SIGNIFICANT PROGRESS HAS BEEN MADE TO IMPROVE OUTCOMES FOR PATIENTS WITH COLORECTAL CANCER. Screening can diagnose patients with precancerous polyps and early stage cancer. We can better identify patients with a genetic predisposition for inherited colorectal cancer. Surgical technique has improved in recent years and is often combined with chemotherapy for stage II-IV colon cancer and chemoradiation for stage II-IV rectal cancer. The 5-year survival ranges from 90% for stage I disease to 10% for stage IV disease, highlighting the importance of early detection and treatment.

EPIDEMIOLOGY AND TUMOR BIOLOGY
The American Cancer Society estimates there will be 93,090 new cases of colon cancer and 39,610 new cases of rectal cancer in the United States in 2015. Colorectal cancer is the third leading cause of cancer-related deaths in the U.S. when men and women are considered separately, and the second leading cause of death when both genders are combined. In 2015, there will be an estimated 49,700 deaths due to colorectal cancer.

The mortality rate from colorectal cancer has decreased 35% since 1990 due to earlier diagnosis attributed to the increased use of screening colonoscopy and more effective treatment. The majority of cancer cases are sporadic and related to chromosomal instability. Chromosomal instability results in loss of function of key tumor suppressor genes, such as APC, p53, k-ras, DCC, and SMAD4 that result in the development and progression of precancerous polyps to invasive cancers over years to decades.

SCREENING AND PREVENTION
More than 80% of colorectal cancers arise from premalignant adenomas. Therefore, diagnosis and treatment of precancerous polyps via colonoscopy is both preventative and therapeutic. Tests used to screen for colorectal cancer include guaiac-based fecal occult blood test (gFOBT), fecal immunochemical test (FIT), stool

(continued on page 2)
DNA, sigmoidoscopy, colonoscopy, double contrast barium enema, and CT colonography (virtual colonoscopy).

The most common and preferred approach to colorectal screening in the US is complete colonoscopy. Colonoscopy allows both evaluation of the entire length of the colon and therapeutic treatment with removal of polyps. A recent estimate suggests that colonoscopic removal of adenomatous polyps reduces the relative risk of colorectal cancer death by greater than 50%. A recent randomized trial compared colonoscopy to fecal occult blood screening and found that colonoscopy was four times more likely to identify advanced adenomas and 26 times more likely to identify early adenomas. Drawbacks of colonoscopy include an extensive bowel preparation, the requirement for either conscious sedation or anesthesia, and the small (0.5%) risk of major complications including bleeding, hypotension, bradycardia and perforation.

For patients who are unwilling or unable to undergo colonoscopy, alternate methods of colorectal cancer screening are recommended. Annual guaiac-based fecal occult blood screening of three consecutive stools is a validated approach that reduces the risk of death from colorectal cancer by 16%. The primary drawback is that fecal occult blood screening has lower sensitivity for identifying adenomas than endoscopic approaches and should the gFOBT be positive, further testing such as colonoscopy needs to be performed.

Flexible sigmoidoscopy is another test which can be performed in the office without sedation. Bowel preparation involves a self-administered enema. Sigmoidoscopy evaluates 45 to 60 cm of sigmoid colon and rectum where 60% of colorectal cancers are located. In a randomized trial, sigmoidoscopy reduces the risk of colorectal cancer incidence by 25 to 30% and the risk of colorectal cancer death by 30 to 40% compared to usual care. Patients with multiple or advanced adenomas on flexible sigmoidoscopy require follow-up colonoscopy.

CT colonography or virtual colonoscopy is a test sensitive for the detection of large adenomas measuring ≥1 cm. However, it requires full bowel preparation, involves radiation exposure and requires follow-up colonoscopy to further evaluate and treat suspicious lesions. This approach has not yet been proven to improve survival.

