Improved Survival Results from Early Detection and Diagnosis of Testicular Cancer

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Testicular cancer is the most frequently occurring solid tumor in men between the ages of 18 and 34 years and was, until recently, one of the leading causes of death in this age group. Fortunately, at a time when the incidence appears to be rising, the mortality is showing a decline. This decline in mortality can be directly attributed to two factors. First, the diagnosis is being made earlier as a result of the efforts expended by a number of organizations, among them the American Cancer Society and its local branches, to (1) educate young men at risk for developing the disease as to its signs and symptoms (see accompanying table) and (2) increase physicians’ index of suspicion, leading to earlier performance of diagnostic studies (such as scrotal ultrasonography and serum biologic marker measurement). Second, this improvement in survival can be attributed to the major advances made during the past decade in developing and employing effective chemotherapy programs. That a prompt diagnosis correlates with a lower stage of disease, less morbidity, and more effective therapy has been demonstrated.

Testicular Self-Examination

Since nine out of every 10 testicular tumors are discovered by the patient himself, young men should learn to practice a two- to three-minute “testicular self-examination” (see drawings) every month and make self-examination a lifetime habit. Testicular self-examination is best performed during or immediately after a warm shower or bath, since heat causes the scrotum to relax, allowing the testes to be in a more descended position. The man takes one testis in his hand, fixes it in a comfortable position, and slowly and gently rolls it between the thumb and index finger of his other hand, checking for a lump, an area of increased firmness, or slight enlargement. He then repeats the examination on the other testis. A man who makes monthly self-examination a lifetime habit can detect promptly any changes that occur in the testes and can immediately seek medical consultation.

Types of Testicular Tumors

In addition to the findings on physical examination, the physician today has a number of noninvasive procedures that usually allow him to establish the diagnosis of a testicular tumor before recommending surgery. When a tumor is present, however, its surgical removal is essential, not only to eliminate the local disease but also to establish the type and extent of the tumor. This information is prerequisite to determining the need for and type of any additional therapy.

More than 95% of testicular tumors arise from the germ cells and must be considered malignant. Although they have a wide range of histologic appearances, they can be conveniently divided into two categories for treatment planning: seminoma and nonseminoma. The remaining 3% to 5% of testicular tumors (nongerminal) arise from specialized elements (Leydig or Sertoli cells) or from connective tissue and muscle and may be either benign or malignant. Since these latter tumors are rarely encountered, we will not discuss them further here.

Seminoma

Seminomas account for 34% to 55% of germinal tumors. Their biologic aggressiveness is relatively low grade, as evidenced by the findings that most patients present with early-stage disease and metastatic progression that is usually systematic, extending first to the retroperitoneum and then to the mediastinal and supraclavicular lymph nodes. Early hematogenous spread is rare. Among 240 patients with seminomas seen at UT M. D. Anderson Hospital over 25 years, only 3 (1%) had pulmonary disease at diagnosis, and initial relapse occurred in the lungs in only 3 of 225 patients with stage I or II disease. This predictable spread pattern together with an unusual radiosensitivity results in a high radiocurability of this disease.

 Signs and Symptoms of Testicular Cancer

A lump on the testicle
Any enlargement of the testicle
Pain or discomfort in the testicle or scrotum
A change in the way the testis feels from month to month
Enlargement or tenderness of the breasts
Testicular Cancer...

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Clinical assessment should include a carefully performed physical examination as well as a careful review of the results of a chest roentgenogram, computed tomography (CT) scan of the retroperitoneum and pelvis, and blood chemistry studies including liver function tests and serum titers for beta human chorionic gonadotropin (B-HCG) and alpha-fetoprotein (AFP). In the past we relied heavily on pedal lymphangiograms to identify small metastatic deposits within the regional lymph nodes, but we have eliminated this examination as a routine staging procedure. We accept the fact that in a few patients the lymphangiogram would have identified regional disease below the resolution power of CT scans, thereby altering stage assignment. Recent analysis of our data showed that neither treatment planning nor prognosis is adversely affected by the absence of a lymphangiogram. Consequently, in attempting to contain medical costs without sacrificing the quality of medical care, we chose to eliminate routine lymphangiography in evaluating patients with seminoma. Furthermore, since CT scanning is performed with contrast medium, which visualizes the kidneys, we were also able to eliminate excretory urography as a separate procedure.

