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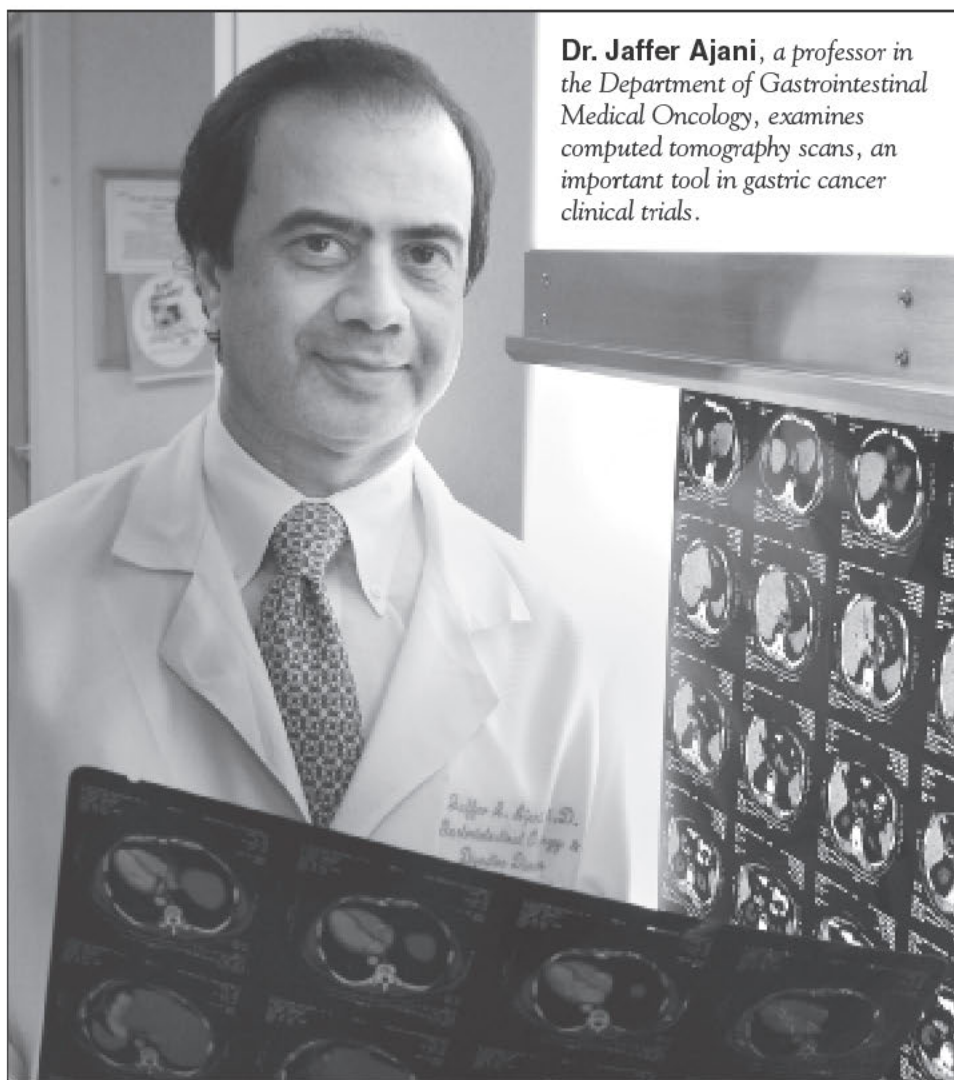


REPORT TO PHYSICIANS

APRIL 2004 Vol. 49, No. 4

Oncology

Gastric Cancer Studies Focus on Prolonging Survival and Finding Molecular Markers for Targeted Therapies



Dr. Jaffer Ajani, a professor in the Department of Gastrointestinal Medical Oncology, examines computed tomography scans, an important tool in gastric cancer clinical trials.

by Katie Prout Matias

During the last century, the incidence of gastric cancer in the western hemisphere decreased dramatically with the advent of better nutrition, refrigeration, and lower rates of *Helicobacter pylori* infection. What used to be the number one cause of cancer-related death among U.S. men is now uncommon, with about 21,000 cases diagnosed annually in the United States. Because patients are not typically screened for gastric cancer, most cases are diagnosed at a late stage, and many patients in whom it develops die of the disease.

