Proactive Management of Li-Fraumeni Syndrome Benefits Patients

By Sarah Bronson

Li-Fraumeni syndrome is a hereditary disorder that confers an extremely high likelihood of developing cancer on affected individuals.

Deciding who should be tested for this rare but potentially devastating hereditary syndrome and how to best care for those who test positive can be a challenge. Ongoing research at The University of Texas MD Anderson Cancer Center is helping to clarify the guidelines for Li-Fraumeni syndrome identification and surveillance and to improve the early detection of cancers in people with the disorder.

“Patients with Li-Fraumeni syndrome, and often many of their family members, are very prone to cancer, including recurrences and additional, new cancers,” said Louise Strong, M.D., a professor in the Department of Genetics. “Some individuals with the syndrome have gone on to develop five or more cancers.” The most common cancers in these patients are breast carcinoma, sarcoma of the soft tissue or bone, brain cancer, and adrenal cancer. These cancers tend to occur at a younger age—in children and young adults—in people with Li-Fraumeni syndrome than in the general population. Leukemia, lung cancer, colon

A sample pedigree chart shows the incidence of cancer in a family affected by Li-Fraumeni syndrome. The number below each entry represents the person’s age in years at first cancer diagnosis or, for those never diagnosed with cancer, age at last examination. Circles represent females. Image courtesy of MD Anderson’s Li-Fraumeni Syndrome Study Group.
cancer, and melanoma are also frequently seen in families with Li-Fraumeni syndrome.

In 1976, Dr. Strong initiated a long-term study that has since created one of the largest data sets of Li-Fraumeni syndrome families and has helped characterize these patients’ cancer risks. More recently, Dr. Strong began MD Anderson’s Li-Fraumeni Education and Early Detection program, or LEAD program, to test a new surveillance strategy for patients with Li-Fraumeni syndrome. Findings from these and similar efforts underscore the importance of recognizing and closely monitoring patients with this syndrome.

Genetic testing

Data from Dr. Strong’s long-term study helped determine that Li-Fraumeni syndrome is caused by germline (i.e., hereditary) mutations in the TP53 gene. Missense mutations or other changes to TP53 interfere with the body’s recognition and repair of genetic damage, allowing cancer cells to propagate. These mutations can be identified through a blood test.

Individuals should be tested for Li-Fraumeni syndrome if they meet the criteria defined by the National Comprehensive Cancer Network (NCCN). In general, patients who develop any of the cancers associated with the syndrome at a relatively young age—for example, women who develop breast cancer before age 35 years and do not carry BRCA mutations—should be tested for the syndrome. Patients with certain rare childhood tumors—including sarcomas, brain tumors, and adrenal cortical tumors—should also be tested because such patients are at increased risk of carrying the mutant TP53 gene. In addition, all first-degree relatives of patients with the syndrome should be tested. Characteristics such as having multiple cancers in the Li-Fraumeni syndrome spectrum at any age or having first-degree relatives diagnosed with any cancer at a young age can also warrant genetic testing.

Surveillance

Patients diagnosed with Li-Fraumeni syndrome should undergo frequent surveillance for new cancers at many sites. In accordance with the NCCN guidelines, adult participants in the LEAD program typically undergo a physical examination every 6–12 months that includes whole-body and brain magnetic resonance imaging (MRI), dermatological and neurological evaluations, and blood tests for thyroid and adrenal function and various cancer biomarkers. Colonoscopy and breast cancer screening are begun at an earlier age than in the general population. Other types of cancer screenings at specific sites may be undertaken depending on the individual. The program’s surveillance strategy for children with Li-Fraumeni syndrome varies by age but includes whole-body and brain MRI.

The necessity of such close monitoring was starkly demonstrated in a small Canadian study of patients with Li-Fraumeni syndrome in which one group received comprehensive screening that included rapid whole-body MRI every 6 months and another group declined the systematic screening. MRI, which does not use ionizing radiation, was chosen over modalities such as radiography or computed tomography because patients with Li-Fraumeni syndrome are uniquely vulnerable to new cancers in irradiated regions. During the first 8 years of screening, individuals in both groups developed new cancers. However, all patients who received comprehensive screening were alive after 8 years. In contrast, only 20% of the patients who received no screening were alive after 5 years; the others died of cancer. These results helped shape recent updates to the NCCN guidelines for screening patients with Li-Fraumeni syndrome and the similar screening guidelines used in the LEAD program.

