

OncoLog

MD ANDERSON'S REPORT TO PHYSICIANS ■ March 2014 Vol. 59, No. 3

Expanding the Use of Laparoscopic Liver Resection

By Bryan Tutt

Minimally invasive surgical resection of liver tumors once was used only in select patients with easily accessible lesions located in the anterior parts of the liver.

However, recent improvements in surgical techniques and the use of preoperative imaging have made laparoscopic approaches possible for even complex liver resections.



Dr. Claudius Conrad (right) performs a laparoscopic liver resection. The two-dimensional image provided by the laparoscope is supplemented with images from preoperative computed tomography and intraoperative ultrasonography.

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Expanding the Use of Laparoscopic Liver Resection

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“Procedures that until recently could only be performed as open surgery are now being performed laparoscopically,” said Claudius Conrad, M.D., Ph.D., an assistant professor in the Department of Surgical Oncology at The University of Texas MD Anderson Cancer Center.

Dr. Conrad explained that the increased use of laparoscopic surgery for primary liver tumors and metastatic tumors to the liver is the result not of a single technological advance but rather of collaborative efforts by multidisciplinary team members to apply multiple advances in imaging technology, surgical tools, and surgical technique.

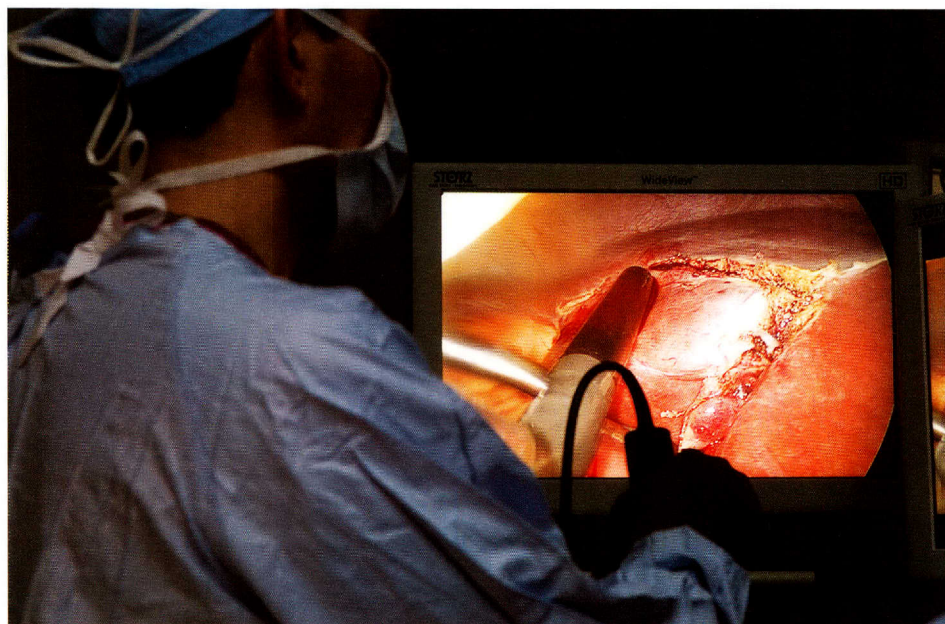
“In the past 3 years, we have performed over 100 minimally invasive liver resections at MD Anderson with very good outcomes,” said Thomas Aloia, M.D., an associate professor in the Department of Surgical Oncology. An increasing number of minimally invasive pancreatic procedures also are being performed (see “Minimally Invasive Pancreatic Surgery,” page 3).

