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REPORT TO PHYSICIANS
MARCH 2002 Vol. 47, No. 3

OncoLog

Largest-Ever Cancer Prevention Study to Examine the Effects of Selenium and Vitamin E on Prostate Cancer Occurrence

by Vickie Williams and Michael Worley

In the largest study of its kind ever conducted, researchers are investigating the possibility that two naturally occurring substances found in common foods might be able to prevent prostate cancer. More than 32,000 men are being recruited to participate in the Selenium and Vitamin E Cancer Prevention Trial (SELECT) at more than 400 study sites in the United States, Canada, and Puerto Rico, including The University of Texas M. D. Anderson Cancer Center.

In the United States, prostate cancer is the second most common cancer in men (after nonmelanoma skin cancer), and the American Cancer Society estimates that it will kill 30,200 men in 2002. However, most men with prostate cancer will die of other causes, and it is impossible to predict which prostate cancers will progress and which will remain indolent and innocuous throughout a man's lifetime.

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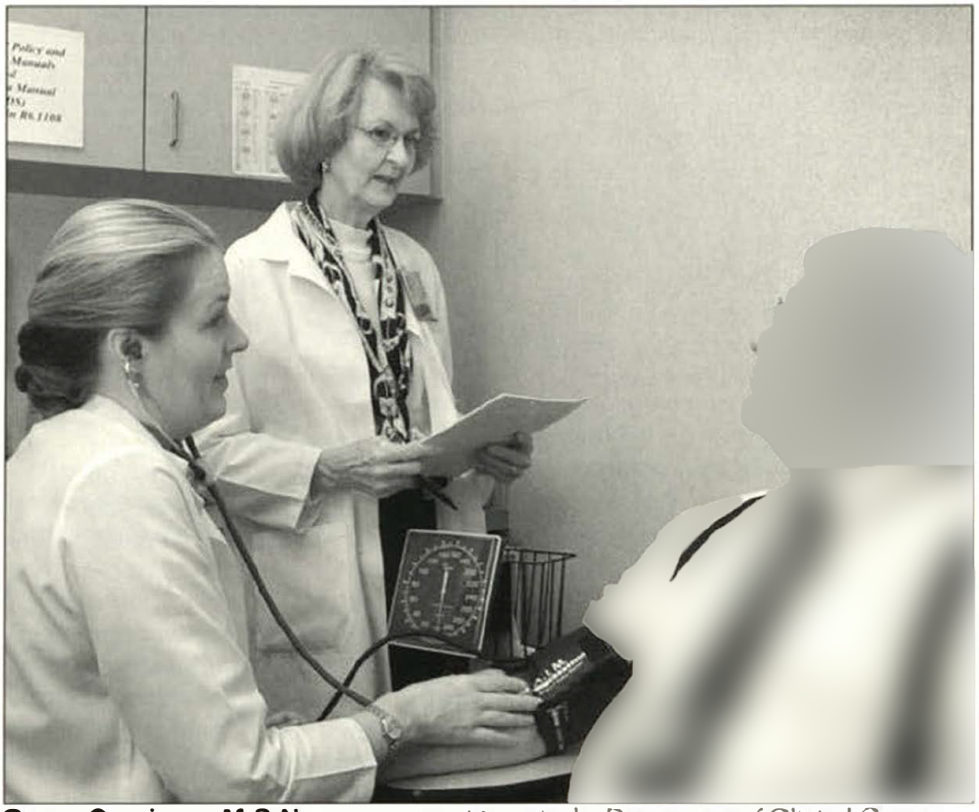

Gwen Corrigan, M.S.N., *a nurse practitioner in the Department of Clinical Cancer Prevention, examines M. D. Anderson employee* [redacted] *while* **Patti Reed, R.N.**, *a senior research nurse in the department, talks* [redacted] *about his participation in the Selenium and Vitamin E Cancer Prevention Trial (SELECT).*

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER

Selenium, Vitamin E, and Prostate Cancer Occurrence

(Continued from **page 1***)*

"Because of successful early detection efforts, there has been a shift to a more favorable stage at diagnosis," said Elise Cook, M.D., an assistant professor in the Department of Clinical Cancer Prevention and principal investigator of the M. D. Anderson SELECT center. "Treatment for localized prostate cancer usually results in long-term survival but can cause serious and life-long side effects of incontinence and impotence. Untreated prostate cancer can cause sexual and urinary dysfunction, bone pain [due to metastatic disease], and pain in the lower back during bowel movements and ejaculation, and these conditions can also seriously affect quality of life. SELECT attempts to avoid the issue of prostate cancer treatment decisions entirely by preventing the disease."

Selenium and vitamin E are both essential nutrients, and most people get some of each on a regular basis in their diets. Selenium is a nonmetallic trace element found in many foods and in water. It is especially prominent in seafood, meats, and Brazil nuts. Vitamin E is found in a variety of foods, most commonly leafy green vegetables, vegetable oils, nuts, and egg yolks. Both substances are antioxidants that are believed to play a role in controlling cell damage that can lead to cancer.

Initial clues to the potential of selenium and vitamin E for preventing prostate cancer emerged from secondary analyses of data from two previous prevention studies. In a 1996 nonmelanoma skin cancer prevention study, selenium did not reduce the incidence of skin cancer, but in secondary analysis, it was associated with a 66% reduction in the incidence of prostate cancer. In a lung cancer prevention study conducted in Finland, vitamin E had only a marginal effect on the occurrence of lung cancer in smokers; however, secondary analysis showed a 33% reduction in the incidence of prostate cancer and a 40% reduction in the prostate cancer mortality rate.

Because neither of these studies was designed specifically to evaluate prostate cancer, their results cannot be considered conclusive. "SELECT will enable us to tailor the research questions precisely to prostate cancer and to the populations at risk for this disease," said Richard J. Babaian, M.D., a professor in the Department of Urology at M. D. Anderson and co-principal investigator of the M. D. Anderson SELECT center.

"SELECT attempts to avoid the issue of prostate cancer treatment decisions entirely by preventing the disease."

– Elise Cook, M.D., assistant professor, Department of Clinical Cancer Prevention

SELECT is funded by the National Cancer Institute and coordinated by the Southwest Oncology Group. The recruitment goal for the M. D. Anderson site is 2,000 participants over a five-year period.

"We hope that because this is a cancer center, men who have a family member or friend being treated here and who understand the importance of cancer screening will be interested in SELECT," said Dr. Cook, who also serves as chair of the National SELECT Minority and Medically Underserved Committee. "Family members of men with prostate cancer are a high-risk group, and their participation in this study will provide valuable research data."

The study is open to healthy men age 55 years or older (50 years or older if African American) who have never had prostate cancer and who have been free of all other types of cancer, with the exception of nonmelanoma skin cancer, for at least five years. Prospective study subjects must also have normal results from a digital rectal examination and a prostate-specific antigen (PSA) blood test. Unlike most clinical trials, the SELECT trial is open to both English- and Spanish-speaking men. Study brochures are available in Spanish, and informational sessions are conducted in Spanish as well as in English.

