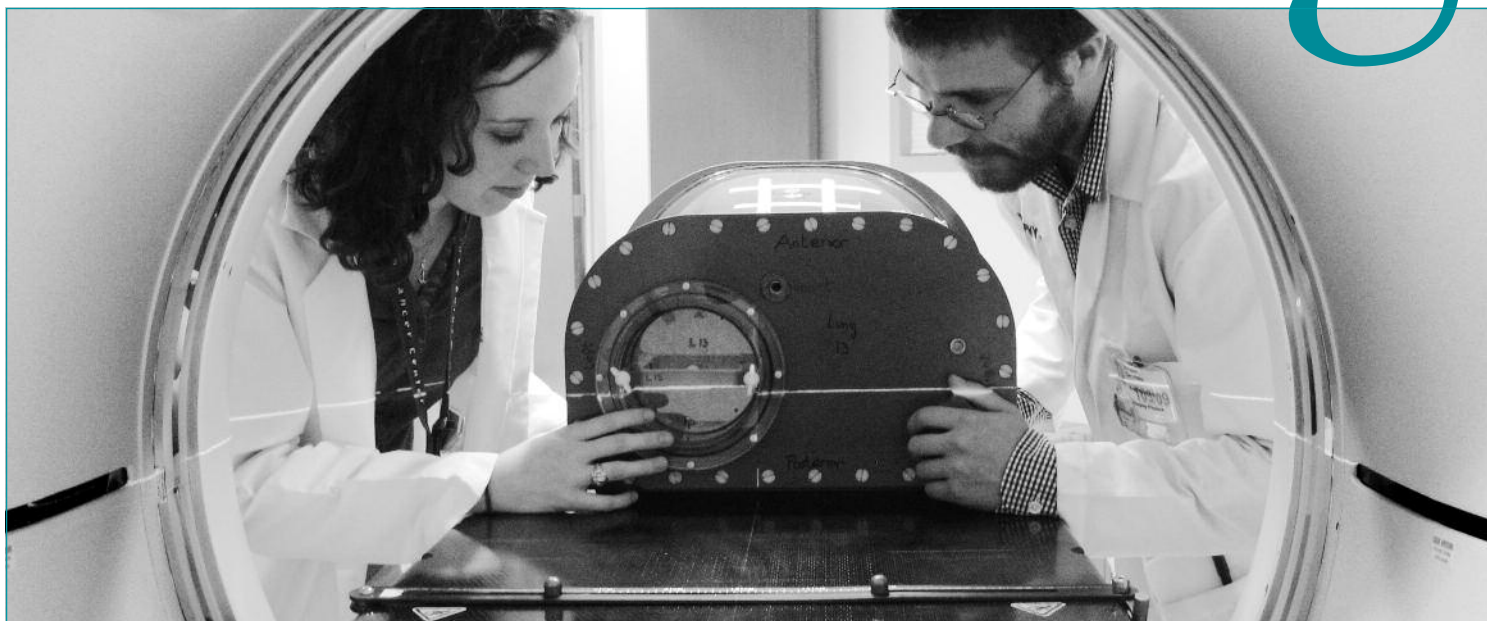




REPORT TO PHYSICIANS

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Oncology



Photograph: Dr. Geoffrey Ibbot

Graduate students at MD Anderson's Radiological Physics Center position a thorax phantom on a CT scanner.

Protecting the Patient during Radiation Therapy

Staff expertise and equipment accuracy are essential to safe and effective treatment

By **Stephanie Deming**

Delivering radiation therapy effectively and safely requires a team effort. Cooperation is needed between skilled physicians, who prescribe the best treatment, and a host of other team members, who make sure that treatment is implemented correctly and that quality and safety checks are done meticulously.

According to Thomas A. Buchholz, M.D., professor in and chair of the Department of Radiation Oncology at The University of Texas MD Anderson Cancer Center,

“You can be the greatest doctor in the world, but if you don’t have the greatest team, things can go wrong.”

Quality through teamwork

In addition to radiation oncologists, the radiation therapy team includes radiation physicists, who ensure that the treatment machines and treatment planning computers are working correctly; medical dosimetrists, who help translate the radiation oncologist’s prescription into a detailed treatment plan; and radiation therapists, who position patients on the treatment machines and deliver the radiation treatment.