**SCREENING RECOMMENDATIONS for Average Risk Patients per US Preventive Services Task Force and American Cancer Society**

Beginning at age 50, both men and women at average risk for developing colorectal cancer should undergo colorectal cancer screening:
- Fecal occult blood test (FOBT) annually or
- Colonoscopy every 10 years or
- Flexible sigmoidoscopy every 5 years with FOBT every 3 years*

For patients who are unwilling or unable to undergo endoscopy
- FOBT or fecal immunochemical test (FIT) every year**+

* Colonoscopy should be done if test results are positive.
+For FOBT or FIT used as a screening test, the take-home multiple sample method should be used. An FOBT or FIT done during a digital rectal exam in the doctor’s office is not adequate for screening.

Average risk patients are defined as patients without clinical symptoms related to colorectal cancer, no personal history of colorectal cancer or adenomatous polyps, no family history of colorectal cancer or adenomatous polyps, and no history of inflammatory bowel disease.

**FIGURE 1.** Note that the American College of Gastroenterology recommends colonoscopic screening of African American patients beginning at age 45 due to their increased risk of developing colorectal cancer.
RISK FACTORS AND GENETICS

Colorectal cancer is associated with:

- Advanced age
- Male gender
- Racial and ethnic background (African Americans, Ashkenazi Jews)
- History of prior colon polyps
- Diets low in fiber and high in processed meat or red meat
- Physical inactivity and obesity
- Personal history of inflammatory bowel disease (Ulcerative Colitis, Crohn’s disease)
- Family history of colorectal cancer or adenomatous polyps
- Inherited syndromes (FAP, HNPCC)

Approximately six percent of colorectal cancers are associated with hereditary syndromes. The most common syndrome is hereditary non-polyposis colon cancer (HNPCC) or Lynch syndrome, which accounts for two to four percent of all colorectal cancer cases. HNPCC involves mutations of MLH1, MSH2, and MSH6 DNA mismatch repair proteins. Patients with Lynch syndrome have an 80% lifetime risk of developing colorectal cancer and a high risk of developing other cancers, especially endometrial cancer.

Identifying individuals with HNPCC is of utmost importance as their medical management significantly differs from that of the general population. Indications for an evaluation for HNPCC as well as medical management guidelines for those with this genetic syndrome are included below for your reference. Involvement of a cancer genetics professional in this evaluation can be invaluable for many reasons, some of which include ensuring the testing strategy is most informative, test results are interpreted in the context of patient’s personal/family history and informed consent for testing is obtained in accordance with New York State law.

Patients with a Personal or Family History of the Following Should be Evaluated for HNPCC:

- Colorectal cancer diagnosed before age 50
- Colorectal cancer diagnosed before age 60 with high microsatellite instability (MSI-H)
- Endometrial cancer diagnosed before age 50
- Two primary HNPCC-associated malignancies in one person, regardless of age at diagnosis
- Two or more family members with HNPCC-associated malignancies, with one diagnosed before age 50
- Confirmed HNPCC in family (mutation in MLH1, MSH2, MSH6, PMS2 or EPCAM gene)

HNPCC-associated malignancies include: colorectal, endometrial, stomach, ovarian, small bowel, ureteral/renal pelvis, pancreatic, hepatobiliary tract, brain/CNS (often glioblastomas), sebaceous gland neoplasms

Medical Management Guidelines for Individuals with HNPCC (adapted from NCCN Guidelines V1.2013):

- Colonoscopy every 1-2 years starting at age 20-25
- Consideration of prophylactic total hysterectomy and bilateral salpingo-oophorectomy after childbearing is complete
- Consideration of transvaginal ultrasound, endometrial sampling and serum CA-125 annually for those who do not undergo prophylactic surgery
- EGD with extended duodenoscopy every 3-5 years starting by age 30-35
- Urinalysis annually starting by age 25-30
- Physical examination annually
- Dermatological examination annually

Frequency of and ages at which to begin cancer surveillance may be altered based on an individual’s personal and/or family history.

