In 2014, nearly 131,000 new cases of colorectal cancer (CRC) will be diagnosed in the United States, making it the third most common malignancy in both men and women. More than half of these new cases will be found when they have already spread to regional lymph nodes or to other sites in the body. Because of this, CRC is also the third most common cause of death from cancer, with an average 5-year relative survival rate of 65%.

This poor prognosis could be improved by finding and removing precancerous lesions and early stage malignancies before they have the chance to develop further. Screening individuals older than 50 with colonoscopy addresses this need, but more than half of the people who should receive this test avoid it because of concerns about cost, sedation, unpleasant bowel preparation, and the risk of serious complications. Ajay Goel, PhD, director of epigenetics and cancer prevention at Baylor Research Institute on the campus of Baylor University Medical Center at Dallas, has been working with colleagues to develop a blood-based screening test for CRC that should have broader public acceptance. (See story on p. 10.)
Imagine a simple blood test that replaces a majority of all colonoscopies currently performed. Imagine accessing the data from hundreds and thousands of surgical cases at the push of a button. Imagine a common spice that prevents and treats cancers.

The current issue of CancerUpdate focuses on progress in colorectal cancer research and treatment. Refinements in imaging and surgical techniques allow for more efficient surgery with fewer potential complications and earlier discharge from the hospital. A blood test based on microRNA may help determine which individuals do or do not need a colonoscopy. By automatically testing for genetic predisposition to cancer, we may identify family members who have increased cancer risk and help them to take preventive measures. The surgical oncology research database allows us to collect data on all patients treated and, from that data, help determine the best options for specific populations.

And what about curcumin, a simple spice that is not so simple? Ajay Goel, PhD, is conducting studies examining epigenetic effects of curcumin and the potential to enhance colon cancer sensitivity to one of our standard chemotherapy agents.

John Lennon wrote, “You may say that I’m a dreamer, but I’m not the only one.” Fortunately we have dreamers who can turn some of those dreams into reality.
For those individuals diagnosed with CRC, the focus is on providing the best possible care, maximizing patient survival while preserving quality of life. With the strong advocacy of James W. Fleshman, Jr., MD, the chief of the Department of Surgery for Baylor University Medical Center at Dallas, Baylor Dallas is on the road to becoming a center of excellence for the treatment of CRC. This development is based on a commitment to:

1. Providing our patients quality care. This requires multidisciplinary input for a treatment plan that is custom-tailored to the individual patient.
2. Capturing and analyzing patient data, not only demographic data, but real-time information about how treatment is delivered and what treatment outcomes are.
3. Exploring new treatment approaches through an active clinical research program.
4. Providing excellence in training residents in the area of colon and rectal surgery.

The Multidisciplinary Tumor Conference: Developing Custom-Tailored Treatment Plans

When Dr. Fleshman first arrived at Baylor Dallas a year ago, one of his first actions was to inaugurate a multidisciplinary tumor (MDT) conference for CRC. This new conference is in addition to the long-standing excellent GI tumor site-specific conference. The colorectal MDT conference focuses on colorectal cancer, allowing the team to review a larger number of cases as well as permitting them to go into more depth for each case. This conference is chaired by Dr. Fleshman. Clinicians representing all the disciplines involved in the diagnosis and care of patients with CRC (medical oncology, gastroenterology, genetics and genetic counseling, radiology, radiation oncology, colon and rectal surgery/surgical oncology) meet biweekly and review every case of colon and rectal cancer. If a patient is referred to medical oncology after surgery, a patient navigator may be brought in to provide the patient appropriate follow-up care.

Colon and rectal surgery fellows in training at Baylor Dallas gather and present patient data, which is discussed by attendees. The goal is to create a treatment plan that is customized for a specific patient and that meets guidelines from the National Comprehensive Cancer Network and the American Society of Colon and Rectal Surgeons. Checks are made at appropriate points during the patient’s treatment to make sure that quality is maintained: Were surgeons able to obtain a complete resection? Was the surgery done properly? Was chemotherapy started in a timely manner?

Special attention is paid to rectal cancer cases which frequently tend to be very complex, requiring a special magnetic resonance imaging (MRI) protocol for proper staging and, in some cases, neoadjuvant treatment with radiation and/or chemotherapy. The case is reviewed again before surgery but after the completion of neoadjuvant therapy, and yet again after surgery to review the pathology and the adequacy of the surgery. According to Dr. Fleshman, “We are working to improve quality control by coming at it from different directions. For example, after surgery for a rectal tumor, we look at pathology slides prepared using a bread-loafing technique to determine the circumferential margins and the adequacy of surgery, and we compare those observations with the MRI images used in staging. We are all communicating with each other and improving surgery, staging, and imaging at the same time.”
The Surgical Oncology Clinical Research Database (SOCRD): A CRC Platform That Combines Historic and Real-Time Patient Data

SOCRD was established by the Division of Surgical Oncology to serve as a metaregistry where multiple databases can be connected in a useful way. In the beginning, it was developed as a research tool that contained largely retrospective data uploaded from existing databases within the Baylor Dallas system. SOCRD includes information that is reported regularly to the Commission on Cancer of the American College of Surgeons and to the State of Texas.

