises the mesorectal fascia to decrease the risk of leaving disease behind. Nevertheless, despite this improved surgical technique, radiation still confers a local control benefit (6). Because of the accepted increased risk of local recurrence of locally advanced rectal cancer, the current standard course of therapy is preoperative chemoradiation, followed by surgery (Fig. 1). As a result of the significant downstaging that occurs with chemoradiation, however, the original nodal status is never known, and patients are recommended to complete a course of adjuvant chemotherapy.

The most typical adjuvant chemotherapy after surgery for either colon cancer or rectal cancer is FOLFOX, a 3-drug regimen of 5-fluorouracil, leucovorin, and oxaliplatin. The rationale for this regimen derives largely from the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial (7), in which investigators showed an improved disease-free survival and overall survival in patients with stage III colon cancer. Even though a similar trial has not been completed for rectal cancer, it is widely assumed that the overall survival between colon and rectal cancer is similar stage-for-stage, given current therapeutic approaches. Retrospective studies that have evaluated this question have been mixed in terms of whether there might be any differences in response between the diseases. These analyses are complicated, however, by changes in the standard approach to adjuvant therapy for both colon and rectal cancer over time, as well as the fact that the neoadjuvant approach for rectal cancer makes it difficult to be certain of the true pathologic stage for all patients.

### CLINICAL DIFFERENCES BETWEEN COLON CANCER AND RECTAL CANCER: BEYOND LOCAL FAILURE

In addition to the greater incidence of local recurrence, differences in clinical patterns of failure have been noted between colon cancer and rectal cancer. Colon cancer relapse is most commonly manifested by primary recurrence in the liver or lung, with liver metastases up to 4 times as likely as lung metastases. In contrast, rectal cancer carries a greater risk of lung metastases, which in some studies has equaled or exceeded the risk of liver metastases (8).

![Table 1. Colorectal cancer staging](image-url)
Similar to local recurrence, the discrepancy in metastatic recurrence is thought to be determined on the basis of anatomy, rather than on biology. Embryologically, the rectum and left side of the colon (from the distal one-third of the transverse colon) arise from the hindgut, whereas the colon proximal to that arises from the midgut. This is accompanied by a difference in blood supply, which may account for the difference in the pattern of metastases. There is a closed portal venous loop by which the intraperitoneal colon drains directly to the portal vein and thus the first major organ that any circulating tumor cells encounter is the liver. The inferior rectal vein, which drains the distal rectum, flows directly to the inferior vena cava, which in turn circulates through the heart and into the pulmonary artery by way of the right atrium and ventricle. Thus, again, the first major organ encountered, in this case the lung, is the greatest-risk site of metastasis. Although anatomy provides a convenient explanation for differences in metastatic potential, robust data are lacking as to whether this simple hypothesis is completely accurate or whether there might be differences in the biology of cancers arising in the colon versus rectum that might account for some of the difference in the pattern of metastases. In other systems, for example breast cancer, differences in metastatic potential cannot be explained anatomically but instead have been linked to the activity of specific genes in distinct subsets of breast cancers (9).

The distinct metastatic behavior of colonic and rectal cancers is clear; however, little is known about whether there might be any difference in survival of patients with metastatic colon or rectal cancer because most of the recent trials that have evaluated this question include patients with either cancer and have not been analyzed for a possible difference between the two. Given the overall evidence suggesting that any difference that might exist once differences in stage at presentation are eliminated may primarily result from differences in genetics between subsets of patients with colon cancer (right-sided vs. left-sided) and rectal cancer, most of the current emphasis has been on evaluating the potential genetic differences (10, 11).

**EPIGENETIC AND GENETIC DISTINCTIONS BETWEEN COLON AND RECTAL CANCERS**

The advent of genomic technologies has allowed for the molecular characterization of cancers in unprecedented detail. For rectal cancer in particular, gene expression profiling has been used to identify a gene signature of local recurrence after chemoradiation therapy, but, for reasons described previously, there is no colon cancer comparison in this study (12). In addition, gene expression profiling has led to the identification of biomarkers related to colorectal cancer staging, metastatic behavior, and clinical response, but these studies typically have not evaluated colon cancer and rectal cancer separately (13–15). For studies in which data are available for anatomic location, there are significant differences in mRNA and miRNA expression between colon cancers and rectal cancers (15, 16). It remains unclear, however, whether these gene expression differences result from the distinct developmental origins of the colon and rectum and whether they affect clinical parameters such as metastatic behavior or therapeutic response.
Genome sequencing provides perhaps the most compelling evidence that colon and rectal cancers are related but distinct. A survey of publicly available sequencing data that are annotated for anatomic location (http://www.sanger.ac.uk/genetics/CGP/cosmic/) identifies several genes that are mutated at similar frequencies in both types of cancers, including FBXW7, KRAS, NFI, NRAS, PIK3CA, PTEN, and SMAD4 (Table 2). However, several genes are also identified that discriminate between colon and rectal cancers. Colon cancers have relatively frequent mutations in BRAF, CTNNB1, PIK3R1, and SRC, whereas rectal cancers are more commonly mutant for APC, ERBB2, STK11, and TP53 (Table 2). Some of these data are consistent with known differences between colon and rectal cancers. For example, BRAF mutations occur most commonly in serrated polyps, a specific subtype of colorectal cancer precursor that arises predominantly in the right-side colon (17). Although the link between rectal cancer and the STK11 mutation has not been studied in detail, single-nucleotide polymorphisms in STK11 have been associated with increased risk of developing the disease (18). By contrast, although SRC mutations have been reported in colorectal cancer, the distinct separation between colon cancer and rectal cancer has not been explored (19). These genetic data suggest that cancers in the colon and rectum select for mutations in an overlapping, but distinct, set of signaling pathways. As with differences in gene expression profiles, the clinical significance of these distinct mutational profiles is unclear.