DIAGNOSIS, STAGING AND PATHOLOGY

Following the diagnosis of colorectal cancer, CT scan of the chest, abdomen and pelvis with contrast is necessary to rule out lymph node and distant metastases. For rectal cancers, either phase array MRI or endoscopic rectal ultrasound is necessary to provide accurate assessment of local tumor extension through the rectal wall (T stage) and lymph node involvement (N stage) which helps to stage the patient and lead to informed treatment decisions. PET/CT is used selectively in colorectal cancer, particularly to define the extent of distant metastases. A complete blood count (CBC) and serum carcinoembryonic antigen (CEA) should be performed prior to surgery.

Staging of the primary tumor is based on depth of invasion (see Figure 1). Locally advanced T3 and T4 tumors have invasion through the muscularis propria into pericolorectal tissues or involvement of visceral peritoneum or adjacent organs. Patients with stage I disease have T1 or T2 tumors with negative lymph nodes and no distant metastases. Patients with stage II disease have T3 or T4 tumors with negative lymph nodes and no distant metastases. Patients with stage III disease have positive lymph nodes and no distant metastases.
nodes but no distant metastases. Patients with stage IV disease have distant metastases. Survival estimates by stage are shown in Table 1.

**TABLE 1  Colorectal Cancer survival by stage**

<table>
<thead>
<tr>
<th>STAGE</th>
<th>5-YEAR SURVIVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>97%</td>
</tr>
<tr>
<td>II</td>
<td>78%</td>
</tr>
<tr>
<td>III</td>
<td>70%</td>
</tr>
<tr>
<td>IV</td>
<td>13%</td>
</tr>
</tbody>
</table>

**SURGICAL TREATMENT FOR COLON CANCER**

Surgery is the mainstay of treatment for nonmetastatic colorectal cancer. Surgery for colon cancer includes partial colectomy with wide mesenteric resection and proximal ligation of the primary feeding vessel. Proximal and distal resection margins for colon cancer should be 5 cm and the pathologist needs to examine at least 12 lymph nodes within the mesentery in order to adequately determine if lymph node involvement is present.

There are different types of laparoscopic techniques used for colon resection including single-incision laparoscopic surgery (SILS), hand-assisted laparoscopy, and robotic surgery. Laparoscopic surgery may not be appropriate for patients with locally advanced T4 tumors or patients presenting with bowel obstruction. In a randomized controlled trial, laparoscopic partial colectomy achieved both equivalent recurrence rates and overall survival compared to open partial colectomy with the advantages of reduced pain, shorter hospital stay, decreased use of pain medication and decreased ileus for right, left and sigmoid colon cancers.

High volume colorectal cancer centers, such as Good Samaritan Hospital Medical Center, are strongly linked to a lower rate of complications.

**ADJUVANT CHEMOTHERAPY FOR COLON CANCER**

Patients with stage I disease have a 5-year survival rate of 97% with surgery alone. Additional chemotherapy is not needed. Chemotherapy for stage II colon cancer is controversial and debated in the literature but is often offered to those patients with T4 tumors, obstruction, poorly differentiated disease, perineural or lymphovascular invasion, <12 lymph nodes sampled or positive margins. Although not yet a standard approach, molecular profiling using microsatellite instability or 12-gene test may provide further information to guide the decision to administer adjuvant chemotherapy for patients with T3N0 colon cancer. Patients with stage 3 colon cancer receive chemotherapy after they have recovered from colon surgery.

The standard adjuvant chemotherapy regimen includes 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX) for six months. The absolute survival benefit for adjuvant chemotherapy for stage III disease is 15 to 20%. To date, adding newer biological agents to FOLFOX has not yet been proven successful. For elderly patients with stage III or high-risk stage II disease, intravenous 5-fluorouracil or oral capecitabine without oxaliplatin is a reasonable alternative that reduces toxicity. There is a limited role for radiation to improve local control for the uncommon patient with perforation, fixation to pelvic structures (ie. bladder or pelvic sidewall), positive margins or recurrent disease.
**SURGICAL TREATMENT FOR RECTAL CANCER**

For rectal cancer, surgery involves removal of the rectum in the form of a low anterior resection (LAR) or abdominoperineal resection (APR) based on location of the tumor and whether or not there is involvement of the sphincter complex. Both of these procedures include total mesorectal excision (TME) with negative circumferential and distal margins and inferior mesenteric lymph node dissection. TME involves sharp dissection of the mesorectum with preservation of pelvic autonomic nerves in order to preserve sexual and bladder function. Compared to historical controls, TME has significantly reduced the risk of local failure compared to traditional low anterior resection without TME.