Dr. Strong said that the LEAD program has been under way for only 2 years but has yielded some notable findings. “Over the past year, we have screened 23 asymptomatic individuals whose ages ranged from 18 to 61 years, and 21 of these patients had findings of interest,” Dr. Strong said. Most of these findings were cysts or hemangiomas, and only four of those required follow-up. In addition, three invasive cancers were identified, including gastric cancer and high-grade breast ductal carcinoma in situ in a 42-year-old patient and metastatic thyroid cancer in an 18-year-old patient. Dr. Strong said that both patients underwent treatment and are doing well. She added, “Our screening program has identified tumors that likely would have been life threatening at a later stage.”

Counseling and educating patients

In addition to testing people for Li-Fraumeni syndrome and screening affected individuals for cancer, a major focus of the LEAD program is educating patients with the disorder and their family members about diagnostic testing, surveillance, and other strategies.
Clinical Trial Tests High-Dose Radiation Therapy for Limited Stage Small Cell Lung Cancer

By Bryan Tutt

Small cell lung cancer carries a poor prognosis, even for patients without metastatic disease. But a phase III trial of high-dose daily or accelerated twice-daily thoracic radiation therapy for limited stage small cell lung cancer may lead to longer survival.

“Small cell lung cancer is not the same as other cancers, and it needs to be treated differently,” said Ritsuko Komaki, M.D., a professor in the Department of Radiation Oncology at The University of Texas MD Anderson Cancer Center. Small cell lung cancer is very aggressive. More than two-thirds of patients present with extensive stage disease (i.e., distant metastasis). Of the patients with limited stage small cell lung cancer (i.e., disease limited to one side of the chest with no distant metastasis), only a small minority are candidates for definitive surgery; the rest are treated with concurrent chemotherapy and thoracic radiation therapy.

Because almost all small cell lung cancer cases are caused by smoking, the tumors tend to have TP53 mutations but lack the EGFR mutations that are often present in non–small cell lung cancer and can be targeted with tyrosine kinase inhibitors; therefore, small cell lung cancer is currently treated with cytotoxic drugs. Although ongoing trials of systemic treatments such as immune checkpoint inhibitors or poly(ADP-ribose) polymerase (PARP) inhibitors show promise for patients with small cell lung cancer (see “Small Cell Lung Cancer Studies May Increase Treatment Options,” *OncoLog*, March 2015), radiation therapy combined with platinum drugs and etoposide remains the standard treatment for limited stage disease.

Improvements in radiation therapy

Radiation therapy for limited stage small cell lung cancer has improved in recent decades. In the 1990s, Dr. Komaki and her colleagues studied accelerated radiation therapy, in which fractions of the 45-Gy dose were given to the affected region in twice-daily fractions over 3 weeks. They found that the accelerated dose resulted in a higher survival rate than the same total dose given in once-daily fractions over 5 weeks among patients with limited stage small cell lung cancer treated with concurrent cisplatin and etoposide. However, the disease tends to spread to the bilateral mediastinal lymph nodes, and treating these nodes resulted in the esophagus receiving a dose of radiation similar to that received by the tumor volume; therefore, many patients who received the accelerated regimen suffered grade 3 or 4 esophagitis. As a result, accelerated radiation therapy was not widely adopted until the advent of three-dimensional conformal and intensity-modulated ra-

FOR MORE INFORMATION
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ADDITIONAL RESOURCES


Physicians and patients can contact the LEAD group at 713-794-5323 or LEADProgram@mdanderson.org.

The NCCN Guidelines for screening and surveillance in patients with Li-Fraumeni syndrome and other hereditary cancer syndromes are available at http://bit.ly/1NubIl0.

“Small cell lung cancer is not the same as other cancers, and it needs to be treated differently.”

– Dr. Ritsuko Komaki
Radiation Therapy for Small Cell Lung Cancer

[Continued from page 3]

Positron emission tomography/computed tomography images from a patient with limited stage small cell lung cancer before (left) and after (right) treatment in the CALGB30610-RTOG0538 trial. Thoracic radiation (45 Gy in twice-daily fractions over 3 weeks) with concurrent etoposide and cisplatin resulted in a complete response with no severe side effects. Images courtesy of Dr. Ritsuko Komaki.

diation therapy, which deliver a higher radiation dose to the target area than to adjacent structures.