Study participants will be randomly assigned to one of four treatment groups: 200 mg of selenium and a placebo, 400 mg of vitamin E and a placebo, 200 mg of selenium and 400 mg of vitamin E, or two placebos. Each participant will be offered a daily supplementary multivitamin that does not contain selenium or vitamin E. Participants will not have to alter their regular diets. The study drugs and the multivitamins will be provided free of charge to participants.

Said Dr. Babaian, "SELECT is designed to enable us to answer all the relevant questions: Is the preventive effect of these agents greatest when they are used together? Does one or the other work more effectively alone? Is either of them protective against prostate cancer at all?"

Each patient will receive treatment for about seven to 12 years from the date of enrollment. Study completion is projected for the end of 2013. While on the study, participants will be required to return to the study site every six months for follow-up examinations. The M. D. Anderson SELECT Study Center recommends a yearly digital rectal examination and PSA blood test. The follow-up examinations are performed to monitor for prostate cancer development and any side effects of the study drugs.

Dr. Cook explained that although there is some risk for side effects with both drugs, the study is designed to minimize that risk. "High doses of selenium can cause changes in hair and nails, abdominal pain, and changes in taste buds," she said. "In this study, however, selenium is administered at a low dose, and these effects are not expected. Vitamin E can increase the risk of stroke in men with uncontrolled hypertension. To diminish this risk, SELECT incorporates strict blood-pressure guidelines for participants."

Some subpopulations of men are at greater risk for prostate cancer, including African-American men, who have

a 60% higher incidence and who are twice as likely to die of the disease than any other population of men; men older than 50; and men with a family history of the disease. The SELECT trial will include these high-risk groups but will not focus exclusively on them.

"Autopsies of men around the world show the prevalence of prostate cancer to be identical globally," said Dr. Babaian. "However, we have also found that the clinical expression of the disease differs on the basis of ethnicity and geography. It is possible, then, that the high-risk groups will not derive the most benefit from SELECT; we may find that the study results will be more beneficial to the low-risk groups. This is why we are hoping to get participation from all populations of men."

Recruitment for SELECT began in July 2001 and is expected to continue through 2006. "We predict that it will take five years to accomplish our nationwide recruitment goal of 32,400 men. Twenty percent of the recruits will be African-American men," Dr. Cook said, "but all participants will be important to this study and to the prevention of this disease, which has such a widespread incidence and such a varied expression among different populations of men." ●

Men interested in participating in SELECT at any one of the 400 sites *can log on at the Southwest Oncology Group Web site (www.swog.org) and click on the link titled "SELECT" or the National Cancer Institute Web site (www.cancer.gov/clinical_trials/), or they can call the National Cancer Institute at (800) 4-CANCER (TTY: [800] 332-8615). The number to call in Canada is (888) 939-3333 (the Canadian Cancer Society's Cancer Information Service). To inquire about participating at the M. D. Anderson site, men may call (713) 794-4440, or they can log on at www.mdanderson.org/SELECT and complete the "Interest Survey Form." Once the form is received at M. D. Anderson, a SELECT study team member will review it, and the inquirer will be notified about his eligibility. Information is provided in both English and Spanish.*

Prostate Cancer Clinical Trials

Clinical trials in progress at The University of Texas M. D. Anderson Cancer Center include the following for patients with prostate cancer.

- A phase III trial of androgen ablation alone versus chemohormonal therapy as initial treatment of unresectable or metastatic adenocarcinoma of the prostate (DM95-231). *Physician: Randall Millikan, M.D., Ph.D.*

  Patients must have histologic proof of acinar adenocarcinoma of the prostate with metastatic disease or locally advanced disease that is either not appropriate for radiation therapy or has recurred following local therapy.

- Phase III trial of radiation therapy with or without casodex in patients with PSA elevation following radical prostatectomy for PT3NO carcinoma of the prostate (RTOG96-01). *Physician: Deborah A. Kuban, M.D.*

  Participants must have no clinical evidence of disease following a radical prostatectomy and pelvic lymphadenectomy for prostate carcinoma (pathologic stage T3N0/pT2pN0) at least 12 weeks prior to study entry.

- A phase III randomized prospective trial of adjuvant hormonal therapy in surgically treated patients at high risk for recurrence (ID97-077). *Physician: Curtis A. Pettaway, M.D.*

  To be eligible for this outpatient study of leuprolide acetate and flutamide, patients must have had a radical prostatectomy with bilateral pelvic lymph node dissection for organ-confined prostate cancer and been determined to be at high risk for recurrence after pathologic assessment of surgical specimens.

- Impact of dietary intervention in men with hormone-refractory and nonrefractory prostate cancer (DM98-054). *Physician: Richard J. Babaian, M.D.*

  Histologically confirmed adenocarcinoma of the prostate with no small-cell component is required for participation in this study, which evaluates an algorithm in men who undergo biopsy for PSA levels between 2.4 ng/mL and 10 ng/mL. Patients' PSA levels must have dropped to undetectable levels after prostatectomy before beginning to rise again. Patients with confirmed metastatic or locally recurrent disease are not eligible.

- A multiple randomized phase II selection trial of four chemotherapy regimens in prostate cancer (DM98-223). *Physician: Randall Millikan, M.D., Ph.D.*

  Participants must have histologic confirmation of adenocarcinoma of the prostate with androgen-independent disease progression. Antiandrogen therapies such as flutamide, bicalutamide, and nilutamide must have been discontinued at least four weeks earlier, with no evidence of response to therapy or disease progression.

- Investigation of acupuncture immune stimulation in patients with prostate cancer (ANS99-074). *Physician: Joseph S. Chiang, M.D.*

  This study is designed for patients who have histologic proof of prostate adenocarcinoma and in whom conventional hormonal therapy and antiandrogen withdrawal have failed. Participants must have evidence of progressive disease (two consecutive increases in PSA levels over eight weeks).

- A phase III protocol of androgen suppression and radiation therapy versus androgen suppression and radiation therapy followed by chemotherapy with paclitaxel, estramustine, and etoposide for localized, high-risk prostate cancer (RTOG99-02). *Physician: Deborah A. Kuban, M.D.*

  Participants must have histologically confirmed prostate cancer and be at high risk for recurrence. Patients with a PSA > 200 or evidence of metastatic disease or pathologically positive lymph nodes will not be eligible.

- L-selenium–based chemoprevention of prostate cancer among men with high-grade prostatic intraepithelial

(Continued on **page 4***)*

Prostate Cancer Clinical Trials

(*Continued from* **page 3**)

neoplasia (SWOG99-17). *Physician: Anita L. Sabichi, M.D.*

Study participants must be at least 40 years old and have documented high-grade prostatic intraepithelial neoplasia, a PSA level < 10, and no evidence of cancer. Participants will be randomly assigned to receive selenium or a placebo. The treatment period is three years, with follow-up visits every six months.