With the increasing development of tumor conferences that focus on prospective evaluation, a new dimension was needed for SOCRD. John Preskitt, MD, medical director of the Division of Surgical Oncology, commented: “We began to talk about what information the doctor, or the surgeon, or the oncologist needs to have so that the patient receives the best possible care and nothing falls through the cracks. We wanted to prospectively put data into SOCRD to track in real time what is going on with patients. At the request of Dr. Fleshman, and with his enthusiastic support, this process began with the CRC multidisciplinary tumor conference.”

Dr. Preskitt and the SOCRD team worked with Dr. Fleshman and colleagues to develop a “short form,” a data template that is completed for each patient whose case is reviewed at the tumor conference. After extensive discussion, a form was finalized that includes the following information:

- Demographics
- Results of preoperative testing, including colonoscopy/sigmoidoscopy, pathology review of biopsy, imaging, and blood work
- Type of neoadjuvant therapy, if any

SOCRD Strategy

Graphic provided by Remedy Informatics. www.remedyinformatics.com

* Under investigation
• Surgery
• Pathology review of surgical specimen, including stage, margins, number of lymph nodes removed, completeness of mesorectal excision (rectal cancer)
• Genetic testing
• Adjuvant therapy
• Preoperative and postoperative recommendations

This short form is initiated by a research nurse who attends each tumor conference and is completed before the next conference. The colon and rectal surgery fellows collect information about stage, imaging results, kinds of cancer, etc. After validation by a senior physician, the data are entered into the computer system.

During the first 12 months, 244 cases were presented to the multidisciplinary tumor conference with data collection begun or completed. Data accrued thus far show that:

• Of the 244 patients reviewed, 62% were colon cancer cases, 35% were rectal cancer cases, and 3% were cancer of the anus.
• Total mesorectal excision (TME), as assessed by the surgical pathologist, is the ideal goal for the best surgical outcomes in treating rectal cancer. Of the patients who were eligible to have this surgery, 75% had complete or nearly complete TME.
• Our guidelines dictate that 12 or more lymph nodes should be removed and analyzed with each colon resection. In our patients, 92% had 12 or more lymph nodes removed and analyzed.
• All cases of colon or rectal cancer at Baylor are analyzed or screened for possible Lynch syndrome by our pathologists. (See related article on p.14.) In our patient population, 11% of patients had microsatellite instability, indicating a predisposition to this condition, and will be further tested with genetic counseling. This is nearly twice the reported national incidence of 7%.

A similar data collection and entry system is now being constructed for pancreatic, liver, musculoskeletal, and breast cancer. “This is how we begin to define centers of excellence,” said Dr. Preskitt. “By collecting these data in real time, we can analyze what we are doing and see where our problems are. This whole process is receiving a lot of momentum by having a new chief of surgery who is such a strong advocate.”

Pushing the Envelope: Clinical Research

“The best treatment” for patients with CRC is a work in progress, with continual improvements and refinements being made based on the results of clinical research trials. This is well illustrated in changes that have been made in surgical approaches over the last 15 years.

• Minimally invasive, laparoscopic surgery was first considered in 1990 for patients undergoing colectomy for colon cancer. Surgeons were initially concerned that complete resection and adequate lymph node harvesting might not be possible with this technique. As a result of a series of large prospective clinical trials (ALCCAS [Australasian Laparoscopic Colon Cancer Study]; COLOR [Colon Carcinoma Laparoscopic or Open Resection]; CLASICC [Conventional versus Laparoscopic-Assisted Surgery in Colorectal Cancer]; and COST [Clinical Outcomes of Surgical Therapy]) showing equivalent outcomes and faster recovery times in laparoscopic versus open surgery, laparoscopic procedures are now standard for CRC. (Dr. Fleshman was one of the organizers and lead investigators in the COST study.)

• Unlike most colon cancers, rectal cancers, contained in a bony box in the pelvis, are difficult to access surgically. Historically, it was challenging to obtain good circumferential margins, and local recurrence rates were around 30%. When rectal cancers recur, the recurrence is often in the tissue or lymph nodes lying in the mesorectum, a fatty tissue directly adjacent to the rectum. With the growing use of TME as definitive surgery for rectal cancer, the recurrence rates have dropped to about 10%.