Treatment recommendations are based on the extent of disease detected by the above-mentioned studies. Patients whose disease is limited to the testis or adnexa (stage I) receive elective regional lymphatic irradiation. Treatment is given with a 6-MeV linear accelerator delivering 25 Gy in 15 fractions over three weeks to the periaortic nodes through parallel opposed rectangular portals and to the iliac and inguinal nodes through an anterior field. A recent review of 263 patients with stage I seminoma of the testis treated by orchiectomy and adjuvant radiation at UTMDAH indicated a total survival rate, corrected for deaths during that period, of 97% from 5 through 20 years. No recognizable long-term complications were noted in this group of patients.

Patients presenting with retroperitoneal tumor masses less than 10 cm in diameter (stage IIa) receive a similar amount of radiation with an additional 5-Gy boost to the involved area through reduced fields. Whereas in the past we believed it necessary to treat prophylactically the next echelon of lymph nodes (those in the mediastinal and supraclavicular regions) for possible occult metastasis, reevaluation of the sites of relapse proved that this is not required. Consequently, we do not believe that patients with seminoma need routine irradiation above the diaphragm. The five-year disease-free survival rate was 95% for 40 patients recently treated at UTMDAH who were in this category and who received radiation therapy.

Patients presenting with advanced retroperitoneal disease (a mass larger than 10 cm), with nodal disease above the diaphragm, or with extranodal disease such as pulmonary or bony metastasis (stages IIb and III) are treated primarily with systemic chemotherapy. This represents a marked change in treatment philosophy. Only a few years ago, patients with bulky retroperitoneal disease would have received total abdominal irradiation followed by prophylactic irradiation to the mediastinum and the supraclavicular regions, and patients with disease confined to the lymph nodes above the diaphragm (supraclavicular and mediastinal regions) would also have received radiation as primary treatment.

Today, for these patients, cisplatin-based chemotherapy has replaced irradiation as primary therapy. Treatment consists of intravenous cyclophosphamide, 1 gram per square meter of body surface area, followed by sequential cisplatin at a dose of 100 milligrams per square meter of body surface area given on days 1, 7, and 14. After 4 to 6 weeks' rest, a second course is given on days 1, 7, and 14. If a complete response is obtained before the second course of treatment, no additional therapy is delivered. If, however, a complete response is not achieved until after the second course of treatment, a third course is administered in 4 to 6 weeks. A review of 52 patients with advanced disease treated in this manner has revealed a 92% long-term disease-free survival rate (range: 44 to 188 weeks). Eighty-five percent of these patients achieved a complete response with chemotherapy alone. However, when the retroperitoneal mass has been significantly reduced but a residual three-dimensional mass remains, postchemotherapy irradiation is considered.
As a result of the judicious use of our therapeutic options, the five-year survival rate for all patients with testicular seminoma currently exceeds 95%.

Nonseminomatous Tumors

The management of nonseminomatous germ cell tumors of the testis (NSGCTT) is in a state of flux as a result of the recent development of chemotherapy regimens that effectively eradicate metastases. Consistently curative chemotherapy was first introduced into the management of NSGCTT by Dr. Melvin Samuels at UTMDAH during the early 1970s; he used a combination of vinblastine and bleomycin. Later, Einhorn at the University of Indiana demonstrated that a combination of cisplatin, vinblastine, and bleomycin was likewise effective. Today, because improved diagnostic studies (ultrasonography, CT, and radioimmunoassays) detect metastatic foci earlier and a number of combination chemotherapy programs are available to treat metastatic disease, our attitudes about the roles of surgery and radiotherapy are undergoing major changes.