The team members work together to develop and deliver a customized treatment plan for each patient (see box, page 3).

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Protecting the Patient during Radiation Therapy

(Continued from page 1)

For radiation therapy to be successful, the treatment plan must strike an appropriate balance between maximizing the number of tumor cells killed and minimizing damage to normal tissue. However, careful treatment planning is not sufficient—it is also critical that the treatment planning computers and treatment machines function correctly so that patients receive the planned radiation therapy.

According to Dr. Buchholz, the incidence of medical errors with radiation has been very low nationwide. “However, if something goes wrong, it can be devastating,” he said, adding that every member of the radiation therapy team must be aware of the potentially serious consequences of errors. “We have teamwork to assure that everything is done perfectly,” said Dr. Buchholz. “Quality in radiation therapy is paramount. Radiation oncology is a specialty that prides itself on taking these quality steps, and we at MD Anderson have very much been part of that for decades.”

Radiological Physics Center

For more than 40 years, MD Anderson’s Radiological Physics Center (RPC) has been overseeing the quality of all radiation therapy delivered in U.S. National Cancer Institute (NCI)-sponsored clinical trials, including trials conducted at MD Anderson. According to Geoffrey Ibbott, Ph.D., director of the RPC, “We started in 1968, when the NCI decided that there needed to be a quality assurance mechanism to make sure that patients who were treated with radiation in their clinical trials were getting the correct radiation doses.” Today, the RPC works with approximately 1,800 institutions, including about 200 outside the United States.

The RPC runs four formal programs for institutions that are members of the cooperative study groups that participate in NCI-sponsored clinical trials:

Credentialing program. Credentialing is done to ensure that institutions wishing to participate in specific NCI-sponsored trials involving advanced radiation therapy techniques can treat patients according to the protocol’s specifications. The RPC uses a number of credentialing approaches. The simplest is to ask physi-



Photograph: Dr. Geoffrey Ibbott

A head-and-neck phantom is positioned for irradiation with a linear accelerator.

cians at the participating institution to fill out a questionnaire to demonstrate their understanding of the protocol. A more in-depth approach is to mail the institution a set of computed tomography scans for a hypothetical patient, showing the tumor and surrounding normal tissues. Using the information from these scans and following the treatment protocol, the institution designs an appropriate treatment plan, which is then checked by the RPC. For the most complicated trials, the RPC mails the institution an anthropomorphic phantom—a model of part of the human body, such as the pelvis, thorax, or head and neck—that can be placed on a treatment machine and irradiated. Phantoms contain sensors, called thermoluminescent dosimeters (TLDs), that measure the amount of radiation received. The institution creates a treatment plan for the phantom according to the protocol specifications, irradiates the phantom, and mails the phantom back to the RPC, which analyzes the TLDs to determine whether radiation was delivered correctly.

Annual treatment machine audits.

Every year, the RPC checks all the treatment machines at the centers participating in NCI-sponsored clinical trials to make sure that the radiation beams are calibrated correctly—in other words, to make sure that the amount of radiation the institution thinks is being delivered by the machine is what is actually being delivered. The RPC mails TLDs to the participating institutions, which then position and irradiate the

TLDs as instructed and mail them back to the RPC for analysis. According to Dr. Ibbott, about 15% of the institutions checked each year have at least one beam whose delivered dose disagrees with the expected value.

Site visits. Physicists from the RPC travel to 30–40 institutions a year for on-site evaluations. During the day, while patients are being treated, the RPC physicists review the institution’s quality assurance programs and check some of its patient treatment records to make sure that the institution is consistent in the way it applies its calculations. Each evening, after patient treatments are finished, the RPC physicists spend 4–6 hours checking the treatment machines. At about 70% of institutions, RPC staff find a discrepancy in the treatment machine measurements during the site visit. These discrepancies are generally minor but occasionally are large enough to affect the quality of treatment. “Institutions usually respond very quickly and are very concerned about our findings,” said Dr. Ibbott.

Audits of treatment records. Finally, the RPC reviews patient treatment records for some of the cooperative groups that take part in NCI-sponsored clinical trials to make sure that institutions are accurately reporting how they treated patients and accurately delivering the intended doses. These audits turn up documentation errors (e.g., someone writes “5,400 cGy” instead of “4,500 cGy”) in about 25% of cases and dosing errors in about 10% of cases.