(Continued on next page)

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Gastric Cancer Studies Focus on Prolonging Survival

(Continued from page 1)

Localized cancer

The five-year overall survival rates for patients with localized gastric cancer are daunting: 78% for patients with stage Ia cancer, 58% for stage Ib, 34% for stage II, 20% for stage IIIa, and 8% for stage IIIb. Currently, the only known curative therapy for nonmetastatic gastric cancer is a gastrectomy performed by experienced surgeons.

However, even with successful surgery, the five-year survival rate is approximately 35%; with adjuvant chemoradiotherapy in selected patients, the survival rate is 40%.

To improve survival rates in patients with localized gastric cancer, clinicians and researchers at The University of Texas M. D. Anderson Cancer Center have developed a strategy for treating select patients with preoperative therapy, a practice that is still investigational, cautioned Jaffer Ajani, M.D., a professor in the Department of Gastrointestinal Medical Oncology. In an ongoing clinical trial at M. D. Anderson, patients with operable gastric cancer are receiving chemotherapy followed by chemoradiotherapy followed by surgery.

According to Dr. Ajani, patients with operable gastric cancer tolerate therapy better before the stomach has been removed. Furthermore, preoperative therapy likely increases the chances of a successful surgery, and several studies have shown that a response to preoperative therapy is a powerful predictor of survival. "One thing we know for sure is that good surgery is an important factor for cure," Dr. Ajani said. "One approach is to reduce the size of the cancer before surgery. If you can reduce the stage before surgery, that patient's cancer is going to behave as if it were [always] at an earlier stage, and this could mean an advantage for the patient."

The results of a multi-institutional study of preoperative chemoradiotherapy, which was led by Dr. Ajani, were presented at the 1998 annual meeting of the American Society of Clinical Oncology and will soon be published. A significant number of

"Gastric cancers are relatively aggressive tumors. Although they respond to treatment, they quickly become resistant to treatment."

— James Yao, M.D.,
assistant professor,
Department of Gastrointestinal
Medical Oncology

patients—approximately 30%—had had a complete pathologic response by the time of surgery. However, only phase III trials will determine the value of the preoperative approach for patients with localized gastric cancer, said Dr. Ajani.

Metastatic disease

The five-year survival rate for patients with metastatic, stage IV gastric cancer is 7% or less. Because most metastatic gastric cancers are inoperable, they are treated with combination chemotherapy. "This is one disease where response to chemotherapy doesn't always translate into improvement in survival," said James Yao, M.D., an assistant professor in the Department of Gastrointestinal Medical Oncology. "Gastric cancers are relatively aggressive tumors. Although they respond to treatment, they quickly become resistant to treatment."

New research initiatives and more effective therapies are clearly needed for patients with metastatic gastric cancer. In the largest clinical trial ever completed in patients with advanced gastric cancer, the interim results of which were presented at the 2003 annual meeting of the American Society of Clinical Oncology, Dr. Ajani led researchers from 14 nations in studying the addition of docetaxel to 5-fluorouracil (5-FU) and cisplatin, which is the most commonly used regimen. In this phase III trial of 223 patients, adding docetaxel caused more tumors to shrink, delayed tumor growth, and prolonged

survival. This is the first study in which more than 50% of patients with late-stage gastric cancer lived for almost one year (10.2 months or longer), compared with a median survival duration of 8.5 months for patients receiving the control regimen.