- A phase III randomized study comparing intensity-modulated external beam radiation therapy to iodine-125 seed implant boost for prostate cancer (ID99-053). *Physician: Deborah A. Kuban, M.D.*

  Adenocarcinoma of the prostate confirmed by biopsy is required for study admission. Patients must be at high risk of recurrence after radiation therapy and be able to return for follow-up at three-month intervals during the first two years after study entry and every six months thereafter. Patients who have metastatic disease or have had prior pelvic radiotherapy or prior or planned radical prostate surgery are not eligible.

- A randomized trial of preoperative chemotherapy and androgen ablation compared with androgen ablation alone followed by radical prostatectomy for select patients with locally advanced adenocarcinoma of the prostate (ID99-061). *Physician: Christopher J. Logothetis, M.D.*

  Participants must have histologic proof of prostatic adenocarcinoma without regional or distant metastasis and be appropriate surgical candidates for radical prostatectomy. A Zubrod performance status of 2 and a life expectancy of at least 10 years are required, as is a recent negative bone scan.

- A feasibility study of l-selenomethionine and α-tocopherol in patients with clinically organ-confined adenocarcinoma of the prostate prior to prostatectomy (ID99-332). *Physician: Jeri Kim, M.D.*

  Patients must be scheduled to undergo radical prostatectomy. Except for those provided through the study, participants cannot take vitamin supplements while on the study. Other exclusion criteria include prior radiation therapy to the primary tumor and concomitant therapy.

- Phase I/II study of paclitaxel, estramustine phosphate, and thalidomide for patients with metastatic androgen-independent prostate carcinoma (ID00-087). *Physician: Danai Daliani, M.D.*

  To be eligible, patients must have histologically confirmed adenocarcinoma of the prostate with evidence of androgen-independent progression. (Patients with variant histologies are eligible for phase I only.) Patients must have disease progression following antiandrogen therapy withdrawal, and at least one but not more than two chemotherapy regimens must have failed.

- A tolerance and efficacy trial of preoperative thalidomide treatment followed by radical retropubic prostatectomy in select patients with locally advanced prostate cancer (ID00-089). *Physician: Danai Daliani, M.D.*

  Participants must have adenocarcinoma of the prostate without evidence of metastases and be candidates for radical prostatectomy. Patients with clinical stage T1c to T2c disease with a Gleason score ≥ 7 on initial biopsy or clinical stage T3 disease are eligible. Patients who have received prior hormonal therapy, immunotherapy, radiation therapy, or chemotherapy for prostate carcinoma are not eligible.

- A phase III intensity-modulated radiotherapy dose-escalation trial for prostate cancer using hypofractionation (ID00-381). *Physician: Deborah A. Kuban, M.D.*

  Patients with proven adenocarcinoma of the prostate, clinical stage T1b to T3b, are eligible to participate. Participants must return for follow-up every six months for the first two years and annually thereafter. Patients who have received prior pelvic radiation therapy will not be eligible.

- Phase I trial of fixed-dose STI-571 with escalating doses of docetaxel in patients with metastatic androgen-independent prostate cancer (ID01-271). *Physician: Paul Mathew, M.D.*

  To participate, patients must have histologic proof of adenocarcinoma of the prostate that has progressed on conventional hormonal therapy as well as bone metastasis demonstrated on bone scans. Participants must discontinue any antiandrogen therapy at least four weeks before study entry (eight weeks for patients taking bicalutamide).

- A randomized, phase II trial evaluating the importance of early erectile dysfunction rehabilitation and unilateral autologous sural nerve grafting in patients undergoing a unilateral cavernous nerve-sparing radical prostatectomy for clinically local prostate cancer (ID01-304). *Physician: Christopher G. Wood, M.D.*

  Participants must be 65 years old or younger and have no discernable preoperative erectile dysfunction. Patients will return for follow-up three weeks after surgery for catheter removal and then at six weeks, four months, and every four months for two years or until spontaneous erectile function returns.

- Phase II, open-label trial to assess the activity of ZD1839 in patients with recurrent prostate cancer who have rising serum PSA levels despite serum testosterone < 50 mg/dL (ID01-361). *Physician: Nizar Tannir, M.D.*

  Patients in this study must have histologic or cytologic confirmation of prostate cancer with no evidence of metastatic disease. Exclusion criteria include prior chemotherapy for the treatment of recurrent prostate cancer and radiation therapy completed less than 28 days before study enrollment. ●

For more information *about these clinical trials, physicians or patients may call the M. D. Anderson Information Line. Those within the United States should call (800) 392-1611; those in Houston or outside the United States should call (713) 792-6161. Visit the M. D. Anderson Cancer Center clinical trials Web site at http://www.clinicaltrials.org for a broader listing of treatment research protocols.*

Trouble Spots: Early Detection Is Key to the Successful Treatment of Melanoma

by Noelle Heinze

Scattered across the skin, signs of sun damage in the form of freckles, moles, wrinkles, and lines mimic markings on a map, depicting where we've been and where we might go. Some skin lesions will grow or change over time and—without some type of intervention—may eventually become cancerous.

"Well, it's not a melanoma," said Madeleine Duvic, M.D., chief of the Section of Dermatology at The University of Texas M. D. Anderson Cancer Center, as she examined my mole to demonstrate an investigational tool called a Dermlite, which was built by researchers at M. D. Anderson for use in skin-imaging studies. The Dermlite resembles a small hand-held magnifying glass with a polarized light ring and, unlike other dermatoscopes, is designed to be used without applying oil to the patient's skin. The technique is called dermascopy, or epiluminescent microscopy, and it helps physicians detect small changes in skin moles.

The Dermlite reveals lines in junctional nevi (flat moles) similar to the veins in a leaf. A normal junctional nevus has visible lines, indicating an even distribution of melanocytes. A change in this pattern is a sign of an abnormal distribution of melanin—and of a mole that should be biopsied for histologic examination. Other techniques, such as mole-mapping, which involves taking high-resolution pictures of moles, help to identify changes in moles or new lesions that could be melanomas.

