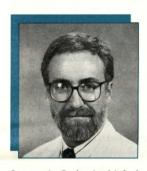
# MDAnderson Oncolog

Difficult tumor inspires varied approaches

## Creative strategies key in fight against liver cancer

## **Treatment Update**



Steven A. Curley is chief of Gastrointestinal Tumor Surgery



Mark S. Roh is chief of Liver Tumor Surgery

Liver cancer remains one of the most challenging tumors faced by the oncologist. Ninety-four percent of people who are diagnosed with primary liver cancer die as a result of it. The majority of patients with hepatocellular cancer, the most common type of liver tumor, do not live even a year after diagnosis. There are two problems behind these discouraging statistics: first, because the liver is such a large organ, tumors can grow quite large before they start causing symptoms and are diagnosed. By then, it is often too late for curative treatment. Second, many traditional cancer treatments are toxic to the normal liver tissue or to other tissues when they are given in doses sufficient to kill the tumor.

One physician who refuses to be daunted by these statistics is Steven A. Curley, M.D., associate professor of surgery and chief of Gastrointestinal Tumor Surgery in the Department of Surgical Oncology at The University of Texas M. D. Anderson Cancer Center. "I got interested in liver tumors because they are such a major clinical problem," Curley said. "There are no good treatments." His interest arose at the University of New Mexico, where he did both his surgical training and laboratory research on the kinetics of tumor cell growth. In 1988, he came to M. D. Anderson Cancer Center to focus on liver tumor treatments. Curley now divides his time between treating patients with hepatobiliary cancers or colorectal cancers (which commonly metastasize to the liver) and working in the laboratory to find better therapies. He and his colleagues at M. D. Anderson have developed some alternative approaches to treating liver cancer that they hope will prolong patient survival.

### Surgery is first line of treatment

When a liver tumor is diagnosed, the first treatment considered is complete surgical removal of the tumor. However, only 20 to 30 percent of liver tumors are completely resectable, said Mark S. Roh, M.D., associate professor of surgery and chief of Liver Tumor Surgery, also in the Department of Surgical Oncology. The tumors may be too large to remove or in an awkward location, perhaps surrounding an essential blood vessel. Cirrhosis, too, can make resection impossible. Thus, in most cases, another treatment approach is necessary.

Unfortunately, traditional nonsurgical therapy options, such as radiation therapy and chemotherapy, have had disappointing results in liver tumors. Standard radiation treatments are toxic to the liver long before they have an effect on the tumor; there is a high risk of liver failure. Similarly, systemic chemotherapy produces toxic effects in other organs before it affects the tumor. "No matter what kinds of drugs are used, the results are pretty dismal," Curley said. "Usually 10 percent or less of the patients respond to systemic chemotherapy."

### Regional chemotherapy minimizes side effects

For treating liver metastases from stomach or pancreatic cancers, whole-body treatment is necessary because the cancers often will have metastasized elsewhere. For primary liver tumors, however, systemic toxicity has limited the tolerable dose of standard chemotherapy drugs to ineffective amounts. M. D. Anderson investigators are therefore trying to deliver high-dose chemotherapy directly to the liver. Yehuda Z. Patt, M.D., associate professor of medicine and chief of the Regional Therapy Service in the Department of Gastrointestinal Oncology and Digestive Diseases at M. D. Anderson, found that infusing drugs directly into the liver through the hepatic artery would dramatically shrink tumors in a carefully selected subset of patients with advanced

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# "Multidisciplinary strategies in liver cancer are made possible by the team efforts of 12 to 15 specialists."



Yehuda Z. Patt is chief of the Regional Therapy

hepatocellular cancer. In 12 of 31 patients, hepatic arterial infusion of FLAP—a combination of floxuridine (FUDR), leucovorin, doxorubicin (Adriamycin), and cisplatin (Platinol)—decreased tumor size by more than 50%. In several patients, tumors that were originally unresectable became resectable after treatment with FLAP. Patients who did not have hepatitis B or C infection survived an average of more than three years after this treatment, while patients who were positive for hepatitis B or C experienced complications during treatment. In modified doses, however, this regimen may prolong life for hepatitis patients who had an adequate amount of healthy liver before treatment.

