# Cancerupdate

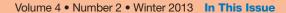
BAYLOR Charles A. Sammons Cancer Centers

# Women's Cancers Yesterday, Today, and Tomorrow

This issue of *CancerUpdate* focuses on women's cancers, malignancies that occur solely or predominantly in women. The most common are breast cancer (an estimated 234,580 new cases in 2013), endometrial cancer (49,560 new cases), and ovarian cancer (22,240 new cases). Despite significant advances in the detection and treatment of these cancers, they continue to be deadly diseases. Breast cancer is one of the leading causes of death from cancer in women in the United States, second only to lung cancer. Although ovarian cancer constitutes only 3% of all cancers in the US, it is the fifth leading cause of cancer death. Endometrial cancer ranks number 8.

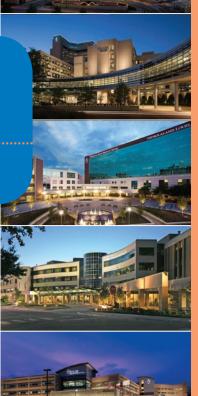
Throughout recorded history and until relatively recently, the treatment options available to fight these cancers were very limited. Because breast cancer is located in a visible organ and, especially in later stages, is often detectable by physical examination, early treatments (some dating back to 1500 BCE) focused on physically destroying or removing the tumors. The development of radiotherapy in the early 20th century offered an additional option for local treatment. The use of systemic chemotherapy in conjunction with surgery to reduce the possibility of recurrence was not methodically pursued until the 1960s, with the inauguration of the National Surgical Adjuvant Breast Project.

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\*Baylor Medical Center at Carrollton and Baylor Medical Center at McKinney offer oncology services and are expected to carry the Baylor Charles A. Sammons Cancer Center name in the future.













# Cancerupdate

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#### BaylorHealth.edu 1.800.9BAYLOR

Editor in Chief: Alan M. Miller, MD, PhD
Chief of Oncology, Baylor Health Care System
Medical Director, Baylor Charles A. Sammons
Cancer Center at Dallas
Writers and Assistant Editors: Lorraine Cherry, PhD,
Margaret Hinshelwood, PhD, and Jana Pope

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## From the Medical Director

## **My Heroes**

I think a hero is an ordinary individual who finds strength to persevere and endure in spite of overwhelming obstacles. Christopher Reeve said it well: One does not need to be a Superman or Wonder Woman to be a hero. People like Michelle Berndt, profiled in this issue of *CancerUpdate*, are true heroes. Not only do they find strength and persevere in the face of their own cancer, but they go further and tell their stories to others so that perhaps those people will be able to face their own struggle, knowing they are not alone.



Alan M. Miller, MD, PhD

I have been fortunate to know many of these heroes. Some are physicians who now treat the very diseases that they themselves fought. There is my friend, a long-term survivor of lymphoma, who just completed another 110-mile bike ride to raise funds and awareness for the Leukemia and Lymphoma Society. For the past 3 years I have joined with others in participating in the Swim Across America open water swim here in Dallas, and many of those who swam past me were themselves survivors doing their part. I would be remiss if I didn't mention April Samuels, a remarkable young woman, noted drummer, and survivor of triple-negative breast cancer. April is getting the message out, and has started a foundation to raise breast cancer awareness and funds called "Breast Cancer Can Stick It." She has a line of clothing and paraphernalia which carries that slogan.

There is so much we can learn from these heroes. If there is cancer in your family, ask your physician if you should be tested for familial cancer genes. Do not put off recommended screening because you are afraid of what you might learn; knowledge is power. Finally, if you do have cancer or another serious disease, follow the example of the heroes that have gone before you: persevere, endure, and then help others. Together you form a legion of superheroes.

Alan M. Miller, MD, PhD

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Chief of Oncology, Baylor Health Care System

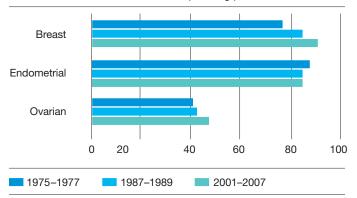
Medical Director, Baylor Charles A. Sammons Cancer Center at Dallas

#### (Continued from page 1)

For endometrial and ovarian cancers, the development of effective therapies has been slower. Although attempts at vaginal hysterectomies date to ancient times and oophorectomy was attempted by the early 1800s, the dangers involved in abdominal surgery before widespread anesthesia and antisepsis caused most surgeons to shy away from treatment. Radiation therapy has proven to be of benefit for patients with endometrial cancer, but generally of only palliative use for patients with ovarian cancer, which is typically advanced at the time of diagnosis. Because these cancers are relatively rare compared with breast cancer, research aimed at more effective systemic treatments has remained underfunded during the last half of the 20th century.

Over the last 40 years, better treatment approaches have resulted in a significant increase in 5-year survival rates for breast and ovarian cancers. The 5-year survival rate for endometrial cancer has decreased over the same time period for reasons that are unclear, but may be related to the cellular or molecular heterogeneity of the disease and/or changing demographics in the US population.

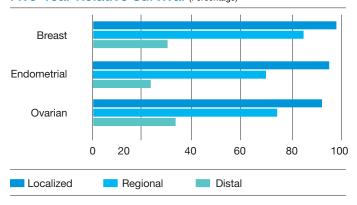
#### Five-Year Relative Survival (Percentage)



Trends in 5-year relative survival rates in breast, endometrial, and ovarian cancers (1975-2008). Based on data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute.

The SEER data illustrate the continued grim prognosis associated with ovarian cancer, with an average 5-year survival rate ≤50% of that seen in breast or endometrial cancer. Is ovarian cancer twice as aggressive as breast cancer? Not necessarily. As shown in the following figure, 5-year survival rates are similar across all three cancer types when considered by cancer stage at diagnosis. In fact, the survival rate for advanced ovarian cancer is actually somewhat higher than that seen in advanced breast or endometrial cancer.

#### Five-Year Relative Survival (Percentage)



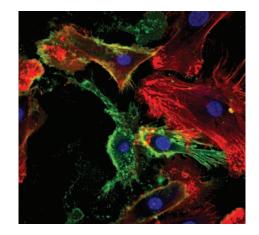
5-year relative survival rates for breast, endometrial, and ovarian cancers by stage at diagnosis. Based on data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute.