Overcoming challenges

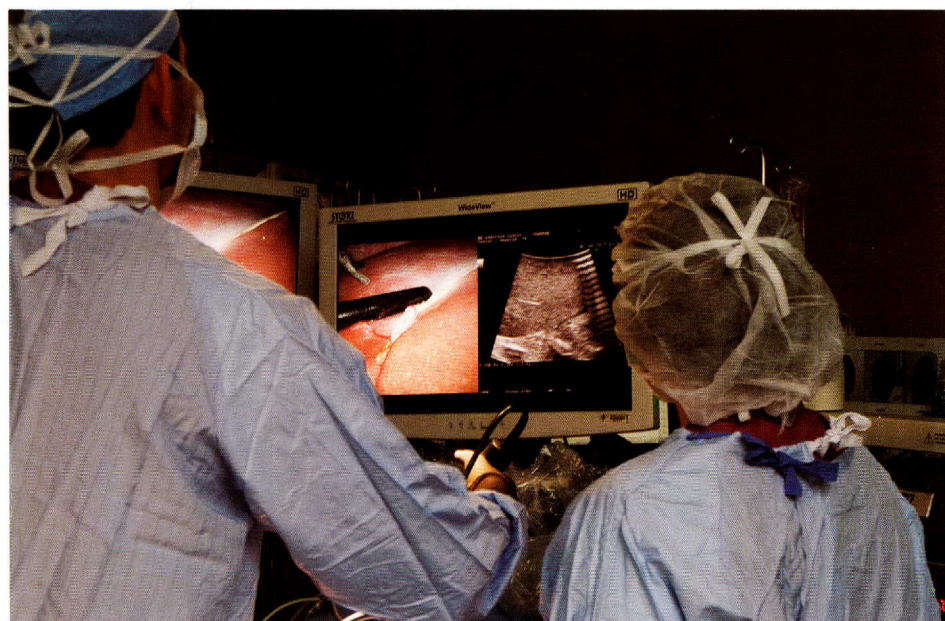
Advanced laparoscopic liver resection presents challenges that open surgery does not, and overcoming these challenges requires teamwork and planning. “More than in open surgery, the complexity of laparoscopic surgery requires close collaboration between all members of the operative team,” Dr. Conrad said.

The laparoscope provides the surgeon a clear view, but the image is two-dimensional. The surgical team supplements this view with preoperative images and intraoperative ultrasonography. “Preoperative cross-sectional imaging and intraoperative ultrasonography not only help identify lesions and critical structures but also facilitate the conversion of the two-dimensional image of the laparoscope into the three-dimensional motor performance of the surgery,” Dr. Conrad said.

A limitation of laparoscopic surgery has been the ability to adequately control intraoperative bleeding, as compression and suturing are technically



Dr. Conrad uses advanced parenchymal transection tools to minimize intraoperative blood loss during a laparoscopic resection of a hepatic lesion.



During a laparoscopic liver resection, intraoperative ultrasonography helps the surgical team locate lesions and avoid critical structures.

more difficult. However, Dr. Conrad said, advanced parenchymal transection devices allow the surgeon to divide liver tissue in such a way that bleeding is minimized. “Most importantly,” he said, “bleeding is minimized through accurate preoperative imaging and careful planning, as these allow the surgeon to avoid major vessels in the liver and optimize the transection plane.”

Preoperative imaging and surgical planning

Computed tomography (CT) is the mainstay of preoperative imaging for liver resections and plays a central role in planning laparoscopic procedures. “In the past 5 years, CT scanners have gotten faster, which enables us to scan the liver in multiple phases of contrast enhancement,” said Harmeet Kaur,

M.D., an associate professor in the Department of Diagnostic Radiology. Dr. Kaur said that CT is not only fast and reliable but also more likely than other modalities to detect extrahepatic lesions. She added that the ability to scan thin cross-sections, which enables two- or three-dimensional reconstructions in different planes, makes CT useful for visualizing a patient's anatomy.

In fact, incremental advances in technology are making possible increasingly detailed reconstructions from CT. MD Anderson's Department of Diagnostic Radiology is developing a system of three-dimensional vascular reconstruction that will allow surgeons to rotate the image of a patient's hepatic vascular structure on screen so that it can be viewed from any perspective.

CT is supplemented by magnetic resonance imaging in a growing number of patients, according to Dr. Kaur. The spatial resolution of CT allows radiologists to see the liver anatomy and vasculature, while the contrast resolution of magnetic resonance imaging enables radiologists to detect small lesions that may be missed by CT.

"To succeed in doing laparoscopic liver surgery, you need radiologists who are dedicated to understanding the liver anatomy and who are familiar with all the variants of the hepatic and portal veins and the hepatic arteries," Dr. Kaur said.

At MD Anderson, surgeons and medical oncologists work closely with radiologists to understand each patient's anatomy and determine the best surgical approach as well as the timing of neoadjuvant and adjuvant chemotherapy. Dr. Kaur said this collaborative approach also helps select patients who would benefit most from liver resection.