Identifying moles that change may be important in the early identification of melanoma, the most deadly form of skin cancer. Based on statistics from the American Cancer Society, 53,600 new cases of melanoma will be diagnosed and approximately 7,400 people will die from the disease this year. "The incidence has gone up to about 1 in 90 people with a diagnosis of melanoma, and they are getting it at younger ages; however, it is being detected earlier because of increased public awareness," said Dr. Duvic. "Melanomas are the most likely skin cancers to metastasize and to kill a patient, and yet, if they

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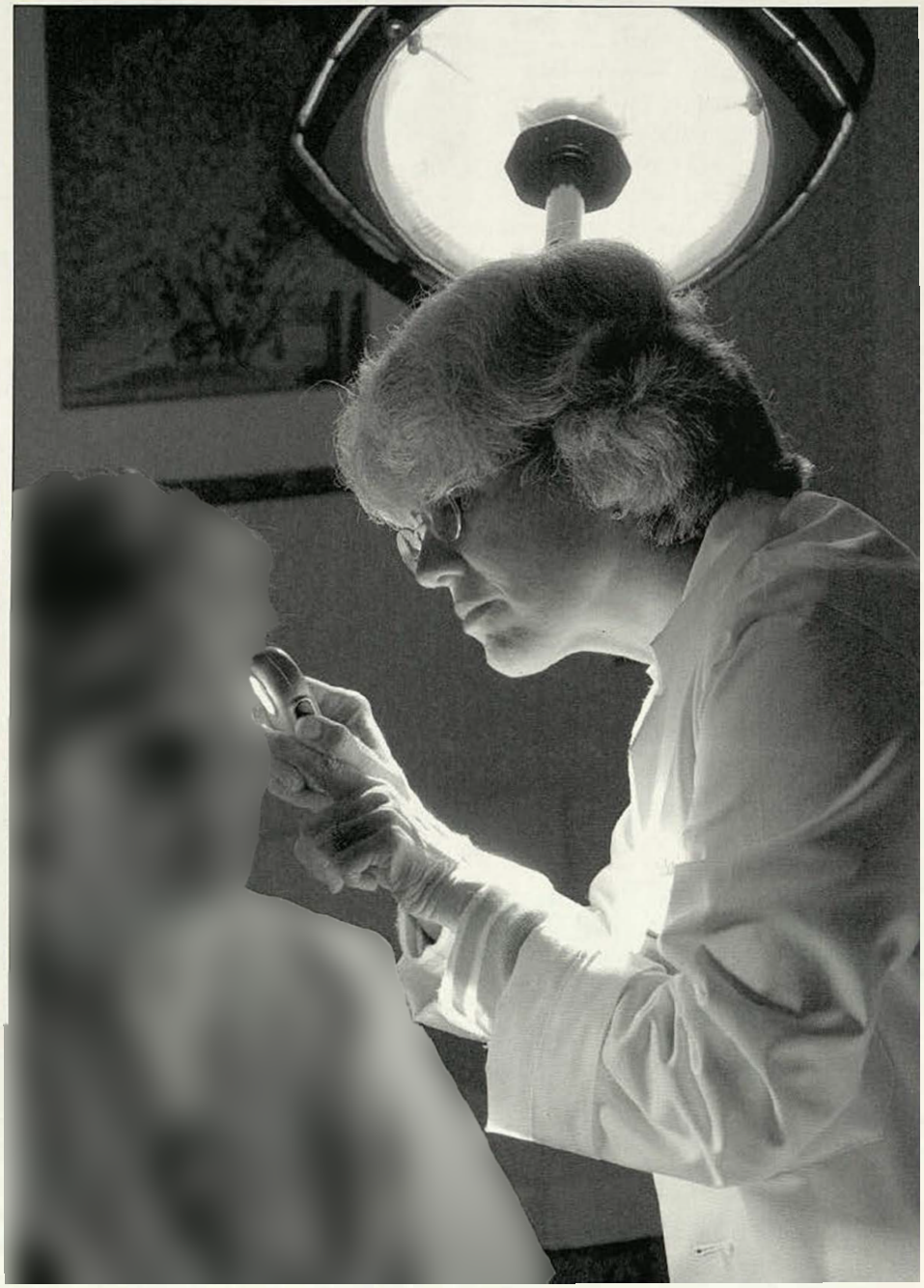


Dr. Madeleine Duvic, *chief of the Section of Dermatology, uses a Dermlite to detect minute changes in certain types of moles that could indicate melanoma. According to Dr. Duvic, the incidence of melanoma has risen in recent years, but early detection of the disease has also increased.*

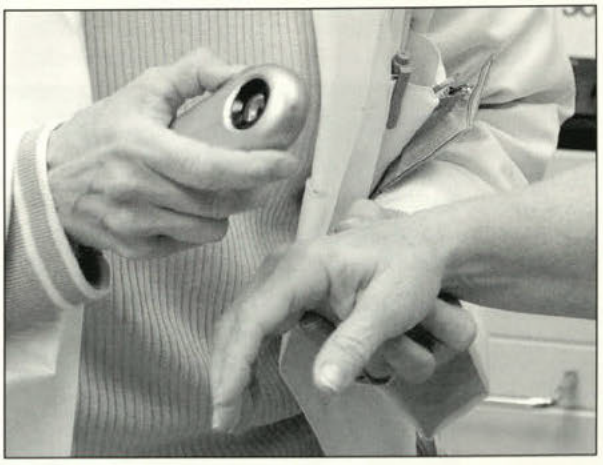
Early Detection is Key to Treatment of Melanoma

(Continued from **page 5***)*

are detected early, before they become invasive, they can be cured by surgery with wide local excision."

Melanocytes are normal cells derived from the nervous system that travel to the skin to give it protection by making the pigment melanin. Melanomas are nests of malignant melanocytes. "We now know that melanoma is often a genetic cancer. There is a gene called p16 that is associated with some familial melanomas," said Dr. Duvic. Melanomas occur most frequently on areas of skin that are intermittently exposed to the sun, especially the lower legs of women and the backs of men. Other risk factors include blistering sunburns as a child, a family history of melanoma, having more than 50 moles, and having unusual dysplastic moles.

The most common nonmelanoma skin cancers are squamous cell and basal cell carcinomas, which are also the most common cancers in humans. Squamous cell carcinoma arises in sun-damaged skin, and its precursor is called actinic keratosis, which is a thickening that usually occurs on sun-exposed areas of the skin. Squamous cell carcinomas of the lips or mucous membranes are more likely to become metastatic than those that occur elsewhere. Basal cell carcinomas are less aggressive and almost never metastasize, but locally they can be very destructive. They most often occur on sun-exposed areas in people who have very fair skin.



The Dermlite, a skin-imaging device developed at M. D. Anderson, detects changes in patterns of melanocyte distribution in junctional nevi.

"There is no recommendation for a clinical skin exam every year like there is for a Pap smear or a mammogram, but certainly people who are at a high risk for skin cancer ought to have an exam once a year," Dr. Duvic said. The American Cancer Society recommends that any skin lesion that changes in size, color, or shape or that bleeds or ulcerates be examined by a physician. Anyone who has had a melanoma or whose family member has had one is considered to be at high risk for melanoma. "If a person has a lot of normal moles or has dysplastic nevi syndrome, they should have a skin exam every six months," stated Dr. Duvic. "If a person has a lot of suspicious lesions for melanoma, then full-body photographs to complement the skin exam are probably needed. So the level of screening is geared to the level of risk."

