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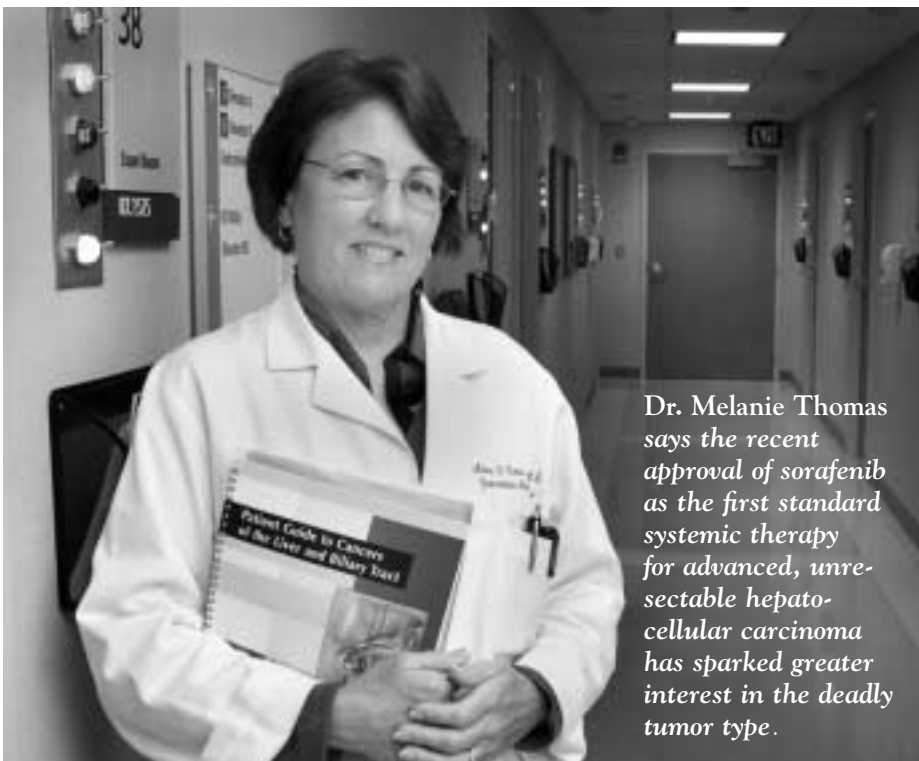
OncoLog

Hepatocellular Carcinoma: *New Standards in Therapy Emerging*

By John LeBas

For decades, oncologists have been trying to turn the tide against hepatocellular carcinoma (HCC). It's a daunting challenge. HCC is typically refractory to systemic chemotherapy, and the great majority of patients are not candidates for treatments that can potentially cure or slow the disease, such as surgery, radiation therapy, and nonsurgical ablation. Moreover, treatment can be made difficult by preexisting liver disease, which is very common in HCC patients.

The merging of these factors makes HCC an exceptionally lethal tumor type, with a median overall survival duration of less than 1 year for patients diagnosed with advanced disease. And the human toll is vast: HCC is the sixth most common cancer in the world and the third leading cause of cancer-related death, resulting in at least 500,000 deaths per year worldwide. While HCC is a relatively rare tumor in the United States, with about 18,000 new cases expected in 2008, the incidence has approximately doubled in the past 30 years.



Dr. Melanie Thomas says the recent approval of sorafenib as the first standard systemic therapy for advanced, unresectable hepatocellular carcinoma has sparked greater interest in the deadly tumor type.

Progress against HCC, which accounts for up to 90% of all liver cancers, has been slow, but that may be changing. Not only has recent research established sorafenib, a multi-kinase inhibitor, as the first-ever standard systemic therapy for advanced, unresectable HCC, but other agents are showing even better results in clinical trials. At the same time, advances in radiation therapy and nonsurgical abla-

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Hepatocellular Carcinoma

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tion may make those already-proven approaches more effective in certain patients.

