Frontiers in Radiosurgery

Gamma Knife offers precise treatment of difficult tumors in the brain, skull base, and head and neck.

By John LeBas

Multiple brain metastases, deep or enmeshed intracranial tumors, and tumors of the skull base and upper cervical spine can be difficult to treat, owing mainly to the delicate adjacent anatomy. Conventional therapies are sometimes too risky or of limited effectiveness.

Fortunately, patients with such lesions may benefit from stereotactic radiosurgery, which selectively targets tumor tissue to receive highly focused radiation with the help of computer-assisted treatment planning. At The University of Texas M. D. Anderson Cancer Center, the Division of Radiation Oncology in conjunction with the Departments of Neurosurgery and Head and Neck Surgery is now offering advanced stereotactic radiosurgery with the Leksell Gamma Knife Perfexion (Elekta, Stockholm, Sweden) system.

Like the earlier-generation stereotactic radiosurgery system it replaced, the Perfexion system integrates imaging and customizable dosing parameters to treat intracranial tumors with minimal damage to surrounding structures. (Continued on page 2)
healthy tissue. However, the new device is fully automated and has improved treatment-planning capabilities, which will allow more efficient treatment of patients, treatment of more lesions per patient, and treatment of more anatomically complex locations than the earlier model.

With this technology, the multidisciplinary oncology team can create a radiation target that fits the lesion almost perfectly. Using a computer that displays images of the target in multiple planes, the physicians direct a cursor to “drop shots,” or place ray paths, around the tumor. From this interaction, the software computes a three-dimensional field that can be finely adjusted for size, dose, and position. After the treatment plan is finalized, the patient is secured into the treatment machine, and a customized dose of radiation is delivered according to the exact specifications of the field created by the team.

**Precise targeting**

The primary appeal and clinical importance of the Gamma Knife lie in its precision and ability to safely reach deep tumors; its treatment efficiency is potentially very high. While surgery is the most common treatment approach for tumors in and around the skull, surgery is not feasible in all cases. “Some tumors aren’t optimally treated with surgery, some need radiation therapy after surgery, and some cannot be treated with chemotherapy,” said Franco DeMonte, M.D., professor and medical director of M. D. Anderson’s Brain and Spine Center. “For those tumors, the Gamma Knife may be a good option.” Surgeons at M. D. Anderson partner closely with their radiation oncology colleagues when treating patients with the Gamma Knife.

The precision of the Gamma Knife results from a combination of attributes. The treatment plan is created using high-resolution maps based on magnetic resonance imaging (MRI) and computed tomography (CT) scans. The patient’s head is secured in a frame to create a stereotactic targeting space. And the gamma radiation beams are shaped by channels as small as 4 mm, allowing tumors of various shapes and sizes to be effectively treated with minimal danger to surrounding healthy tissue.

The Gamma Knife directs multiple beams of gamma radiation at individual doses that are considered clinically insignificant. However, the sum of those small doses as they intersect at the target is clinically significant. As the physician drops shots and adjusts the eight-sector collimators during planning, the computer calculates the exact amount of radiation that will be built up at each point within the target. The approach spares healthy tissues that lie in the paths of the beams while allowing a tumor-killing level of radiation to be delivered within a well-defined area.

In addition to the 4-mm size, the Gamma Knife’s tungsten collimators offer 8-mm and 16-mm shots emitted by 192 cobalt-60 sources in the machine. The machine uses four pins to hold the skull in position; the slightest movement could mean the difference between hitting or missing the tumor, and a miss could deliver damaging radiation to healthy tissues instead. “It’s a one-shot deal. There’s only one chance to get it right since you can’t take back the treatment once you give it,” said Eric L. Chang, M.D., associate professor and director of M. D. Anderson’s central nervous system stereotactic radiosurgery program. “That’s why the delivery needs to be robust and highly precise.”

Because the Gamma Knife can so precisely treat small lesions without damaging normal brain tissue, the device is ideally suited for the treatment of patients with multiple brain metastases. Frequently, patients with brain metastases have already received whole-brain irradiation, and further whole-brain irradiation may carry an increased risk of toxicity. Gamma Knife radiosurgery, however, can obviate the need for repeating whole-brain irradiation, and some patients may be able to avoid whole-brain irradiation altogether by receiving Gamma Knife radiosurgery as initial therapy.