Curley has been studying a system that combines this hepatic arterial infusion technique with hepatic venous isolation and extracorporeal chemofiltration. A chemotherapy drug is infused into the liver through the hepatic artery; the blood coming out of the liver is then captured and filtered to remove the drug (see figure). Thus the liver and tumor get a high dose of the drug, but

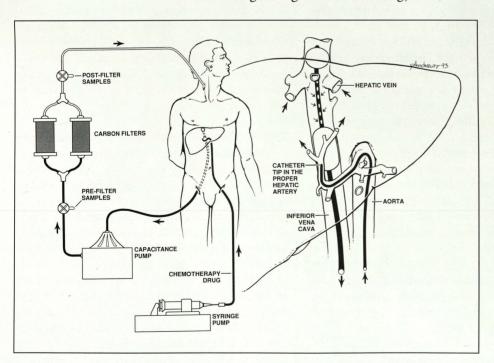
the rest of the body does not. The infusion and the filtering are done through catheters in the neck and groin.

In trials, this system allowed delivery of doses of doxorubicin of 120 mg/m², twice what can normally be tolerated by patients. Seven of ten patients had a reduction in tumor volume of at least 25 percent; in two patients, Curley was able to resect a tumor that had previously been unresectable. Now he is awaiting Food and Drug Administration approval to add mitomycin C and cisplatin to the doxorubicin to try to increase the effectiveness of the treatment even more. Both these agents have shown activity against hepatocellular cancers, and the three-drug combination has shown promise in hepatic arterial infusion studies.

Curley is also planning a clinical study of a drug-delivery medium called matrix collagen gel. This compound, when mixed with a chemotherapy drug like cisplatin, encapsulates the drug; the drug then does not disperse into other tissues when it is injected into the tumor. "Again, we get

higher doses of the chemotherapy drug in the tumor but reduce the dose of drug that goes to the rest of the body," Curley said. Tumor kill is enhanced, while side effects are minimized. Pilot studies of this technique were done at M. D. Anderson; although measuring patient response was not a primary focus of these studies, Curley noted that in all 20 patients the size of tumor was reduced at least 50 percent, and in nine the reduction was at least 90 percent.

Researchers are also trying other drugs that attack the tumors in different ways. Curley has begun studying some experimental compounds that, rather than being directly toxic to the hepatocellular cancer cells themselves, may cause the normal liver cells (hepatocytes) to excrete substances that slow or retard the growth of the cancer cells. These compounds have had promising results in clinical trials in Europe, producing anticancer responses. Curley will study the interaction of the compounds with normal



Delivery system used for hepatic arterial infusion of chemotherapy with complete hepatic venous isolation and extracorporeal chemofiltration. (Reprinted with permission from The Cancer Bulletin. Copyright 1994, The University of Texas M. D. Anderson Cancer Center, Houston, Texas.)

Current Liver Cancer Protocols	
	Current practice of cryosurgery for unresectable hepatic metastases (Study chair- man: Dr. Roh)
	A Phase II trial of intravenous 5-fluorouracil and subcutaneous recombinant interferon- $lpha$ for treatment of fibrolamellar hepatoma and cancer of the biliary tree (cholangiocarcinoma and gall bladder carcinoma) (Study chairman: Dr. Patt)
	A Phase II trial of hepatic arterial infusion of floxuridine (FUDR), leucovorin, doxorubicin (Adriamycin), and cisplatin (Platinol) for the treatment of hepatocellular cancer confined to the liver (Study chairman: Dr. Patt)
	A case-control study of hepatitis C virus and its interaction with hepatitis B virus in the development of hepatocellular cancer in Harris County, Texas (Study chairman: Dr. Patt)
	A two-arm Phase II trial of cisplatin (Platinol), recombinant interferon-α, doxorubicin (Adriamycin), and 5-fluorouracil for the treatment of hepatocellular cancer: arm A by hepatic arterial infusion, arm B by systemic administration confined to the liver (Study chairman: Dr. Patt)

hepatocytes and with hepatocellular cancer cells in the laboratory to determine whether they indeed produce an effect and, if so, how they can be used to treat cancer patients.

### Cryotherapy takes up where surgery leaves off

Roh, with Bruno D. Fornage, M.D., of the Department of Diagnostic Radiology, has helped a number of patients with liver tumors—including metastases from colorectal cancers, hepatomas, and sarcomas—by using cryosurgery. "I cut out what I can and freeze the remainder of the tumor," he said. This technique, which was developed in Boston and Pittsburgh in the late 1980s, involves inserting into the tumor a thin probe that fills with liquid nitrogen, freezing the surrounding tissue. The freezing (at least 10 minutes at 30°C) destroys the tumor tissue, which is then slowly absorbed by the body over time. The probe insertion and freezing process are monitored precisely by ultrasound.