“For years, long-term survival or cure was considered possible only in a minority of HCC patients,” said Melanie Thomas, M.D., an assistant professor in The University of Texas M. D. Anderson Cancer Center’s Department of Gastrointestinal Medical Oncology. “While we’re still a long way off from curing HCC in the majority of patients, we are finally finding therapies that may enable long-term disease control for most.”

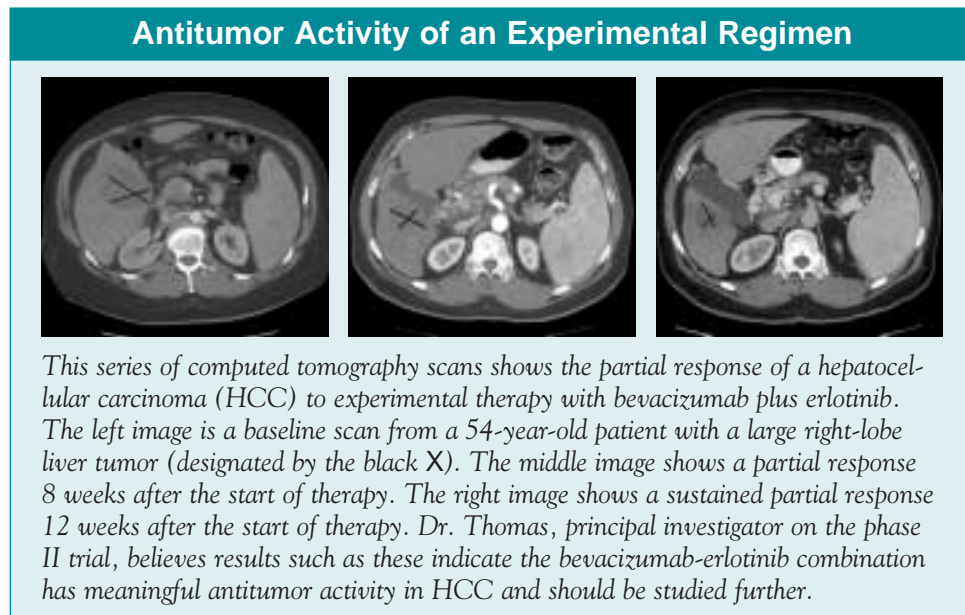
Understanding HCC

To appreciate the importance of recent advances in HCC, it helps to understand some of the etiologic and clinical variations that make the disease such a wily foe.

HCC usually develops in patients with liver damage caused by alcohol abuse, fatty liver disease, or, most commonly, chronic hepatitis infection. The vast majority of HCC cases occur outside the United States, particularly in Asia, which is home to about 80% of cases worldwide. The main cause of the disease in Asia is hepatitis B infection, primarily because of high rates of child-birth transmission. Children infected at birth are extremely likely to develop a chronic infection, and over time the virus causes cirrhotic changes that can lead to cancer.

The global incidence of hepatitis B is staggering—there are an estimated 350 million chronic infections, and up to 25% will lead to HCC. Fortunately, inroads have been made since the introduction of the hepatitis B vaccine, which has cut HCC incidence by half in some countries with robust vaccination efforts.

But the hepatitis B vaccine has had limited impact on HCC rates in the United States, where that strain of the virus causes very few HCC cases. Rather, 60% of U.S. cases of HCC arise from hepatitis C infection, which is becoming more common and for which no vaccine exists. Consequently, the incidence of HCC is increasing in the United States as well. “This is one of



the few tumors that’s rapidly on the rise in the United States, and much of that rise is related to an increase in hepatitis C cases,” Dr. Thomas said. Even so, HCC is still considered an “orphan disease” in the United States—that is, the incidence is so low that there is little financial incentive for pharmaceutical companies to develop new therapies.