• In the 1990s, when most CRC patients received open surgery, patients were required to remain in the hospital for up to 2 weeks. Even with laparoscopic surgery, recovery time was up to 10 days. Enhanced Recovery is a program designed to speed recovery after surgery for CRC through avoidance of fluid overload, minimization of opioid consumption and intrathecal analgesia, and early feeding and ambulation. The program requires close cooperation among the surgeon, anesthesiologist, nurse, physical therapist, and stoma therapist in following a concise set of procedures, as well as extensive education of the patient beginning in the preoperative period. Dr. Fleshman commented: “Enhanced Recovery decreases complication rates and average length of stay.”
Researchers at Baylor Dallas are participating in two randomized, prospective, multicenter trials investigating improved surgical approaches for rectal cancer:

1. ROLARR, RObotic versus LAparoscopic Resection for Rectal cancer, an international multicenter, prospective, randomized, controlled, unblinded, parallel-group trial of robotic-assisted versus laparoscopic surgery for the curative treatment of rectal cancer. This study is sponsored by the University of Leeds and run by the Clinical Trials Research Unit in England. The purpose of this study is to compare laparoscopic rectal resection to robotic-assisted laparoscopic rectal resection for individuals diagnosed with rectal cancer.

2. Z6051: A phase III prospective randomized trial comparing laparoscopic-assisted resection versus open resection for rectal cancer. This is a cooperative study group trial with the Alliance for Clinical Trials in Oncology (formerly the American College of Surgeons Oncology Group—ACOSOG). The primary objective of this study is to test the hypothesis that laparoscopic-assisted resection for rectal cancer is not inferior to open rectal resection, based on a composite primary endpoint of oncologic factors that are indicative of a safe and feasible operation.

Two additional randomized, prospective, multicenter studies looking at systemic therapy regimens for neoadjuvant or adjuvant therapy in CRC are scheduled to begin recruitment next summer.

In addition to the multicenter studies, three local studies are currently underway:

1. Effect of a multidisciplinary approach to treatment of rectal cancer on delivery of care. This is a retrospective study comparing the care patients received before and after initiation of a multidisciplinary approach to the evaluation and overall treatment of patients with rectal cancer.

2. Use of model for end-stage liver disease (MELD) score for guiding clinical decision making in patients undergoing colorectal surgery. This retrospective study evaluates the outcome of patients with a high MELD score who undergo colorectal surgery. This will allow for appropriate patient counseling when discussing morbidity and mortality as it relates to colorectal surgery.

3. N1c pathology in colorectal carcinoma: impact on treatment and outcomes. This retrospective study is looking at patients with a pathological designation of N1c to determine if there is any impact on their treatment and outcome.

Dr. Fleshman, who arrived at Baylor Dallas a little over a year ago, commented on the quality of care available for patients with CRC: “We have surgeons, pathologists, medical oncologists, radiation oncologists, and radiologists, all focused specifically on colorectal cancer. That kind of emphasis always results in better patient outcomes. If an improvement is made in any aspect of the treatment of colorectal cancer, our clinicians are aware of it and ready to adopt it for their patients. People here come together to improve quality of care on an ongoing basis, not just as a one-time thing.”

In the remainder of this issue of CancerUpdate, we discuss new developments in the management of CRC at Baylor Dallas: new imaging approaches to improve disease staging; the development of a blood-based screening test for CRC; and the initiation of a Lynch syndrome testing program.
Accurate staging of tumors is necessary to determine the most appropriate treatment options. While local T stage does not currently play a major part in the staging of colon cancer, it now has a critical role in rectal cancer staging. According to Gregory dePrisco, MD, a diagnostic radiologist on the medical staff at Baylor University Medical Center at Dallas: “For rectal cancer in particular, there has been a major paradigm shift, with the use of high-resolution magnetic resonance imaging (MRI) for preoperative staging as well as restaging after the completion of neoadjuvant treatment.”

Staging for colorectal cancer is based in part on how far the tumor has grown into the layers that form the wall of the intestine and whether it has spread into adjacent areas (T stage). These layers, from inside to outside, include the mucosa (inner lining); muscularis mucosae (thin muscle layer); submucosa (fibrous tissue beneath the thin muscle layer); muscularis propria (thick muscle layer); and subserosa and serosa (thin layers of connective tissue that cover most of the colon, but not the rectum). T stages range from Tis (in situ disease that involves only the mucosa) to T4 (cancer that has penetrated the serosa [T4a] and may have attached to or invaded nearby tissues or organs [T4b]).

Staging is also based on the degree of spread to regional lymph nodes (N category) and whether cancer has metastasized, most commonly to the liver, lungs, or peritoneum (M category).

Rectal Cancer

High-resolution MRI for staging and treatment planning: Rectal cancer is typically found incidentally during a routine physical or when a patient comes in with symptoms (bleeding, fullness, pain). If a malignant tumor is confirmed by biopsy, high-resolution MRI is used for local staging, providing an accurate determination of exactly where the tumor is and the depth of tumor invasion. For this application, diagnostic radiologists at Baylor University Medical Center at Dallas use 3-tesla high-field-strength MRI with a protocol designed specifically for rectal cancer (Figure 1 A, B, C).