Although chemotherapy can delay or prevent distant metastasis in patients with limited stage small cell lung cancer, the blood-brain barrier prevents most chemotherapy drugs from reaching the brain, a common metastatic site for these tumors. Decades ago, Dr. Komaki and her colleagues found that a low dose of radiation (25 Gy over 2 weeks) to the brain can prevent or slow the development of brain metastases, and prophylactic cranial irradiation is now the standard of care for patients whose limited stage disease completely or mostly responds to thoracic radiation therapy and chemotherapy.

Although advances such as accelerated radiation therapy and prophylactic cranial irradiation have improved survival outcomes and quality of life for patients with limited stage small cell lung cancer, the 5-year survival rate remains only 25%. “Local [thoracic] therapy fails for about 40% of these patients,” Dr. Komaki said. “So we asked whether a higher radiation dose would improve their outcomes.” This question may be answered by an ongoing phase III trial of high-dose radiation therapy.

High-dose radiation therapy

The multicenter clinical trial known as CALGB30610-RTOG0538 has enrolled nearly 500 patients with small cell lung cancer and will eventually enroll 729. The patients are randomly assigned to receive a standard chemotherapy regimen of etoposide and either cisplatin or carboplatin every 21 days for four cycles with concurrent radiation therapy at the standard dose of 45 Gy in fractions given twice daily over 3 weeks or the experimental dose of 70 Gy in fractions given once daily over 7 weeks.

The trial’s primary endpoint is 2-year overall survival. In a previous study, the 2-year overall survival rate was 47% among patients receiving 45 Gy over 3 weeks in twice-daily fractions with concurrent etoposide and cisplatin. It is hoped that the high-dose radiation regimen will increase this rate to at least 58%. Blood samples taken during the trial will be studied to look for biomarkers and to determine the effect of circulating tumor cells on patients’ outcomes.

Although results of the phase III trial are not yet available, Dr. Komaki, MD Anderson’s principal investigator for the study, is optimistic. “The trial should tell us which regimen is best for patients with limited stage disease,” she said. “We hope that this and other ongoing studies will help us cure more patients with small cell lung cancer.”

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Smoking and Small Cell Lung Cancer

Although small cell lung cancer is deadly, it is also preventable: 97% of cases are related to smoking. “I have been seeing patients with small cell lung cancer for 40 years,” Dr. Komaki said, “and I’ve only seen about five patients who never smoked—and some of those were exposed to passive smoke.”

In an effort to educate young people about the dangers of tobacco use, Dr. Komaki has visited schools throughout Texas to share her observations on the devastating effects of lung cancer on patients and their families.

As the rate of smoking has gone down in recent decades, so has the incidence of small cell lung cancer. However, smoking remains a public health concern, and Dr. Komaki continues her efforts to urge smokers to quit and nonsmokers not to start.

If you are a smoker who wants to quit, visit MD Anderson’s Tobacco Treatment Program at www.mdanderson.org/quitnow or call 713-792-QUIT.
Reducing Complications and Hospital Readmissions after Liver Surgery

By Bryan Tutt

Hepatectomy carries a risk of complications that can lead to hospital readmission and even death. Even as modern surgical techniques make liver surgery safer and less invasive, a series of initiatives at The University of Texas MD Anderson Cancer Center has resulted in reduced rates of complications and hospital readmission for patients who undergo hepatectomy.

For any surgical procedure, readmission to the hospital after discharge has been recognized in recent years as an indicator of the quality of care. Even before the Affordable Care Act reduced Medicare payments for hospitals with high readmission rates, many institutions sought ways to improve various areas of patient care to reduce the occurrence of complications that lead to readmission.

At MD Anderson, ongoing efforts led by Jean-Nicolas Vauthey, M.D., a professor and chief of the Liver and Pancreas Section in the Department of Surgical Oncology, aim to reduce complications stemming from hepatectomy. Among the most important of these efforts has been the development of surgical techniques that reduce the occurrence of bile leaks and intraoperative blood transfusions, both of which are associated with hospital readmission.

Efforts to reduce complications

Preventing bile leaks

Bile leak has long been recognized as a serious complication that can lead to life-threatening sepsis after liver surgery. Several years ago, Dr. Vauthey and Thomas Aloia, M.D., an associate professor in the Department of Surgical Oncology, began working on a novel technique to detect and repair bile leaks during hepatectomy.