Sphincter-sparing surgery is attempted if negative distal margins of ≥1 cm can be obtained, although coloanal anastomosis can be done for low rectal cancer patients, these patients are at increased risk of fecal incontinence. A coloanal anastomosis is usually protected with a temporary diverting ileostomy until adjuvant treatment is completed; this is also commonly used for patients who have undergone neoadjuvant radiation treatment. For patients with very low rectal tumors who are not candidates for resection with anastomosis, an APR with permanent colostomy is the only viable surgical option. Recently, laparoscopic and robotic techniques have emerged as alternatives to open surgery for selected patients when performed by experienced surgeons.

**NEOADJUVANT CHEMORADIATION FOR STAGE II-III RECTAL CANCER**

Patients with rectal cancer have a higher risk of local failure when compared to patients with colon cancer. Preoperative chemoradiation is recommended for patients with T3/T4 disease or positive lymph nodes based on endoscopic ultrasound or MRI. Preoperative chemoradiation has proven more effective and less toxic when compared to post-operative chemoradiation. In a randomized controlled trial, the 5-year locoregional control for stage II-III rectal cancer treated with neoadjuvant chemoradiation followed by TME was 94%. Neoadjuvant chemoradiation also increased the probability of successful sphincter preservation by reducing tumor size. The standard radiation regimen is 30.4 Gy with concurrent 5-fluorouracil and leucovorin. Intensity modulated radiation therapy allows for selective sparing of small bowel and judicious application of this technology holds promise for reduced acute and late gastrointestinal toxicity. Following surgery, adjuvant FOLFOX for six months is offered to high-risk patients, particularly those with unfavorable stage II and stage III disease.

**TREATMENT OF STAGE IV COLORECTAL CANCER**

Distant metastases limited to one to five liver or lung metastases are considered potentially curable oligometastases. Combined surgery and chemotherapy is more effective than surgery alone for resectable liver metastases. Stereotactic radiotherapy and radiofrequency ablation are other approaches used to ablate inoperable metastases (Figure 2). Approximately 25 to 30% of patients with limited liver metastases remain alive and free of recurrence 10 years following combined local and systemic therapy.

For the majority of patients with more widespread metastases, major advances in systemic therapy have increased median survival of newly diagnosed patients to two years. Common first-line regimens include FOLFOX and 5-fluorouracil, oxaliplatin and irinotecan (FOLFIRI) or 5-fluorouracil, oxaplipatin and irinotecan (FOLFOXIRI). Adding biologically targeted agents to conventional chemotherapy regimens improves survival for patients with stage IV disease. Bevacizumab, an inhibitor of blood vessel growth that works by blocking vascular endothelial growth factor receptor (VEGF), improves survival but is associated with a small incidence of potentially serious toxicities including hypertension, bleeding, blood clot formation, delayed wound healing and perforation. Newer inhibitors of vascular endothelial growth factor receptor include ziv-afilberecept and regorafenib, which are typically used in second and third line settings.

EGFR inhibitors are well tolerated except for acneiform rash, diarrhea and uncommon anaphylactic reaction. Biological therapies that block epithelial growth factor receptor (EGFR), cetuximab and panitumumab, are effective for the 60% of patients with k-ras wild-type tumors. However, combining anti-EGFR with VEGF inhibitors has not yet been proven effective. Further, anti-EGFR inhibitors may actually be detrimental to progression-free survival for patients with k-ras mutations. Although biologically targeted therapies offer a clinically relevant palliative benefit and improved overall survival ranging from one to five months, the high cost of treatment has emerged as an important public health issue.
**FOLLOW-UP**

After treatment, patients should be carefully followed by the oncologist and surgeon with serum CEA tumor markers every three months for the first three years and then every six months for the next two years. CT scan imaging should be performed annually. Colonoscopy is recommended one year after surgery and every three to five years thereafter.