M. D. Anderson screening guidelines recommend monthly skin self-examinations beginning at age 18 to detect any changes in moles. Melanoma most often appears as a changing black or brown mole with irregular borders. Less commonly, lesions are red or small and dark (less than 6 mm in diameter). Other symptoms include a mole that burns, stings, or itches. The most common kind of basal cell carcinoma usually presents as glassy, waxy papules on the skin in which blood vessels can be seen. They can also resemble scaly spots or scars. Squamous cell carcinomas look like warty, crusted lesions, or they can form ulcerations.

"Just looking at your own skin and then getting a doctor to examine you will lead to the early detection of skin cancer," Dr. Duvic said. "It is a more observable cancer because it is on the outside, so it should be easier to detect." ●

FOR MORE INFORMATION, *contact Dr. Duvic at (713) 745-1113.*

Studies of Chemoprevention for Skin Cancer

In addition to efforts aimed at the screening and early detection of skin cancer, researchers are studying the use of chemoprevention agents such as retinoids and celecoxib to prevent or delay the development of skin cancer in patients who are at high risk for the disease because of environmental or genetic causes. At The University of Texas M. D. Anderson Cancer Center, ongoing studies are investigating a retinoid-inducible tumor suppressor as well as other transcription factors. Also under way is a double-blind, placebo-controlled prevention trial of the arthritis medication celecoxib to determine if it reduces the number of actinic keratoses and skin cancers in study participants over the course of eight months.

According to Madeleine Duvic, M.D., chief of the Section of Dermatology at M. D. Anderson, patients with actinically damaged skin may get many skin cancers, so most of these patients will benefit from an application of fluorouracil to the face and arms to remove any premalignant cells. Because cancer arises in a field of sun-damaged skin, the application of fluorouracil or other, newer agents is advantageous compared with waiting to freeze or treat lesions after they have occurred. Fluorouracil has been used in this manner for many years with good success, but there is little published data on its beneficial effect.

HOUSE•CALL

Understanding Metastasis

Metastasis is the spread of cancer from one part of the body to another. Any malignant tumor has the potential to spread. Cancerous tumors metastasize when individual cells break away from the tumor, enter the bloodstream or the lymphatic vessels, and travel to other parts of the body and develop into a new tumor.

When a cancer spreads to nearby lymph nodes, doctors call this regional metastasis, and when a cancer spreads to a remote part of the body, they call it distant metastasis. Knowing whether metastasis is regional or distant can affect a patient's prognosis because regional metastasis can sometimes be more effectively treated than distant metastasis.

The original tumor is called the primary tumor, and distant tumors that have metastasized from it are called secondary tumors. The secondary tumor is made up of the same type of cells as the primary tumor. So, a secondary tumor found in the lungs that spread from a primary tumor in the colon will be called metastatic colon cancer.

Metastases are directly responsible for most cancer deaths. Metastases can cause problems by invading an essential organ such as the brain, by growing so large that the body's normal metabolism is disrupted, or by pressing against vital tissues like blood vessels or nerves.

The American Cancer Society reports that about one third of patients with cancer (not including those with non-melanoma skin cancer) have metastases that are detected at the time the primary tumor is diagnosed. Another third of patients have metastases that were too small to be detected by blood tests and imaging at diagnosis. These are called micrometastases. If the cancer is only treated locally, there remains a risk of the cancer recurring in another part of the body because of micrometastases. For this reason, the doctor may recommend chemotherapy. The possibility of undetectable micrometastases is important to keep in mind when making decisions about therapy.

Researchers are working on ways to keep primary tumors from spreading. They hope to find treatments that will keep cancer cells from entering the bloodstream or lymphatic vessels or slow or prevent the development of blood vessels that feed tumor growth (angiogenesis).

Right now, the best way to prevent the metastasis of a cancer is to detect and treat the primary tumor before it spreads. Effective screening is available for many types of cancer. M. D. Anderson Cancer Center recommends the screening guidelines listed at left. ●

Preventing Metastasis Through Early Detection:
M. D. Anderson's Cancer Screening Guidelines

Breast:
- Monthly breast self-examinations from age 20
- Clinical breast exam every one to three years from age 20 to 39
- Begin annual mammograms and clinical breast exams at age 40
- Try to schedule clinical breast exam at the time of regularly scheduled mammogram
- For women at increased risk of breast cancer, screening may begin earlier and/or may be required more frequently

Cervical:
- Annual Pap test with pelvic exam beginning at age 18, or earlier if sexually active
- Depending on risk factors, after three or more consecutive exams with normal findings, a physician and patient may choose to do them less frequently

Colorectal:
- Begin screening at age 50
- Fecal occult blood test (FOBT*) every year
- Flexible sigmoidoscopy every five years
- Double-contrast barium enema every five years
- Colonoscopy every 10 years
- Colonoscopy may be recommended to begin earlier and/or be done more frequently if individual is at increased risk

Endometrial:
- Screening is not recommended for most women
- For women with hereditary non-polyposis colorectal cancer, annual endometrial biopsy is recommended beginning at age 35

Prostate:
- Annual digital rectal exam beginning at age 50
- Annual prostate-specific antigen blood test beginning at age 50
- Begin screening at age 45 for men at increased risk (African-American men, men with a family history of prostate cancer)
- Screening is not recommended for men with a life expectancy of less than 10 years

Ovarian:
- Benefits of screening for women at average risk have not yet been proven, and screening is therefore not recommended
- For women with a hereditary ovarian cancer syndrome, annual or semi-annual pelvic exam, CA 125 measurement, and transvaginal ultrasonography may be considered on the advice of their physician

Skin:
- Monthly self-exam beginning at age 18

**The take-home multiple-sample method of FOBT should be used. All positive FOBTs should be followed up with colonoscopy.*

For more information, contact your physician or contact the M. D. Anderson Information Line:

✆ **(800) 392-1611** *within the United States, or*

✆ **(713) 792-6161** *in Houston and outside the United States.*

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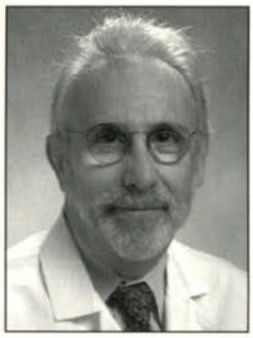
DiaLog

The Prostate-Specific Antigen Test: Reliability and Recommended Use

Richard J. Babaian, M.D.
Professor, Department of Urology



The prostate-specific antigen (PSA) test has revolutionized the early detection of prostate cancer and remains the best tumor marker available in clinical practice, but it is not perfect. Because PSA can be found in both malignant and benign cells, its use for the early detection of prostate cancer has some limitations.