At M. D. Anderson, patients with difficult tumors in and around the skull are evaluated in a multidisciplinary fashion. “A multidisciplinary approach is essential to ensure that we choose the best treatment modality and produce the best possible plan for each patient,” Dr. Chang said. That approach carries into treatment planning for Gamma Knife sessions, involving specialists in radiation oncology, neurosurgery, head and neck surgery, and radiation physics.

**Improved technology**

The Gamma Knife Perfexion system, available for about 3 years, has been tested in controlled studies at other institutions. Experience from those studies suggests its treatment potential is greater than that of the earlier radiosurgery system. “The earlier system, which was 10 years old, was not fully automated. As
There’s only one chance to get it right since you can’t take back the treatment once you give it. That’s why the delivery needs to be robust and highly precise.”  
– Dr. Eric L. Chang

In a result, it was just not efficient to use it to treat more than four lesions per patient at a time,” said Almon S. Shiu, Ph.D., professor and supervising radiation physicist. “We believe the new system is the most automated radiation therapy system available, which will allow us to target a greater number of lesions.”

The new machine automatically positions the radiation sources at the correct collimator channels; in the old device, the channels had to be manually configured to customize the gamma rays’ path for each patient. With the automated system, Dr. Chang said, multiple targets in the brain can be treated more efficiently.

The automation and configuration of the Gamma Knife will also allow the treatment of different types of lesions, including acoustic neuromas, meningiomas, pituitary tumors, and other benign brain tumors; skull base tumors; malignant gliomas; and possibly tumors in the upper cervical spine. On the opening days in the Gamma Knife suite, specialists successfully treated two skull base tumor patients—one with a recurrent nasopharynx carcinoma and one with a recurrent salivary gland cancer in the skull base—who previously would not have been candidates for radiosurgery because the earlier-generation machine could not reach the skull base.

The integration of CT and MRI studies, which are essential to developing the treatment plan, has also been improved with the Perfexion system. The previous version of treatment planning software did not allow the treatment plan to be worked up until the day of the treatment, after the patient was secured in the frame. The new planning software does allow the flexibility of preplanning, which could improve operational efficiency—important since about 300 patients are treated each year, and the number is expected to grow.

Increasing options
The advances in the technology translate primarily into a wider range of treatment options for patients with brain, skull base, and upper cervical spine tumors. “We wanted to be able to offer all modalities to the patient and improve continuity of care,” Dr. DeMonte said. “It is important to offer choices in treatment, and for many patients, the risk-benefit ratio and preferences will support one choice or another. For example, an elderly patient with a skull base tumor may not be a candidate for surgery, but that patient may be successfully treated with the Gamma Knife.”

Paul Gidley, M.D., an associate professor in the Department of Head and Neck Surgery who specializes in the treatment of acoustic neuromas, said similar choices will apply to some patients he sees. “The same complications—namely, facial weakness or paralysis and hearing loss—can occur whether we treat acoustic neuromas with surgery or radiation therapy,” he said. “However, for patients who are infirm or have other medical problems and thus cannot tolerate surgery, Gamma Knife may be an excellent choice.” More specifically, Gamma Knife radiosurgery is an option for medium-sized (2.5 cm) and smaller acoustic neuromas or those that have regrown after surgery.

The advantages for patients with brain metastases are important when considering that such cases are increasing in both complexity and number. “We started out using radiosurgery for treating patients with single brain metastases, but treatments have evolved to the point where we are now routinely treating newly diagnosed brain metastasis in patients with up to three or four tumors,” Dr. Chang said. “Cancer patients in general are surviving longer as more effective systemic treatments become available, but as survival increases, patients are also developing more brain metastases. To help those patients over the long term, we need to safely and efficiently treat brain metastases when they appear while preserving neurocognitive function and minimizing any damage to the brain. Radiosurgery is also chemo-friendly, allowing patients to return to their chemotherapy program with minimal delay.”

For more information, visit the Brain and Spine Center at www.mdanderson.org, or contact Cindy Kişer, R.N., at 713-563-2405.
Advanced Ovarian Cancer

Deciding Whether Chemotherapy Should Precede or Follow Surgical Resection

By Sunni Hosemann

Introduction

Ovarian neoplasms comprise several pathologic subtypes. Epithelial ovarian cancers are the most common and cause the most deaths among patients with gynecologic cancers.