In deciding whether laparoscopic surgery is appropriate for a patient, Dr. Conrad said, "Most important are safety and the oncologic aspects; we have to minimize the risk of complications, and we want to remove all the cancer and suspected lymph nodes. Only secondary is whether the laparoscopic or open approach is best for the patient's recovery."

When planning a laparoscopic procedure, the surgeon will also plan for performing open surgery if needed. "We are always prepared to complete the operation through a traditional incision if safety or oncologic aspects

dictate that this is best for the patient. However, preoperative imaging and collaborative planning make conversion from the laparoscopic to the traditional approach a rare event," Dr. Conrad said.

The multidisciplinary approach

Minimally Invasive Pancreatic Surgery

Not only can the laparoscopic approach be used to perform complex hepatobiliary procedures, it can be used in pancreatic surgery. Even an extremely difficult procedure such as a pancreaticoduodenectomy can be performed using a laparoscopic approach.

"We routinely remove lesions in the pancreatic body and tail laparoscopically or robotically, and we're beginning to develop a laparoscopic program for lesions located in the pancreatic head," said Claudius Conrad, M.D., Ph.D., an assistant professor in the Department of Surgical Oncology.

Matthew Katz, M.D., an assistant professor in the Department of Surgical Oncology, pointed out the challenges of caring for patients with pancreatic neoplasms. "These are complex clinical problems that require a thoughtful approach," he said. "Through carefully integrated care, we have achieved excellent outcomes."

Dr. Conrad said, "To date, there are no published randomized controlled trials comparing minimally invasive—either robotic or laparoscopic—pancreaticoduodenectomies to open procedures, nor are there any registered trials ongoing, to my knowledge." He added that although the published data suggest that minimally invasive pancreaticoduodenectomy is safe and has short-term benefits, "the findings of low operative blood loss and high rate of negative-margin resection must be viewed in



"Minimally invasive surgical therapy requires unique skill sets."

– Dr. Jason Fleming

the setting of highly selected patients with significantly smaller-than-usual tumors."

Nevertheless, for this select group of patients, the benefits of advanced laparoscopic pancreatic surgery are very important. "Minimally invasive surgical therapy requires unique skill sets, and we have recruited outstanding surgeons with specific expertise in this area," said Jason Fleming, M.D., a professor in and deputy chair of the Department of Surgical Oncology and service chief of pancreas surgery. "Moving forward, we will investigate these new approaches and hope to integrate them into our existing clinical strategies to further improve the survival of our patients with these aggressive malignancies." ■

[Continued on page 8]

Physicians Refining Lung Cancer Screening Programs

By Joe Munch

Lung cancer screening with low-dose computed tomography (CT) has been shown to reduce the rate of lung cancer–specific mortality in people at high risk for the disease.

Three years after the National Lung Screening Trial (NLST) showed this definitively, physicians and researchers at The University of Texas MD Anderson Cancer Center have implemented the NLST's findings in a screening program and are developing new methods of identifying patients who would most likely benefit from screening.

"We're working to better understand who we should screen and what we should do with any abnormal results we find," said Therese Bevers, M.D., a professor in the Department of Clinical Cancer Prevention.

MD Anderson's CT screening program

Established shortly before the publication of the NLST's primary findings in 2011, the CT screening program at MD Anderson's Lung Cancer Screening Clinic follows the criteria set forth by that landmark study. Annual screening with low-dose, thin-slice multidetector CT of the lungs is recommended for asymptomatic individuals at a high risk of lung cancer—those 55–74 years old who have a smoking history of at least 30 pack-years and are current smokers or former smokers who quit within the past 15 years. Screening is not recommended for individuals at low risk—those with no current or former history of smoking.

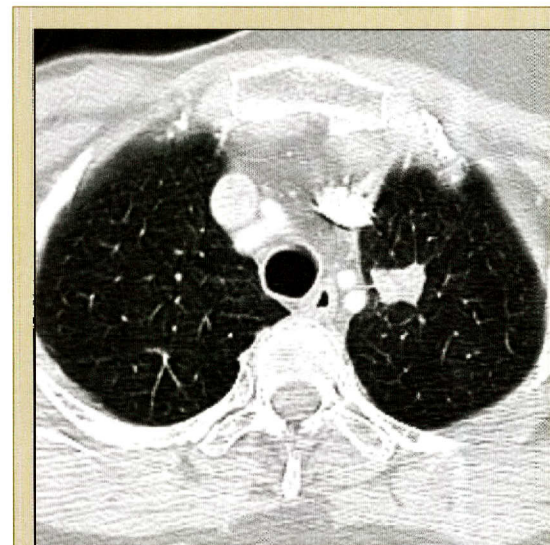
For individuals who have a moderate risk of lung cancer (i.e., those at neither a high nor a low risk of the disease), the recommendation to undergo screening is ultimately left to the discretion of the patient's physician. People in the moderate-risk category do not meet the screening criteria established by the NLST but have a combination of variables that suggest that the benefits of screening could outweigh its risks.