PREPARING FOR RADIATION THERAPY

According to Sandra Hayden, administrative director of Radiation Therapy Services at MD Anderson, developing a patient's individual radiation therapy plan is a multistep process—one that often takes several days.

BEFORE THE INITIAL CONSULTATION. By the time a patient comes for the initial radiation oncology consultation, he or she has already been diagnosed with cancer. One or more radiation oncologists will review information about the patient's cancer from imaging studies and other diagnostic tests.

INITIAL CONSULTATION. During the initial consultation, the patient undergoes a physical examination, and the radiation oncologist may order additional diagnostic tests. The radiation oncologist explains the potential benefits of radiation therapy, describes what the patient can expect in terms of the treatment and its side effects, and answers the patient's questions. "Patient education is paramount," said Ms. Hayden. "We want the patient to understand what will take place for the next several days, weeks, or months." Educational materials from MD Anderson are available in print, on line, and on DVD and CD.

SIMULATION. During the simulation appointment, the radiation therapist positions the patient on the simulator or treatment machine in the position that will be used during radiation therapy, and then computed tomography is performed to show the location of the tumor and surrounding normal tissues for treatment planning. The radiation therapist draws marks or makes small tattoos on the patient's skin; these are used to ensure that the patient is in exactly the same position for treatment. The simulation appointment usually takes about 1 hour.

CONTOURING. The computed tomography scans from simulation are reviewed on a computer by a radiation oncologist and a medical dosimetrist, who delineate the planning volumes via the computer by contouring the areas to be treated (e.g., tumor and lymph nodes) and the areas to be protected (e.g., critical structures like the spinal cord).

TREATMENT PLANNING. The information from simulation and contouring is fed into a treatment planning computer system, and the medical dosimetrist works with the computer to find a treatment plan. The radiation oncologist reviews suggested treatment plans until he or she finds one that is ideal. "The computer can go through millions of iterations and eventually come up with the best solution," said Thomas Buchholz, M.D., chair of the Department of Radiation Oncology.

PEER REVIEW. The patient's proposed radiation treatment plan is discussed by several physicians at an in-house conference. Once the plan is approved, the medical physicist must review and approve it.

QUALITY ASSURANCE. In this final pretreatment step, the medical physicist's assistant runs the treatment plan on the treatment machine without the patient on the machine, and sensors are used to make sure that the machine will actually deliver the radiation prescribed by the radiation oncologist.

RADIATION THERAPY. Once the preceding steps are complete, radiation therapy can begin. A patient typically will receive treatment once a day Monday through Friday, and each session typically takes from 15 minutes to an hour depending on the treatment plan. Each day, the radiation therapist responds to any questions or concerns the patient might have, positions the patient on the treatment machine, and delivers the radiation. ●

When RPC staff find problems at an institution, they notify the radiation physicist and, if the problem may have resulted in serious consequences for patients, the radiation oncologist. The cooperative study groups—and, through them, the NCI—are also notified of the findings. In the case of major problems, which fortunately are extremely rare, membership in a study group may actually be revoked, meaning that an institution can no longer participate in NCI-sponsored trials.

In addition to these formal programs, the RPC offers informal assistance to institutions participating in NCI-sponsored clinical trials. For example, radiation physicists at other institutions may ask the RPC to double-check complicated treatment plans. "Often, they ask us if we'll send an extra set of TLDs even though it's not the right time of the year, but they have a new machine that they want to have checked independently before they start treating patients," said Dr. Ibbott. "We strongly encourage that."

To help institutions that don't participate in NCI-sponsored trials, the RPC has a sister program, Radiation Dosimetry Services (RDS), which is also based at MD Anderson and can help these institutions for a modest fee. According to Dr. Ibbott, "Nearly 1,000 radiation therapy departments took advantage of that service last year. There is some overlap between the two groups of customers—we have a number of clinical trial participants who think that TLDs once a year isn't often enough, so they'll buy another set at the midpoint from RDS. And then there is a completely separate set of customers who just take advantage of RDS's service."