---

*Figure 3. Complete radiographic and metabolic response of liver metastases with image-guided radiotherapy.*

- a) Pre-treatment CT with arterial contrast demonstrated two enhancing 9 mm lesions in the dome of the liver.
- b) T1 fat saturated MRI with contrast redemonstrates two enhancing lesions in the dome of the liver.
- c) Pre-treatment planning CT with superimposed radiation dose distribution. Note fiducial marker placed adjacent to tumor to allow for image-guided radiation delivery. The patient received 50 Gy in 10 fractions. The 5 Gy isodose line covers the gross tumor volume with excellent sparing of normal tissue.
- d) CT performed at 57 months following completion of radiation demonstrates a complete radiographic response on CT. Tumor markers also normalized after treatment.

*Reprinted from Kao, Cancer 115: 3571, 2009 with permission.*
TABLE 2  Selected randomized trials of anti-VEGF biological agents for metastatic colorectal cancer

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Treatment groups</th>
<th>Patients</th>
<th>Median progression-free survival (months)</th>
<th>Median overall survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously untreated</td>
<td>Irinotecan, 5-fluorouracil, leucovorin ± bevacizumab</td>
<td>813</td>
<td>6.2 vs. 10.6 (p&lt;0.001)</td>
<td>15.6 vs. 20.3 (p&lt;0.001)</td>
</tr>
<tr>
<td>Previously untreated</td>
<td>XELOX or FOLFOX ± bevacizumab</td>
<td>1401</td>
<td>8.0 vs. 9.4 (p=0.0023)</td>
<td>19.9 vs. 21.3 (p=0.77)</td>
</tr>
<tr>
<td>Previously untreated</td>
<td>FOLFIRI ± bevacizumab vs. FOLFOXIRI ± bevacizumab</td>
<td>508</td>
<td>9.7 vs. 12.1 (p=0.003)</td>
<td>25.8 vs. 31.0 (p=0.05)</td>
</tr>
<tr>
<td>Second-line, prior FOLFOX</td>
<td>FOLFIRI ± afibercept</td>
<td>1226</td>
<td>4.7 vs. 6.9 (p&lt;0.001)</td>
<td>13.5 vs. 12.1 (p=0.003)</td>
</tr>
<tr>
<td>Second-line, prior FOLFIRI</td>
<td>FOLFOX ± bevacizumab</td>
<td>597</td>
<td>4.7 vs. 7.3 (p=0.0001)</td>
<td>10.8 vs. 12.9 (p=0.001)</td>
</tr>
<tr>
<td>Second-line, prior chemotherapy + bevacizumab</td>
<td>Oxaliplatin or irinotecan-based chemotherapy ± bevacizumab</td>
<td>810</td>
<td>4.1 vs. 5.7 (p=0.001)</td>
<td>9.8 vs. 11.2 (p=0.006)</td>
</tr>
<tr>
<td>Third-line, failed all prior standard therapy</td>
<td>Best supportive care ± regorafenib</td>
<td>753</td>
<td>1.7 vs. 2.0 (p&lt;0.001)</td>
<td>5.0 vs. 6.4 (p=0.005)</td>
</tr>
</tbody>
</table>

TABLE 3  Selected randomized trials of anti-EGFR biological agents for metastatic colorectal cancer. Please note that the benefit for anti-EGFR therapy is limited to patients with k-ras wildtype phenotype. *Furthermore, treatment with EGFR inhibitors may be detrimental for patients with k-ras mutations.