"A moderate-risk individual might be a person who is only 50 years old but has a 40 pack-year smoking history," Dr. Bevers said, "or maybe a patient who quit smoking 20 years ago but has a 50 pack-year smoking history. Those patients would have a moderate risk because they don't meet the exact high-risk criteria as defined by the NLST but still have significant risk of lung cancer due to their enormous smoking histories."

People who have a history of cancer other than lung cancer related to tobacco use are also included in the moderate-risk category. Acknowledging the mounting evidence that individuals who have chronic obstructive pulmonary disease (COPD) as a result of their smoking are at higher risk of lung cancer, Dr. Bevers also suggested that such people be included in the moderate-risk category.

"We've already shown a 20% reduction in mortality using the NLST indications for CT screening. Now, we're simply asking what contribution a blood-based test would add to lung cancer screening."

– Dr. Samir Hanash



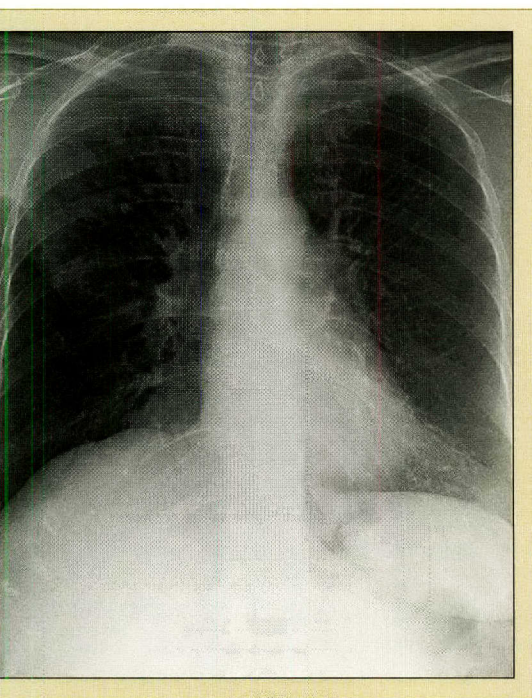
A lung tumor in the left upper lobe is visible in a low-dose computed tomography scan (left) but not in a posteroanterior chest radiograph (right) of the same patient.

Although the NLST showed a benefit through 3 years of screening with CT, MD Anderson recommends that individuals at high risk of lung cancer undergo annual screening with low-dose CT for as long they remain in good health and able to undergo additional interventions if lung cancer is discovered. In addition, through its Tobacco Treatment Program, MD Anderson offers tobacco cessation services to all the institution's patients who currently smoke or have quit smoking within the past year.

Patients must have an order from a physician to be able to undergo lung cancer screening at MD Anderson, and the screening results are sent to the physician. However, Dr. Bevers said that she or other physicians in the Cancer Prevention Center can order screening for patients who do not have a primary care physician or for those whose primary care physician is not comfortable managing the outcomes of CT screening.

Cost and coverage

Currently, few insurance plans cover lung cancer screening, and many people



have to pay for the service out of pocket. At MD Anderson, screening costs \$250, which includes the charge for performing CT as well as a radiologist's interpretation of the study. For many individuals, this cost is prohibitive.

This may soon change, however. In late December, the U.S. Preventive Services Task Force issued a statement recommending annual lung cancer screening with low-dose CT for adults who meet the NLST criteria. Per the 2010 Affordable Care Act, private insurance companies participating in the Health Insurance Marketplace established by the legislation must cover services the Task Force recommends with no cost to patients.

Dr. Bevers expects that the added coverage will result in an influx of patients to the screening program. "We've seen it with all other screenings: once they're covered by insurance, patients are more likely to participate," she said.