Figure 1. 3-tesla high-field-strength MRI with a protocol designed specifically for rectal cancer.

A. Metastatic nodes— Eccentric mass along the right lateral aspect of the rectum with three metastatic perirectal lymph nodes (arrows). The circumferential resection margin is negative indicating this patient is a good candidate for total mesorectal excision following pre-operative radiation therapy.

B. Venous invasion—Long segment low rectal tumor with tumor extending into and expanding the perirectal venous plexus on the left (arrows). Such venous invasion heightens risk of hepatic metastatic disease.

C. Cancer invading vagina and levator—Large low rectal mass invading the right aspect of the vagina (arrowheads) and the right and left levator ani muscles (arrows). Additional images (not shown) showed extensive tumor involvement of the sphincter complex. Adequate resection in such cases requires vaginectomy and levator resection with or without reconstruction.
The determination of tumor location and invasion is important, because it is a deciding factor in whether the patient should be recommended for presurgical neoadjuvant therapy consisting of radiation therapy with or without chemotherapy (CRT). Radiation can carry significant morbidities in this region of the body, including continence issues, scarring, and radiation-induced secondary tumors, so it is important to identify patients who can safely avoid it.

Tumors that do not extend beyond the muscularis propria (T1, T2) and some that extend <1 mm beyond the muscle but are node negative (T3a) may have a primary resection without CRT. For tumors invading beyond the muscularis propria, MRI can estimate the depth of tumor invasion and the circumferential resection margin. If the latter is <1 mm, CRT is usually recommended to lower the risk of local recurrence.

For tumors that penetrate beyond the mesorectal fascia envelope, MRI can assist in surgical planning by determining which way to extend the surgery: How far is the tumor from the presacral fascia? Does it extend into the coccyx or sacrum? Does it involve the pelvic sidewall? Is it a low rectal tumor invading the muscular floor of the pelvis or sphincteric complex? Is it a mid or high rectal tumor with peritoneal invasion?

High-resolution MRI is also useful for assessing lymph nodes in the mesorectal fascia. Nodal involvement carries a recommendation of CRT before surgery. Importantly, MRI can identify nodes outside the mesorectal fascia that can be a source of local recurrence. MRI can also be used to visualize extramural venous invasion of the network of venous channels in the perirectal fat that drains into the portal system and then to the liver. Extramural venous invasion is a significant predictor of metastatic disease and local recurrence.

As an adjunct to MRI in detecting metastases, a computed tomography (CT) scan of the chest, abdomen, and pelvis is used to look for carcinomatosis, which may determine the need for chemotherapy. Any equivocal findings discovered on CT may be further evaluated with positron emission tomography (PET)-CT. If liver metastases are discovered, MRI with the contrast agent Eovist® (gadoxetate disodium) is the most sensitive exam for lesion detection.

Restaging rectal tumors after neoadjuvant chemotherapy: Restaging tumors after the completion of neoadjuvant CRT may result in altered treatment recommendations, depending on the degree of downstaging and tumor regression. With high-resolution MRI, the radiologist can differentiate between fibrotic scar tissue and viable tumor. In cases where there is a complete response (tumor regression grade = 1; only fibrosis is visible), it may be possible to avoid surgery altogether. This would be especially important, for example, for a larger low rectal tumor in proximity to the sphincteric complex, where the surgery would normally include the anus and sphincters, leaving the patient with a lifetime colostomy. If posttreatment restaging shows a significant or complete response, it may be possible to defer surgery and follow the patient with a serial MRI every 3 months. A patient who shows a favorable response to therapy but still requires surgery may be candidate for a less morbid procedure, for instance a transanal local excision rather than a low anterior resection.

**Colon Cancer**

Colon cancers are usually found with colonoscopy, either as a screening modality or when used to obtain a tissue diagnosis as follow-up to a report of symptoms. Unlike rectal cancer, MRI does not currently play a prominent role in the staging of colon cancer. The mainstay for staging of colon cancer is a contrast-enhanced CT scan of the chest, abdomen, and pelvis. If staging CT reveals equivocal findings or the patient is unable to have contrast, PET-CT may be performed.

Almost all nonmetastatic colon cancers are resected, and they can be definitively staged after surgical exploration of the abdomen and pathologic examination of the surgical specimen. Patients with metastatic disease may undergo synchronous or staged resection of resectable liver and/or lung metastases, as patient survival can be substantially prolonged and patients may be cured if the primary tumor is removed and hepatic and pulmonary metastases are eradicated.