Treatment of HCC with the therapies that do exist often proves difficult for multiple intertwined reasons. Usually, the surrounding organ is already diseased by the time the tumor develops, increasing the risk of complications. “The worse the liver is, the worse the prognosis is,” Dr. Thomas explained. Since a diseased liver performs its metabolic detoxification functions poorly, a toxic chemotherapy is more likely to make the patient very sick.

Moreover, HCC is considered to be chemoresistant; historically, cytotoxic drugs have been minimally effective at killing this type of cancer cell, especially compared to their efficacy in chemosensitive cancers such as lymphoma or leukemia. In addition, the window for treatment is short; the underlying liver disease can progress faster than the cancer and often is what kills the patient.

Checked history, promising future

The history of HCC therapy has been a story of limited and somewhat isolated

successes. Surgical resection and liver transplant are the only curative options, and only for patients who present with a limited tumor burden and limited liver disease burden—perhaps 20% of all patients. Some success in controlling localized tumors has been achieved with cryotherapy, ablative therapies, radiation therapy, and chemoembolization. But systemic chemotherapies—the only real option for patients with advanced or metastatic disease—have largely yielded low response rates and virtually no survival benefit.

Finally, it was a biologic agent—not a cytotoxic chemotherapeutic agent—developed for another cancer type that bucked the negative trend in systemic therapy for HCC. This agent, sorafenib, was originally approved by the U.S. Food and Drug Administration (FDA) in 2005 for the treatment of renal cell carcinoma. But investigators desperate to find effective therapies for liver cancer also tested sorafenib against HCC, and encouraging results from early studies led to the phase III SHARP trial presented at the 2007 American Society of Clinical Oncology meeting.

The SHARP trial showed that sorafenib extended the overall survival of patients with advanced HCC by 44%, or nearly 3 months—the first agent to cause a significant increase. Approval of sorafenib for unresectable HCC was granted by the FDA in November 2007.

The SHARP trial has already made an important impact on the evolution of HCC therapy, Dr. Thomas said. Patients who are not eligible for other therapies finally have a systemic therapy option. Also, sorafenib provides a control arm for future clinical trials of other agents. And importantly, the SHARP trial has generated greater interest in HCC by proving that a biologic agent has activity in the disease.

This heightened interest has led investigators to launch clinical trials of other agents, with early results even more promising than those from sorafenib. Two of these agents are the targeted therapies bevacizumab (Avastin) and erlotinib (Tarceva), which have shown good results in other cancer types. Bevacizumab is an anti-angiogenic agent that is FDA-approved for the treatment of metastatic colorectal cancer and non-small cell lung cancer. Erlotinib targets epidermal growth factor receptors (EGFR) and is approved for the treatment of metastatic or locally advanced non-small cell lung cancer and pancreatic cancer.

Dr. Thomas began testing bevacizumab in HCC after reviewing the positive results of a trial of the drug in renal cell cancer. “I suspected bevacizumab would also work in HCC, since HCC and renal cell carcinoma are quite similar in that both tumors are highly vascular and both are very chemoresistant,” Dr. Thomas

said. “So, we started a trial of bevacizumab in combination with erlotinib for HCC. Erlotinib was a rational choice in HCC because 80% of these cancers overexpress EGFR.”

The phase II trial, which has not yet been published, showed that the combination therapy prolonged progression-free survival in patients with advanced HCC by 50% compared to sorafenib—for a median progression-free survival interval of 9.75 months. Also significant, the investigators observed a 25% overall response rate, which is considered exceptionally high for clinical trials of agents in HCC. Based on these results, a phase III trial of bevacizumab and erlotinib is planned to open this summer at M. D. Anderson and seven other cancer centers in the United States.

“I am hopeful that bevacizumab and erlotinib will be the new standard for advanced HCC after this trial,” Dr. Thomas said. “We will also be seeing sorafenib tested in combination with other agents. I think that these therapeutic agents will eventually make HCC much more treatable for a wider population, as has happened with other historically difficult-to-treat cancer types such as renal cell carcinoma.”