Educational programs

MD Anderson also serves as a national resource for quality in radiation therapy through a number of educational programs. Twice a year, MD Anderson offers "Introduction to Physics and Administrative Aspects of Radiation Oncology for Administrative Staff," a 2.5-day course that draws attendees from all over the country who want to learn how to establish and maintain a high-quality radiation treatment facility. MD Anderson's School of Health Professions

offers bachelor of science degrees in medical dosimetry and radiation therapy; the most recent graduating class included 35 students in those programs. MD Anderson's radiation physics faculty also teach 1- and 2-week Continuing Medical Education short courses on medical dosimetry throughout the year. The RPC plays a major educational role as well: the RPC trains graduate students in radiation physics, and in fact most of the an-

thropomorphic phantoms that the RPC uses were designed by radiation physics graduate students during their training.

"We have a very conservative stance on quality," said Dr. Buchholz, "and we're educating people on how to do this right." ●

For more information about the Radiological Physics Center or Radiation Dosimetry Services, please call 713-745-8999.

Stage II Colon Cancer: Adjuvant Therapy?

After surgery, some patients benefit from chemotherapy

By **Sunni Hosemann**

Introduction

The primary treatment for stage I–III colon cancers is surgical resection. There is agreement that surgery alone is adequate for American Joint Committee on Cancer stage I disease, in which the tumor is confined within the submucosa or muscularis propria, and that additional therapy is needed for stage III disease, which by definition has invaded regional lymph nodes. But for stage II colon cancer—which includes tumors that have invaded beyond the muscularis propria but have not involved regional lymph nodes or metastasized to distant sites—clinical studies to date have not provided a clear treatment directive. Current standard guidelines give clinicians the options of adjuvant chemotherapy or observation only following surgery for this intermediate category of disease, which represents a quarter of all cases of colon cancer.

The purpose of adjuvant chemotherapy is to eliminate any unseen tumor cells that might remain after surgical resection, with the intent of reducing the risk of disease recurrence. According to Scott Kopetz, M.D., an assistant professor in the Department of Gastrointestinal Medical Oncology at The University of Texas MD Anderson Cancer Center, patients with stage II colon cancer have a good prognosis overall, with a 5-year overall survival rate of approximately 85%. Because chemotherapy itself is not without risk and adjuvant therapy typically requires 6 months of treatment, physicians wish to avoid giving adjuvant chemotherapy to patients who would derive no significant benefit from it. The challenge lies in deciding which individuals would benefit.

For patients who may benefit from adjuvant therapy, chemotherapy regimens available include 5-fluorouracil (5-FU) alone and combination chemotherapy. However, when the benefit of chemotherapy is less certain, deciding on a course of treatment for an individual patient with stage II disease involves a complex risk-benefit analysis and an in-depth conversation with the patient about the options, according to Michael Overman, M.D., an assistant professor in the Department of Gastrointestinal Medical Oncology.

Understanding the evidence

To date, large randomized trials and meta-analyses have failed to show a significant survival benefit from adjuvant chemotherapy in patients with stage II colon cancer. However, trials of adjuvant therapies large enough to produce significant results have

seldom focused specifically on patients with stage II disease. The majority of these phase III trials compared observation following surgery to adjuvant 5-FU (the longtime standard) and often included patients with stage III disease. Furthermore, Cathy Eng, M.D., an associate professor in the Department of Gastrointestinal Medical Oncology, pointed out that many of the definitive trials took place before the newest standard regimen—oxaliplatin, 5-FU, and leucovorin (FOLFOX)—was in use. “Oxaliplatin was approved in 2004,” she said. “All the trials before that time consisted only of single-agent 5-FU.”

According to Dr. Kopetz, although several statistically underpowered studies have not shown significant evidence of prolonged survival with adjuvant chemotherapy for patients with stage II colon cancer, a reduced risk of recurrence was seen retrospectively in the MOSAIC trial of adjuvant FOLFOX therapy for patients with high-risk stage II disease. “So while we lack definitive proof of a survival benefit, there are credible reasons to believe that there is some meaningful benefit for patients with stage II disease,” he said. Indeed, expert panels from both the National Cooperative Cancer Network and the American Society of Clinical Oncology have recommended that adjuvant therapy for stage II disease be considered and discussed with patients. Both panels strongly recommended that such treatment be given within clinical trials, when possible.