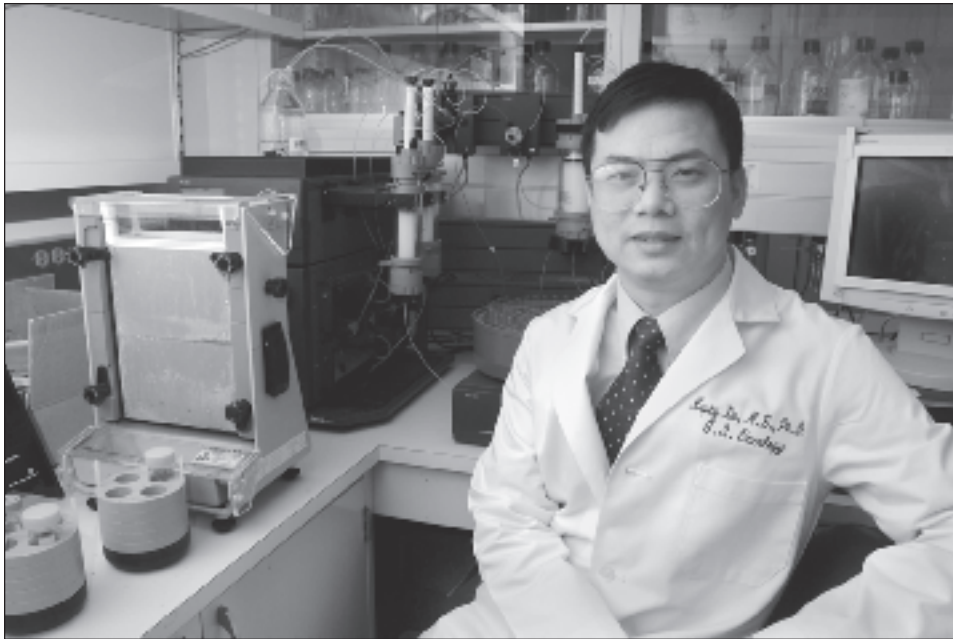
Dr. Ajani is also investigating the efficacy of S-1 (a prodrug of 5-FU that contains a compound that prevents the breakdown of 5-FU) combined with cisplatin in phase II trials of patients with advanced gastric cancer. This combination has been tested in Japan, where the response rates were as high as 70% but the effects on survival were limited.

The key to prolonging survival with chemotherapy, according to Dr. Ajani, lies in increasing the time to tumor progression: "The longer that time to progression, the longer the patient is going to live."

To prolong the time to tumor progression in patients with gastric cancer, Dr. Ajani proposes that oncologists change the treatment agent the moment they know that maximum response has occurred rather than continuing treatment once the cancer has started to progress. "That is the period where you're treating unnecessarily," he explained. "Essentially, the cancer is growing, and you're giving the same treatment that may be harming the patient. So, we would like to [achieve the maximum response with chemotherapy and then] bring in another [nonchemotherapy] treatment, something very simple that is not going to lower the patient's quality of life."

Molecular biology and translational research

At M. D. Anderson, a number of people from a variety of disciplines are coordinating translational and molecular research efforts to discover new targets for therapy and to understand the mechanisms of resistance to chemotherapy and radiotherapy. "To make an impact, we probably need to go beyond the chemotherapy paradigm and incorporate newer treatment strategies,



In his research of Sp1, a transcription factor that is overactivated in human gastric cancers, **Dr. Keping Xie**, an associate professor in the departments of Gastrointestinal Medical Oncology and Cancer Biology, and his research group are using small inhibitory molecules and genetically engineering a gene similar to Sp1 to compete with Sp1 and block it from binding with DNA and activating gene expression.

molecular and targeted treatments,” Dr. Yao said.

One approach is to add targeted biologic therapy to chemotherapy and chemoradiotherapy. “Targeted agents may selectively increase the response to chemoradiation, which is important since many of the combinations of chemotherapy and radiotherapy in past gastric cancer studies have had significant gastrointestinal side effects,” said Christopher Crane, M.D., an associate professor in the Department of Radiation Oncology. According to Dr. Crane, future studies will include targeted agents with chemoradiation based on preliminary work done at M. D. Anderson in pancreatic cancer.