### Table 2. Genes for which mutational data are available for colonic and rectal cancers

<table>
<thead>
<tr>
<th>Genes</th>
<th>Anatomic site</th>
<th>Colon (F)</th>
<th>Rectum (F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>Colon</td>
<td>28% (208/738)</td>
<td>51% (48/94)</td>
</tr>
<tr>
<td>BRAF</td>
<td>Rectum</td>
<td>14% (1079/7618)</td>
<td>4% (102/2810)</td>
</tr>
<tr>
<td>CTNNB1</td>
<td>Colon</td>
<td>7% (38/528)</td>
<td>0% (1/236)</td>
</tr>
<tr>
<td>ERBB2</td>
<td>Rectum</td>
<td>0% (0/30)</td>
<td>6% (3/52)</td>
</tr>
<tr>
<td>FBXW7</td>
<td>Colon</td>
<td>17% (20/121)</td>
<td>21% (8/39)</td>
</tr>
<tr>
<td>KRAS</td>
<td>Rectum</td>
<td>35% (1736/4958)</td>
<td>36% (489/1343)</td>
</tr>
<tr>
<td>NF1</td>
<td>Colon</td>
<td>10% (8/78)</td>
<td>7% (1/14)</td>
</tr>
<tr>
<td>NRAS</td>
<td>Rectum</td>
<td>2% (5/223)</td>
<td>1% (1/69)</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>Colon</td>
<td>12% (63/509)</td>
<td>10% (44/441)</td>
</tr>
<tr>
<td>PIK3R1</td>
<td>Rectum</td>
<td>3% (6/174)</td>
<td>0% (0/14)</td>
</tr>
<tr>
<td>PTEN</td>
<td>Colon</td>
<td>9% (18/203)</td>
<td>12% (9/77)</td>
</tr>
<tr>
<td>SMAD4</td>
<td>Rectum</td>
<td>10% (15/151)</td>
<td>10% (5/52)</td>
</tr>
<tr>
<td>SRC</td>
<td>Rectum</td>
<td>5% (9/191)</td>
<td>0% (0/101)</td>
</tr>
<tr>
<td>STK11</td>
<td>Colon</td>
<td>12% (5/41)</td>
<td>33% (4/12)</td>
</tr>
<tr>
<td>TP53</td>
<td>Rectum</td>
<td>49% (1530/3138)</td>
<td>66% (402/610)</td>
</tr>
</tbody>
</table>

### IMPLICATIONS FOR THERAPY

The distinctions between colon cancer and rectal cancer have important implications for therapeutic development. To begin, the current therapeutic paradigm for rectal cancer—neoadjuvant chemoradiation—provides a different framework for the identification of new therapies. Several randomized trials have shown that patients who had a pathologic complete response to chemoradiation have a significantly better outcome, particularly in regard to distant metastases (20, 21). The link between pathologic complete response and disease outcomes has prompted a generation of phase I/II studies for rectal cancer that have evaluated the impact of new agents in an attempt to improve the pathologic complete response rate.

Nevertheless, these trials typically are not designed to evaluate the same agent in the setting of postoperative chemotherapy. Rather, patients are treated postoperatively with FOLFOX based on the MOSAIC trial, which specifically excluded patients with rectal cancer (7). This type of trial design represents a potential conflict in therapeutic development. On the one hand, new agents are added to radiation in hopes of improving disease outcomes. On the other hand, the component of therapy most likely to impact overall survival is the postoperative chemotherapy. On the basis of the results of the trials referenced previously, if a new agent convincingly improves pathologic complete response rates, one should consider studying it in combination with postoperative chemotherapy, unless there is scientific evidence that the drug’s mechanism of action is strictly the result of radiosensitization.

Moving forward, this discrepancy will need to be resolved before further resources are invested in the integration of new agents into chemoradiation. Patterns of failure clearly indicate that the metastatic risk in rectal cancer greatly outweighs the local recurrence with current standard therapy (20). Thus, a pathway of development to improve the pathologic complete response rate without an attempt to mitigate the metastatic risk via the same agent will likely be unsuccessful.

The finding of genetic differences between colon and rectal cancers also has potential practical implications for evaluating investigational agents. Elucidation of the genomic landscape of specific cancers has ushered in the era of genotype-driven targeted therapy. As such, the anatomic and physiologic distinction between cancers of the colon and rectum may become less significant when, in the long term, cancers are classified primarily on the basis of mutational profiles. Nevertheless, the distinction between the mutational spectra of colon cancer and rectal cancer is still important. Because broad tumor genotyping is not currently commonplace in the clinic, it can be extremely difficult to identify the patients who will benefit from a particular targeted therapy, especially when a particular mutation is rare. This concept is readily apparent in the case of EGFR-mutant non–small cell lung cancer. Although activating mutations in EGFR occur at a frequency of 10% in patients with non–small cell lung cancer, they are strongly enriched in female Asian nonsmokers with adenocarcinomas (22). By extension, clinicians are aware that these patients are more likely to benefit from EGFR inhibitors. Similarly,
activating SRC mutations are rare in the general colorectal cancer population. However, these mutations appear to be entirely absent in rectal cancers, so perhaps they are enriched in a specific subpopulation of patients with colon cancer. Identification of the "at-risk" populations for all of the mutations involved in colon cancer and rectal cancer is the first step toward the establishment of genotype-based therapeutic paradigms.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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REFERENCES

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