The standard treatment of epithelial ovarian cancer is surgery and chemotherapy. Traditionally, surgery is done first, and chemotherapy is given postoperatively (adjuvantly). However, some patients benefit from receiving chemotherapy prior to surgery (neoadjuvant chemotherapy). Usually, patients who receive neoadjuvant chemotherapy also receive adjuvant chemotherapy, but this approach does not necessarily involve more treatment; rather than receive a course of six chemotherapy cycles after surgery, a patient might receive three before surgery and three after surgery.

This article discusses the treatment alternatives for epithelial ovarian cancer, including factors to consider in deciding whether to give chemotherapy first, how many cycles to give, and when to perform surgery. No simple treatment plan for ovarian cancer exists, and the decisions in developing a personalized plan require careful evaluation, monitoring, and collaboration among specialists.

Understanding Ovarian Cancer

What gynecologic oncologists see when they look into the abdomen of a patient with ovarian cancer is not just a diseased ovary. A hallmark of ovarian cancer is abundant fluid manifesting as abdominal ascites and pleural effusion; whether this fluid is produced by the cancer itself or by the distressed organs is unknown. Presumably, the fluid is the vector of another curious behavior of ovarian cancer: the tendency of the tumor to spread by depositing cancer cells throughout the abdomen rather than by invading adjacent tissues before metastasizing via lymph and blood to distant locations. Ovarian cancer appears to initially “fall away” from the primary tumor into the fluid and then adhere to the surfaces of organs and membranes it contacts. Small surface tumors develop, appearing to have been “sprayed” onto the uterus, bladder, bowel, diaphragm, mesentery, liver, omentum—in fact, no abdominal organ or surface is immune. Later, the cancer can also spread via lymph and blood as many other cancers do.

The surgery for ovarian cancer is therefore a major and extensive operation that includes a thorough exploration and possible resection of multiple organs. Every surface of every tissue in the abdomen must be examined for cancer. At M. D. Anderson, surgery for ovarian cancer is always led by gynecologic oncologists who have training and expertise in performing complex procedures.

Initial Evaluation

Patients who are seen by a gynecologic oncologist for the treatment of ovarian cancer have usually been referred after the discovery during physical examination of an abnormal pelvic mass, which is often confirmed by imaging (ultrasonography or computed tomography [CT]). It is also common for the disease to have been discovered during a surgical procedure, in which case there are usually tissue samples.

“When ovarian cancer patients come to us, they may have had one of a number of procedures, including a CT scan, open biopsy, paracentesis, and thoracentesis, to make the diagnosis,” said Charles F. Levenback, M.D., professor and deputy chairman of M. D. Anderson’s Department of Gynecologic Oncology and clinical medical director of the Gynecologic Oncology Center. Histologic confirmation is not needed for a referral to M. D. Anderson, however.

In fact, according to Kathleen M. Schmeler, M.D., an assistant professor in Gynecologic Oncology, it is preferable for the patient to be seen prior to any invasive procedure. That is not always possible, since ovarian cancer is sometimes discovered during an unrelated abdominal surgery.

By the time the patient is seen by an oncologist for treatment, she may be suffering from a range of symptoms—from vague “bloating” and loss of appetite to considerable abdominal distention, pleural effusion, and frank malnutrition. Patients are often depressed as well, according to Dr. Levenback.

Treatment

As stated earlier, the standard treatment for ovarian cancers advanced beyond the earliest stage (localized) involves both cytoreductive surgery and chemotherapy (usually a course of six cycles). Chemotherapy usually consists of a taxane plus carboplatin.

The surgery involves a full exploration of the abdomen and maximal removal of the cancer, or “debulking.” The operation can be extensive and may include a total hysterectomy and removal of the ovaries, fallopian tubes, omentum, and sometimes aortic and pelvic lymph nodes. All peritoneal surfaces are scrutinized for evidence of cancer, which is excised if found. To achieve maximal or optimal cytoreduction, the surgery can...
also include bowel resection, splenectomy, radical pelvic dissection, liver resection, and stripping of the surfaces of the diaphragm and other peritoneal organs and structures. Like any large and long operation with risks of serious complications, this surgery is best performed at an institution that has a high volume of such operations, a full complement of supportive care services, and the availability of other surgical specialists. “Depending on the extent of tumor involvement, we may need a liver surgeon and perhaps a vascular surgeon involved as well,” said Michael M. Frumovitz, M.D., an assistant professor in Gynecologic Oncology. Added Dr. Levenback: “We recommend to the patients we see that they have their surgery here, but they’re often able to have their chemotherapy closer to home if that is desirable.”