The SEER data indicate that the major factor underlying the poor prognosis for ovarian cancer is late diagnosis more than 70% of patients with ovarian cancer are initially diagnosed with advanced disease, compared with 24% of patients with breast cancer and 16% of patients with endometrial cancer. This is the result of the location of the ovaries and the biology of the disease. Early stage ovarian cancer is associated with vaque, nonspecific symptoms, including bloating, pelvic or abdominal pain, feeling full quickly, or urinary symptoms, all of which are relatively common in older women. (The median age at diagnosis for ovarian cancer is 63 years.) In contrast, early stage breast cancer can be detected with screening mammography, and early stage endometrial cancer is frequently associated with vaginal bleeding in postmenopausal women. Clearly, improved approaches for early detection and prevention are desperately needed for ovarian cancer. For all three cancers, ongoing clinical trials are searching for more effective treatment approaches that will improve survival while limiting toxicity.

Our growing understanding of the genetic and immunologic mechanisms underlying tumorigenesis is pointing the way toward more effective treatments, as well as new approaches to early detection and prevention. For example, we already know that some women may require aggressive prevention or screening strategies because of the presence of specific genetic mutations (e.g., *BRCA1/BRCA2*, Lynch syndrome) that place them at very high risk for the development of these cancers.

In the remainder of this issue, we discuss some of the newest approaches currently being used or tested in clinical trials by clinicians at Baylor Sammons Cancer Centers and their academic and clinical research partners for the prevention, detection, and treatment of women's cancers.

# Breast Cancer: New Approaches for Treatment and Prevention



In the last half of the 20th century, the management of breast cancer was transformed. In the mid-20th century, the majority of breast cancers were discovered by accident, usually when they were relatively advanced. Extensive and disfiguring surgery was the standard of care, often to little avail. Today, due to the widespread use of screening mammography, most women diagnosed with breast cancer in the US have very small tumors and are good candidates for breast-conserving surgery. A broad menu of adjuvant therapies is available, offering patients a chance of remaining disease-free for an extended period of time.

But breast cancer still kills over 40,000 women each year in the US. Many questions remain unanswered, some of which are being studied by researchers at Baylor Sammons Cancer Centers and their academic and clinical research partners.

#### **Helping the Body Fight Cancer**

The possibility of destroying and/or preventing neoplastic disease by enlisting the patient's own immune system has excited clinical scientists for decades. During the past 10 years, new and powerful tools in immunology and molecular biology have allowed a more complete understanding of the immune process and the design of better strategies for vaccine development. Now, a vaccine to fight breast cancer is ready to launch at Baylor Charles A. Sammons Cancer Center at Dallas.

Joyce O'Shaughnessy, MD, Celebrating Women Endowed Chair in Breast Cancer Research at Baylor Charles A. Sammons Cancer Center, is the principal investigator on two related clinical trials aimed at testing the efficacy of a dendritic cell vaccine for the treatment of advanced or metastatic breast cancer. The vaccine, which has been developed by Karolina Palucka, MD, PhD, director of the Ralph M. Steinman Center for Cancer Vaccines at Baylor Institute for Immunology Research, is based on the ex vivo generation and antigen loading of the patient's own dendritic cells.

The first clinical trial is a pilot study to assess the safety of the interleukin (IL)-1 receptor antagonist, anakinra, plus the physician's chemotherapy choice in patients with HER-2–negative metastatic breast cancer. The IL-1 family of cytokines plays an important role in inflammation and host defense. Increased IL-1-beta levels correspond with a more advanced clinical stage of breast cancer, and are associated with an immune-suppressive microenvironment around the tumor. Secondary objectives in this study are objective response rate, clinical benefit rate, progression-free survival, and determination of anakinra-induced anti-IL-1 blood transcriptional signatures.

The second clinical trial will assess the safety and feasibility of combining dendritic cell vaccination with preoperative chemotherapy, with or without the addition of anakinra, in patients with locally advanced triple-negative breast cancer. Recent studies have shown that human breast cancers can be immunogenic, and that enhancing the immune effector function already present may augment the cytotoxic effects of chemotherapy. The blockade of IL-1-beta by anakinra is a novel approach to breast cancer immunotherapy, involving a complex system of cross-talk and feedback between cancer cells and cells of the immune system. In addition to assessing safety and feasibility, other objectives of this study are to determine pathologic complete response rates with and without anakinra, disease-free survival, and biomarkers of immunity in breast cancer biopsy specimens and blood samples.

According to Dr. O'Shaughnessy, "The focus of this work is to both counteract the negative effects of the immune system that exist in high-risk breast cancer and to unleash the powerful positive effects of the immune system to work together with chemotherapy to kill cancer cells."

#### **Preventing Breast Cancer**

While better approaches to early detection and effective treatment are significant factors in reducing the mortality and morbidity associated with breast cancer, clearly the ultimate solution would be to prevent the cancer from ever starting. Two large clinical trials—the National Surgical Adjuvant Breast Project P-1 trial and the STAR trial—have demonstrated that long-term treatment (5 years) with antihormonal therapy (tamoxifen or raloxifene) is effective in preventing invasive breast cancer in high-risk women.

The principal investigator for both of those studies at Baylor University Medical Center at Dallas was Michael Grant, MD, a breast surgical oncologist on the medical staff at Baylor Dallas. "The efficacy of these agents in preventing breast cancer was significant, with an almost 50% risk reduction," said Dr. Grant. "Unfortunately, a lot of patients who would be good candidates for these drugs are afraid of the potential side effects and just don't want to take them when they aren't sick."

Dr. Grant has now turned his attention to another approach for breast cancer prevention, this one using high-dose vitamin D3 (cholecalciferol). This phase IIb study is a randomized, double-blind, placebo-controlled biomarker modulation study of high-dose vitamin D3 in premenopausal women at high risk for breast cancer. There is preclinical and clinical evidence that vitamin D deficiency, which is surprisingly common, may be involved in the development of breast cancer. The primary outcome measure is mammographic breast density, which has been associated with increased breast cancer risk. The secondary outcome measure is Ki-67, a molecular marker of cellular proliferation.

This study is also recruiting patients at Baylor Medical Center at Irving under the direction of Edward Clifford, MD, a surgical oncologist on the medical staff at that institution. According to Elizabeth Broyles, RN, BSN, CRN, who serves as project

manager on the Irving campus, the study will continue for a year, with follow-up occurring at 3, 6, 9, and 12 months. "Mammographic density will be assessed using image analysis of digitized images," she explained, "while serum and blood samples will be sent to a core laboratory for standardized assessment of markers."