M. D. Anderson is also participating in a multicenter phase II trial of brivanib (an inhibitor of vascular endothelial growth factor receptor 2) in HCC and is

studying DHA-paclitaxel (a conjugate of paclitaxel and a natural fatty acid that enhances the drug’s ability to inhibit cell division and induce apoptosis) in a separate phase II trial.

Other novel approaches

For the minority of HCC patients whose tumors can be treated without systemic agents—namely, those with localized disease—groundbreaking work continues to refine the standards of care. Exciting results are being seen with proton therapy and an experimental type of thermal ablation that uses radio waves to heat carbon nanoparticles injected into tumors.

Proton therapy

Radiation therapy was once thought to have very limited application in HCC. The rationale was that the tumors were resistant to radiation and that the surrounding liver was too sensitive to tolerate an effective dose. Additionally, the risk of radiation-induced toxicity was considered high.

But over time, radiation oncologists came to understand that so long as the patient had no more than a solitary tumor with a few satellites and so long as a sufficient amount of healthy liver could be spared, effective doses of radiation could be given to the tumor-bearing tissue with a low risk of toxicity. Proton

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Clinical Trials in Hepatocellular Carcinoma

- **Phase II Open-Label Study of Brivanib (BMS-582664) in Subjects with Unresectable, Locally Advanced or Metastatic Hepatocellular Carcinoma (2006-0860).** Principal investigator (PI): Melanie Thomas, M.D. The primary objective of this study is to estimate the 6-month progression-free survival rate in patients who receive daily doses of brivanib. To be eligible, patients must have received no prior systemic therapy or not more than one prior regimen of angiogenesis inhibitor therapy.
- **Phase II Study of the Combination of Avastin and Erlotinib in Patients**

with Unresectable Hepatocellular Carcinoma (2004-0874). PI: Melanie Thomas, M.D. The primary objective of this study is to assess the progression-free survival rate at 16 weeks after the start of therapy with a combination of Avastin (bevacizumab) and erlotinib.

- **Phase I Study of Proton Radiotherapy and Bevacizumab for Primary Liver Tumors (2005-0881).** PI: Sunil Krishnan, M.D. This study will evaluate dosing and safety during concurrent treatment with proton radiotherapy and bevacizumab in patients with technically or medically

inoperable hepatocellular carcinoma or cholangiocarcinoma.

- **Phase II Open-Label Study of Weekly Taxoprexin (DHA-Paclitaxel) Injection as Second-Line Therapy for Patients with Advanced Primary Cancers of the Liver, Including Hepatocellular Carcinoma and Carcinoma of the Gallbladder or Biliary Tract (2006-0566).** PI: Melanie Thomas, M.D. This study will evaluate response rate, duration of response, and safety. ●

For more information on trials at M. D. Anderson, visit www.clinicaltrials.org.

Overweight, Obese Patients Fare Worse with Breast Cancer, Researchers Find

A higher body-mass index (BMI) indicates a worse prognosis for women with locally advanced breast tumors, M. D. Anderson researchers recently reported. The retrospective study of more than 600 patients suggests that dietary interventions should be included in the treatment of locally advanced breast cancer, including inflammatory breast cancer.

Researchers assigned women to one of three BMI score groups: 24.9 or lower (normal weight/underweight); 25 to 29.9 (overweight); and 30 or higher (obese). All patients had stage III (locally advanced, nonmetastatic)

inflammatory or noninflammatory breast cancer. Overweight and obese patients with noninflammatory breast cancer had 5-year overall survival rates of 58.3% and 58.6%, respectively, whereas normal weight/underweight patients with noninflammatory breast cancer had a 5-year overall survival rate of 69.3%. Similarly, overweight and obese patients with inflammatory breast cancer had 5-year overall survival rates of 45.3% and 49.3%, respectively, compared with 55.1% for normal weight/underweight patients with inflammatory breast cancer. Overweight and obese patients also had a higher incidence of recurrence than normal weight/underweight patients, researchers found.