Using a tumor database developed from almost 3,000 patients’ tissue samples, Dr. Yao and other researchers at M. D. Anderson are looking for molecular markers of gastric cancer that could be targeted in therapy and trying to correlate them with patient outcome and survival. These markers include tumor suppressor genes p53 and fragile

histidine triad, the adhesion molecules E-cadherin and cluster of differentiation 44, the tyrosine kinases epidermal growth factor receptor and platelet-derived growth factor, and vascular endothelial growth factor (VEGF), which plays an important role in angiogenesis.

Keiping Xie, M.D., Ph.D., an associate professor in the departments of Gastrointestinal Medical Oncology and Cancer Biology, was recently awarded a five-year grant from the American Cancer Society to study molecular markers for gastric cancer. “If certain molecular markers can consistently predict a patient’s outcome,” explained Dr. Xie, “we can better understand gastric cancer development and progression and design more effective strategies to block or reverse its malignant phenotype.”

Based on his previous research with pancreatic cancer, Dr. Xie is focusing on a transcription factor called Sp1. Sp1 is overactivated in human gastric cancers, and abnormal Sp1 activation has been

linked with the overexpression of many genes downstream of Sp1 that are involved in aggressive tumor behavior.

For example, Sp1 controls the expression of VEGF. Using human gastric cancer specimens, Dr. Xie and colleagues at M. D. Anderson investigated the expression level of Sp1 and its relationship to VEGF and microvessel density, or the angiogenic phenotype. They found that elevated Sp1 expression and the related overexpression of VEGF were directly associated with microvessel density and predicted a poor outcome for the patient. The results of their study were published in *Clinical Cancer Research* in December 2003.

Dr. Xie and his research group are also investigating Sp1’s relationship to other prognostic markers, including genes related to metastasis, apoptosis resistance, and proliferation, as well as other factors involved in angiogenesis.

“Sp1 is much, much better than the molecules we have looked at so far in predicting patients’ outcomes. Because this molecule is pivotal in controlling many aspects of cancer biology, it can be a consistent tumor marker as well as a very good target for therapy. [Through Sp1], you can trap the tumor quite easily and control tumor growth and eventually metastasis,” Dr. Xie said.

Future directions

According to Dr. Ajani, gastric cancer should be investigated from all angles. By joining efforts, gastroenterologists, pathologists, medical oncologists, radiation oncologists, and surgical oncologists can improve the clinical outcomes of patients with gastric cancer. At the same time, the discoveries made by molecular biologists, molecular pathologists, gastrointestinal biologists, and molecular epidemiologists are helping to overcome the challenges posed by gastric carcinoma. ●

FOR MORE INFORMATION, contact Dr. Ajani, Dr. Yao, or Dr. Xie at (713) 792-2828 or Dr. Crane at (713) 563-2340.

Clinical Ethicists Help Patients, Families, and Staff Resolve Difficult Dilemmas

by Karen Stuyck

A patient lies in the intensive-care unit, in critical condition and unable to communicate. He has no living will and no family member or friend with medical power of attorney to make health-care decisions for him. Who, then, decides whether life-sustaining measures such as ventilation or nutritional support are started? Who decides at what point these measures should be stopped?

Another patient refuses treatment that her doctors agree would be medically beneficial. What recourse do her physicians and family members have? What if the patient doesn't understand what the health professionals are telling her?

Fortunately, there are professionals available at many hospitals to help resolve these and other dilemmas. At The University of Texas M. D. Anderson Cancer Center, the Clinical Ethics Service conducts about 100 ethics consultations a year, according to Martin L. Smith, S.T.D., chief of the service. About 95% of the consultation requests come from M. D. Anderson health professionals, with the rest requested by patients and their families.

More than half of these consultations, Dr. Smith said, center around end-of-life issues, such as whether to stop or start life support, including whether to put a patient on a ventilator, start dialysis, or initiate resuscitation. About 30% of the Clinical Ethics Service's consultations involve patients in the intensive-care unit. Often "in the intensive-care unit, there is a critically ill patient with multiorgan failure, for example, and the health-care professionals are questioning how aggressive they should be," Dr. Smith said.