If CT findings are discordant with PET-CT findings in patients with hepatic metastatic disease, the patient should be further examined using MRI with the contrast agent Eovist®. This allows an accurate determination of the distribution and number of hepatic metastases. By using MRI imaging with this contrast agent, the radiologists can tell surgeons precisely where the metastases are in relation to major blood vessels and the biliary tree. This information will assist in deciding whether to use surgery, ablative therapy, or radiation therapy to eradicate the metastatic lesions.
Long-term Surveillance of Rectal and Colon Cancer

For both types of cancer, follow-up is conducted using CT scans, peripheral blood assessment of carcinoembryonic antigen (CEA), and liver function tests. If CEA levels rise over time and a restaging CT of the chest, abdomen, and pelvis is unrevealing, PET-CT may be performed. If no recurrent tumor or metastases are found on PET-CT, repeat CT is performed after 3 months.

It may be possible to use a CT scan to determine whether metastatic disease to the liver is present even if it cannot yet be visualized. In an article by Hung and colleagues (Acad Radiol 2006;13:713), it was reported that hepatic metastases are associated with a differing texture that can be identified through postprocessing of the CT data. If this approach could be used to identify patients before the development of overt metastatic disease, alternative management approaches (e.g., heightened surveillance, chemotherapy) could be instituted very early. Dr. dePrisco and colleagues are recruiting a cohort of patients to receive portal venous phase CT scans in order to further investigate this approach.

With regard to the current use of diagnostic imaging for colon and rectal cancers, Dr. dePrisco emphasized: “Every clinician working with these patients needs to recognize the paradigm shift to MRI in the staging and restaging of rectal cancer that both lowers the risk of local tumor recurrence and improves patient survival. If the physicians caring for rectal cancer patients adopt routine use of staging and restaging MRI for rectal cancer, it will make a big difference in how our patients are doing.”

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Welcome to New Members of the Medical Staff at Baylor Charles A. Sammons Cancer Centers

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<tr>
<th>Name</th>
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<tr>
<td>Daniel D. Von Hoff</td>
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<td>Jessamy A. Boyd</td>
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<td>M. Ahad Athar</td>
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Screening for Colorectal Neoplasia: Development of a New Blood Test Based on MicroRNAs

A new blood test based on the genetic marker microRNA-21 (miR-21) has shown very promising results for the early detection of colorectal cancer (CRC) and premalignant advanced adenomatous polyps (adenomas). This new test, developed in the Baylor Research Institute’s (BRI) Gastrointestinal Cancer Research Lab at Baylor University Medical Center at Dallas, may make it possible to catch the disease at an early stage where it is both treatable and curable.

Why a New Test Is Needed
Since the invention of the colonoscope by William Wolff and Hiromi Shinya in 1969, colonoscopy has become the gold standard for CRC screening, with an overall accuracy of around 80%. From 94% to 95% of malignant tumors and large adenomas (>1 cm) are identified, although there is about a 20% chance that smaller polyps will be missed. Colonoscopy allows detection and treatment in one procedure, effectively preventing the development of future cancers. According to C. Richard Boland, MD, chief of gastroenterology at Baylor Dallas, “If we can remove these premalignant polyps, there is a 95% chance that these patients will not develop colon cancer in their lifetimes.”

The growing use of colonoscopy over the ensuing 45 years has aided in reducing the mortality associated with CRC. Nonetheless, public acceptance of colonoscopy is low, with fewer than 50% of individuals 50 years or older receiving colonoscopies. A combination of cost, an unpleasant colon-cleansing regimen required prior to the screening, the need for sedation or anesthesia in many patients, and fears about potential mishaps during the procedure discourage many
eligible adults from having this screening test. Even when
patients do agree to undergo a colonoscopy, detection of
lesions can be affected by the experience of the clinician,
the physical characteristics of the lesion (protruding into the
lumen versus flat), and anatomical bias (with the proximal
end of the colon being harder to access).

To overcome these difficulties, researchers have worked for
many years on developing more acceptable screening tests,
including fecal occult blood tests and virtual colonoscopy.
Unfortunately, approved tests that have a higher rate of patient
compliance usually tend to suffer from lower accuracy. For
example, tests that measure fecal occult blood have a sensi-
tivity and specificity of 50% to 60%. Accuracy is substantially
lower for adenomas, giving these tests a limited role in cancer
prevention. In the case of virtual colonoscopy, where detec-
tion accuracy for CRC and polyps is close to that observed
with standard colonoscopy, the unpleasant colon-cleansing
procedure is still required, and a positive finding requires a
follow-up procedure to remove or biopsy the lesion.

Now with the identification of an miRNA marker for CRC
and adenomas that can be identified in blood as well as
other bodily fluids, there is the promise of a test that will
be inexpensive, noninvasive, and accurate, removing the
major roadblocks to consumer acceptance of regular colon
screening.