#### Assessing Risk from Early, Noninvasive Lesions

Major technical advances have occurred in the last 30 years in breast cancer imaging and in biopsy techniques for sampling suspicious lesions. One of the problematic aspects of this improved technology for breast cancer detection is the increasing discovery of noninvasive lesions (ductal atypia [DA] and ductal carcinoma in situ [DCIS]). According to Dr. Clifford, "You may find DA by histological analysis of a core needle biopsy. If you subsequently do an excisional biopsy, you will upgrade from DA to DCIS about 20% of the time. But then you face the issue of whether the DCIS should be treated as a cancer."

DCIS now constitutes about 20% of all newly diagnosed breast tumors in the US. It can become invasive, but does not invariably do so. Because of the chance of additional current or future invasive disease associated with DCIS, the standard treatment until recently was mastectomy. Several large clinical trials have subsequently demonstrated that excisional biopsy with negative surgical margins followed by radiation therapy is an acceptable approach for the treatment of DCIS.

The question now being addressed is whether there is a subgroup of women at such low risk for local recurrence that they can be treated with excisional biopsy alone with no radiation therapy. Dr. Clifford is hopeful about a new multigene test that may be able to distinguish between low-risk and high-risk patients with DCIS. A low-risk patient might be treated with biopsy alone and no further treatment. "There is some controversy remaining about how well the data supporting this test has been validated, so some caution is in order right now," he commented. "But this definitely is a further progression toward the concept of individualized medicine."

"The focus of this work is to both counteract the negative effects of the immune system that exist in high-risk breast cancer and to unleash the powerful positive effects of the immune system to work together with chemotherapy to kill cancer cells." Joyce O'Shaughnessy, MD

# Assessing Hereditary Cancer Risk at Baylor Sammons Cancer Centers: Growing a Program

Approximately 20% of the women who are diagnosed with breast cancer each year have a positive family history of the disease. The degree of risk for a woman in such a family is a function of the type of relative affected (first or second degree), how many relatives are affected, and the age at which they were affected.

Ovarian cancer also tends to run in families. If a woman has a first-degree relative with ovarian cancer, her risk is 3 to 4 times higher than that of a woman in the general population. The risk increases if additional first- or second-degree relatives have had ovarian cancer.

In some cases, the increased risk for breast or ovarian cancer is due to the presence of a harmful mutation in BRCA1 or BRCA2, tumor suppressor genes that normally prevent uncontrolled cell growth. Mutations in these autosomal dominant genes increase the lifetime risk of breast cancer from 12% in the general population to 56% to 87%. For ovarian cancer, the lifetime risk increases from 1.4% in the general population to 15% to 40% in women who carry a BRCA1 or BRCA2 gene mutation.

Mutations in other genes (e.g., TP53, PTEN, MLH1, MSH2) may also be involved with increased risk for women's cancers. For example, women with Lynch syndrome (associated with mutations in MLH1, MSH2) have a 9% to 12% chance of developing ovarian cancer and a 40% to 60% chance of developing endometrial cancer. Several rare genetic syndromes, such as Li Fraumeni syndrome or Cowden syndrome, also increase the risk of breast or other cancer.

The Hereditary Cancer Risk Program at Baylor University Medical Center at Dallas is under the medical direction of Joanne L. Blum, MD, PhD, a physician on the medical staff at Baylor Dallas. The program offers genetic testing and counseling to patients about their risks for breast and ovarian cancer. Over 80% of patients who come to the program are referred by physicians; the remaining 20% self-refer after

hearing about the program from a participant, a health fair, or another source.

Women who come into the program meet with a genetic counselor to learn about genes, mutations, and genetic testing, and to review their own medical and family history for risk factors. The counselor also discusses what the patients' options are if they test positive for a mutation, and is available for additional counseling as necessary.

Between the program's inception in 1998 and September 2013, 3,981 patients have been seen for genetic testing and counseling, with the number of patients enrolled increasing every year. With three full-time genetic counselors now available, the program is gradually expanding across the Baylor Health Care System. Starting in 2012, the counselors began seeing patients in Plano and Fort Worth. Those clinics have expanded significantly since then; as of last September, 120 patients had been seen in Plano during 2013 compared with 55 in 2012, and 112 had been seen in Fort Worth compared with 19 in 2012. Further expansion of the program to other centers is anticipated, pending the hiring of additional genetic counselors.

Most patients who participate in the Hereditary Cancer Risk Program agree to enroll in the patient registry, which maintains information about them and their genetic status. Most are willing to participate in research studies, especially questionnaire studies. Dr. Blum is enthusiastic about what she calls "the power of numbers" to get enough information to answer some of the complex questions about breast and ovarian cancer heritability.

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Family History of Breast Cancer	Relative Risk
No family history	1.0
First-degree relative diagnosed at age < 50	3.3
First-degree relative diagnosed at age $\geq 50$	1.8
Two first-degree relatives	3.6
Second-degree relative	1.5



Dr. Blum mentioned that there has been a spike in interest in the program since the recent publicity surrounding movie actress Angelina Jolie, a BRCA mutation carrier who opted to have a prophylactic mastectomy. "It's an exciting time for clinicians who deal with these patients," she said, "since not only do we have prevention strategies to offer our patients that can improve survival, but we're also beginning to learn how to specifically target these cancers at the molecular level. It's a rapidly evolving field, with important questions still to be answered."

In some cases, the increased risk for breast or ovarian cancer is due to the presence of a harmful mutation in *BRCA1* or *BRCA2*, tumor suppressor genes that normally prevent uncontrolled cell growth. Mutations in these autosomal dominant genes increase the lifetime risk of breast cancer from 12% in the general population to 56% to 87%. For ovarian cancer, the lifetime risk increases from 1.4% in the general population to 15% to 40% in women who carry a *BRCA1* or *BRCA2* gene mutation.