Previous studies have identified such factors as tumor size, lymph node involvement, estrogen receptor status,

and protein expression profile as prognostic indicators for breast cancer. "We believe our study is the first to evaluate BMI as a prognostic tool for women with breast cancer," said senior author Massimo Cristofanilli, M.D., an associate professor in M. D. Anderson's Department of Breast Medical Oncology. With a link now established between BMI and outcome, clinicians should consider lifestyle interventions and more frequent follow-ups for overweight and obese patients with locally advanced breast cancer, Dr. Cristofanilli said.

Next, the research team plans to study other factors related to obesity in breast cancer patients, including leptin (a hormone involved in the regulation of appetite and metabolism), insulin, and estrogen levels.

The study was published in the journal *Clinical Cancer Research*. ●

Hepatocellular Carcinoma (Continued from page 3)

therapy, a relative newcomer in radiation therapy, appears to fit the bill perfectly.

"The best way to spare maximum healthy tissue is with a beam that has little scatter, concentrates its energy deposition within the tumor, and does not deposit its energy after it exits the tumor," said Sunil Krishnan, M.D., an assistant professor in radiation oncology at M. D. Anderson. "That's exactly what a proton beam does."

The use of proton beams for HCC is still under study—M. D. Anderson's Proton Therapy Center opened just last year—but initial results from investigators elsewhere are promising. In one study from Japan, a 5-year overall survival rate of 23% was seen in patients who were ineligible for other therapies and were treated with proton radiation. More impressive, the 5-year overall survival rate was 50% among patients who had a single tumor and preserved liver function and were treated with proton radiation. This result rivals what can be achieved with surgical resection and has helped propel further study on proton therapy for HCC. "We can also use

photon beams to treat this tumor type, but we think that we can spare more good liver with proton therapy, which is especially important for a patient who has cirrhosis," Dr. Krishnan said. M. D. Anderson is also running a phase I clinical trial in which the patient receives one cycle of bevacizumab prior to proton therapy, followed by two cycles administered concurrently with radiation.

“We think that we can spare more good liver with proton therapy.”

— Dr. Sunil Krishnan

Radiofrequency ablation

In traditional radiofrequency ablation, otherwise harmless radio wave energy is converted to heat via needle electrodes inserted into a tumor. The technique can be used to control localized liver cancers and some other tumor types. But incomplete ablation occurs in up to 40% of cases, and complications occur in 10% of patients because of damage to healthy tissue

from the procedure. Thus, a more precise method is needed.

Recently, researchers collaborating at M. D. Anderson and Rice University reported that carbon nanotubes might offer such precision. In their study, nanotubes injected into rabbit tumors and heated with externally administered radio waves destroyed all tumor cells with minimal damage to healthy liver cells and no side effects. Results were published in the December 2007 issue of the journal *Cancer*.

"Our next step is to look at ways to more precisely target the nanotubes so they attach to, and are taken up by, cancer cells while avoiding normal tissue," said Steven Curley, M.D., senior author of the nanotube study and a professor in the Department of Surgical Oncology at M. D. Anderson. He estimated that a clinical trial is at least 3 years away.

If effective in humans, the technique could give oncologists one more inventive option for turning the tide against HCC. ●

For more information, call Dr. Thomas at 713-792-2828, Dr. Krishnan at 713-563-2377, or Dr. Curley at 713-794-4957.

A Reverse Approach to Adrenal Gland Resection

By Joe Munch

For more than a decade, using transperitoneal laparoscopy to treat patients with benign adrenal neoplasms has been the norm. However, surgical endocrinologists at M. D. Anderson are finding that for some of these patients, a different approach may be warranted. Today, these surgeons are using retroperitoneoscopic posterior adrenalectomy (RPA), a procedure that has become commonplace in Germany (where it was initially developed) but is seldom employed in the United States, to resect adrenal glands containing benign tumors and small metastases.