**About miRNAs**

MiRNAs are short RNA molecules that bind to and inactivate
or degrade messenger RNA (mRNA) transcripts, effectively
silencing genes. Each miRNA may regulate up to several
hundred genes. Compared to DNA and mRNA, which can be
technically difficult to adapt to the clinical setting, miRNAs
(perhaps because of their small size) are resistant to endog-
eous degradation and thus are extremely stable.

MiRNAs are involved in multiple types of cancer, and it appears
that specific patterns of miRNA expression are associated
with different cancers. Because of this, they are being studied
as candidate biomarkers for the early detection of cancer.

**miR-21 Is a Biomarker for CRC**

Ajay Goel, PhD, director of epigenetics and cancer prevention
at BRI, and his team have been working to identify an
appropriate miRNA for the detection of CRC and adenomas.
He originally explored the possibility of using miRNA expres-
sion profiles in fecal specimens and was able to show
increased expression of miR-21 in patients with adenomas
and CRCs compared with controls. MiR-21 is an oncogenic
miRNA that modulates the expression of multiple cancer-
related genes such as PTEN, TPM1, and PDCD.

In recent work published in the Journal of the National Cancer
Institute (2013;105:849), Dr. Goel was able to demonstrate
that miR-21 is secreted from CRC cell lines and upregulated
in preoperative blood samples of patients with CRCs as well
as patients with advanced adenomas. In a validation study
that included 186 CRC patients, 43 advanced adenoma
patients, and 53 control subjects, blood levels of miR-21
accurately identified 83% of patients with CRC and 77%
of patients with advanced adenomas and were negative in
91% of people without CRC, for an overall test accuracy of
92%. High miR-21 expression in both serum and tissue was
significantly associated with tumor size, distant metastasis,
and poor survival.

The blood test may also have value in detecting recurrence
after a patient has undergone surgery for adenomas or colon
cancer. MiR-21 expression dropped in postoperative blood
samples from patients who underwent curative surgery.
Rising levels could indicate the need for further evaluation
by a gastroenterologist.

The use of a blood test based on a genetic biomarker will
address an important gap in current screening strategies. In
low-risk patients over the age of 50, colonoscopies are rec-
O
ommended every 10 years, based on the typical slow growth
rate of CRCs. However, a small percentage of cancerous
or precancerous lesions may be missed on colonoscopy. In
addition, a small number appear to be much faster growing.
Either of these factors can give rise to interval cancers that
manifest in the extended period between colonoscopies.

Now with the identification of an miRNA marker for CRC and adenomas that can be identified in blood
as well as other bodily fluids, there is the promise of a test that will be inexpensive, noninvasive, and
accurate, removing the major roadblocks to consumer acceptance of regular colon screening.
A blood test that is inexpensive, noninvasive, and accurate can be administered annually or even more frequently in high-risk patients, substantially raising the probability of detecting interval cancers at an early stage.

While miR-21 has shown great promise as the basis of a blood-based colon cancer test, Dr. Goel pointed out that, in practice, additional markers will be needed. “Circulating expression of miR-21 has been described in other solid cancers besides CRC, including glioblastoma, pancreatic cancer, and breast cancer,” he said. “Incorporating additional markers associated with colon cancer will refine the test and make it even more accurate.”

Drs. Goel and Boland caution that this test is intended not to eliminate the need for colonoscopy, but to allow it to be used more selectively. One of the reasons that colonoscopy is such a hard sell to asymptomatic, low-risk individuals is that the lifetime risk of developing colon cancer is only about 6%. Thus, many believe that the discomfort and risks associated with colonoscopy outweigh the potential benefit. The advantage of a blood-based test is that it can “prescreen” these individuals, identifying those who are likely to benefit from more intensive screening.

Dr. Goel and colleagues at BRI are currently in the process of prospectively validating the performance of the miR-21 test. The goal is to obtain a blood sample from 200 healthy subjects who are scheduled for colonoscopy at Baylor Dallas and from 200 treatment-naïve patients who are diagnosed with colorectal cancer. In addition to the local patient sample, collaborations are being established with other researchers in Europe, Asia, and Australia to determine if there are population-specific variations in test results.

Curcumin: Modern Validation of an Agent from Indian Ayurvedic Medicine

Curcumin is the active ingredient in turmeric, the spice that provides the characteristic yellow-orange color in Indian foods and in mustard. In addition to its uses in the kitchen, curcumin has long been used as a powerful antiinflammatory agent in the traditional Indian Ayurvedic system of medicine.

Because of epidemiologic evidence indicating that the incidence of colorectal cancer (CRC) is 15- to 20-fold higher in North America than in rural India, there has been growing interest in identifying factors that may contribute to this striking difference. Curcumin has been of interest because of its antiinflammatory properties and because it is consumed multiple times a day by a large segment of the population in India, while being consumed only rarely in North America.