"It's quite well tolerated," Roh said. Since September 1993, he has performed cryosurgery on about 35 patients. "This treatment is exciting because it increases the number of patients who can be treated with potentially curative therapy," Roh said. Initial data suggest survival rates as good as those for patients who undergo surgical resection.

## Radio-frequency current destroys tumors

In the laboratory, Curley is studying another technique called bipolar radio frequency ablation (BRFA). "It's the opposite of cryosurgery," he

explained. "Instead of freezing the tumor, we're heating it." Two needles are placed in the liver, one on each side of the tumor, and a radio frequency current is run through the tumor, coagulating it. As for cryosurgery, the dead tumor tissue is slowly absorbed by the body over time. The potential advantage over cryosurgery is that the needles used are much smaller than cryosurgery probes and therefore less traumatic to the liver.

In the United States this research is still in the preclinical stage; Curley is studying BRFA in pigs. "When it comes to the anatomy of the liver and blood vessels, pigs are strikingly similar to humans," he said. The technique has been used in patients in Asia and Europe. "It looks promising," Curley said, "but these are early studies."

## Early detection and new research are increasing options

"Promising" means a lot when there are so few good treatment options for patients with liver cancer. The chances for the patient would be better if the tumors were detected earlier, when there are more options for therapy. "We're doing better at early detection by screening patients at higher risk with blood tests and ultrasound," Curley said. People appropriate for such screening include those with cirrhosis or chronic hepatitis B or C infection.

Because the cancer is usually advanced by the time it is diagnosed, any treatments that even prolong survival could benefit the patient, Curley said. He feels that multimodality treatments will be the key to success. A significant number of

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Primary care physicians play an important role in prevention

## Teaching physicians how to prevent cancer

#### Prevention



Robert M. Chamberlain is director of the Cancer Prevention Education and Teaching Program

Ten years ago, a physician might have seen a tanned teenager with a broken arm and just treated the arm. "These days it would not be unusual for the physician to also counsel the patient about the possible harmful effects of tanning," said Robert M. Chamberlain, Ph.D., associate professor of cancer prevention and Director of the Cancer Prevention Education and Teaching Program at The University of Texas M. D. Anderson Cancer Center. Our increasing knowledge of how cancer arises has enabled us to devise effective ways to prevent it. However, physicians themselves must be taught how to prevent cancer before they can advise their patients about it; through research and training, this is the mission of the Cancer Prevention Education and Teaching Program.

Until recently cancer prevention was not part of medical school curricula. When Chamberlain began his work in cancer education ten years ago at Baylor College of Medicine, most medical students never even saw untreated cancer patients. Even today, most medical students learn about cancer only in basic science courses such as Cell Biology and Introduction to Medicine. They seldom receive formal training in how to diagnose or prevent cancer unless they intend to become oncologists. Chamberlain pointed out, "Many physicians graduated from medical school never having palpated a breast lump. Most medical students saw breast cancer patients only after surgery. If you weren't on duty before the patient had surgery, you missed it."

### Texas a leader in cancer prevention education

If you were a medical student or have practiced medicine in Texas, you (and your patients) may have been luckier than most. "Nationally, Texas has been a leader in cancer prevention education. In fact, we had the national meeting for the American Association for Cancer Education in Houston in 1993," said Chamberlain, who is secretary of the association. "People were amazed at how much is going on in Texas, much of it thanks to the Texas Cancer Council." In 1987, Joseph T. Painter, M.D., then Vice President for Health Policy at M. D. Anderson Cancer Center,

ensured that funding for cancer research and education became a line item in the Texas state budget by forming the Council, which funds cancer education. As a result, Texas educators have addressed the gaps in physicians' knowledge about cancer prevention in several ways.

At Baylor, Chamberlain helped organize an elective class devoted to cancer for the medical school curriculum. The medical students themselves may have recognized the need for the class: it rapidly became the most popular elective. Over half of the students took it, and more would have if the classroom had been larger. The class has become a model for other medical school classes throughout the nation.