Clinical ethicists at M. D. Anderson help identify, analyze, and resolve ethical issues by gathering information and discussing the problem with the involved health professionals, the patient, and the family. The ethicists offer advice, make recommendations, and help identify options, but they don't make decisions for the persons involved.

Making sure that those involved have a common understanding of the issue is a big part of these consultations, Dr. Smith said. He related one case in which an ethicist was asked to help determine who should make decisions for a heavily sedated patient in intensive care who had left no written instructions. The patient had told his physician earlier that he did not want his wife to make any medical decisions for him because he was planning to divorce her once he recovered. Now the patient was unable to communicate his wishes. Was he serious about his intentions? If so, who instead should make the decisions?

The ethicist talked to some of the staff members involved with the patient, and a nurse suggested decreasing the patient's medication so that they could have a conversation with him. The ethicist supported the nurse's recommendation. When the patient's level of sedation was reduced, the nurse and a social worker spoke to him, and he said that he wanted his wife to be the decision maker.

About 85% of the ethics consultations are conducted by one ethicist, Dr. Smith said, but sometimes "very significant conflicts or tough dilemmas" require



The members of the Clinical Ethics Service —**Dr. Martin L. Smith** (left, background), chief; **Anne L. Flamm** (center, background), a clinical ethicist; and **Dr. Barbara J. Evans** (right, background), a clinical ethics fellow, consult with **Vanessa L. Davis**, a clinical nurse in the Symptom Control and Palliative Care Center.

the services of a four-person Clinical Ethics Consult Team. In addition to an ethicist, this team consists of an M. D. Anderson physician, a nurse, and an "ancillary other," such as an allied health professional, or a social worker, chaplain, or patient advocate, none of whom is involved in the patient's care. The physician, nurse, and ancillary other are always members of M. D. Anderson's Clinical Ethics Committee. More than half of these difficult cases concern end-of-life issues. "A frequent theme is that a patient, in the judgment of the health-care team, is dying, but the family

continues to insist on aggressive treatment," Dr. Smith said, whereas the medical team believes that the disease process cannot be reversed and that the goal should now be to keep the patient comfortable.

The consult team meets with the patient's family and the professionals who are treating the patient. Everyone is assembled in one room to voice their different perspectives, and the consult team makes sure that each understands the others. After that, the consult team meets alone to arrive at ethically supportable options, strategies, and recommendations, which are then communicated to the family and the medical team.

In addition to conducting ethics consultations, the Clinical Ethics Service has developed an online clinical ethics course designed to help medical professionals address ethical issues. The course is available at <http://netmedical.ethics.mdanderson.org>.

"Assessing decisional capacity and informed consent are a daily occurrence for physicians," Dr. Smith said. "Part of good patient care is knowledge and information about good ethics."

The clinical ethicists at M. D. Anderson come from different educational backgrounds. Dr. Smith has a doctorate in theology. The other M. D. Anderson clinical ethicist, Anne L. Flamm, has a law degree, and the service's clinical ethics fellow, Barbara J. Evans, has a Ph.D. in earth science and a law degree.

Despite their varied backgrounds, clinical ethicists base their recommendations and advice on a shared body of knowledge regarding ethical norms and standards, Dr. Smith said. These common values include supporting patient autonomy, respecting a patient's confidentiality, promoting patient benefit while minimizing harms and risks, and applying basic principles of justice and fairness to patient care.

"We have an obligation to treat medically similar patients similarly. We owe everyone equal quality care. For most people of good will, these basic principles reflect shared values and generally acceptable professional responsibilities," Dr. Smith said. ●

FOR MORE INFORMATION, contact Dr. Smith at (713) 792-3204.