Early in this century, when patients whose disease appeared confined to the testis (stage I) were followed after orchiec tomy by observation alone, only 25% survived for significant periods. This unacceptable survival rate led to the routine use of retroperitoneal lymphadenectomy or radiotherapy, both of which produced potentially devastating long-term complications. Because today's sensitive diagnostic studies can determine so much more reliably that disease is really stage I, we would like to avoid this unnecessary morbidity for patients with limited NSGCTT. Accordingly, in October 1981 we began a pilot study to evaluate the feasibility of a postorchiectomy surveillance program in a carefully controlled setting for patients with NSGCTT. Preliminary experience with surveillance alone after orchiectomy in patients with clinical stage I disease confirmed that a "watch and wait" policy was safe and that those patients who relapsed could be rendered free of disease with chemotherapy.

Eighty-two patients with NSGCTT whose evaluation at UTMDAH following orchiectomy was negative for metastatic disease (normal B-HCG and AFP serum levels, lymphangio-gram, CT scan, and chest x-ray) have been followed for at least one year; 70% have been continuously free of disease. As expected, 30 patients developed metastasis, but all but one were rendered free of disease with chemotherapy and are alive, doing well, today. In view of our experience, which has been confirmed by other investigators at a number of institutions worldwide, we continue to recommend careful surveillance following orchiectomy for patients who have NSGCTT but no obvious regional or visceral metastasis.

Current treatment options for patients presenting with regional retroperitoneal metastases whose disease is not advanced (≤ 10 cm mass; stage IIa) include (1) retroperitoneal lymphadenectomy followed by adjuvant chemotherapy for patients at high risk for recurrence and (2) lymphadenectomy followed by expectant observation, adding chemotherapy only if metastatic disease develops. Unfortunately, distant metastases have occurred in 30% to 50% of the patients under expectant observation. The recent demonstration of an 89% continuous disease-free status for 100 patients with advanced presentations treated by Dr. Christopher Logothetis in the Section of Genitourinary Medical Oncology, alternating cisplatin, cyclophosphamide, and doxorubicin with vinblastine and bleomycin (cycloscisplatin/VLB), has given us cause to adopt an individualized approach to patients with clinical stage IIa disease. On one hand, by introducing primary chemotherapy for patients with highly metastatic pure embryonal carcinoma, we find we have effectively eliminated the need for "double" therapy (retroperitoneal lymphadenectomy followed by chemotherapy) and have maintained a 96% complete-response rate. On the other hand, we have found that patients with teratomatous elements in the primary tumor benefit most from a primary retroperitoneal lymph node dissection, since they have a lower visceral metastatic potential and are most likely to have a persistent retroperitoneal mass requiring surgery after primary chemotherapy. These patients, therefore, now undergo primary retroperitoneal lymphadenectomy and are followed carefully, reserving chemo-

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Gastrointestinal Radiotherapy Team Creates Atmosphere of Com
templation.

Radiotherapists ask all their pa-

tients not to lose weight.

In the rockbottom basement of
UT M. D. Anderson Hospital, the
Department of Clinical Radiother-
apy promotes this theme by offering
patients eggnog instead of coffee,
even at 7 a.m. And because most
patients come at least once a day, five
days a week for five or six weeks,
patients and clinic staff members
know each other, and the place has
an aura of welcome, as if having
body parts x-rayed once or twice a day were the way the world
turns. Staff members rarely walk down a hall without greeting
everyone on all sides. Patients share information about their ill-
ess and treatment, and often the conversation turns to where
they come from and how they need to get back there, to the job
or the children or the home in Odessa, Texas.

For patients from out of town who will go home for the week-
end, the radiotherapy staff's custom is to make their appoint-
ments early on Fridays and late on Mondays. For Houston peo-
ple who work while they are being treated—and there are many who
manage to do this—the custom is to make the appointments con-
venient and to keep people waiting as little as possible. That, any-
way, is the intent.