She also believes that, although they have no legal obligation to do so, Medicare, Medicaid, and private insurance companies not participating in the exchanges will eventually cover the

"We're working to better understand who we should screen and what we should do with any abnormal results we find."

– Dr. Therese Bevers

screening if data show the procedure to be cost-effective.

Improvements to screening

Lung cancer screening is not without risk. Although the amount of radiation exposure from low-dose CT (1.5 mSv) is considerably less than that from diagnostic CT (7 mSv) or even that of yearly background levels (3–5 mSv), increasing evidence suggests that cumulative radiation effects may have harms associated with them, including an increased risk of cancer.

And the screening is not perfect: the NLST found a high false-positive rate, largely owing to the detection of benign lesions. In many patients whose CT findings were positive, a watch-and-wait approach with follow-up CT that revealed no changes confirmed the absence of lung cancer. Other patients required interventions.

"At worst, you end up having to perform a needle biopsy to determine whether cancer is present," Dr. Bevers said.

To help address these issues, researchers at MD Anderson are developing a blood test to guide decision-making in the face of abnormal findings on lung cancer screening CT. The blood test will include a panel of biomarkers found to be associated with increased lung cancer risk. A clinical trial of the blood test will soon be open to patients who undergo lung cancer screening at MD Anderson.

"If you have a blood test that could discriminate what is cancer from what

is not cancer, you could save a lot of unnecessary procedures and encourage people to undergo CT screening," said Samir Hanash, M.D., Ph.D., a professor in the Department of Clinical Cancer Prevention, noting that such a blood test could allay people's concerns about possibly having to undergo unnecessary procedures because of false-positive findings.

"We've already shown a 20% reduction in mortality using the NLST indications for CT screening," Dr. Hanash said. "Now, we're simply asking what contribution a blood-based test would add to lung cancer screening."

Dr. Hanash said there are plans to expand the trial to include other institutions nationally and worldwide. As the test is evaluated and refined, its role in lung cancer screening may change.

"If a test turns out to be good at detecting cancer, then one can imagine down the road that perhaps it would be more logical to first get a blood test, and if the blood test is positive, then that would be an indication to get a CT study," Dr. Hanash said. "But we're not there yet. We have to crawl before we walk and walk before we run. What is very compelling to do now is to figure out a way we can improve on CT screening." ■

FOR MORE INFORMATION

Dr. Therese Bevers.....713-745-8048

Dr. Samir Hanash.....713-745-5242

To view MD Anderson's lung cancer screening algorithm, visit www.mdanderson.org/education-and-research/resources-for-professionals/clinical-tools-and-resources/practice-algorithms/screening-algorithms.html.

To refer a patient to MD Anderson's Lung Cancer Screening Clinic, call 877-632-6789 or visit www.mdanderson.org.

Should the Primary Tumor Be Treated in Patients With Metastatic Prostate Cancer?

By Bryan Tutt

Researchers at The University of Texas MD Anderson Cancer Center hope to determine whether treating the primary tumor has any oncologic benefit in patients with metastatic prostate cancer.

A new clinical trial aims to find which patients, if any, are most likely to benefit from such treatment.

The prostate tumor usually is not treated in patients with metastatic disease unless the tumor progresses and causes local symptoms. Instead, patients typically undergo a sequence of systemic therapies, starting with hormone therapy (also called androgen deprivation), which can be done by orchiectomy but is most often done with injections of luteinizing hormone–releasing hormone agonists or antagonists. Unfortunately, complications from local progression occur in 30%–45% of patients whose primary prostate tumors have not been previously treated with radiation or surgery.

“There are two schools of thought about local therapy in the setting of metastatic prostate cancer,” said Brian Chapin, M.D., an assistant professor in the Department of Urology. “Some believe that treating the primary tumor may have a biologic effect on the metastatic sites. These people theorize that such treatment could delay disease progression and even death.

“Other physicians believe that treating the primary tumor will have no effect on metastatic disease and should be done only in the setting of symptomatic



Dr. Brian Chapin



Dr. Ana Aparicio

local progression for palliative reasons,” Dr. Chapin continued. “But there has never been a study to determine whether that is true.”

Clinical trial

Dr. Chapin is the principal investigator of a phase II trial in which patients with metastatic prostate cancer receive systemic hormone treatment for 6 months and then are randomly assigned to continue hormone treatment only or continue hormone treatment and also undergo definitive treatment of the primary tumor.