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



#### **Baylor University Medical Center at Dallas**

Sarah Y. Boostrom, MD—Colon and Rectal Surgery

#### **Baylor Medical Center at Garland**

Korie L. Flippo, MD-Internal Medicine/ Hospice Palliative Medicine Hematology-Oncology

#### **Baylor Regional Medical Center at Grapevine**

Prasanthi Ganesa, MD-Internal Medicine/ Medical Oncology

#### **Baylor Medical Center at McKinney Baylor Regional Medical Center at Plano**

Mohammed A. Athar, MD-Internal Medicine Hematology, Medical Oncology

#### **Baylor Medical Center at McKinney**

Mary E. Cavalier, MD-Pediatrics/Pediatric Hematology-Oncology

#### **Baylor Regional Medical Center at Plano**

Khusroo M. Qureshi, MD-Internal Medicine Hematology, Medical Oncology

# Michelle Berndt A *Dallas Hope* Star Who Keeps on Giving

Little did Michelle Berndt realize that going to her gynecological checkup that day would change her life forever. In a conversation with her doctor about her medical family history, she mentioned that her mother, grandmother, and great-grandmother all had fought breast cancer.

Her doctor said she really needed to be tested for a BRCA1/ BRCA2 gene mutation; she tested positive for a BRCA2 mutation, the only one of her siblings to do so. Like Angelina Jolie, who tested positive for a mutation in the BRCA1 gene, Michelle decided to undergo a preventive bilateral mastectomy that would be followed by a preventive oophorectomy. She was only 29 years old at the time. Just before her mastectomy procedure, Michelle detected a lump in her breast. What followed was a double mastectomy and reconstruction, eight rounds of chemotherapy, and 6 weeks of radiotherapy for her aggressive, node-positive stage 2 tumor. At one point Michelle became so sick she ended up in the hospital, unsure whether she would make it out alive. But somehow, with the support of her family and friends and sheer strength of will, she made it through.

Michelle Berndt, married mother of two with a career in higher education, went on to do one of the things she knew best: compete in pageants. Four weeks after coming home

Above: A video frame from Dallas Hope shows a very sick Michelle recovering in the hospital. Right: The radiant Mrs. Texas International.

from the hospital, she competed and won the Mrs. Texas International pageant. As Mrs. Texas International, her goal is to make 100 appearances, speaking about the importance of cancer screening and raising awareness for young adults with cancer. In addition to her forum with the Mrs. Texas International pageant, she has given her time freely to many events at Baylor Sammons Cancer Center and the American Cancer Society, and most recently served as a mentor with Imerman Angels, an organization that



Four weeks after coming home from the hospital, she competed and won the Mrs. Texas International pageant. As Mrs. Texas International, her goal is to make 100 appearances, speaking about the importance of cancer screening and raising awareness for young adults with cancer.

provides one-on-one support among cancer fighters, survivors, and caregivers. This has truly become a calling in Michelle's life, one that involves not only her, but the rest of her family and friends. Even her 6-year-old daughter now emulates her mother, and in the checkout line at the supermarket tells the checkout person, "You know, my mommy had breast cancer."

For more information about Michelle's inspiring journey, see the Dallas Hope website at http://www.baylorhealth.com/ dallashope/Pages/default.aspx.

# Mobile Mammography





Baylor Health Care System Foundation hosted its 2013 Celebrating Women luncheon on October 23 in Dallas, using the opportunity to introduce the first mammography vehicle in the state of Texas with three-dimensional imaging capability. This mobile mammography unit will allow women to undergo quality breast screenings almost anywhere. Internet capabilities will allow the machine to sync patient data with the hospital. In addition to the mammogram unit, the bus functions as a doctor's office with two changing rooms that open directly to the mammogram area for privacy. The mobile clinic can screen up to 50 women a day. With the aid of the mobile mammography unit, they don't have to take off a day of work as the clinic can actually go to them.

Mark Spradley of Hologic, the company that manufactured the mobile breast screening center, said it is only the second mammography unit of its kind in the Southwest. Ethel Randall, MBA, RT (R)(M), director of breast imaging at Baylor Health Care System, said the plan is to set up schedules for the bus stops weeks in advance so appointments can be made easily.

Celebrating Women has raised more than \$20 million over the last 14 years, including nearly \$2 million at this year's luncheon, to benefit Baylor Health Care System's fight against breast cancer. Building on decades of care and research, Baylor is fighting against breast cancer through a commitment to patient care, education, research, and clinical trials. In addition to the purchase of this mobile mammography vehicle, Celebrating Women has impacted many other areas, including technology, medical education, patient-centered programs, and research. Joyce O'Shaughnessy, MD, the Celebrating Women Endowed Chair in Breast Cancer Research at Baylor, and Karolina Palucka, MD, PhD, director of the Ralph M. Steinman Center for Cancer Vaccines at Baylor Institute for Immunology Research, part of Baylor Research Institute, are awaiting regulatory approval to proceed with a clinical trial that will test the efficacy of a vaccine for triple-negative breast cancer, an aggressive form of the disease. Circle of Care honoree Bruce Selkirk, in conjunction with the Baylor Foundation, has generated more than \$1 million to support this research. Thus, with the help of the funds generated by Celebrating Women, the Baylor Health Care System is better armed to continue its fight against breast cancer.

# **Integrative Medicine: Focusing on the Needs** of Cancer Patients from a Holistic Viewpoint

Carolyn Matthews, MD, a gynecologic oncologist on the medical staff at Baylor University Medical Center at Dallas, is the medical director of the integrative medicine program. The program has been open and seeing patients since December 2011. It focuses on lifestyle recommendations such as nutrition, sleep, exercise, and stress reduction that will help patients feel better mentally and physically, as well as enable them to better withstand the challenges and side effects of cancer therapies.

The center is open for initial consults, follow-up visits, and acupuncture treatments 2 days a week. The initial consult includes an in-depth medical history and interview of the patient to determine that individual's unique requirements. Each patient will leave with an integrative medicine prescription that may include recommendations about diet, exercise, stress reduction, additional tests (e.g., metabolic tests, sleep studies), additional therapies (relaxation biofeedback, massage, acupuncture, body work), and possible supplements (e.g., probiotics, omega-3 fish oil, vitamin D).

The program has a full schedule of new patients, follow-up visits, and acupuncture treatments as word about this center spreads. Dr. Matthews commented, "I'd like to see this service available to anyone who would like to learn how to take better care of themselves. My favorite consult is the individual who comes in and tells me, 'I want to know what I can do to be as healthy as I can."