Since its introduction in 1992, laparoscopic adrenalectomy has become the standard of care for patients with benign adrenal disease. Traditional transperitoneal laparoscopic adrenalectomy is performed with the patient in a supine position; surgeons must navigate through the patient's abdomen to approach the adrenal glands anteriorly, carefully moving organs aside to access the retroperitoneum. In contrast, RPA is performed while the patient is in a face-down "jack-knife" position, and the adrenal glands are accessed through the lower back. This provides quick, direct access without disturbing the intraabdominal organs. Not only does RPA have all the usual advantages of laparoscopic surgery—including minimal blood loss, shorter hospital stay, less pain, and quicker recovery—but because it allows more direct access to the adrenal glands, RPA also provides a superior field of view.

Who benefits?

While RPA is not indicated for patients with primary adrenal cancer—these tumors are often too large and have invaded too much of the sur-

rounding tissue to be removed laparoscopically—the procedure can lessen the impact on recovery for patients with benign disease or small metastatic tumors.

According to Nancy D. Perrier, M.D., an associate professor in and chief of the Section of Endocrine Tumor Surgery in the Department of Surgical Oncology, patients who particularly benefit from RPA include:

- **Patients with prior abdominal surgery.** Scarring and adhesions caused by prior abdominal surgery create a "nonfriendly" abdomen in which tissues have fused together, making it difficult to access the adrenal glands from an anterior approach.
- **Patients who need a bilateral adrenalectomy.** Traditionally, bilateral adrenalectomy requires either a large, open operation or two completely separate laparoscopic surgeries. "This would involve turning the patient in the middle of a case, which is very tricky when a patient

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Dr. Nancy D. Perrier readies a patient for retroperitoneoscopic posterior adrenalectomy. The procedure, in which surgeons access the adrenal gland (inset, white arrow) through the back, provides superior results for some patients.

Adrenal Gland Resection

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is intubated and asleep,” Dr. Perrier said. “To unprep, undrape, reposition the patient, then re-prepare and re-drape can add an hour and a half to the anesthesia time.”

- **Patients with Cushing syndrome caused by a benign adrenal adenoma.** The syndrome, which is characterized by high levels of cortisol in the blood, prevents normal wound healing. In these cases, the most direct and minimally invasive operation is best, since it requires the least amount of tissue healing.
- **Patients with metastatic cancer in the adrenal glands.** These patients need to receive chemotherapy or radiation therapy. A traditional, anterior adrenalectomy in such patients, who often have had multiple prior abdominal operations, would likely require a long recovery period. RPA, with its shorter recovery period, may allow the rest of their treatment to proceed more quickly.

The use of RPA is not limited to patients with these conditions; in fact, Dr. Perrier said, the approach may be used to resect other types of tumors in the same region. However, RPA is not indicated for large tumors because the modest operating space afforded by RPA makes manipulation of large tumors difficult. RPA is also not appropriate for very obese patients; even in the prone position, the retroperitoneum in these patients becomes compressed, and sufficient operative space cannot be created.

A precipitous learning curve

Yet despite the benefits RPA offers and despite the fact that RPA has been around for more than a decade now, few U.S. surgeons have embraced the procedure. Many of those who attempted to do so, Dr. Perrier said, abandoned the procedure after only a few cases.

“There is a learning curve, and it is steep,” Dr. Perrier said.

RPA is a technically challenging procedure. Not the least of these

To perform an RPA, surgeons must completely reorient themselves. It would be like asking you to drive home backward, according to Dr. Nancy Perrier.

challenges is approaching the adrenal glands from an entirely unfamiliar direction. Surgeons are trained to navigate human anatomy head-on; in a conventional laparoscopic adrenalectomy, for instance, surgeons approach the adrenal glands anteriorly, guided in part by familiar anatomical “landmarks” within the abdomen—the liver, the spleen, the pancreas, and so on. But to perform an RPA, surgeons must completely reorient themselves.

“It would be like asking you to drive home backward,” Dr. Perrier said. “You’ve never driven backward before. You’ve always driven forward, right? If you just randomly try to do it, it’s very frustrating and very difficult.”