Prognostic factors

Whether or not any cancer patient will likely benefit from adjuvant chemotherapy depends on the risk of disease recurrence. For stage II colon cancer, several well-known pathological and clinical factors are associated with a higher risk of recurrence.

Perhaps the initial factor to be considered is a molecular marker for microsatellite instability (MSI), an alteration that results in faulty replication of repetitive nucleotide chains in the DNA of tumor cells—signaling a deficient DNA mismatch repair mechanism. Testing standardized by the U.S. National Cancer Institute includes a panel of five microsatellite markers (BAT-25, BAT-26, D2S123, D5S346, and D17S250). Tumors are classified as high-frequency MSI (MSI-H) if two or more markers are unstable, low-frequency MSI (MSI-L) if only one is unstable, and microsatellite stable (MSS) if no instability is found in any of the five markers. Immunohistochemistry is now routinely performed to check for loss of key components of the DNA mismatch repair mechanism, which can also indicate the

presence of an MSI-H phenotype.

MSI-H is sometimes seen with hereditary nonpolyposis colon cancer (Lynch syndrome), although tumor cells of sporadic cancers also can be MSI-H. Although only about 15% of colon cancer patients are found to have MSI-H tumors, it is important to identify these patients because they have a better overall prognosis regardless of stage. Prior trials indicated that patients with MSI-H tumors do not benefit from single-agent 5-FU. In fact, an updated pooled analysis of several studies showed that patients with MSI-H stage II tumors who received adjuvant 5-FU actually fared worse in both disease-free and overall survival compared with those who received no adjuvant therapy. Dr. Eng pointed out that these results apply only to single-agent 5-FU; the role of FOLFOX in patients with MSI-H is currently unknown.

Regardless of a patient's MSI status, several factors are considered to be signs of increased risk of recurrence. They are:

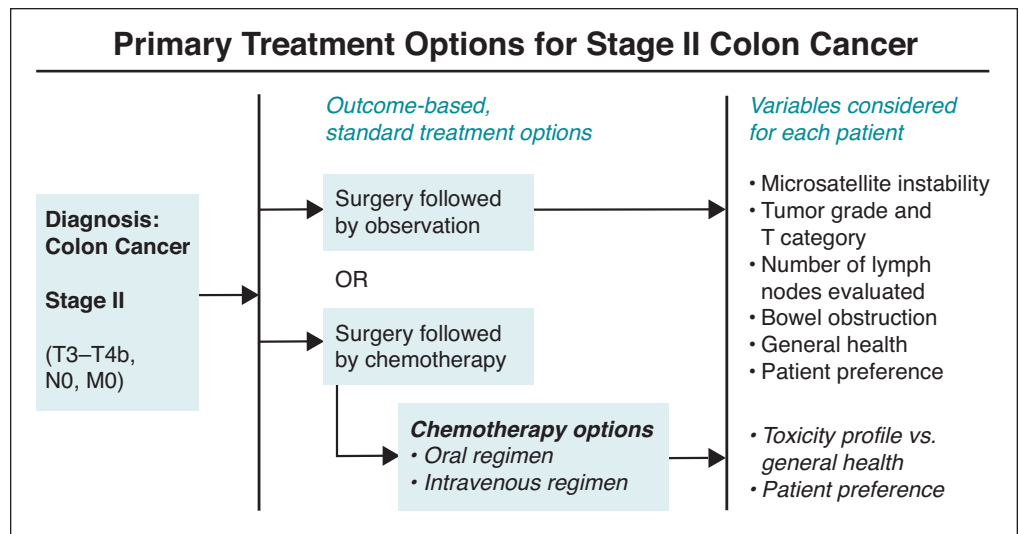
T category: An indication of the depth of tumor invasion, T category is considered a major prognostic marker. By definition, stage II colon cancers are T3 or T4, and T4 tumors are associated with an increased risk of recurrence. T4 tumors are those that extend into adjacent structures (T4a) and those that perforate into the visceral peritoneum (T4b). Gross perforation is associated with substantial morbidity and even death from the immediate event, as well as a high risk of colon cancer recurrence; but microperforations noted pathologically are also associated with poor outcomes.