#### **Integrative Medicine and Women's Cancers**

An increasing amount of data suggests that lifestyle approaches, including diet and exercise, are valuable not only in improving day-to-day quality of life, but also in assisting with cancer prevention and control. In breast cancer, for example, increased physical activity is significantly associated with decreased risk of breast cancer and with increased survival after a diagnosis of breast cancer. In addition, excess weight and alcohol consumption are known risk factors for initial and recurring disease, and evidence is emerging that dietary changes can change the background of inflammation, making the microenvironment less conducive to tumor growth. Women who are overweight are at higher risk for endometrial cancer, so weight loss through diet and exercise is especially relevant for this disease. In the first study of its kind in ovarian cancer, the GOG-225 trial being conducted at Baylor All Saints Medical Center at Fort Worth is testing to see if diet and exercise can affect progression-free survival in patients with advanced disease.

#### A Dietary Approach to Improved Quality of Life

The program is interested in dietary approaches that may improve quality of life in patients being treated for cancer. One method that has shown promising results calls for eliminating many foods that typically trigger sensitivities in large numbers of people: soy, wheat, dairy, corn, coffee, alcohol, and sugar. In a group of women who followed this diet for 3 weeks, cutting out all processed and refined food and eating a diet consisting of vegetables, fruits, nuts, and seeds, almost all of the women lowered their scores on a symptom assessment instrument by about 50%, and most reported sleeping better, having less pain in their joints, and experiencing more energy. There is also the intriguing possibility that this kind of dietary intervention may have a direct beneficial effect on the disease process, in addition to improving symptoms and quality of life, as important as those are.

#### **Exercise and Adjuvant Chemotherapy in Breast Cancer**

One of the ways that exercise may help to improve outcomes in breast cancer is by helping patients to cope with the







side effects of treatment. Cynthia Osborne, MD, a medical oncologist on the medical staff at Baylor Dallas, is conducting a study looking at the interactive effects between exercise and adjuvant chemotherapy in women undergoing treatment for breast cancer. Two issues are being considered.

First, exercise compliance is poor in the US, with about 50% of people stopping programs within 6 months. This study will determine if breast cancer patients who exercise at the cancer center on the day that they receive each dose of chemotherapy will show increased compliance with an exercise program in the 6 months after completion of their treatment. Second, chemotherapy schedules are frequently delayed or attenuated because of the severity of side effects. This study will determine if exercise is associated with decreased side effects and/or decreased chemotherapy dose attenuation or delay.

Study subjects will be enrolled in the FitSTEPS for Life® program. This program is offered free of charge to cancer patients at multiple sites, including Baylor Charles A. Sammons Cancer Center at Dallas. Staff members are trained as exercise physiologists. They use the patient's clinical information and doctor's recommendations to design exercise programs tailored specifically to each patient.

Programs use a combination of aerobic exercise, core strengthening, and light weight work, escalated every few weeks as the individual becomes stronger.

For this study, women will be encouraged to exercise a minimum of 3 days a week, including the day that they receive chemotherapy. Twenty-four patients have already been enrolled, with a goal of 200. According to Dr. Osborne, "We have good data showing that women who exercise regularly, even at a moderate level, have a lower risk of incidence and recurrence from breast cancer. But long-term compliance with an exercise program is a real problem. How do we get people excited about doing it? How long does it take for exercise to become a habit? It's a hard problem, because we've become a sedentary society."

"I'd like to see this service available to anyone who would like to learn how to take better care of themselves. My favorite consult is the individual who comes in and tells me, 'I want to know what I can do to be as healthy as I can." Carolyn Matthews, MD Ovarian cancer is the leading cause of death from gynecologic cancer in the US. Over 70% of patients are initially diagnosed with advanced disease, at which point the 5-year survival rate is less than 30%. This grim prognosis has seen only modest improvement over the last 40 years, pointing to several critical needs:

- 1. The ability to diagnose ovarian cancer earlier, when the chance of a cure is much higher
- The development of more effective treatments to prolong survival in patients with advanced disease
- 3. Improved approaches to prevention

Researchers at Baylor Charles A. Sammons Cancer Centers and their academic and clinical partners are pursuing exciting new research directions for the improved management of patients with ovarian cancer. An important component of this process is affiliation with the Gynecologic Oncology Group (GOG), a National Cancer Institute–funded research group comprising 50 principal centers and 160 affiliate institutions nationwide that collaborate on clinical trials. Over 3,300 patients are registered each year in GOG research trials.

Noelle Cloven, MD, a gynecologic oncologist on the medical staff at Baylor All Saints Medical Center at Fort Worth, commented, "We are really pleased and proud that, through our affiliation with the GOG, we are able to offer these clinical trials to our patients. These large collaborative trials are often practice-changing, and we want North Texas women to be able to participate without having to travel long distances to a study site." These sentiments were echoed by Mark Messing, MD, a gynecologic oncologist on the medical staff at Baylor Regional Medical Center at Grapevine: "Through the work of Baylor, US Oncology, and Texas Oncology, and our affiliations with GOG, we are able to bring advanced clinical care and research into the community. People really want that—they want the best possible care near home."

#### **Early Detection of Ovarian Cancer**

Ovarian cancer has been called "the silent disease" because its symptoms are vague and nonspecific, making it difficult

to diagnose at an early, potentially curable stage. Possible symptoms include:

- Bloating
- Pelvic or abdominal pain
- · Difficulty eating or feeling full quickly
- Urinary symptoms (urgency or frequency)
- · Change in bowel habits
- Unexplained vaginal bleeding

These symptoms may be related to other conditions, but are more likely to be associated with ovarian cancer if they are new and unusual and if they persist for more than 2 weeks.

A better approach for screening is the use of biomarkers that can be measured in a blood sample. Traditionally, cancer antigen CA-125 has been used as a marker for ovarian cancer, but it is not specific enough to be used as a regular screening tool. Many conditions can cause elevation of CA-125, and nearly half of stage I ovarian cancers have normal values. Because each woman has a personal baseline value for CA-125, recent studies have been exploring the use of serial CA-125 measurement in combination with transvaginal ultrasound as a screening approach.

As more is learned about the molecular biology of ovarian cancer, genetic screening tests are being developed to assist in detecting ovarian cancer. The OVA1 test uses five markers (transthyretin, apolipoprotein A1, transferrin, beta-2 microglobulin, and CA-125), while the OvaSure test uses six

markers (leptin, prolactin, osteopontin, insulin-like growth factor II, macrophage inhibitory factor, and CA-125). Neither of these tests is currently recommended as a screening tool for ovarian cancer. Additional markers, including HE4, mesothelin, B7-H4, decoy receptor 3, and spondin-2, are associated with ovarian cancer but do not increase early enough in the disease process to be useful for screening.