Ajay Goel, PhD, director of epigenetics and cancer prevention at Baylor Research Institute, recently published the results of an in vitro study looking at the effectiveness of curcumin in enhancing chemosensitization of 5-fluorouracil (5-FU)-resistant human colon cancer cells (PloS One; January 3, 2014). Many cancer patients develop resistance to chemotherapeutic drugs, and it has been hypothesized that this resistance is due to the preferential survival of a drug-resistant subpopulation of cancer stem cells. In this study, high-density 3D cultures of CRC cell lines and their 5-FU–chemoresistant derivative clones were treated with 5-FU with or without curcumin or with curcumin alone. Cultures treated with curcumin alone or in combination with 5-FU showed decreased proliferation, increased apoptosis, and down-regulation of colon cancer stem cell markers. This suggests that the effect of curcumin in enhancing 5-FU sensitivity was correlated with its ability to effectively suppress cancer stem cell pools.
Site-Specific Tumor Conferences at Baylor Charles A. Sammons Cancer Center at Dallas

At Baylor Sammons Cancer Center at Dallas, a key element at the heart of our approach to patient care and education is the site-specific tumor conference program. Rather than focusing solely on recommendations for patient care, the site-specific conferences also aim at educating the medical professionals attending the conference.

Unlike tumor boards, continuing medical education credit is available for physicians who attend. Because several patients with the same diagnosis are presented at each conference, attendees are provided with an in-depth view from specialists, accompanied by lively discussion. Below please find the schedules for tumor conferences at Baylor Charles A. Sammons Center at Dallas.

Conference Schedules

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</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>2nd and 4th Tuesdays</td>
</tr>
<tr>
<td>Neuro-oncology</td>
<td>2nd and 4th Wednesdays</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1st and 3rd Fridays</td>
</tr>
<tr>
<td>Skin</td>
<td>1st and 3rd Wednesdays</td>
</tr>
<tr>
<td>Skull Base</td>
<td>1st Wednesday</td>
</tr>
<tr>
<td>Urology</td>
<td>3rd Wednesday</td>
</tr>
</tbody>
</table>

Baylor Dallas

The site-specific tumor conferences are on the 10th floor conference center in the outpatient cancer center. The exceptions to this are the liver and pancreas tumor conferences, which are held in the transplant large conference room on the 9th floor of the outpatient cancer center, as well as the gynecology tumor conference, which is in room 8 of the lower level of Truett, and the skull base tumor conference, which is in the Radiology resident classroom.

For more information about site-specific tumor conferences at Baylor Charles A. Sammons Cancer Center at Dallas, please call 214.820.4073.
Genetics and Colorectal Cancer: Lynch Syndrome Testing at Baylor Dallas

Hereditary nonpolyposis colorectal cancer (CRC), also known as Lynch syndrome, is the most common hereditary cancer syndrome predisposing individuals to CRC, accounting for approximately 3% of all cases. It is associated with mutations in four DNA mismatch repair (MMR) genes: *MLH1*, *PMS2*, *MSH2*, and *MSH6*. Loss of MMR gene expression can result in microsatellite instability, which is seen in more than 90% of the CRCs associated with Lynch syndrome. In general, a person has about a 5% lifetime risk for developing CRC. However, in people with Lynch syndrome, the risk increases to almost 40% in women and 70% in men. In addition to CRC, both men and women with Lynch syndrome also have increased risks for urinary tract, renal pelvis, stomach, and other cancers. Women are also at increased risk for ovarian and uterine cancer.

According to C. Richard Boland, MD, gastroenterologist on the medical staff and chief of gastroenterology at Baylor University Medical Center at Dallas, most of the approximately 1 million people in the United States who have Lynch syndrome are not aware of it. “These people would greatly benefit if they knew,” he said, “because the disease must be managed differently compared with sporadic colon cancer.”

Various sets of diagnostic criteria based on demographic data (age, family history, clinical history, including extraintestinal manifestations) have been used by doctors to help identify families that are likely to have Lynch syndrome and should be referred for genetic testing. However, these screens fail to detect nearly 13% of Lynch syndrome cases. In order not to miss any cases, a new Lynch syndrome reflex testing program was instituted at Baylor University Medical Center at Dallas in June 2013 to screen all patients with CRC at first diagnosis. The screening uses immunohistochemical staining to detect expression of the 4 MMR gene products, along with assessment for the presence or absence of microsatellite instability (MSI) by polymerase chain reaction. If the findings are abnormal in tumor tissue, a consultation for genetic counseling with confirmatory germline testing for the MMR gene dysfunction associated with Lynch syndrome is made. Patients who test positive with germline testing are placed under surveillance algorithms specific to their circumstances. Moreover, germline testing is available for family members of Lynch syndrome patients at a reduced fee if the family member can provide the testing laboratory with the findings of the relative’s test. Including immunohistochemistry as part of the initial screen helps direct the germline testing in a cost-effective manner, as only the proteins that have loss of expression are tested. (As of March 2014, the National Comprehensive Cancer Network now recommends universal Lynch syndrome testing in all patients with newly diagnosed colorectal cancer.)