Inadequate lymph node analysis: Lymph node status is an important risk marker, but the number of nodes evaluated is also prognostic. Dr. Eng said that 16 of 17 studies included in a recent systematic review found that increased survival in patients with stage II colon cancer was associated with increased numbers of lymph nodes evaluated. One study found that 8-year overall survival increased from 56% when 10 or fewer nodes were sampled to 90% when more than 40 nodes were evaluated. Current guidelines from the American Society of Clinical Oncology, American College of Surgeons, and National Quality Forum recommend examination of at least 12 lymph nodes to achieve proper evaluation—examination of fewer nodes constitutes a risk factor for recurrence, even when the nodes examined are negative.

Lymphovascular invasion: Pathological evidence of tumor cells in the microvasculature or lymphatic vessels is considered a strong prognostic risk factor for recurrence.

Tumor grade: Tumors classified as poorly differentiated or undifferentiated have a worse prognosis than those deemed well or moderately differentiated.

Bowel obstruction: Patients who present with clinical obstruction of the bowel are considered to have an adverse disease feature.



Finally, variables other than tumor factors, such as age and general health, must be considered for individual patients. For two patients with identical tumor characteristics, the treatment decision might differ for the patient in otherwise good health and the one who has significant comorbidities because each patient's tolerance for chemotherapy must be considered.

Chemotherapy choices

When the decision is made to use adjuvant chemotherapy, additional choices must be made, such as whether a single-agent therapy will suffice or a more potent (and therefore more toxic) combination is needed and whether to use an oral agent or one that requires infusion.

For the past 2 decades, 5-FU has been the basis of adjuvant therapy for colon cancer, first as a single agent, then in combination with levamisole, and still later with leucovorin. The latter combination proved superior and has been the standard adjuvant treatment for stage III colon cancer since 1998. Oxaliplatin was added to this combination (producing FOLFOX) in the 2004 MOSAIC trial. FOLFOX was accepted as an approved standard adjuvant therapy regimen for stage III colon cancer after showing a dramatic (23%) reduction in the risk of recurrence and an improvement in the 6-year overall survival rate.

The standard adjuvant chemotherapy regimens recommended for stage II colon cancer are FOLFOX and single-agent 5-FU or capecitabine. Capecitabine, an oral prodrug of 5-FU, has been shown to be equivalent to intravenous bolus 5-FU in treating stage III colon cancer.

The side effects of chemotherapy regimens must be considered for individual patients. The effects of 5-FU are well documented—in general, 5-FU therapy is well tolerated, although return to baseline quality of life can take as much as a year after the end of therapy, according to one study. Oxaliplatin is associated with increased toxicity and increased potential for unremitting neurotoxicity that will last for several weeks to months following discontinuation of the drug. Oxaliplatin would therefore not be appropriate for patients with baseline neuropathy and would be considered more cautiously for patients whose tolerance for chemotherapy is in question.

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When there is a choice of using the oral agent capecitabine or an infusion of 5-FU, patient preferences must be discussed. “Lifestyle issues play an important role in that decision for individual patients,” said Dr. Kopetz. The long-term effects are the same, but during treatment, side effects are more pronounced and concentrated within the few days following infusion of 5-FU. With the oral agent, side effects are milder but tend to be spread over a longer time.

Weighing the factors

The clear-cut candidate to forego adjuvant chemotherapy would be a patient with none of the risk factors noted above. If the patient’s tumor were MSI-H, the choice would be doubly clear, as MSI-H not only confers a better prognosis but also is known to reduce the response to the least toxic chemotherapy. But in cancer care, the ideal and the clear-cut are seldom the reality, and most patients present with a combination of prognostic factors that must be assessed to determine the risk-benefit ratio for the individual.

For example, Dr. Kopetz said, “Occasionally, patients with MSI-H, and therefore a good prognosis, present with other pathological features consistent with high risk, such as perforation and a very low number of retrieved lymph nodes. In such cases, we would have considerable unease about observation alone.” One option in such a case would be to treat with FOLFOX because although 5-FU may not be effective alone in these patients, the combination may provide some protective benefit.

For other patients who have less ominous risk factors or are not in robust health, single-agent 5-FU or capecitabine might be chosen rather than a combination that includes oxaliplatin.

Discussing risk with patients

Adjuvant therapy reduces the risk of recurrence by approximately 30% for colon cancer of any stage, but many patients would be misled by that figure because it doesn’t reflect the individual’s absolute benefit.