The intraoperative air leak test is a two-step process. In the first step, a cholangiography catheter is inserted into the cystic duct to inject air into the biliary tree while the distal common bile duct is closed by finger compression. Ultrasonography is used to visualize pneumobilia, which indicates a patent biliary system. If pneumobilia is not seen on ultrasonography, a bile leak may be present. In the second step, the right upper quadrant of the abdomen is filled with sterile saline solution or water. A second injection of air into the cystic duct causes bubbles to emerge from any leaking bile ducts. The water is slowly drained so that each leak can be located and repaired with a polypropylene suture.

Drs. Aloia and Vauthey got the idea for the test from colorectal surgery, in which air is injected into the anus and the pelvic cavity is filled with water to check for colon leaks.

“You have to cut a lot of bile ducts when you do a liver resection,” Dr. Vauthey said. “But any bile duct that is leaking can be found with this technique. It’s an advance in liver surgery.”

The effectiveness of the technique was confirmed by a retrospective study in which postoperative bile leaks occurred in 10.8% of hepatectomy patients who did not undergo the air leak test but in only 1.9% of those who did undergo the test.

Avoiding blood transfusion

Another advance in liver surgery developed by Drs. Aloia and Vauthey, along with other MD Anderson colleagues, is a two-surgeon technique to reduce blood loss during hepatectomy. In this technique, the primary surgeon...
dissects the liver parenchyma while a second surgeon controls bleeding using a saline-linked cautery device. An added benefit of the technique is reduced operative time.

This technique, which has been in use for more than a decade, has reduced the need for blood transfusions during liver surgery at MD Anderson, as has the use of minimally invasive laparoscopic procedures. Dr. Vauthey said, “Less than 5% of our patients currently undergoing liver resections receive blood transfusions.”

**Readmission rates**

The benefit of reducing bile leaks and blood loss during hepatectomies was underscored by a recent study of factors leading to hospital readmission. In the study, Dr. Vauthey and his colleagues reviewed the records of 3,041 patients who underwent hepatectomies at MD Anderson between 1998 and 2013.

An important aspect of the study was its distinction between planned and unplanned readmissions. “In cancer patients, it is important to differentiate between planned and unplanned readmissions because many patients return to the hospital for chemotherapy or other procedures that were planned before discharge,” Dr. Vauthey said. The researchers found that most unplanned readmissions that can be attributed to liver surgery occur within 45 days of discharge from the hospital.

The initiatives to minimize bile leaks and blood loss, along with other efforts to ensure quality of care, appear to have helped prevent unplanned readmissions. Only 10.3% of the liver surgery patients in the study had unplanned remissions within 45 days of hospital discharge.

In addition, a separate review of post-operative mortality rates among patients who underwent hepatectomy between October 2014 and September 2015 at National Cancer Institute–designated cancer centers found that, despite having the highest case volume, MD Anderson had no deaths within 30 days of the surgery or during the same hospitalization. Dr. Vauthey is pleased with both the low mortality and readmission rates, especially considering the complex liver surgeries that often are involved.

“Readmission is a reflection of the quality and the extent of the surgery,” Dr. Vauthey said. “At our institution, we do major liver resections. In more than half of our liver cancer patients, we remove a lobe or more of the liver, which is considered a major resection. But despite our doing these extensive resections, we are able to maintain high standards and quality of care.”

**FOR MORE INFORMATION**

Dr. Jean-Nicolas Vauthey ...... 713-792-2022

**FURTHER READING**


When Should Women Begin Breast Cancer Screening?

Guidelines vary, but annual screening is best for most women 40 years and older

Breast cancer screening saves lives. Cancer specialists and researchers agree with this statement and encourage women to be screened. But experts’ opinions vary about exactly how often screening should be done and at what age screening should begin. These differences of opinion among experts lead to varying guidelines from multiple sources and cause confusion for patients and even doctors.

Benefits of annual mammography

For women at average risk of breast cancer, The University of Texas MD Anderson Cancer Center recommends annual clinical breast examination and screening mammography (x-rays of the breast) beginning at age 40 years. Women at high risk of breast cancer may need to begin screening at an earlier age or undergo screening at more frequent intervals.

“We know that annual screening results in fewer women dying from breast cancer,” said Therese Bevers, M.D., a professor in the Department of Clinical Cancer Prevention. “And that’s what MD Anderson is about. We want fewer women to die from breast cancer, and that’s why we recommend annual mammograms beginning at age 40.”

Dr. Bevers added that these guidelines are in accordance with those of the National Comprehensive Cancer Network, an alliance of 26 leading cancer centers, including MD Anderson.