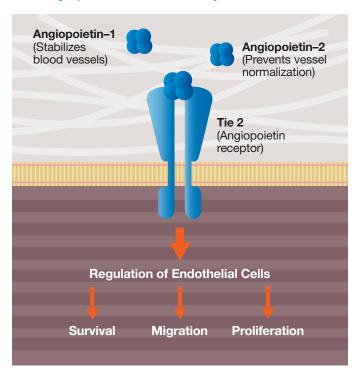
#### **Developing More Effective Therapies**

Primary treatment for newly diagnosed ovarian cancer consists of surgery, followed in most cases by chemotherapy. E. Colin Koon, MD, PhD, a gynecologic oncologist on the medical staff at Baylor University Medical Center at Dallas, pointed out that ideas about optimal surgery have changed significantly over the last 10 years. "In the past," he said, "nodules as large as 2 cm would be left behind; when this limit was reduced to 1 cm, we found that patients lived longer, and this became the standard. As of 8 years ago, that was reduced again. Now, our goal is to leave no visible disease at all." In some patients with advanced disease, debulking might be a fairly morbid procedure requiring extensive surgery. "If we give three to four cycles of chemotherapy up front to these patients who are poor candidates for debulking, we can still approach the goal of no visible disease, but with much less morbidity," he said.

Adjuvant chemotherapy for primary ovarian cancer typically uses a combination of a platinum-containing compound and a taxane. With these standard drugs, researchers have found that altering the route of delivery and timing of the drugs can significantly affect treatment outcomes. For example, the GOG 172 study showed a significant increase in overall survival when the chemotherapy was delivered intraperitoneally rather than intravenously. Altering the treatment schedule and delivery can also have an impact on side effects.

The major thrust of research, however, is away from "shotgunstyle" systemic agents like carboplatin and toward biologic therapies that target specific processes important for tumor development and growth. One such process is angiogenesis, the growth of new blood vessels to support tumor cell growth and metastasis. Angiogenesis involves multiple signaling pathways, including the vascular endothelial growth factor (VEGF)/VEGF receptor pathway and the angiopoietin/Tie-2 pathway. Bevacizumab (Avastin®) was the first agent to target the VEGF/VEGF receptor pathway. Although it has shown modest success in the treatment of some cancers (e.g., lung, colorectal), results have not been as dramatic as originally

#### The Angiopoietin/Tie-2 Pathway



anticipated, and the side effect profile, including an increased risk of blood clots, has been more significant than expected.

A new drug that targets the angiopoietin/Tie-2 pathway is now being tested in patients with ovarian cancer. AMG-386 is a hybrid compound comprising a peptide with angiopoietin-binding properties that is fused to the Fc region of an antibody; the compound acts to inhibit angiopoietin 1 and 2. The TRINOVA-3 study is a phase 3 randomized, double-blind, placebo-controlled, multicenter study of AMG-386 with paclitaxel and carboplatin as first-line treatment for patients with stage III/IV epithelial ovarian, primary peritoneal, or fallopian tube cancers. The trial is designed so that all patients still receive the standard of care, with half also receiving the study drug and half receiving placebo. The primary outcome measure is progression-free survival. Principal investigators on this study are Dr. Koon at Baylor Dallas and Dr. Messing at Baylor Grapevine.

#### **Preventing Ovarian Cancer**

Genetic factors can increase the risk of ovarian cancer. This includes mutations in the BRCA1/BRCA2 genes, Lynch syndrome, or positive family history with unspecified genetic linkage. However, only about 5% to 10% of patients with

"Cancer is incredibly intelligent and constantly changing. To have a chance of hitting this moving target, we have to strike at multiple different levels: detect it earlier, decrease the chance of getting it, improve the drugs we have available and how they are given, improve our surgical approach. We've made huge advances in the last 10 years, but we're still only scratching the surface." E. Colin Coon, MD, PhD

ovarian cancer come from these high-risk families. For other women, the risk appears to be associated with the amount of ovulation that occurs over a reproductive lifetime. Thus, the risk is decreased by up to 60% when there are multiple births and the first pregnancy and birth occurs at or before 25 years of age, whereas risk is increased if the first birth occurs after age 35 or if a woman is nulliparous. Hormone replacement therapy and fertility drugs are also linked to an increased risk, while the risk decreases with the use of oral contraceptives and/or breast feeding.

According to Dr. Koon, women at very high risk can reduce that risk somewhat by taking birth control pills. Alternatively, they may opt to have a prophylactic oophorectomy. This will greatly reduce their risk of future disease, although they retain a small risk of ovarian cancer in the peritoneum.

Cancer prevention trials are studying other ways to lower the risk of developing a primary ovarian cancer or a recurrence after initial treatment. Drugs that have resulted in significant risk reduction in breast cancer (i.e., tamoxifen and raloxifene)

have shown disappointing results in preclinical studies of ovarian cancer. Other preclinical studies suggest that vitamin D may be of value in this setting, and a small clinical trial testing this hypothesis is underway in Chicago. Dr. Cloven at Baylor All Saints is participating in GOG-225, a clinical trial designed to see if diet and exercise can affect progressionfree survival in patients who have been treated for advanced ovarian cancer. Similar studies of modifiable lifestyle factors have yielded positive results in breast cancer, but this is the first such study done in gynecologic cancer.

These and other clinical studies continue to push the boundaries of care for ovarian cancer, but much remains to be done. According to Dr. Koon, "Cancer is incredibly intelligent and constantly changing. To have a chance of hitting this moving target, we have to strike at multiple different levels: detect it earlier, decrease the chance of getting it, improve the drugs we have available and how they are given, improve our surgical approach. We've made huge advances in the last 10 years, but we're still only scratching the surface."



## **Endometrial Cancer: Good Outcomes Getting Better**

Endometrial cancer (also known as adenocarcinoma of the endometrium or carcinoma of the uterine corpus) is the most common malignancy of the female genital tract in the US. Most cases are the result of sporadic mutations, although about 5% are associated with the defective DNA mismatch repair genes found in Lynch syndrome. Women in the general population have an approximate 3% lifetime risk of endometrial cancer, compared with 60% for women in Lynch syndrome families.