“This can be a complex conversation,” said Dr. Overman. “For patients to appreciate absolute benefit, it is critical for them to understand the starting point. For example, two patients might have a potential 30% risk reduction, but if one person’s initial risk is 50%, the reduction by 30% results in an absolute reduction of about 15%. But a person whose initial risk is only 10% would derive an absolute reduction of only about 3%,” he explained. “Put another way, a 15% benefit means that one in eight people will benefit. With a 3% benefit, only one in 33 will.”

This conversation necessarily involves understanding the patient’s preferences and viewpoints. “Some patients want treatment even if it changes the ratio by 1%,” said Dr. Overman. “Others don’t want chemotherapy unless it is absolutely necessary.” In either case, it is important for patients to have a factual basis for their decision. *Adjuvant! Online*

(www.adjuvantonline.com) is one of several decision tools available to help physicians describe the risks and benefits of adjuvant therapy to individual patients.

Moving forward

The development of additional molecular markers will help individualize therapy for patients. Although several gene profile tests are in development and one, OncoType DX Colon, has been approved by the U.S. Food and Drug Administration, Dr. Kopetz said these tests have prognostic value but are not predictive of which patients are most likely to benefit from chemotherapy.

Some questions about adjuvant treatment for patients with stage II colon cancer may be answered by an ongoing Eastern Cooperative Oncology Group trial, ECOG 5202. It is the first clinical trial to stratify patients with stage II colon cancer as having low or high risk of recurrence depending on their molecular marker analysis. Participants are considered to have a high risk of recurrence if their tumors are MSS or MSI-L with loss of heterozygosity at chromosome 18q (LOH 18q, indicated as a risk factor for recurrence in prior studies in patients with stage III colon cancer). Participants considered to have a high risk of recurrence are randomized to one of two adjuvant chemotherapy arms, while patients considered to have a low risk—those whose tumors are MSI-H and those whose tumors are MSS or MSI-L without LOH 18q—are followed by observation only. MD Anderson is one of the participating accrual sites for ECOG 5202.

Until more data are available, stage II colon cancer remains a condition for which clinicians must assess a complex set of factors and use the art of clinical judgment to determine the best course of treatment for each patient. ●

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Managing Cancer-Related Pain



For many cancer patients, pain is a distressing symptom of their disease. Yet, thanks to advances in pain management, cancer-related pain is now very treatable.

Approximately one-third of people undergoing cancer treatment experience some degree of pain. This pain may be short-lived or long-lasting, mild or severe. Cancer pain has several causes. Most results from a tumor pressing on bones, nerves, or organs; however, pain can also result from chemotherapy, radiotherapy, or surgery.

Treatment for cancer-related pain varies from patient to patient. Since every cancer patient's pain is unique, effective pain management must be tailored to the individual's specific needs. The good news is that the vast majority of patients can find relief using one or more medications.

Taking medication for pain relief is not a sign of weakness or the first step to addiction. Unfortunately, some patients do not seek treatment for their pain because they believe it is a normal part of their disease. Others are afraid that if they report their pain, their doctors will stop treating their cancer. And still others fear that pain is a sign that their cancer is spreading or believe that pain medicines cause addictions and disabling side effects. In fact, these are myths that can prevent patients from getting the help they need.

Taking control

Controlling pain is a part of effective cancer treatment. Here are some steps you can take to ensure that you get the best pain relief:

- **Tell your doctor about your pain.** Your health care team needs detailed information about what you're experiencing in order to create the best pain control plan for you.
- **Keep a record.** Where do you feel pain? What does it feel like? Is it sharp, dull, throbbing, constant,

burning, or shooting? How long does it last? What makes the pain better or worse?

- **Rate the severity of your pain** on a scale of 0–10, with 0 indicating no pain, 5 moderate pain, and 10 the worst pain you can imagine. Or you can describe it with words: none, mild, moderate, severe, or worst possible.

Available medications

Many medicines are now used for managing cancer pain. Some drugs are general pain relievers, while others target specific types of pain. Physicians typically use one group of drugs for mild to moderate pain, another for moderate to severe pain, and others for tingling and burning pain or for pain caused by swelling.

For mild to moderate pain, your doctor may recommend non-opioid pain medications, which include such familiar over-the-counter drugs as acetaminophen and nonsteroidal anti-inflammatory drugs (for example, aspirin and ibuprofen).