The primary tumor may be treated with surgery or radiation; the modality is chosen according to the physicians’ discretion and the patient’s preference. “Each patient is seen by a urologist, a radiation oncologist, and a medical oncologist,” Dr. Chapin said. “We get together and determine which modality is appropriate for a particular patient.”

In patients who undergo surgery, Dr. Chapin may perform an open or a robotic prostatectomy with pelvic lymph node dissection, depending on the extent of the disease. Patients who undergo radiation therapy may receive intensity-modulated radiation therapy or proton therapy.

The trial is enrolling men with metastatic, androgen-dependent prostate cancer who are candidates for surgery or radiation therapy. The trial is currently available only at MD Anderson, but Dr. Chapin said the trial will soon be opening at additional sites.

The primary endpoint of the trial is the time to disease progression, which is determined by an increase in the level of prostate-specific antigen or by clinical evidence of progression.

Several correlative studies will be performed to determine which subgroups of patients are most likely to benefit from treatment of the primary tumor. The researchers hope that biomarkers found in immunological profiling, magnetic resonance imaging, or surgical biopsies can be used to guide future treatment.

Looking forward

“We think treating the primary tumor will help some people a lot, some people a little, and some people not at all,” said Ana Aparicio, M.D., an assistant professor in the Department of Genitourinary Medical Oncology and a co-investigator of the trial. “It is too early to recommend definitive intervention to the primary tumor as standard therapy in patients with metastatic prostate cancer outside a clinical trial,” she said.

Dr. Chapin agreed, adding that it will likely be 2 years before preliminary results are available. However, he was optimistic. “We’re hoping we can improve outcomes for patients with metastatic prostate cancer,” he said.

Dr. Aparicio concurred. “I’m excited about the trial,” she said. “It could potentially change the landscape of how we treat the disease.” ■

FOR MORE INFORMATION

Dr. Ana Aparicio.....713-563-6969
Dr. Brian Chapin.....713-792-3250

To learn more about the ongoing study of systemic therapy plus definitive treatment of the primary tumor in patients with metastatic prostate cancer, visit www.clinicaltrials.org and select study No. 2012-0705.



Vaccines That Prevent Cancer

Hepatitis B and HPV vaccines protect against cancer-causing viruses

While most people are familiar with vaccines that prevent diseases such as smallpox or polio, fewer are aware that vaccines can protect against certain cancers.

The U.S. Food and Drug Administration (FDA) has approved two types of vaccines that can prevent cancer in healthy people. One is used to protect against the hepatitis B virus, which can cause liver cancer as well as cirrhosis (scarring) of the liver. The second protects against human papillomavirus (HPV), which is responsible for almost all cervical cancers and more than half of oropharyngeal (throat) cancers. HPV is also linked to some other cancers and is responsible for 5% of all cancers worldwide, according to the U.S. National Institutes of Health.

The hepatitis B and HPV vaccines don't target cancer cells directly; instead, they prevent the infections that lead to specific cancers. Most common cancers, such as colorectal, lung, prostate, and breast cancers, are not caused by viral infections.

The hepatitis B and HPV vaccines are made from antigens (substances that are present on the surface of a virus) that the immune system will recognize as foreign. These antigens do not cause a viral infection, but they train the immune system to fight off the virus if the vaccinated person is exposed to it later.

The hepatitis B vaccine

The original hepatitis B vaccine, developed in 1981, was made from plasma and is no longer available in the United States. The current hepatitis B vaccine is made synthetically with no blood products. The Hepatitis B Foundation describes the current vaccine as "one of the safest and most effective vaccines ever made" and emphasizes that recipients cannot develop hepatitis B from the vaccine.

Both the U.S. Centers for Disease Control and Prevention (CDC) and the



American Academy of Pediatrics recommend that all infants at birth and unvaccinated children up to age 18 years receive the hepatitis B vaccine. Three shots are required to get lifetime protection from hepatitis B. The second shot is given at least 1 month after the first, and the third injection is given at least 6 months after the first.

The CDC also recommends that unvaccinated adults in high-risk groups be vaccinated against hepatitis B. High-risk groups include health care professionals and emergency personnel, patients who have kidney disease or are receiving dialysis, sexually active people who are not in a monogamous relationship, and anyone living with an infected person. Travelers to regions where hepatitis B is common (Asia, Africa, South America, the Pacific Islands, Eastern Europe, and the Middle East) and families considering international or domestic adoption should also be vaccinated.