## First step: physician education

In 1988 Chamberlain moved to the Division of Cancer Prevention at M. D. Anderson, which had already begun to educate primary care physicians in cancer prevention. He later became part of the newly formed Department of Epidemiology within that division. Margaret R. Spitz, M.D., M.P.H., professor of cancer prevention and acting chairman of the Department of Epidemiology, and the late Guy R. Newell, M.D., M.S.Hyg., then chairman of the Division of Cancer Prevention, had written a loose-leaf guidebook for physicians called ReCaP: Recommendations for Cancer Prevention. ReCaP begins with an overview of cancer trends in the United States and a brief introduction to cancer screening. Separate chapters are devoted to the most important cancer sites: breast, cervix, endometrium, colorectal system, head and neck, lung, skin, and prostate. Each chapter begins with graphs showing the incidence and survival rates for that cancer. Then, the risk factors for that cancer are discussed and prevention strategies are outlined.

The Texas Cancer Council distributed copies of ReCaP to 10,000 primary care physicians in Texas. A mail-back card in the book solicited feedback on its usefulness. ReCaP proved to be so helpful to these physicians that eventually it was published for nationwide distribution by Mosby-Year Book. "It is now the family physician's desk

# "While many are aware of the need to educate their patients about how to reduce their risk of developing cancer, it is not always clear to busy physicians what they should do."

reference book for cancer," said Chamberlain. (Instructions for obtaining the book are provided at the end of this story.)

Chamberlain used the successful ReCaP formula to address the remaining weak link in cancer education for physicians—resident training. He helped develop and test ReCaP for Residents, a complete cancer course consisting of an instructor's manual with slides and outlines of lectures. With the detailed information in ReCaP for Residents, an instructor can prepare a one-hour lecture in only about one hour's time. ReCaP for Residents is currently used in about 100 primary care residency programs in this country.

## Training opportunities for physicians in practice

But what about the physicians already in practice who missed these educational opportunities? While many are aware of the need to educate their patients about how to reduce their risk of developing cancer, it is not always clear to busy physicians what they should do. For instance, it may seem obvious that a physician in Miami should spend more time educating patients on the dangers of tanning and skin cancer than a doctor in Minneapolis. However, other risk factors and practices may not be so obvious. For example, few physicians can say what percentage of their women patients are complying with the National Cancer Institute guidelines for mammography screening. "Primary care physicians see patients one at a time and only rarely collect statistics on compliance," said Chamberlain.

So that physicians do not have to read all their patient records to collect this information, Chamberlain created *Profile*, a computerized system that ascertains the cancer risk profile of all adult outpatients, as a group, in a medical practice. To use *Profile*, a physician or office staff member randomly selects 200 patient charts and enters into the computer such patient characteristics as sex, age, history of smoking, family history of cancer, dates of last mammogram and Pap smear, and date of last prostate examination. *Profile* then compares this information to the National Cancer

Institute guidelines and tells the physician which screening tests or other prevention strategies should be emphasized in that practice. Chamberlain estimates that the risk profile of a practice is accurate for about two years or until the composition of patients in a practice changes significantly.

In some cases, a physician's solution to better cancer prevention may be as simple as placing in the waiting room pamphlets from the American Cancer Society or the National Cancer Institute. For physicians who want to improve their own understanding of cancer prevention, Chamberlain recommends consulting ReCaP and taking Continuing Medical Education classes. "Physicians, researchers, and other professionals in the Houston area are also welcome to attend our Friday morning cancer prevention seminars," invited Chamberlain.

Two of the offerings of the Cancer Prevention Education and Teaching Program are a multiyear predoctoral and postdoctoral fellowship and a three-month fellowship for graduate students in any field related to cancer prevention. Both fellowships are funded by the National Cancer Institute. Each fellow chooses a mentor from the M. D. Anderson faculty, works in the mentor's lab or on his or her project, and participates in seminars and courses on cancer prevention research. In this way, M. D. Anderson faculty prepare for the next generation of cancer prevention strategies.