For moderate to severe pain, opioids are often prescribed. These include morphine, hydromorphone, oxycodone, hydrocodone, codeine, fentanyl, and methadone.

For tingling and burning pain, your doctor may prescribe an antidepressant or an antiepileptic drug. Such drugs are used in these instances to control pain rather than for depression or epileptic seizures. Antidepressants that may be used include amitriptyline, imipramine, doxepin, and trazodone. An anti-epileptic drug that may be prescribed is gabapentin.

Steroids, such as prednisone and dexamethasone, can help combat pain caused by swelling.

Use as directed

Most pain medicine is taken by mouth, but sometimes pain drugs can be administered with rectal suppositories, transdermal patches, or injections. It is important to take your pain medicine exactly as your doctor prescribed.

Never skip a dose or wait until your pain gets bad to take your medication. The best way to control pain is to stop it from starting or to keep it from getting worse.

Be sure to tell your doctor about any other medications you are taking, including any over-the-counter medicines or alternative remedies, as these may interfere with your pain medicine. Also tell your doctor about any new symptoms that occur once you begin taking pain medicine. Some pain medications have side effects that are easily treated, such as constipation. Call your doctor right away if you have trouble breathing, are suddenly dizzy, or develop a rash after taking your pain medication. You may be having an allergic reaction.

Sometimes, after you have been taking a pain medication for a while, the drug becomes less effective. Your doctor may then increase your dose, add a new kind of medicine, or change your pain medication. Medicine tolerance is not the same as addiction, and increasing the dose to overcome tolerance does not lead to addiction.

Additional treatments

Your doctors and nurses may recommend non-drug treatments such as bio-feedback, massage, or transcutaneous electrical nerve stimulation as a supplement to pain medication. When pain medications fail to relieve a patient's pain, doctors may recommend procedures such as nerve blocks, radiotherapy, or surgery.

Above all, remember that your cancer pain can be managed. ●

For more information, talk to your physician, or:

- visit www.mdanderson.org
- call askMDAnderson at 1-877-632-6789

OncoLog, October 2010
K. Stuyck

IN BRIEF

Researchers Identify Enzyme Involved in Chemotherapy Resistance

Researchers at MD Anderson Cancer Center and at the Life Sciences Institute of Zhejiang University in China have discovered an enzyme that causes resistance to platinum-based chemotherapy drugs by helping cancer cells repair DNA damage.

The discovery of the enzyme, called FAN1, and of its role in repairing DNA damage was recently reported in the *Science Express* advance online publication of the journal *Science*.

The platinum-based chemotherapy drugs cisplatin, carboplatin, and oxaliplatin work by causing cross-linking of the DNA strands in cancer cells, which blocks the cells' ability to divide and leads to cell death. Although it has been known that the protein complex FANCI-FANCD2 responds to DNA damage and repairs cross-linking, the details of how the complex works were unknown.

"This pathway that repairs cross-linking damage is a common factor in a variety of cancers, including breast cancer and especially ovarian cancer. If the pathway is active, it undoes the therapeutic effect of cisplatin and similar therapies," said Junjie Chen, Ph.D., a professor in and chair of MD Anderson's Department of Experimental Radiation Oncology and one of the report's corresponding authors. "The breakthrough in this research is that

"The breakthrough in this research is that we finally found an enzyme involved in this repair process."

— Dr. Junjie Chen

we finally found an enzyme involved in this repair process."

In a series of experiments, the researchers demonstrated how the FANCI-FANCD2 protein complex summons the FAN1 enzyme by acquiring a single ubiquitin molecule, connects with the enzyme by binding at the ubiquitin site, and moves the enzyme to the site of DNA cross-linking. They also showed that FAN1 cleaves branched DNA, which can result from DNA damage, but leaves the normal, double-stranded DNA alone. Mutant versions of FAN1 were unable to slice branched DNA.

Dr. Chen said that analyzing the activity of this repair pathway could guide treatment with platinum-based agents, which could be administered when the cross-linking repair mechanism is less active.

The FANCI-FANCD2 pathway is associated with the BRCA1 and BRCA2 pathways, Dr. Chen said. Mutations of the BRCA1 and BRCA2 genes are found in 5%–10% of women with ovarian and breast cancers. ●

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