An Unexpected Finding: Male Breast Cancer Is Rare and Often Overlooked

by Katie Prout Matias

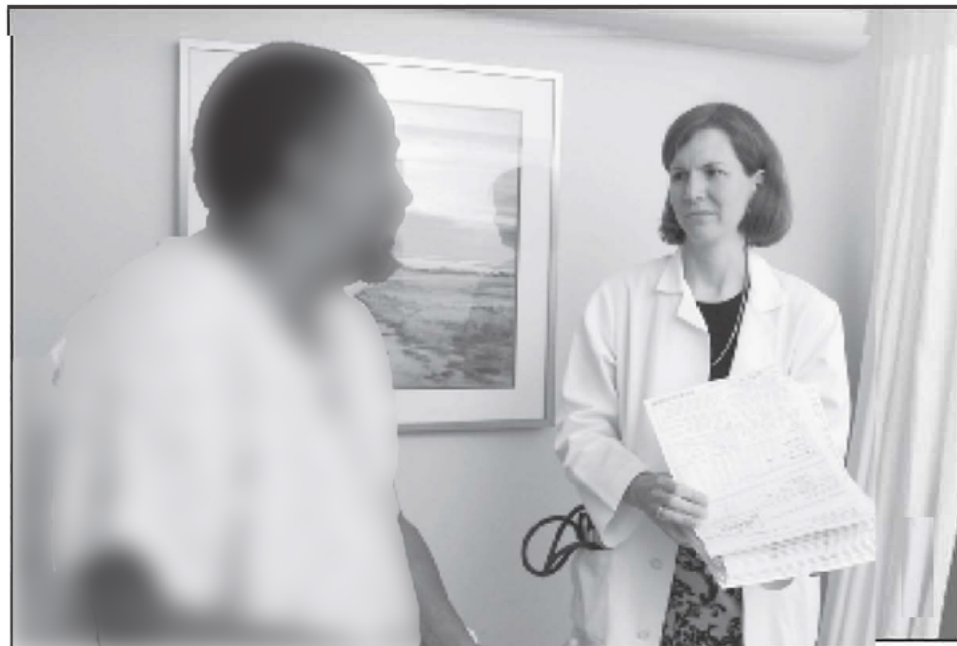
██████████ was lying in bed one night talking with his wife when they discovered a hard knot behind one nipple—his nipple. Alarmed, they made an appointment with his physician, who ordered a fine-needle biopsy of the lump. When the results came back negative for cancer, the physician told Mr. ██████████ that it was probably fatty tissue. But when Mr. ██████████ returned five months later for follow-up mammography and ultrasonography, the results shocked him: breast cancer.

"That is the last thing I thought I would have," said Mr. ██████████

In 2002, 1,500 men were diagnosed with breast cancer in the United States; 21 of them were treated at The University of Texas M. D. Anderson Cancer Center. Each year, approximately 400 men die of the disease.

Because breast cancer is so uncommon in men, no large, population-based studies have been conducted, and very little is known about the disease's epidemiology, risk factors, pathology, and treatment in men. "There is a huge void in information that needs to be filled," said Sharon Giordano, M.D., M.P.H., an assistant professor in the Department of Breast Medical Oncology who treats most of M. D. Anderson's male patients with breast cancer. "All the men who come here are wondering, 'Why did I get breast cancer?' We can't really answer that right now."

To shed light on this and other unanswered questions, Dr. Giordano has led two retrospective studies. In "Breast Cancer in Men," published in the *Annals of Internal Medicine* in (Continued on page 6)



Patient ██████████ who was diagnosed with breast cancer last year, speaks with Dr. Sharon Giordano, an assistant professor in the Department of Breast Medical Oncology, who treats most of M. D. Anderson's male patients with breast cancer.

Male Breast Cancer

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October 2002, she reviewed 114 articles published between 1942 and 2000. In a report accepted for publication in *Cancer*, she analyzed data from 1973 to 1998 in the National Cancer Institute's Surveillance, Epidemiology, and End Results database, a cancer registry that includes data from 14% of the U.S. population. In this study, 2,524 cases of male breast cancer were compared with 380,856 cases of female breast cancer.