Outer and Inner Changes

"One of our major goals in recent times," said Lester J. Peters,
M.D., head of the Division of Radiotherapy and chairman of the
Department of Clinical Radiotherapy, "has been to deinstitu-

tionalize the place. We've tried to do everything we can to make
the atmosphere friendly and receptive, and we've nowhere near
completed that task."

Peters described redecoration of patient areas and installation
of more comfortable furniture and signs and directions that are
easier to follow, and the creation of a clubroom for the many
patients who come for treatment twice a day. "But none of that
means anything unless we deliver the best possible treatment," he
said. "We try to bring particular skills to bear by having all of
our faculty members subspecialize so that we become experts in
one or two areas of cancer radiotherapy.

"This concentration," Peters said, "makes it easier for our phy-
sicists to interact with the surgeons who specialize in treating
specific types of cancer and with the medical oncologists, so that
we form more cohesive interdisciplinary groups than would be
possible if every one of the radiotherapists were treating many
types of patients."

Anderson Hospital is also fortunate, Peters said, in having a
great deal of technical capability. "Although that's important,
it's less important than the first requirement, which is medical
skill and judgment. You can have fancy equipment and still not
do good radiotherapy. On the other hand, if you're a very good
radiotherapist, you can get by with less fancy equipment. Of
course, if you've got both, you're in great shape, and that's what
we aim to achieve."

"This is not a static specialty," he said. "A lot of people think
that radiotherapy has been around for 80 years and is in a rut.
Nothing could be further from the truth. The practice of radio-
therapy is changing and evolving, and we are constantly adapt-
ing treatment to take advantage of new discoveries—to provide
better control of the cancer and to reduce the side effects of
treatment."

View of the open-tabletop device, the "bellyboard," and of the smallowel shift it produces in patients undergoing radiotherapy for gastroin
testinal cancer.
Fort and Confidence for Patients

Flora Johnson, a technician, at the treatment control console with chief technologist Velda Croy and Tyvin A. Rich look over the patient's record.

The Gastrointestinal Cancer Treatment Team

Tyvin A. Rich, M.D., an associate professor of radiotherapy, specializes in treating patients for gastrointestinal (GI) cancer. Among the leading staff members on his team are head nurse Linda McCallister, who is also the radium curator, clinic nurse Ellen Sitton, and chief technologist Velda Croy. The GI cancer team treats about 25 patients a day. Most are ambulatory, but a third are very ill patients brought from the inpatient unit, usually for palliative treatment.

Rich developed the “bellyboard,” an open-tabletop device with a large hole by which a patient’s small bowel is shifted out of the radiation beam’s way (see drawing). He and his staff know and often hear from their patients that it’s not a great pleasure to lie on this board for up to an hour, immobile, while being marked and measured for radiotherapy during the simulation session. Evidently, the bellyboard’s safety advantages rate higher than the discomfort.

Rich described a patient’s odyssey in his service, from evaluation to treatment simulation to daily treatment. “The simulation,” Rich said, “sets up the geometry of treatment. We take radiographs of the area to be irradiated and obtain a computer contour, a process that involves the technical and dosimetry staff. After that, the actual treatment should flow smoothly, because we know exactly what we want to do. We typically treat patients over a period of four to seven weeks. During that time our technical staff delivers the treatment and our nursing staff makes sure that all details of patients’ tests and quality controls are done correctly.”

On his clinic days, Monday, Wednesday, and Friday afternoons, Rich and his resident physician—earlier this year, this was Lori Hughes, M.D.—see each patient at least once a week to discuss treatment, change it if necessary, answer questions, check on tests. Rich’s team members put a great deal of effort into communicating with patients and with each other. They stay in touch with referring physicians, particularly the doctors patients will return to after they have completed their treatments at Anderson.