PSA is secreted predominantly into the seminal fluid, where it reaches its highest concentrations. Therefore, disease processes that alter the internal architecture of the prostate, such as inflammation (prostatitis) and benign glandular hyperplasia, as well as cancer, can result in elevated PSA levels (serum concentration > 4.0 ng/mL). It is well known that the PSA level is significantly related to tumor volume; however, only 40% to 50% of PSA levels in men with cancer can be explained by tumor volume using a goodness-of-fit analysis. PSA levels also are directly related to prostate gland size and to a man's age. Furthermore, the usefulness of the PSA assay can be significantly limited by variabilities in testing procedures and fluctuations in an individual's PSA level from day to day. Taken together, these observations highlight potentially significant problems with using the PSA test to make clinical decisions.

Enhancing PSA performance is the subject of intense study, and some methods are beginning to decrease the rate of unnecessary biopsies. PSA can exist in at least two isoforms, an active component referred to as complexed PSA and an inactive form called free PSA. There is evolving evidence that a new complexed PSA assay may significantly enhance the specificity of total PSA in the 2.5 ng/mL to 4.0 ng/mL range and significantly decrease unnecessary biopsies, particularly when the PSA value is adjusted for prostate gland volume.

Men age 50 to 75 years (45 years for African-American men or men with a family history of prostate cancer) should be informed about the early detection of prostate cancer using the PSA test and digital rectal examination. They also should be told that the risk of an unnecessary biopsy approaches 75% when the PSA level is in the 2.5 ng/mL to 10.0 ng/mL range.

Since approximately 75% of men have a PSA value of less than 2.5 ng/mL, I believe the benefits of PSA testing exceed the risks associated with early detection. All men with PSA levels greater than or equal to 4.0 ng/mL and select men whose PSA is between 2.5 ng/mL and 4.0 ng/mL should be given a recommendation to undergo further evaluation and biopsy.

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CLINICAL PRACTICE GUIDELINES
Quarterly Supplement to *OncoLog*
SPRING 2002, VOL. 4, NO. 1

About These Clinical Practice Guidelines

These guidelines may assist in the diagnostic evaluation of patients with clinical symptoms or positive screening tests (if such testing exists). The clinician is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care.

M. D. Anderson Cancer Center's Practice Guidelines are continually updated as new information becomes available and are being expanded to include the entire spectrum of cancer management. Access the most current version of all M. D. Anderson Practice Guidelines from M. D. Anderson's Home Page at http://www.mdanderson.org.

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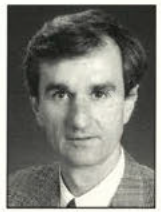

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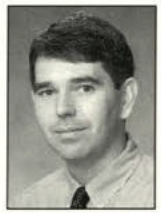

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CLINICAL DISCUSSION: Cancer Pain

Scope of This Guideline

Presented here is M. D. Anderson's guideline for managing pain associated with cancer. The guideline was developed as a one-page "quick reference" that would be clinically useful for physicians who are not pain specialists, with the recognition that the context of cancer pain is often more complex than such an algorithm can reflect and that many situations require consultation with a pain specialist.

Synopsis & Highlights

Overview

Pain can occur at any stage of cancer. It arises from the disease itself, from the effects of treatment, or from causes independent of cancer. Pain may be acute, chronic, or both in combination. It can be constant or episodic. It may concur with a specific activity such as moving or coughing (incident pain) or occur intermittently without a pattern. It may be localized or diffuse or both. The expressions of pain in patients' experiences are as many and varied as the words used to describe them: dull, sharp, shooting, radiating, burning, gnawing, and more. Pain may be nociceptive (somatic and visceral pain) or neuropathic in origin. It is always exacerbated by psychological or spiritual distress. Most people with cancer experience more than one kind of pain during the course of their illness, regardless of disease stage or prognosis.

Comprehensive Assessment

Because there are many types and origins of pain in cancer, each suggesting a different approach to treatment, a thorough assessment is the absolute bedrock of pain management. Regular ongoing reassessment is also featured prominently in the guideline, as cancer and its treatment have a dynamic relationship with pain.

This crucial assessment includes a comprehensive physical examination with relevant laboratory and imaging studies and a thorough medical history. The art and skill of the physician is next employed in the investigation and evaluation of the pain and the meaningful factors that surround it for the individual. "We are more likely to successfully treat a patient's pain if we understand that it is a complex phenomenon wrapped

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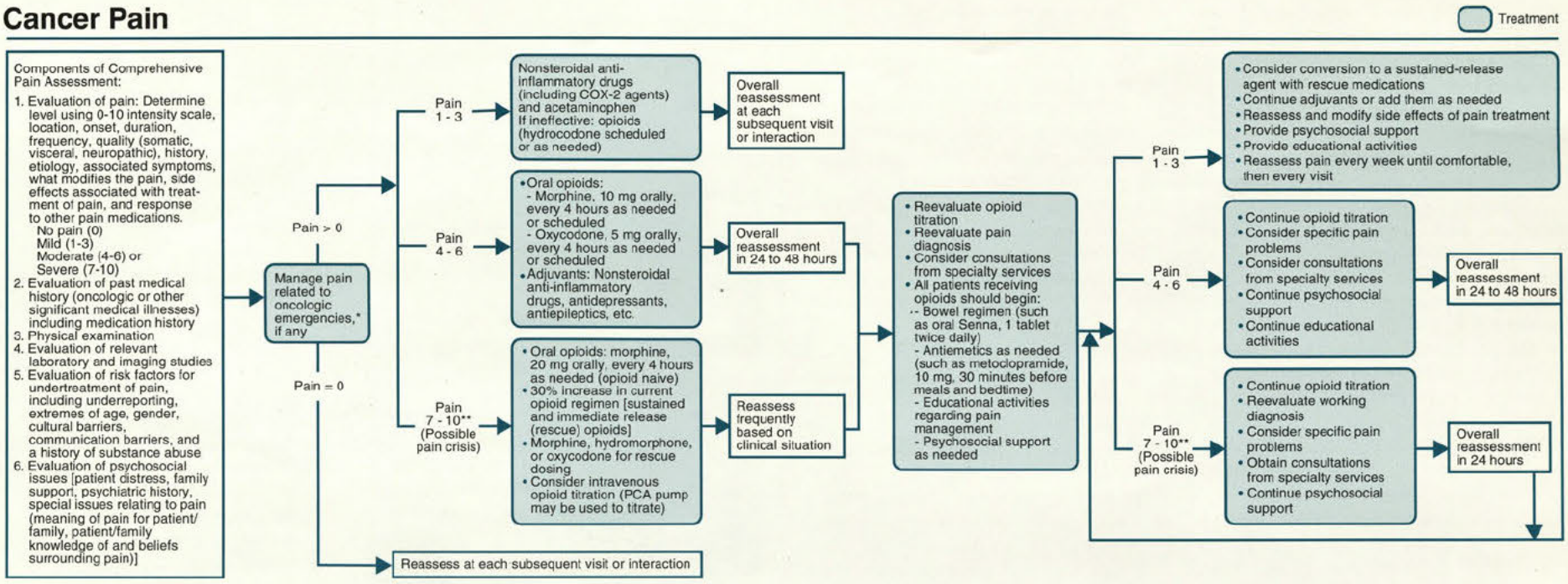
Pull Out

Cancer Pain



* Pain related to an oncologic emergency requires assessment and treatment (e.g., surgery, steroids, radiotherapy, antibiotics) along with an emergent consultation. Oncologic emergencies include:
• Bowel obstruction/perforation • Brain metastasis • Epidural metastasis/spinal cord compression • Fracture or impending fracture of weight-bearing bone • Leptomeningeal metastasis • Pain related to infection

** Some patients with chronic pain syndromes will report high pain scores on an ongoing basis. Generally, this situation is not a crisis.