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Treatment groups</th>
<th>Patients</th>
<th>Median progression-free survival (months)</th>
<th>Median overall survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously untreated, Kras wildtype</td>
<td>FOLFIRI ± cetuximab</td>
<td>666</td>
<td>8.4 vs. 9.9 (p=0.001)</td>
<td>20.0 vs. 23.5 (p=0.009)</td>
</tr>
<tr>
<td>Previously untreated, Kras mutated</td>
<td>FOLFIRI ± cetuximab</td>
<td>397</td>
<td>7.7 vs. 7.4 (p=0.28)</td>
<td>16.7 vs. 16.2 (p=0.76)</td>
</tr>
<tr>
<td>Previously untreated, Kras wildtype</td>
<td>XELOX + bevacizumab ± cetuximab</td>
<td>314</td>
<td>10.6 vs. 10.5 (p=0.30)</td>
<td>22.4 vs. 21.8 (p=0.64)</td>
</tr>
<tr>
<td>Previously untreated, Kras mutated</td>
<td>XELOX + bevacizumab ± cetuximab</td>
<td>216</td>
<td>12.5 vs. 8.1 (p=0.003)*</td>
<td>24.9 vs. 17.2 (p=0.03)*</td>
</tr>
<tr>
<td>Previously untreated, Kras wildtype</td>
<td>FOLFOX ± panitumumab</td>
<td>656</td>
<td>8.0 vs. 9.6 (p=0.02)</td>
<td>19.7 vs. 23.9 (p=0.07)</td>
</tr>
<tr>
<td>Previously untreated, Kras mutated</td>
<td>FOLFOX ± panitumumab</td>
<td>440</td>
<td>8.8 vs. 7.3 (p=0.02)*</td>
<td>19.3 vs. 15.5 (p=0.07)*</td>
</tr>
<tr>
<td>Failed prior irinotecan</td>
<td>Cetuximab ± irinotecan</td>
<td>329</td>
<td>1.5 vs. 4.1 (p&lt;0.001)</td>
<td>6.9 vs. 8.6 (p=0.48)</td>
</tr>
<tr>
<td>Failed prior 5-fluorouracil, irinotecan and oxaliplatin</td>
<td>Best supportive care ± panitumumab</td>
<td>463</td>
<td>1.7 vs. 1.9 (p&lt;0.001)</td>
<td>NR (p&gt;0.05)</td>
</tr>
</tbody>
</table>
From the colorectal cancer experts at Good Samaritan Hospital Medical Center

Department of Surgery
Anthony Capizzi, MD, President of the Medical Staff and Associate Chairman of Surgery
Bradley Cohen, MD
Kazim Doganay, MD
Marc Finkelstein, MD
John Francfort, MD, Chairman of Surgery
John Hsu, MD
Sang Jho, MD
Michael Sacca, MD
John Simon, MD
John Tomasula, MD

Division of Gastroenterology
Neil Lobo, MD
Kourosh Adhami, MD
James Kohlroser, DO
Babak Danesh, MD
Krishaniyer Subramani, MD
Raj Mariwalla, MD, Chief of Gastroenterology
Noel D’Silva, MD
Darius Sorbi, MD
William DiSanti, MD
Katherine Freeman, MD

Division of Medical Oncology
Kenneth Gold, MD, Chairman of Cancer Committee and Chief, Division of Hematology/Oncology
Shabeer Dar, MD
Paul Hyman, MD
John Loscalzo, MD
Sudha Mukhi, MD
Mary Puccio, MD
Hasan Rizvi, MD
Gerry Rubin, MD
Emmanuel Sygaco, MD

Department of Radiation Oncology
Johnny Kao, MD, Chairman of Radiation Oncology
Neha Sharma, MD

Department of Radiology
Michael Benanti, DO, Chairman of Imaging Services

Department of Pathology
William Engellener, MD, Chairman of Pathology

Division of Genetic Counseling
Amanda Laterza, MS, CGC, Director of Genetic Counseling
Melanie Charles, MS, CGC
Olivia Tan, MS, CGC