Avoiding false-positive findings

Last fall, the American Cancer Society (ACS) made headlines when it changed its breast cancer screening guidelines. The ACS had previously recommended annual screening mammography beginning at age 40 years for women at average risk of breast cancer, but the organization’s new guidelines for women at average risk call for screening mammography every year between ages 45 and 54 years and every other year at age 55 years and older. However, the new ACS guidelines also recommend that annual screening be available to women between 40 and 44 years old and those 55 years and older. This last suggestion was ignored or only briefly mentioned in some news reports about the new ACS guidelines.

“If people just see a headline that says the ACS recommends that screening start later and occur less often, they miss the nuances of what the guidelines actually say,” Dr. Bevers said. “If you consider those additional statements, that a woman can begin screening at age 40 and can continue annual screening after age 55, the ACS endorses what MD Anderson is doing.”

Dr. Bevers said that the ACS suggests beginning screening at 45 years because women 45 years and older have a greater incidence of breast cancer and a slightly lower rate of false-positive findings (masses that look like cancer but are not) on mammography than women 40–44 years old.

False-positive findings can lead to additional screening tests, including needle biopsy, and can cause anxiety for the patient. However, Dr. Bevers said, studies have shown that this anxiety is short-lived.

Benefits of clinical breast examinations

Another key difference between the MD Anderson and ACS guidelines is that MD Anderson recommends clinical breast examinations while the ACS does not. “The ACS felt that there were no data to support the clinical breast exam,” Dr. Bevers said. “We acknowledge that the data are limited, but some data show benefit from the clinical breast exam. And we think the value of the clinical encounter extends beyond the clinical breast exam. A woman should see her clinician every year—whether a clinical breast exam is done or not—because the doctor can help determine the patient’s risk of breast cancer.”

Like the MD Anderson guidelines, the ACS guidelines call for starting screening mammography earlier for women at higher risk of breast cancer. But several factors influence cancer risk, and doctors can help their patients weigh these factors to decide on appropriate screening.

“The doctor also can give women advice about reducing their risk of breast cancer by losing weight or avoiding weight gain, following a healthy diet, and exercising,” Dr. Bevers said. “Ultimately, we’d like to not only detect cancers early but also prevent cancers from occurring in the first place.”

Dr. Bevers is concerned that the confusion from conflicting guidelines might discourage women from breast cancer screening. She advises women to discuss their risk factors for breast cancer and the benefits of screening mammography with their doctors. “For women at average risk,” Dr. Bevers said, “annual mammography and clinical breast exams starting at age 40 is the highest level of care, so that’s what we’ll continue to recommend.”

FOR MORE INFORMATION

- Ask your physician
- Call MDAnderson at 877-632-6789
- Read MD Anderson’s breast cancer screening guidelines at http://bit.ly/1kln5fd

PhySiCiAnS: THe SiSS THeN ATtO BEGIN

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Cancer Screening and Risk Reduction Algorithms

Cancer screening is not a one-size-fits-all endeavor. The use of various techniques to screen for different types of cancer is determined by multiple risk factors, such as patients’ age, medical history, and family history of cancer. Patients rely on their physicians to help them weigh the benefits of early cancer detection against the potential harms that could stem from false-positive findings, low levels of radiation exposure from imaging scans, or moderately invasive tests.

To help physicians advise their patients about cancer screening, The University of Texas MD Anderson Cancer Center provides screening algorithms for breast, cervical, colorectal, endometrial, liver, lung, ovarian, and skin cancers. These algorithms list the risk factors that define average, intermediate, or increased risk and suggest which screening tests should be done at what age for patients at each risk level.

In addition to the cancer screening algorithms, there are three risk reduction guides. The first is an algorithm for the use of chemopreventive agents such as tamoxifen, raloxifene, or aromatase inhibitors in patients at high risk for breast cancer. The second offers guidelines for human papillomavirus vaccination according to the patient’s age and sex. The third covers the initial assessment for and prescription of physical activity/exercise programs, as physical activity can reduce the risk of several cancer types.

The screening and risk reduction algorithms were developed by teams of clinicians and researchers at MD Anderson. The algorithms are not a replacement for physicians’ clinical judgement but are intended as tools to help physicians make evidence-based recommendations to their patients.


“Useful Resources” introduces tools for community physicians and other medical professionals available free of charge on MD Anderson’s Web site.