PCA = patient-controlled analgesia

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CONVERSION TABLE FOR OPIOIDS

Conversion ratios are approximate, and clinical conversions should be done carefully.

PROCEDURE:

1. Determine total amount of current opioid taken over a 24-hour period that effectively controls pain.
2. Multiply by conversion factor(s) in the table below. (Convert to a morphine equivalent, then convert to a new opioid.) Give 30% to 50% lower dose of the new opioid to account for partial cross-tolerance between opioids.
3. Divide the calculated 24-hour dosage by number of doses to be given per day.
4. Add adequate PRN doses of new opioid for breakthrough pain (each PM dose should be 10% to 15% of total daily dose of new opioid prescribed).

Opioid	IV/SC opioid to IV/SC morphine	IV/SC morphine to IV/SC opioid	Oral opioid to oral morphine	Oral morphine to oral opioid
Hydromorphone	5	0.2	5	0.2
Meperidine	0.13	8	0.1	10
Oxycodone	—	—	1.5	0.7
Hydrocodone	—	—	0.5	2

Oral morphine to IV/SC morphine: **Divide by 3**

IV/SC morphine to oral morphine: **Multiply by 3**

EXAMPLE: To convert from hydromorphone 4 mg PO every 4 hours plus two extra 2-mg doses of hydromorphone per day (4 mg) to oral morphine immediate release (IR):

1. Total opioid amount: oral hydromorphone 24 mg around the clock plus 4 mg for breakthrough pain = oral hydromorphone 28 mg per day.
2. 28 mg x 5 = oral morphine 140 mg/day; 30% decrease = oral morphine 98 mg/day .
3. New regimen: oral morphine IR 100 mg divided by 6 doses ≈ oral morphine IR 15 mg every 4 hours around the clock plus 7.5 mg every 2 hours PRN for breakthrough pain.

NOTE: Methadone, fentanyl transdermal patches (Duragesic), and oral transmucosal fentanyl citrate (Actiq) do not follow standard conversions and need to be carefully titrated to desired effect.

Long-acting dosage forms are available for morphine sulfate (Oramorph) and oxycodone (Oxycontin) and are given every 8 to 12 hours. Breakthrough doses of IR products should always be prescribed in conjunction with these long-acting products.

TRANSDERMAL FENTANYL

Transdermal fentanyl is difficult to titrate and should be reserved for patients with chronic pain who have exhausted oral opioid options. Prescribing PRN metoclopramide with initiation of opioids may minimize opioid-associated nausea/vomiting and should be attempted before switching to a non-oral opioid.

An equivalency ratio of 100 : 1 (oral morphine in milligrams per 24 hours : fentanyl transdermal patch in milligrams per 24 hours) is suggested by several authors. This ratio translates to:

IV/SC Morphine	Oral Morphine	Transdermal Fentanyl
20 mg	60 mg	25 mcg/hr
40 mg	120 mg	50 mcg/hr
60 mg	180 mg	75 mcg/hr
80 mg	240 mg	100 mcg/hr

- It is important to prescribe breakthrough doses of another opioid with initiation of the patch.
- Do not titrate patch dose more frequently than every 3 days. Increase the patch dose based on the additional amount of breakthrough opioid required during a 3-day period.
- When rotating off the fentanyl patch, remove the patch and start the new opioid 12 hours later. Breakthrough medication should be available during this critical period and afterward.

METHADONE AND EQUIANALGESIC

Equivalency ratios comparing morphine (and other opioids) to methadone are dose-dependent. This ratio may range from 1:1 at low doses of oral morphine to as high as 20:1 for patients receiving oral morphine in excess of 300 mg per day. Because of its long half-life, high potency, and interindividual variations in pharmacokinetics, methadone can be very difficult to titrate and may be associated with life-threatening consequences if a patient is not monitored closely. Therefore, it is recommended that rotation to methadone be undertaken only by experienced physicians and with great caution. Candidates for a trial of methadone might include but are not limited to:

- Patients with poor pain control who have received an adequate trial of other strong opioids, especially if neuropathic pain is a component of the pain syndrome
- Patients experiencing severe or multiple toxic effects from other strong opioids
- Patients receiving high doses of opioids that are difficult to swallow because of numerous tablets per dose

M. D. Anderson's Practice Guidelines were developed by multidisciplinary teams of physicians and nurses and are intended to represent evidence-based cancer care with consensus of opinion used secondarily. The core development team for this guideline included Dr. Eduardo Bruera, Dr. Allen W. Burton, and Dr. Charles Cleeland.

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up in that person's psychological experience," says Dr. Burton. A diagnosis of cancer carries with it, for many patients, substantial emotional implications, but anxiety and worry play a part for anyone, even if these emotions are only indirectly related to the illness. It is important to understand, for example, whether there are financial or family stresses that should be addressed. According to Dr. Bruera, medical pain management will be ineffective for many patients until they gain relief from those stresses.

Evaluating Pain

Evaluation of a specific pain or pain episode is aimed at determining the source or sources of pain and looking first to find and treat conditions that might be considered oncologic emergencies. The most common such conditions include infection, fracture or impending fracture in a weight-bearing bone, obstruction or perforation of the bowel, spinal cord compression, and new metastatic disease (most commonly brain, epidural, or leptomeningeal metastases). Emergency consultations should be sought for such conditions, for which palliative surgery, radiotherapy, or chemotherapy may be used to achieve significant relief.

The guideline also addresses recommendations for medical analgesia, based on the patient's assessment of pain severity using a numerical scale of 1-10, where 10 is the most severe. Several points should be made about these numbers: first, one of the concerns about basing recommendations on such a scale is that it may appear to emphasize the numbers, and the clinician should be wary of viewing them as prescriptive or bypassing a comprehensive assessment. However, the numeric scale is very helpful for patients in describing their pain levels, and this benefit is underscored in situations where language, age, or other communication issues might otherwise present a barrier. In addition, the scale proves useful in documenting pain levels for a given individual and for evaluating response to treatment. According to Dr. Cleeland, when patients use such a scale to report pain, the level of discomfort (severity) as well as the need to treat are reliably conveyed. At reported pain levels of 1-4, most patients find that their ability to enjoy their activities is impaired; at level 4, most find that their ability to work is affected; at pain levels of 5-6, most patients have mood, sleep, and activity impairment. With pain at a level of 7 or higher, many patients have difficulty relating to their family members, indicating that the pain is predominant and consuming. Except for patients with chronic pain syndromes who sometimes report sustained pain levels of 7 or higher, patients with this level of pain may be in "pain crisis," which should be treated as an emergency, preferably in consultation with a pain specialist. As indicated in the guideline, reassessment should be done more frequently in situations where pain is more severe or control is not stable.