"Most men do not even think they can get breast cancer," said Dr. Giordano. Mr. ■■■■■ speculates that many men ignore the signs and delay the doctor visit because they are embarrassed or in denial. Because of his quick action in going to the doctor (and scheduling his mastectomy for the first day available—a Friday the 13th), ■■■■■ cancer was stage I when it was removed.

When men do seek medical attention for their symptoms, 85% of the time they report a painless subareolar mass. Often, this is mistakenly diagnosed as gynecomastia, a benign swelling of the breast tissue that up to a third of men experience in their lifetimes. Other symptoms at presentation include local pain and nipple ulceration, retraction, bleeding, or discharge. In men, the cancer tends to involve the nipple, the skin, and the muscles because there is less breast tissue to invade.

A family history of breast cancer appears to be a risk factor for men: 15% to 20% of men with breast cancer have a family history, compared with 7% of the general male population. Carrying the BRCA1 gene mutation does not seem to increase risk in men, but the BRCA2 gene defect confers significant risk. Many risk factors are related to abnormalities in estrogen and androgen balance; other risk factors include testicular defects or injury, infertility, Klinefelter syndrome, obesity, cirrhosis, benign breast conditions or breast trauma, increasing age, Jewish ancestry, and radiation and estrogen exposure.

Ironically, breast cancers in men are more likely to be estrogen receptor positive and progesterone receptor positive than those in women. "It's counterintuitive because estrogen and

progesterone are female hormones," said Dr. Giordano. Most men's breast tumors (90%) are invasive, and the predominant histologic subtype is infiltrating ductal carcinoma (80%).

Dr. Giordano is very interested in how breast cancers in men differ biologically from those in women. The literature review she published in 2002 showed that breast cancers in men and women express many of the same molecular markers—c-erbB-2, p53, cyclin D1, and epidermal growth factor receptor—to the same degrees. However, men may have higher rates of Bcl-2 overexpression.

Five- and 10-year disease-specific survival rates are similar in men and women, but the overall survival rate is lower in men. As with women, lymph node status, tumor size, histologic grade, and hormone receptor status are significant prognostic factors for men.

Because no large, population-based studies have been conducted, many of these findings have not been verified. Furthermore, no large clinical trials have studied breast cancer treatment for men; most men are treated based on the standard of care guidelines established for women, which often indicate a modified radical mastectomy, axillary lymph node biopsy, and adjuvant therapy. The high rates of hormone receptor-positive tumors in male breast cancer suggest that adjuvant hormonal therapy could be effective, and indeed, the recommendation for men with hormone receptor-positive tumors is daily tamoxifen for five years.

Mr. ■■■■■ whose cancer was estrogen receptor positive, had great reservations about taking tamoxifen because of the increased risk of blood clots and stroke. "All of the hormonal questions, the

"Most men do not even think they can get breast cancer."

– Sharon Giordano, M.D., M.P.H., assistant professor, Department of Breast Medical Oncology

possible impact on sexual activity, none of those things bothered me because I knew that men produce estrogen. The only thing that bothered me was the fact that I didn't want to be cured of breast cancer and die from a stroke or blood clot," said Mr. ■■■■■ who decided after much inner debate to take the pills.

While Mr. ■■■■■ initially had no side effects, he later began experiencing gastrointestinal and vision problems, adverse effects that have been reported by other patients. After six months of taking tamoxifen, he decided to discontinue its use and since then has been feeling much better.

Dr. Giordano is very interested in studying how hormonal therapies may affect men differently. She plans to set up a registry with a standardized treatment algorithm for men, looking at outcomes and toxicity and correlating side effects with prognosis. She also intends to build a tissue bank of breast tumors from men.

In addition to the lack of research or data, the greatest problem for men with breast cancer may be the stigma associated with having what is traditionally considered a woman's disease.

"I am sure there is a psychological burden to it, just because a lot of breast cancer centers are called women's centers. Everyone assumes that they are a woman," said Dr. Giordano. "It is important to keep the public consciousness open. People should be aware that [breast cancer] can happen [to men]."