-Maureen E. Goode

Physicians who desire more information on cancer prevention training fellowships or attending the cancer prevention seminars may write Dr. Chamberlain, Box 189, Department of Epidemiology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, or call (713) 792-3020. The book *ReCaP: Recommendations for Cancer Prevention*, by Margaret R. Spitz, M.D., and Guy R. Newell, M.D., can be obtained from the publisher, Mosby-Year Book, Inc., 11830 Industrial Drive, St. Louis, MO 63146, or from medical bookstores. Specify ISBN 0-8016-6704-6. ■

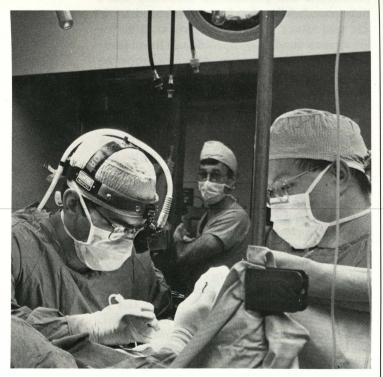
## **Ambulatory Surgery**

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## Range of surgical procedures available

M. D. Anderson surgeons are electing to perform a variety of operations on an outpatient basis. Most breast cancer surgeries can now be performed through the Center, including lumpectomies, simple mastectomies, and modified radical mastectomies. Other outpatient procedures include biopsies, dental surgeries, bone marrow aspiration procedures, revisions to facial and breast reconstruction, bronchoscopies, excisions of head and neck lesions, and many others. In a recent survey, 50 M. D. Anderson surgeons indicated that the Center could have provided a treatment option for about one third of the 8,470 surgeries performed here in 1993.

Kim Vidor, M.S., R.N., C.N.O.R., administrative coordinator of the Ambulatory Surgery Center, recounted that 15 years ago, when she first came to M. D. Anderson, breast cancer patients were hospitalized for up to 12 days after surgery. In recent years, patients have been required to stay only 3 to 4 days. But with the range of support services M. D. Anderson provides, such as preoperative training for patients and family members, and the advanced anesthesia and surgi-



A procedure in progress in the Ambulatory Surgery Center while Dr. Moss (in background, facing camera) looks on.

cal capabilities provided through the Center, some patients are able to go home in an even shorter period of time.

Moss explained that every patient in the Center's recovery room is continuously monitored, which offers a safety net not found in all institutions. Patients must meet certain criteria before they can be discharged. The exact duration of the patient's hospital stay depends on the type of surgery performed and how well and how soon the patient responds. Some patients are discharged directly from the postanesthesia unit, while others are transferred to another recovery area for overnight observation. The service is still considered outpatient if the patient is discharged within 23 hours of arrival at the hospital. If complications do arise, the patient can be admitted as an inpatient for further treatment.

Located in Station 44 on the fourth floor of M. D. Anderson's Clark Clinic, the Center has already assumed a large percentage of the hospital's surgical volume. "On a monthly basis, we perform 25% to 33% of the total bookings for the hospital's operating rooms, and we work out of only three of the 19 rooms designated for surgery," Moss reported.

Robert Jones, M.D., chairman of the Department of Anesthesiology and Critical Care and medical director of the Ambulatory Surgery Center, estimated that 3,000 surgeries had been performed in the Center by the end of 1994. Once construction is complete on new surgical suites that are part of an M. D. Anderson expansion project, additional space will be available to the Center, and this volume will probably increase.

## State-of-the-art anesthesia and pathology services offered

The success of the Center is a testament to M. D. Anderson's goal of constantly improving the quality of patient care. Three factors that have been particularly beneficial to Center patients are M. D. Anderson's comprehensive anesthesia, pathology, and pharmacology services.

"We use the most up-to-date anesthesia management techniques available and appropriate in the cancer setting," said Moss. "Likewise, M. D. Anderson's pathologists can rapidly identify tumor types and analyze tissues because of their experience with these specialized samples. The level of expertise in these particular areas has been essential to our implementation of a successful outpatient surgery program. Also, improved anesthesia medications means patients are alert and functional sooner. Patient recovery is further ac-

# "It is important that patients know exactly what to expect before, during, and after their procedure."

celerated by the use of more effective pain and anti-emetic medications."

## Training sessions for patients, friends, and families

Although pleased with the implications of same-day discharge after surgery, patients naturally have some concerns. Through specialized training sessions, the patient and a designated friend or family member receive information about the surgical procedure they are to undergo and instructions regarding postoperative care. This service is essential because it gives all parties an opportunity to clarify their roles in the caregiving scheme and to become comfortable with outpatient surgery as a treatment alternative. During the sessions, a hospital representative answers questions ranging from "What type of anesthesia will I be given?" to "How long will I be convalescent?"