Dr. Levenback said M. D. Anderson takes an aggressive approach with ovarian cancer surgery, examining and excising tumor deposits from both the lower and upper abdomen. There is good reason to be aggressive: the duration of survival is inversely related to the amount of tumor left behind.

Treatment Decisions

Traditionally, advanced ovarian cancer is treated first with surgery to debulk the tumor and then with chemotherapy to kill any residual or metastasized cancer cells. However, for some patients, it may be preferable to give part of the chemotherapy before surgery. At M. D. Anderson, the decision is based on two major criteria: the likelihood that the tumor burden can be removed surgically, and the patient’s health and nutritional status.

Degree of resectability: Tumor and anatomic factors

According to Dr. Frumovitz, the goal of surgery is to remove all of the cancer. “In some ways, it’s an all-or-nothing proposition,” he said. “If you remove 99% of the cancer but leave a large nodule somewhere, it’s the same as not removing any of it, in terms of long-range cancer control.”

The preoperative evaluation is therefore an assessment of whether surgery is likely to remove all of the cancer. In patients for whom the likelihood is very high, surgery is a reasonable initial step. But if there is a large tumor load and complete resection appears unlikely, Dr. Frumovitz recommends chemotherapy first. The chemotherapy can reduce the tumor extent, boosting the likelihood that the tumor will be completely removed during surgery.

Another anatomic consideration is whether there is disease in very vascular areas where the tumor may not be confined to surfaces—the porta hepatis region behind the liver or in the root of the mesentery, for example. Such findings indicate the cancer is unlikely to be completely resectable, a good reason to consider neoadjuvant therapy.

Patient health, nutritional status, and other factors

Other factors may also tilt the decision toward neoadjuvant therapy. According to Dr. Schmeler, some patients who present with ovarian cancer at M. D. Anderson have multiple medical comorbidities and are not able to undergo extensive surgery. However, such patients may be able to receive chemotherapy.

It may seem paradoxical to recommend chemotherapy for a patient considered too weak for surgery. But in practice, such patients benefit the most from preoperative chemotherapy since they often experience a dramatic reduction in tumor load and ascites with a subsequent relief of symptoms after a few chemotherapy cycles. These patients are then able to resume eating and become more comfortable. “The ascites dries up, there is almost always significant tumor shrinkage, and the patients experience a dramatic relief of symptoms,” Dr. Levenback said. “This makes the surgery less radical.”

Nutritional status also plays an important role in determining whether to give therapy before or after surgery. According to Dr. Frumovitz, patients with an albumin level less than 2 gm/dL, which suggests a poor nutritional status, have more difficulty recovering from extensive surgery. Dr. Levenback agreed. “If a patient hasn’t been eating or has been vomiting, I pay attention to that as well. Poor nutrition compromises wound healing after surgery,” he said. Thus, patients with a poor nutritional status may benefit from neoadjuvant chemotherapy, which can alleviate symptoms and allow the patient to eat again so her nutritional status can improve before surgery.

Other symptoms are also significant in making the case for neoadjuvant chemotherapy. Depression is common, particular-
ly when nutritional status is compromised, and can play an important role in how well patients do postoperatively. “For one thing, depression makes it more difficult to get out of bed and to be active, which slows recovery,” Dr. Levenback said. Mood often improves when the patient experiences relief of other symptoms.

According to Dr. Schmeler, another potential benefit of neoadjuvant therapy is that it provides an earlier indication of tumor response to chemotherapy agents. “The most ideal situation is one in which we have a good surgical outcome and chemosensitivity,” she said. Response to chemotherapy can be gauged prior to extensive surgery. “When chemotherapy is given neoadjuvantly and no response is seen, we usually do not proceed to surgery, but rather we change to a different agent,” she said. If patients do not respond to initial chemotherapy agents, their prognosis is very poor and performing surgery will not improve survival.

When therapy is given neoadjuvantly, surgery is considered following three cycles of chemotherapy. This allows the tumor burden to decrease prior to cancer cells becoming resistant to the chemotherapy. However, determining when to intervene surgically requires careful monitoring and continual assessment of response, and the plan must be individualized for each patient.