According to Mr. ■■■■■ preconceived ideas about what a man is are a problem for all men seeking medical care. "Real men don't cry. Real men don't show pain. It is ludicrous because those real men die," said Mr. ■■■■■ "The [breast cancer] death rate among men is so high because most men ignore it and don't do anything about it, and by the time they do anything about it, it is in an advanced stage. I can tell other people, and if they can discover it as early as I did or earlier, then lives can be saved." ●

FOR MORE INFORMATION, contact Dr. Giordano at (713) 792-2817.



Getting Screened for Oral Cancer

With about 30,000 new cases diagnosed annually, oral cancer has become a significant health problem in the United States. The American Cancer Society estimates that the incidence of oral cancer is almost as high as that of leukemia and its mortality rate is about the same as that of melanoma. Dental examinations play an important role in screening for and diagnosing and treating oral cancer. While the prospect of dental examinations may be intimidating for some people, the vast majority of these examinations are quite painless and, in some instances, quickly performed.



Routine examinations/checkups

According to an American Dental Association survey, most respondents (61%) did not realize that dentists look for oral cancer as part of a routine dental examination; in fact, all dentists and dental hygienists have been trained to perform a visual head and neck examination, as well as an oral soft tissue examination.

During the examination, the dental professional visually inspects all of the oral and gingival tissues, as well as high-risk areas, for the presence of cancer or premalignant changes.

By obtaining a complete and thorough medical and dental history from the patient, the dental professional can learn of any oral cancer risk factors, such as tobacco and alcohol use.

Comprehensive oral cancer examination

When a dental professional examines a patient strictly for cancer detection, he or she often conducts a comprehensive oral examination, which only takes about 90 seconds. The dentist starts by examining the patient's head, face, and neck and then systematically assesses and may palpate the patient's lips, gums, tongue, and tissues inside the mouth, under the tongue, and on the roof of the mouth.

If the dental professional suspects cancer, he or she will likely decide to remove some of the tissue for evaluation. The dentist may elect to do this but is more likely to make a referral to a specialist for this procedure. There are

several ways that a suspicious lesion can be evaluated.

Scalpel and punch tissue biopsy

Biopsy remains the gold standard for diagnosing oral lesions. In a scalpel biopsy, also known as incisional biopsy, a scalpel is used to obtain a sample of the lesion. Another method is punch tissue biopsy, in which a punch tool resembling a small cookie cutter is used to remove a section of the tissue. With the use of a standard anesthetic injection, patients can undergo either of these procedures without experiencing any pain.

Brush biopsy

A brush biopsy technique is increasingly used for questionable lesions that are not obviously cancerous. In this procedure, a circular, stiff-bristled brush is rotated against the surface of the lesion until pinpoint bleeding occurs. Cells are then collected from the area of bleeding and transferred to a glass slide for analysis. Brush biopsy can be performed painlessly without the use of an anesthetic.

Mucosal staining

When a patient has oral surface abnormalities that are considered severe and that cover a large area of tissue, the area may be stained with blue dye called toluidine blue O. After the dye is applied and the patient rinses with an acetic acid solution, any blue-stained areas that remain indicate the need for further pathologic analysis of that area, most likely using a biopsy technique.

Chemiluminescent light

A new, cost-effective method of diagnosing oral lesions is the use of chemiluminescent light. In this procedure, the patient rinses with a mild acid solution to minimize oral secretions. A chemiluminescent light is inserted into the mouth. Precancerous cells will reflect the light, whereas healthy cells will not. Again, the atypical area would most likely be biopsied.

Summary

Regular dental checkups and examinations can lead to the detection of oral and head and neck cancers when they are at an earlier, more treatable stage. These examinations should be part of everyone's routine dental care. Individuals who are not receiving an oral cancer examination from their dental professional should request the screening at least once a year. In addition, the dentist or dental hygienist can teach patients how to self-evaluate oral tissues. ●

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

 **(800) 392-1611, Option 3,** within the United States, or

 **(713) 792-3245** in Houston and outside the United States.

April 2004

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Staff Publications

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