Pharmacological Management

"Most of the time, we can control even very severe pain," says Dr. Burton. Fortunately, there is an extensive and powerful array of medications that can be brought to bear on this complex situation. Besides those used for primary analgesia, there are effective adjuvant or supplemental agents and still others that can be used to alleviate or prevent side effects. The mainstay agents for primary analgesia are nonsteroidal anti-inflammatory drugs (NSAIDS) — including the new COX-2 agents — and opioids. Adjuvant drugs include NSAIDS, local anesthetics, antihypercalcemic agents, antibiotics, and antidepressant and antiepileptic agents, which are used in this setting not for their primary classification but for their pharmacological actions on nervous tissue. Benzodiazepines and phenothiazines are no longer considered first-line adjuvants in pain management.

Effective analgesia for a given pain relies first on a sound assessment of its origin and quality, as these bear directly on treatment choices. In some situations, it is best to provide successful primary analgesia before adding adjuvant agents; in other circumstances, combination therapy works best. Neuropathic pain, for instance, can be somewhat resistant to standard measures and is often better treated by opioids plus early use of adjuvants, particularly anticonvulsants and antidepressants.

Alternative routes of administration for some drugs can enhance their effectiveness for certain patients and may give the physician yet another tool to create the right solution. An example is the combination of a long-acting patch for basic control with rescue doses of quick-acting oral lozenges for breakthrough pain. Liquids, patches, and suppositories are alternatives to tablets and may be more readily absorbed and more easily tolerated by some patients. Opioids that are traditionally given orally or intravenously may instead be given subcutaneously. Where pain is extraordinary or intractable, other routes such as epidural catheters or spinal infusions are sometimes used. Indeed, the availability of such an extensive array of useful drugs and so many creative ways to administer them (while avoiding the dangers of polypharmacy) calls for extraordinary skill on the part of the physician. For most situations, effective management will consist of regular around-the-clock opioid administration with adequate breakthrough dosing, adjuvants as required, and proactive management of side effects such as nausea and constipation. According to Dr. Burton, strategies for managing opioid-related confusion (or delirium) include reducing the opioid dose by 10% to 20% or changing to a different opioid at an equivalent dose

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(opioid rotation), which can be determined utilizing the conversion table provided here. If relief from pain is not attained for the patient, the physician may increase the opioid dose, add an adjuvant medication, rotate to another opioid, or use a combination of these strategies. Nausea and constipation should always be treated proactively, and if they are resistant to treatment, opioid rotation may help. Our experts agree that when those measures prove inadequate, consultation with a pain specialist is recommended.

Education & Psychosocial Support

Psychosocial support may play an adjunct role in treating short-term pain (for example, pain associated with a sprained or broken ankle). But for patients who have cancer, such support is almost always of primary importance. Anxiety and depression—sometimes related to pain or fears about pain—are almost always part of the picture for patients and often for their families as well. Anxiety can be greatly reduced by acknowledging it during a thorough assessment and giving reassurance that most pain can be relieved. Dr. Burton advises physicians to spend time educating patients about pain and its treatment, to encourage them to speak up rather than suffer, and to let them know they have choices. This has an empowering effect, which is very important to patients with cancer. Frequently, patients and their families need information and reassurance about their concerns or fears regarding the use of opioids and the problem of addiction.

In addition to consultation with specialists in psychiatry, social work, nursing, or other areas for educational and psychosocial support, Dr. Cleeland points out that relaxation training, support groups, and counseling are beneficial.

Authors' Perspectives

Pain is almost never an isolated symptom in patients with cancer. According to Dr. Bruera, almost all patients with cancer have other physical and psychological symptoms, and almost always, those other issues have great impact on the patient's experience of pain. It is telling that when other physical symptoms such as constipation, nausea, and shortness of breath are alleviated, the patient's report of pain generally improves, even without changes in analgesia. Dr. Bruera believes in developing all pain management plans in a holistic way—looking at the individual's multiple concerns and treating pain in that context. "Over the years, we have learned that isolating pain is simplistic and does not achieve goals," he says. "We must remember that what patients call pain is not just that discomfort in the right shoulder but all the losses and fears they are experiencing." Reassurance and management of depression, anxiety, and associated psychological and physical symptoms must therefore be a part of the holistic approach.

Treat pain promptly and aggressively, and consult specialists early. "Pain is no longer considered simply a symptom that occurs within the 'important' disease," says Dr. Burton. In fact, unrelieved pain influences the treatment of and recovery from the primary disease. The simplest example is pain that prevents patients from getting out of bed postoperatively. In the setting of cancer treatment, unrelieved or poorly controlled pain associated with chemotherapy or radiotherapy can make patients reluctant to pursue therapy. He adds that effective pain treatment is often multidisciplinary, involving the skills of specialists in surgery, radiation therapy, palliative care, physical and rehabilitative medicine, psychiatry, and nursing. In areas where a pain specialist is not available, Dr. Cleeland suggests that a hospice physician might be consulted.

Numerical pain scales should not be used by rote. The use of a scale to help patients report their pain is very helpful in documenting and tracking changes in the individual. It has also been found to be effective across populations regardless of culture, age, or gender, thus transcending some of the traditional barriers to reporting pain. However, a pain scale does not provide a measurement that reflects or correlates with underlying pathophysiology in the way that blood glucose measurements do, for example, and therefore, the scale or the rating identified by it cannot directly suggest a specific treatment. What the scale does reflect is a patient's experience, of which only part is "pain" that can be addressed with analgesia alone.

Most important: assessment, assessment, and assessment. According to Dr. Cleeland, the most significant barrier to effective pain management is the fact that assessment and reassessment are perceived as time-consuming and ancillary to the task of treating the primary disease process. Our experts recommend a disciplined approach to pain assessment and encourage clinicians to invest energy in the evaluation because of its impact on quality of life for patients, particularly when it results in a very personalized treatment approach. "It's like a puzzle," says Dr. Bruera. "Our job is to place the pieces correctly and use the resources effectively. Find out some of the patient's attributes and strengths that can be used to help them, and you will find ways to help beyond what you would have imagined."

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References & Suggested Reading

Driver L, Bruera E. The M. D. Anderson Palliative Care Handbook, Houston: The University of Texas M. D. Anderson Cancer Center, 2000

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Note: Please see the Cancer Pain Practice Guideline on the Internet at http://www.mdanderson.org for more references.