Around 75% of endometrial cancers occur in women aged 55 or over. Besides age, other risk factors are related to increased exposure to estrogen: increased estrogen levels caused by obesity or diabetes, early age at menarche, nulliparity, late age at menopause, and the use of unopposed estrogen in hormone replacement therapy. The selective estrogen response modifier tamoxifen, taken as preventive or adjuvant treatment for breast cancer, is also associated with increased risk. The incidence of endometrial cancer in the US has been increasing by a little over 1% each year, possibly due to increased life expectancy and obesity.

Unlike breast cancer and ovarian cancer, which have seen significantly improved 5-year survival rates since 1975, the rates in endometrial cancer have decreased during that same time period. One reason for this may again be increased life expectancy. Clinically, endometrial cancers fall into two categories, endometrioid and serous. Endometrioid is associated with increased estrogen and obesity and has a favorable prognosis. Serous is more common in older women and has a less favorable outcome.

Irregular vaginal bleeding in postmenopausal women is an early sign of endometrial cancer that sends many women to a doctor for assessment. The result is that these cancers are usually diagnosed at an early stage when they are still confined to the uterus and can be definitively treated using surgery with or without radiation therapy. Over the last 12 years, major changes have been made in the delivery of these treatment modalities to significantly improve patient comfort, safety, and convenience.

#### Surgery

According to Mark Messing, MD, a gynecologic oncologist on the medical staff at Baylor Regional Medical Center at Grapevine, "The biggest change we've seen in gynecologic oncology is the introduction of robotics into surgical practice. This allows a minimally invasive surgical approach compared with a large open laparotomy. The majority of patients now get to go home the next day and return quickly to normal activities. We are seeing reduced hospitalization, lower infection rates, fewer transfusions, and better quality of life."

The robotic surgery approach involves four to five small incisions that allow the insertion of surgical and imaging instruments. The instruments are guided by the surgeon using a magnified 3D high-definition vision system. The robotic instruments are designed to bend and rotate more completely than the human wrist, allowing easier access to difficult sites. The robotic and computer technologies translate the surgeon's hand movements into precise micromovements of the instruments.

Although the equipment needed for robotic surgery is expensive up front, it broadens the field of practitioners that can perform minimally invasive surgery. Dr. Messing commented, "The use of robotic surgery extends our ability to offer advanced laparoscopic procedures and increases the reproducibility of this surgery in the hands of many physicians. With appropriate training, many more physicians will be able to perform these surgeries successfully."

#### **Radiation Therapy**

Radiation therapy is an integral part of the treatment for endometrial cancer. It is a treatment option for all but the most favorable stage I tumors, and is recommended for intermediate-risk stage Ib and all stage II and III tumors. Treatment may consist of external beam therapy (tumordirected or pelvic) or brachytherapy. External beam therapy is usually given 5 days a week for 4 to 6 weeks. Brachytherapy uses radioactive seeds/elements contained in a cylinder that is inserted into the vagina. The radiation principally affects the area of the vagina in direct contact with the cylinder, while nearby structures such as the bladder and rectum receive less exposure. Vaginal brachytherapy can be administered as low-dose or high-dose therapy. For low-dose therapy, which is no longer common in the US, the radiation cylinder is left in place for several days, during which time the patient needs to stay immobile, leading to an increased risk of blood clots. For high-dose therapy, the cylinder is left in place for less than an hour. Treatment is given on a fixed schedule (daily or weekly) for at least three doses.

Modern adjuvant radiotherapy for the treatment of endometrial cancer is not associated with significant morbidity, but it can result in side effects that while less severe, nevertheless impact quality of life, e.g., diarrhea, bowel symptoms, bladder irritation, and scar tissue causing vaginal stenosis. Continued research into improved delivery of radiotherapy aims at optimizing treatment efficacy while minimizing discomfort and inconvenience for the patient.

Mark Engleman, MD, a radiation oncologist and medical director of oncology on the medical staff at Baylor Regional Medical Center at Plano, commented, "Modern brachytherapy is a huge step forward. Low-dose therapy used to require hospitalization for 24 to 36 hours. Now the patient

treatment can be accomplished in 10 minutes. We have also made tremendous advances in the delivery of external beam radiation. With intensity-modulated radiation therapy, we now have three-dimensional treatment planning and delivery that focuses the radiation dose onto the tumor with pinpoint precision, sparing the surrounding healthy tissue." Baylor Medical Center at Plano is part of the Radiation Therapy Oncology Group (RTOG). RTOG is a cooperative group of 300 academic and community-based facilities around the world who participate in clinical trials aimed at evaluating new forms of radiotherapy delivery and testing new systemic therapies in conjunction with radiotherapy.

Over the last 10 years, the trend has been to decrease the amount of external beam radiotherapy. According to Dr. Engleman, radiotherapy can be omitted entirely for some low-risk tumors. In other cases, the preference is for brachytherapy. It is faster, easier, and less toxic to the patient. Another trend, for use in high-risk patients, is to use a combination of chemotherapy with brachytherapy administered three to five times over 2 weeks. "In the old days," Dr. Engleman said, "we would irradiate the entire abdomen, then the pelvic area, and then use brachytherapy. Now, we use chemotherapy before and after the brachytherapy. It's equally effective and less toxic."

An ongoing clinical trial sponsored by the Gynecologic Oncology Group is looking at another approach to combining chemotherapy with radiation therapy. Noelle Cloven, MD, a gynecologic oncologist on the medical staff of Baylor All Saints Medical Center in Fort Worth, is principal investigator on a multisite study looking at the efficacy of pelvic radiation therapy versus the combination of vaginal cuff brachytherapy and paclitaxel/carboplatin in patients with high-risk, early stage endometrial cancer.