Choosing the optimal treatment sequence can be a delicate matter and requires close monitoring of response and collaboration between gynecologic and medical oncologists. Gynecologic oncologists are unique in that they practice both surgical and medical oncology, so they are ideally suited to manage this treatment timing and ensure that care does not become fragmented between subspecialists.

**Contributing Faculty**

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**IN BRIEF**

**Vaccine Improves Survival in Melanoma**

A vaccine for advanced melanoma has been shown to improve therapeutic response and progression-free survival in patients receiving interleukin-2 (IL-2), according to researchers from M. D. Anderson. The vaccine is the first in melanoma—and one of the first in all cancers—to show clinical benefit in a randomized phase III clinical trial.

“While more follow-up is needed, this study serves as a proof of principle for vaccines’ role in melanoma and in cancer therapy overall,” said Patrick Hwu, M.D., professor and chair of the Department of Melanoma Medical Oncology and a co-investigator on the study. The peptide vaccine, gp100:209-217 (200M), works by stimulating patients’ T cells, which control immune responses. “The T cells then secrete enzymes that poke holes in the tumor cell’s membrane, causing it to disintegrate,” Dr. Hwu said.

The trial opened more than a decade ago, after an earlier study of the vaccine combined with IL-2 showed a response rate of 42% in patients with metastatic melanoma. The phase III trial showed that patients who received IL-2 and the vaccine had a significantly higher response rate (22.1% vs. 9.7%) and progression-free survival (2.9 months vs. 1.6 months) than the patients who received IL-2 alone.

Dr. Hwu said that although the findings are promising, more research with the vaccine is needed, including long-term follow-up of the phase III trial participants.

“Right now, the vaccine can be given to only half of those with melanoma because it has to match a patient’s tissue type, or HLA. A major priority for us is to figure out ways to broaden our approach and use mixtures of peptides so that more patients are eligible,” Dr. Hwu said. “We also would like to improve upon it by including other immune-stimulatory agents, such as anti-CTLA4.”

The study’s findings were presented in May at the American Society of Clinical Oncology’s annual meeting in Orlando.


Colorectal Cancer: Life-Saving Options for Early Detection

Colorectal cancer is easy to prevent or treat when growths are detected early with screening tests. For that reason, doctors recommend that most people start regular screening for colorectal cancer at age 50.

The standard screening test for colorectal cancer is colonoscopy, which allows the physician to see cancerous and precancerous growths in the colon and rectum. However, other options may be available to you. To decide which option is best, talk to your physician.

Understanding the options

During conventional colonoscopy, the doctor examines the rectum and colon using a lighted, flexible tube called a colonoscope, which is inserted through the anus. When a precancerous growth (or polyp) is detected, it can be snipped away during the colonoscopy, preventing a cancer from ever developing. When a cancerous growth is found early, it can usually be treated successfully.

A less invasive technique called virtual colonoscopy offers another option for detection of polyps and colorectal cancer. The main difference between conventional and virtual colonoscopy is how the doctor sees inside the patient. In virtual colonoscopy, computed tomography (CT) is used to scan the colon from outside the body. A computer then assembles the CT images into three-dimensional images that can show polyps and other abnormalities.

Both types of colonoscopy require the patient to prepare for the exam by cleansing the colon. Usually, this is accomplished by taking laxatives 24 hours before the test and not eating or drinking anything after midnight the night before the colonoscopy. Some physicians also require that the patient consume nothing but clear liquids for a day or two before the procedure.

Conventional colonoscopy is the more widely used of the two tests. Patients are usually sedated during the test, which eliminates discomfort but requires someone else to drive them home afterward. If any polyps are discovered during the procedure, they are immediately removed. Removing polyps—which can become cancerous—is considered one of the most effective ways to prevent colorectal cancer.

Virtual colonoscopy does not require sedation, which makes the procedure more convenient. Although preparation requires the same bowel cleansing as for standard colonoscopy, the procedure itself is shorter. Instead of inserting a colonoscope through the entire length of the colon, the physician inserts only a thin tube into the rectum to expand the colon with room air or carbon dioxide. Then, the CT scans are performed.