The trick to performing a successful RPA, Dr. Perrier said, is knowing the right steps.

“There are certain absolutes to this operation,” Dr. Perrier said. “For instance, getting the patient in the right position makes or breaks the operation. Getting into the right surgical plane, knowing the tricks for retracting and exposing the adrenal vein, dissecting the adrenal gland medially off the kidney—if you don’t know how to do these things, you won’t be able to do the operation. It’s too technically demanding.”

Training at the source

To gain the technical expertise necessary to perform a successful RPA, Dr. Perrier and her colleagues went straight to the source. Martin K. Walz, M.D., a professor at the Department of Surgery and Center for Minimally

Invasive Surgery at the Kliniken Essen-Mitte, Essen, Germany, developed the procedure not long after laparoscopic adrenalectomy was first described.

“He really single-handedly designed this operation,” Dr. Perrier said.

In 2005, Dr. Perrier was teaching a course on parathyroid surgery at the European Institute of TeleSurgery when she first observed Dr. Walz perform several RPAs.

“I saw Martin do these surgeries, and I was so impressed,” Dr. Perrier said. “It was really mind-boggling to see him do these operations, to see the technical ease of him doing it—it was just mesmerizing. I came back and said, ‘We have got to learn how to do this.’”

So, later that year, Dr. Perrier, along with Jeffrey E. Lee, M.D., and Douglas Evans, M.D., professors in the Department of Surgical Oncology, traveled to Essen, Germany, where they observed Dr. Walz perform seven RPAs in a matter of 6 hours and noted the critical aspects of the procedure. The team members returned to M. D. Anderson, and, bolstered by their observational experience, performed their first RPA in November 2005. The following spring, Dr. Walz (who had by that time performed the procedure more than 600 times) came to M. D. Anderson and observed the surgeons as they performed RPAs. His input proved exceedingly valuable and helped Drs. Perrier, Lee, and Evans succeed where other surgeons had failed. Since then, the team has done more than 70 RPAs.

“For me, now, there is no doubt that doing this operation is easier than for me to do an anterior operation,” Dr. Perrier said, “but it wasn’t that way at the beginning.” ●

For more information, call Dr. Perrier at 713-794-1345 or Dr. Evans at 713-794-4324.

To see a video of a retroperitoneoscopic posterior adrenalectomy, visit the *OncoLog* Web site at www.mdanderson.org/oncolog.



When Diagnosis Meets Denial

Being diagnosed with a serious illness is a devastating experience for almost anyone. On hearing the news, some people become fearful, while others are angry, anxious, or sad. Still others deny that anything is wrong, telling themselves that the doctor must be mistaken, the diagnosis isn't serious, and everything will be fine.

The basics of denial

Denial is a psychological defense mechanism that protects us from anxiety by allowing us to refuse to admit that a problem exists. Many people initially have trouble believing or accepting the fact that they have a serious illness. As a temporary response, denial can be a helpful buffer, allowing time to adjust to a new diagnosis. Usually, this early period of denial is followed by other, more realistic coping responses.

Denial of a serious medical problem can happen at different times:

- **Before the diagnosis.** A person might ignore symptoms or think that there's no reason to seek medical attention because "it's probably nothing."
- **After a diagnosis.** A denying patient might insist he or she isn't really ill or doesn't need to return for follow-up care.
- **When a cured ailment returns.** In this case, the patient may think, "I've completed my treatment and done everything I was supposed to do. This can't be happening again."

Persistent denial can lead to serious medical complications. Patients who won't accept that they are ill will avoid or delay treatment, miss doctors' appoint-

Deniers don't hear the details of medical treatment or information about the severity of their disease.



ments, and ignore symptoms or warning signs of problems. They often do not follow medical advice.