Preoperative training is coordinated by Tomee Keto, R.N., nurse clinician in the surgery scheduling clinic, who says it is important that patients know "exactly what to expect before, during, and after their procedure." Keto serves as a liaison between the patient, the surgeon, and the anes-

thesiologist. She checks the patients' paperwork to make sure it is complete, makes sure they know when to arrive at the hospital and where to check in, and describes what they will experience during surgery, recovery, and observation. Her role, she says, is "to make the patient feel as comfortable as possible."

"Patient feedback has been very positive," said Moss, "but then, patients don't typically have a problem with a shorter hospital stay. As an institution constantly striving to improve on patient care, we understand that cancer can have an enormous effect on a patient's life. With this service, we hope to minimize that effect by shortening the hospital stay and thereby minimizing the interruption of the patient's regular schedule."

—VICKIE J. WILLIAMS

REFERRALS. Physicians who have questions or would like to refer patients to the Ambulatory Surgery Center may write Dr. Moss, Department of Anesthesiology and Critical Care, Box 42, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, or call (713)792-6907. ■

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Published quarterly by the Department of Scientific Publications, Division of Academic Affairs, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030.

Made possible by a gift from the late Mrs. Harry C. Wiess.

## **Liver Cancer**

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patients develop recurrences in the liver or other organs after surgery alone. "We need to combine surgery with other treatments," he said. "For example, if the tumor is small, we can do surgery first and follow with chemotherapy. Or, if it is large, we can use chemotherapy to reduce the size of the tumor and then use surgery or radiation." Such multidisciplinary strategies are made possible at M. D. Anderson by the team efforts of 12 to 15 specialists, including Curley, Roh, and radiologist C. Humberto Carrasco, M.D., who participate in a liver tumor study group chaired by Patt. The group meets each week to discuss their patients' treatments and future treatment protocols.

The various lines of attack described here all attempt to remove or dissolve the tumor. Novel therapies down the road may be able to change the behavior of the tumor so that it will regress on its own or become more benign. "That's science fiction now," said Curley, "but as we understand the liver better, we'll be able to develop other options."

—SUNITA PATTERSON

REFERRALS. Physicians who have questions or would like to refer a patient may write Drs. Curley, Roh, or Patt at the Departments of Surgical Oncology (Curley, Roh) or Gastrointestinal Oncology and Digestive Diseases (Patt), The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, or call (713) 794-4957 (Curley), 792-7961 (Roh), or 792-2828 (Patt). ■

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## Inside

Liver cancer strategies Prevention for physicians Ambulatory surgery

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Ambulatory Surgery Center offers a wide range of procedures

# Getting patients home and back to their routines more quickly

**Patient Care** 



Edward Moss is clinical coordinator of the Ambulatory Surgery Center

Adjusting to a diagnosis of cancer often means adjusting to a host of lifestyle changes. There are new emotional, financial, and schedule considerations for the patient and the entire family. The possibility of surgery can be particularly burdensome. To ease some of this burden, The University of Texas M. D. Anderson Cancer Center has established an outpatient surgical unit where a range of procedures are performed and patients are typically released the same day.

#### Disruption minimized by quick turnaround

Being sick can create all types of anxieties for a patient, explained Edward Moss, M.D., associate professor of anesthesiology and clinical coordinator of M. D. Anderson's Ambulatory Surgery Center, especially when the cause of the illness is a major disease such as cancer and surgery is prescribed. Parents of young children must arrange for their care. Patients who do not live in the immediate treatment area must consider temporary accommodations for themselves and those who will travel with them. Patients who work

must arrange for time off from their jobs. When the duration of the hospital stay is uncertain, the patients' concerns about time and expense accelerate.

The one-year-old Center was designed to address certain aspects of surgery that can trigger such anxieties. "In general, people do not like being in the hospital," said Moss. "They have to deal with a separation from their families and adapting to a new situation at a difficult period. One of the goals of this service is to get patients home sooner. We have found that patients progress quickly in their own homes and when cared for by loved ones."

Moss said that another goal in establishing the Center was to respond to the managed care industry. "M. D. Anderson is looking for ways to address managed care issues, one of which is cost. By reducing the amount of time a patient has to stay in the hospital, without sacrificing the quality of patient care, we can cut costs considerably, which translates into benefits for both the insurance provider and the patient."

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