## **Recent Publications from Baylor Sammons Cancer Center**

September 1, 2013 to November 30, 2013

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# **New Clinical Trials at Baylor Charles A. Sammons Cancer Centers**

Site	Study ID	Location	Principal investigator	Title
Breast	11276	Texas Oncology-Dallas	Joyce A. O'Shaughnessy, MD	A phase 2/3, multi-center, open-label, randomized study of weekly nab-paclitaxel in combination with gemcitabine or carboplatin, compared to gemcitabine/carboplatin, as first line treatment in subjects with ER, PgR, and HER2 negative (triple negative) metastatic breast cancer (ABI-007-MBC-001)
	13094	Texas Oncology-Dallas	Carlos H. Roberto Becerra, MD	A phase 1b dose escalation study of vantictumab (OMP-18R5) in combination with paclitaxel in patients with locally recurrent or metastatic breast cancer (18R5-002)
	13111	Texas Oncology-Dallas	Joanne L. Blum, MD	(673-301) A phase 3, open-label, randomized, parallel, 2-arm, multi-center study of BMN 673 versus physician's choice in germline BRCA mutation subjects with locally advanced and/or metastatic breast cancer, who have received no more than 2 prior chemotherapy regimens for metastatic disease
	13098	Texas Oncology–Fort Worth	Sanjay P. Oommen, MD	An observational cohort study of treatment patterns and outcomes in patients with HER2 positive (HER2+) metastatic breast cancer (SystHERs)—Genentech protocol ML28259
	013-154	Baylor Dallas	Joyce A. O'Shaughnessy, MD	Pilot safety trial of anakinra combined with chemotherapy and dendritic cell vaccine in patients with locally advanced, triple-negative breast cancer
GI	12177	Texas Oncology–Fort Worth	Robert L. Ruxer, Jr., MD	(2012-PT023) A pivotal phase III study to evaluate overall survival using MABp1 as a monotherapy in metastatic colorectal cancer patients with cachexia
GU	13028	Texas Oncology–Dallas Texas Oncology–Fort Worth	Thomas E. Hutson, DO Stephen L. Richey, MD	A phase III, randomized, controlled study of cabozantinib (XL184) vs. everolimus in subjects with metastatic renal cell carcinoma that has progressed after prior VEGFR tyrosine kinase inhibitor therapy (XL184–308)

Site	Study ID	Location	Principal investigator	Title
Neuro- Oncology	013-172	Baylor Dallas	Karen Fink, MD, PhD	Individual expanded access treatment proto- col of EMD 121974 (Cilengitide) for a single patient with recurrent glioblastoma multi- forme who has been on treatment long term
	013-216	Baylor Dallas	Karen Fink, MD, PhD	A phase II trial of oral pazopanib plus oral topotecan metronomic antiangiogenic therapy for recurrent glioblastoma multiforme (A) without prior bevacizumab exposure and (B) after failing prior bevacizumab
Ovary	12232	Texas Oncology–Dallas Texas Oncology–Fort Worth	Erik C. Koon, MD Noelle G. Cloven, MD	(ET743-OVC-3006) A randomized, open-label study comparing the combination of Yondelis® and Doxil®/Caelyx® with Doxil®/Caelyx® monotherapy for the treatment of advanced-relapsed epithelial ovarian, primary peritoneal, or fallopian tube cancer
Pancreas	013-018	Baylor Dallas	Carlos H. Roberto Becerra, MD	A phase I, prospective, non-randomized eval- uation of the safety of anakinra plus standard chemotherapy regimens in metastatic pan- creatic ductal adenocarcinoma (PDAC) patients
Skin	12184	Texas Oncology–Dallas	Charles L. Cowey, MD	(CMEK162A2301) The NEMO trial (NRAS melanoma and MEK inhibitor): A randomized phase III, open label, multicenter, two-arm study comparing the efficacy of MEK162 versus dacarbazine in patients with advanced unresectable or metastatic NRAS mutation-positive melanoma
Solid Tumor	13053	Texas Oncology–Dallas Texas Oncology–Fort Worth	Carlos H. Roberto Becerra, MD Stephen L. Richey, MD	A phase lb/II Clinical Study of BBI608 administered with paclitaxel in adult patients with advanced malignancies (BBI608-201)

#### **Online Access to Clinical Trials**

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.

# Site-Specific Tumor Conferences at **Baylor Charles A. Sammons Cancer Centers**

At Baylor Sammons Cancer Centers, 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 across the Baylor Charles A. Sammons network.

### **Conference Schedules**

#### **Baylor Dallas**

Bone and Soft Tissue	1st Tuesday
Breast	Thursdays
Chest	1st, 2nd, and 4th Wednesdays
Colorectal Multidisciplina	ry
Tumor (MDT)	Thursdays
Endocrine	3rd Tuesday
GI	Alternating with Colorectal MDT
Gynecology	Wednesdays
Head and Neck	2nd and 4th Tuesdays

Head and Neck Journal Club	5th Tuesday
Hematopoietic Diseases	Wednesdays
Liver	2nd and 4th Tuesdays
Neuro-oncology	2nd and 4th Wednesdays
Pancreas	1st and 3rd Fridays
Skin	1st and 3rd Wednesdays
Skull Base	1st Wednesday
Urology	3rd Wednesday

#### **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.

#### Below please find the schedules for tumor conferences across the Baylor Charles A. Sammons Cancer Center network.

## **Baylor Fort Worth**

Breast	Wednesdays
General	1st Thursday
Gyn Onc	3rd Thursday
Head and Neck	3rd Tuesday

### **Baylor Garland**

Breast	1st Wednesday
General	1st and 3rd Wednesdays

## **Baylor Grapevine**

Breast	4th Wednesday
General	3rd Thursday

## **Baylor Irving**

Breast	1st and 3rd Tuesdays
General	1st Tuesday
Thoracic	1st and 3rd Mondays

## **Baylor Plano**

General/GI	3rd Thursday
Breast	1st Thursday
Lung	2nd Thursday of every EVEN month
GU	2nd Thursday of every ODD month
Head and Neck	4th Thursday
Focus on Research	4th Thursday of the 2nd month of the quarter

## **Baylor Waxahachie**

General	2nd Thursday
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## **Baylor Carrollton**

General	3rd Thursday
General	3rd mursday

## **Baylor McKinney**

General 4th Monday
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For more information about tumor conferences at any of the other Baylor campuses, please call 214.820.6261.



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# North Texas Multidisciplinary LUNG CANCER S Y M P O S I U M



**Baylor Sammons Cancer Center** 10th Floor Conference Center 3410 Worth Street Dallas, Texas 75246



**DIRECTOR**Kartik Konduri, MD

Medical Director, Lung Cancer Center Baylor Charles A. Sammons Cancer Center Dallas, TX

www.CMEbaylor.org | 214-820-2317 cmeregistration@baylorhealth.edu