Tuning out the details

Whether denial is a temporary reaction or a persistent mindset depends on the way the patient has dealt with past crises, said Mary K. Hughes, C.N.S., a psychiatric advanced practice nurse in M. D. Anderson's Psychiatry Service. "People aren't going to change their coping mechanisms because they are ill," she said. "They're going to do what's comfortable." If denial is the way they've coped with past problems, they are likely to tune out what the doctor is telling them.

Deniers don't hear the details of medical treatment or information about the severity of their disease. "They don't pay attention to specifics," Ms. Hughes said. They might tell them-

selves that the doctor will take care of the problem and everything will be fine.

It's vitally important, Ms. Hughes said, to watch for signs of denial in a loved one who is ill. You can accompany the patient to medical appointments and pay attention to the details that he or she may ignore. In the doctor's office, you can serve as an extra pair of ears, ask the physician questions, get treatment specifics, take notes, and generally offer the patient support. You can also ask the doctor about possible side effects from treatment and how those side effects can be managed, which may help the patient feel more comfortable.

Beyond denial: How to cope

Almost everyone diagnosed with a serious illness experiences a wide range of feelings afterward. These feelings can change often and unexpectedly. Having someone who will listen to the patient discuss these often confusing emotions can be a big help. The listener might be an empathetic friend or family member, other patients in a support group, or a member of the clergy. Professional counseling can also be beneficial.

Perhaps most important of all is making sure that patients realize that a wide variety of help is available—from health care professionals, friends, family, and volunteers—and they do not have to carry the burden of illness alone. ●

For more information, talk to your physician, or

- visit www.mdanderson.org/departments/neuro; click on "Quality of Life" and then "Psychiatry Service"
- call askMDAnderson at 1-877-632-6789

OncoLog, May 2008
K. Stuyck

Address Service Requested

DiaLog ASPIRE to Stop Teen Smoking

By Alexander V. Prokhorov, M.D., Ph.D.

As physicians, we can play a valuable role in preventing teen smoking. Trusted health professionals have a unique opportunity to counsel their young patients about the dangers of tobacco.

But as you may have experienced first-hand, it can be difficult to discuss the health risks of smoking in a way that captures the attention of teens. That's why M. D. Anderson created ASPIRE, an interactive Web site that uses animation, real-life scenarios, and teen talk to communicate the dangers of smoking.

ASPIRE ("A Smoking Prevention Interactive Experience") is a free, in-depth resource that you can use to give teenagers the knowledge and skills they need to adopt a tobacco-free lifestyle. The Web site is easy to find—www.mdanderson.org/aspire—and it can be accessed by anyone. I encourage you not only to peruse the ASPIRE site yourself but also to recommend it to your teenage patients and their parents.

The Web site allows teens to choose their current situation—for example, whether they already smoke or are being tempted to smoke—and customizes a presentation based on that choice. Much of the content is streaming video (more than 5 hours in all), including clips from teens who have lost loved ones to smoking and others who apply some positive peer pressure against tobacco use. While clicking through the site, teens also learn facts

about the short- and long-term consequences of smoking on their health, their appearance, the environment, and even their social life.

ASPIRE doesn't take a dry, didactic approach. The site speaks to teens on their terms, and the information is built around scenarios to which they can relate, such as dating, stress, and sports. It also emphasizes that addiction is a form of dependence, appealing to teens' desire to be independent and to make decisions on their own.

We know from experience that this self-paced, interactive method works. During initial testing of ASPIRE, students who used the site reported that they smoked fewer cigarettes, developed stronger aversions to smoking, and experienced less temptation to smoke. Health agencies in several states have adopted ASPIRE as part of their anti-smoking education efforts, and we are now rolling out the program to school districts nationwide.

Every day, nearly 4,000 youths under the age of 18 years start smoking; clearly, "Just say no" is not sufficient to keep teenagers from using tobacco. With ASPIRE, we can inspire them to make wiser choices. ●



Dr. Prokhorov is project director of ASPIRE and a professor in the Department of Behavioral Science at M. D. Anderson.

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