Michelle Shiller, DO, MSPT, a pathologist on the medical staff and co-medical director of the Hereditary Cancer Risk Program at Baylor Dallas, commented on the importance of identifying patients with Lynch syndrome: “It puts them at risk for other malignancies and can also change the management of their disease. Precancerous lesions may grow faster, so that more frequent colonoscopies are recommended. A diagnosis of Lynch syndrome may alter the surgical approach. In addition, Lynch syndrome tumors do not respond as well to conventional chemotherapy. Patients and their family members who carry the same mutation need to be aware of these issues.”
Two Molecular Pathways Key to the Development of Colorectal Cancer (CRC) with Microsatellite Instability (MSI)

Lynch syndrome CRC

- Germline mutations and epimutations in MMR genes
- Second hit (mutations, deletions, methylation)

Sporadic CRC (CIMP positive)

- MLH1 hypermethylation

MMR gene inactivation

MSI

Frameshift mutations in genes with coding “microsatellite repeats”

K-ras mutation

β-catenin mutation

DNA methylation

Other mutations

BRAF mutation

Colorectal cancer

“These people [with Lynch syndrome] would greatly benefit if they knew, because the disease must be managed differently compared with sporadic colon cancer.”

C. Richard Boland, MD
New Clinical Trials at Baylor Charles A. Sammons Cancer Center at Dallas

<table>
<thead>
<tr>
<th>Site</th>
<th>Study ID</th>
<th>Location</th>
<th>Principal investigator</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>13181</td>
<td>Texas Oncology–Dallas</td>
<td>Joyce A. O'Shaughnessy, MD</td>
<td>COMETI Phase 2: Characterization of circulating tumor cells from subjects with metastatic breast cancer using the CTC-Endocrine Therapy Index (COMETI-P2-2012.0)</td>
</tr>
<tr>
<td></td>
<td>13146</td>
<td>Texas Oncology–Fort Worth</td>
<td>Sanjay P. Oommen, MD</td>
<td>A randomized double-blind, placebo-controlled study of LEE011 in combination with letrozole for the treatment of postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who received no prior therapy for advanced disease (CLEE011A2301)</td>
</tr>
<tr>
<td>GU</td>
<td>T0-1313</td>
<td>Texas Oncology–Dallas</td>
<td>Thomas E. Hutson, DO</td>
<td>A multicenter, randomized, double-blind, placebo-controlled, phase III study of ARN-509 in men with non-metastatic (M0) castration-resistant prostate cancer</td>
</tr>
<tr>
<td>Hematology</td>
<td>013-031</td>
<td>Baylor Dallas</td>
<td>Edward D. Agura, MD</td>
<td>A Phase 1/2 single-arm, open-label study to evaluate the safety and efficacy of brentuximab vedotin in combination with bendamustine in patients with relapsed or refractory Hodgkin lymphoma (HL)</td>
</tr>
<tr>
<td></td>
<td>013-269</td>
<td>Baylor Dallas</td>
<td>M. Yair Levy, MD</td>
<td>Phase III, multicenter, randomized, trial of CPX-351 (cytarabine:daunorubicin) liposome injection versus cytarabine and daunorubicin in patients 60–75 years of age with untreated high risk (secondary) AML.</td>
</tr>
<tr>
<td>Ovary</td>
<td>13008</td>
<td>Texas Oncology–Fort Worth</td>
<td>Noelle G. Cloven, MD</td>
<td>A phase 3 randomized double-blind trial of maintenance with niraparib versus placebo in patients with platinum sensitive ovarian cancer (PR-30-5011-C)</td>
</tr>
<tr>
<td>Renal</td>
<td>13096</td>
<td>Texas Oncology–Dallas</td>
<td>Thomas E. Hutson, DO</td>
<td>AP311736 adjuvant axitinib treatment of renal cancer: a randomized double-blind phase 3 study of adjuvant axitinib vs. placebo in subjects at high risk of recurrent RCC.</td>
</tr>
</tbody>
</table>
Physicians and their patients can now access information about open clinical trials in oncology at Baylor Sammons Cancer Center by following these steps:

- Go to BaylorHealth.edu/Sammons.
- Click on “Research” on the left-hand menu, then click on “Clinical Trials” in the drop-down menu.
- Select a condition (e.g., “Cancer”) and then select a specific disease (e.g., “Breast Cancer”)

For additional details or questions about the studies, please contact the Office of Clinical Oncology Research Coordination at 214.818.8472, 817.698.8472 or via e-mail at cancer.trials@baylorhealth.edu.


Recent Publications from Baylor Sammons Cancer Center

December 1, 2013 to May 7, 2014