While virtual colonoscopy can detect polyps, the physician has no way to remove them during the procedure. Instead, polyps have to be removed later that same day or at another time during a follow-up conventional colonoscopy. However, less than 10% of the patients screened have a significant polyp. Research has shown that virtual colonoscopy can be as effective as conventional colonoscopy in finding polyps 5 mm and larger, but virtual colonoscopy is less reliable than the conventional exam for detecting smaller polyps.

The need to have a conventional colonoscopy to remove any polyps is often cited as a disadvantage of virtual colonoscopy. However, David Vining, M.D., a professor in M.D. Anderson’s Department of Diagnostic Radiology and the inventor of virtual colonoscopy, said virtual colonoscopy allows the majority of patients to avoid unnecessary invasive procedures. “About 90% of patients who undergo virtual colonoscopy do not have a significant polyp that requires removal, and thus they don’t need a follow-up colonoscopy,” he said.

One advantage of virtual colonoscopy is that it doesn’t have the risks associated with sedation. The risk of instrument-related complications, such as bleeding or tearing of the colon, also is lower than for the conventional procedure.

Other screening tests for colorectal cancer include the fecal occult blood test and fecal immunohistochemical test, which check for blood in the stool; sigmoidoscopy, which is similar to colonoscopy but is limited to the rectum and lower colon; and double contrast barium enema, during which x-rays are used to check for cancer after the patient receives a barium enema and has air pumped into the colon.

Importance of screening

No matter which test is chosen, it is important for people over age 50 to get some type of regular colorectal screening. “For patients diagnosed with early-stage colon cancer, 90% are still alive after 5 years. But for patients diagnosed with later stages, after the cancer has spread to distant organs, only 10% are still alive after 5 years,” Dr. Vining said. “Getting screened for colorectal cancer means that you’re improving your odds of finding the cancer early, when it’s easiest to treat and you have the best chance of long-term survival. Better yet, you can prevent the disease altogether by detecting and removing precancerous polyps.”

Regular screening for colorectal polyps and cancers is recommended for everyone age 50 years or older, or earlier for people with a family history of colorectal cancer or a personal history of inflammatory bowel disease. A standard colonoscopy is recommended every 10 years, or more often if a polyp is found. A virtual colonoscopy is suggested every 5 years.
Reduced Wait Times Mean Faster Access for New Patients

By Bryan Tutt

First-time patients at M. D. Anderson may not have to wait as long for their initial appointments as they have in the past. The institution has streamlined its medical review process, reducing the average wait from the time a patient first calls for an appointment until the actual appointment from 3 weeks to 1½ weeks.

Also, certain diagnostic and treatment services are now being offered on Fridays and weekends, giving patients increased and faster access to care.

“M. D. Anderson has taken very proactive steps in reviewing and streamlining our access processes,” said Gerard Colman, the institution’s chief of clinical operations. “We have greatly reduced the wait times for new appointments, in most cases by more than 50%.”

M. D. Anderson saw 26,587 new patients in 2008, and Connie Longuet, director of Patient Access Services, said she expects the number to increase to around 29,000 in 2009. With this increase, it is important to make sure all patients continue to receive personal, convenient care, she said.

For physicians, the process of referring patients and sending their records has not changed. The online referral form and the myMDAnderson portal for physicians are available at www.mdanderson.org. Physicians may also refer patients by telephone at 1-800-392-1611, option 1. Patients may refer themselves by submitting a self-referral form at www.mdanderson.org or by calling 1-877-632-6789.

Ms. Longuet said delays can result when physicians try to refer patients to M. D. Anderson by phoning a colleague who works at the hospital instead of using the toll-free number or Web site. “Every patient referral has to be processed by a patient access specialist,” said Ms. Longuet, “so the best way to refer a patient is to refer via the myMDAnderson physician portal or to call the physician referral number. Our patient access specialist will guide each person step by step, keeping them informed of the referral status and answering all their questions.”

Patients who are referring themselves should have insurance information on hand and be prepared to answer a few questions about their diagnosis and current treatment when they call. “We want to make sure they get booked with the correct physician the first time,” Ms. Longuet said.

As recently as February, new patients had to wait for their first appointment an average of 15 weekdays, including several days just to find out whether they would be accepted. Now, one-third of departments are scheduling appointments the same day or next day after the patient first calls, and the average time to the new patient appointment is 8 weekdays.