The HPV vaccine

Two vaccines—Gardasil and Cervarix—have been approved by the FDA to prevent HPV infections. Both Gardasil and Cervarix protect against HPV types 16 and 18, which cause about 70% of cases of cervical cancer as well as

some vaginal, vulvar, anal, penile, and oropharyngeal cancers. Gardasil also protects against two other HPV types, 6 and 11, which are responsible for about 90% of genital warts in males and females. Both of these vaccines are available to females, but only Gardasil has been approved by the FDA for use in males. Either vaccine is given in a series of three shots over 6 months.

The CDC recommends that girls and boys receive the HPV vaccine when they are 11 or 12 years old. The HPV vaccine also is recommended for teenaged boys and girls who did not get the shots when they were younger and for unvaccinated women 26 years or younger and unvaccinated men 21 years or younger. Other groups who should get the vaccine are gay and bisexual men and adults 26 years or younger with compromised immune systems. Although the HPV vaccine can prevent the virus that causes cervical cancer, it does not substitute for routine cervical cancer screening.

Vaccine safety

The hepatitis B and HPV vaccines have been widely used and shown to be safe, with only mild to moderate side effects. The hepatitis B vaccine may cause soreness in the vaccinated arm and a low fever. The most common side effects of the HPV vaccines are soreness, swelling, and redness at the injection site. Less common side effects of the HPV vaccine are fever and headaches, and occasionally people experience dizziness or fainting shortly after the injection. ■

— K. Stuyck

FOR MORE INFORMATION

- Ask your physician
- Visit www.mdanderson.org
- Call askMDAnderson at 877-632-6789
- Visit the Centers for Disease Control and Prevention at www.cdc.gov/vaccines

Expanding the Use of Laparoscopic Liver Resection

[Continued from page 3]

allows minimally invasive surgery to be considered for even complex procedures. As an example, Dr. Conrad described a patient with lesions in the posterosuperior segments of the liver, which were once considered inaccessible by a laparoscopic approach. But Dr. Conrad was able to perform a minimally invasive resection by inserting the trocars through the chest and diaphragm. "We removed the lesions laparoscopically, and the patient had an excellent outcome," he said.

Benefits of laparoscopy

"Laparoscopic surgery provides comparable long-term oncologic outcomes to open surgery and can help to improve resectability in patients with recurrent disease," Dr. Conrad said.

The chief advantages of laparoscopic surgery over open surgery are reduced pain, blood loss, morbidity, risk of surgical site infection, and length of hospital stay. According to Dr. Conrad, the faster recovery time from laparoscopic surgery can enable some cancer patients to begin adjuvant therapy sooner and perhaps tolerate it better.

Many patients with multiple bilateral liver tumors require a two-stage resection, in which tumors are removed from one side of the liver and portal vein embolization is used to help the rest of that side of the liver regenerate before a second surgery is done to remove disease from the other side. This concept has been advanced by Jean-Nicolas Vauthey, M.D.,

a professor and chief of the liver and pancreas section in the Department of Surgical Oncology. Between 2003 and 2011, 134 patients had a planned two-stage hepatectomy, and the two-step liver resection sequence was successfully completed in 112 of these patients.

If the first stage of a two-stage resection is performed laparoscopically, the reduced scarring facilitates the second surgery after the portal vein embolization. The liver tumor study group at MD Anderson is currently investigating the outcomes of patients who underwent two-stage resections with the first stage performed laparoscopically.

An important benefit from the reduced pain and recovery time of the laparoscopic approach is better quality of life. "Many of our patients lead active lives," Dr. Conrad said. "They are not only asking if we can remove the tumor; they are also asking how soon they can get back to their normal daily activities."

Fortunately, the minimally invasive laparoscopic approach is successful in more and more patients as physicians gain experience in planning and performing such procedures. Dr. Kaur said, "More than new technology, the key to success is having a multidisciplinary team dedicated to understanding the liver anatomy." ■

FOR MORE INFORMATION

Dr. Claudius Conrad713-745-1499
Dr. Harmeet Kaur713-745-1519

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MD Anderson Cancer Center

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