Constantly Working on Treatment Flow

As to internal communication, Rich stressed the technical staff’s need to know the patient’s whole treatment, not only the daily requirements. “We are continually trying to refine that process of communicating among ourselves and our patients,” he said. “When the patient comes in for the first treatment and the technician walks out to the waiting room and says, ‘Come in, Mr. Robinson, we’re ready for you,’ that’s the culmination of everything that’s been done so far. We want to make sure that there is no problem and that the patient feels absolutely comfortable and confident. We have to improve this constantly. And if something doesn’t work at the physician’s level, yes, we will change it. That is why the treatment team works so closely with me to develop the flow of treatment, not only from a technical but also a nursing standpoint.”

Sitton, a nurse in the radiotherapy clinic for 11 years, talked about the inevitable side effects, which may vary from mild to severe forms of fatigue, diarrhea, and loss of appetite. That is why patients are asked to try to maintain their weight, often with a dietician’s advice.

Early in treatment, she said, patients usually don’t experience adverse effects. “But as we get into the treatment, we expect to see some evidence of side effects. And the earlier we catch these, the more comfortable a patient will be throughout the treatment. Because the only way to stop side effects is to stop treatment, and that, of course, is not what we want to do.”

“I don’t think radiotherapy will ever be totally rid of all side effects,” Rich said. “But we’ve learned from technology and biology and from understanding each anatomic site how to maximize the effect of radiotherapy on the tumor and minimize the effect on the patient. That’s the name of the game.”

Progress in Techniques

But do the staff members get tired and burned out?

“One in a while,” Sitton said. “It’s a temporary thing, and that’s why we need to take vacations. But I always come back. It’s the area I care about and am interested in, and I enjoy working with those patients.”

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Current Laboratory Research Modernizes Traditional Chinese Herbal Medicine

For more than two thousand years, Chinese physicians have used traditional herbal medicines to build up a patient's natural defenses against cancer and other diseases. During the past several years in the Department of Clinical Immunology and Biological Therapy at UT M. D. Anderson Hospital, Giora Mavligit, M.D., and two visiting Chinese scientists have been studying two of those herbs, attempting to isolate and characterize components that may restore immune function.

"I've always been impressed with traditional medicine, because if it were not good, it wouldn't have lasted for so long. It's human nature to seek the best and filter out what doesn't work," said Mavligit. Yen Sun, M.D., a visiting scientist from the People's Republic of China, was the first to suggest to Mavligit that they use modern research tools to investigate these traditional herbs in the laboratory. The physicians' tests of simple water extracts of two herbs, Ligustrum and Astragalus, indicated the presence of significant immune-restorative agents.

For in vitro testing, the researchers used an immunobioassay—local xenogeneic graft-versus-host reaction—in laboratory rats, a test they have used since the late 1970s to evaluate T-cell function. "This bioassay sets up a competition between the cells that we inject—the graft—and the animal that's supposed to reject that graft. If the animal is immunologically competent, it will reject the graft. If we partially suppress the animal's immune system (for example, with cyclophosphamide, a widely used anticancer drug) but give it a cell graft from a patient with advanced disease, the animal that is only partially immune-suppressed can still reject the graft because its immunity is stronger than that of the patient," said Mavligit. "What we have is a very delicate balance of two systems, one of which is artificially suppressed and the other suppressed by the growing cancer," he said.

Complete Immune Restoration

The results showed that cells (from cancer patients) incubated in vitro with the herbs had their immunity restored completely so that they were as immune competent as cells from normal donors. Other immune-restorative agents the researchers tested, such as cimetidine, indomethacin, and isoprinosine, restored immunity only partially.

When Da-Tong Chu, M.D., followed Sun in the exchange program, Chu and Mavligit decided to determine the nature of the active component in the crude extract of Astragalus membranaceus. With the help of Newport Pharmaceuticals, they obtained eight fractions from a column-fractionated extract of the herb. They tested all eight and determined that fraction 3, with a molecular weight of 20,000–25,000, was the most potent. In testing fraction 3 in vitro, they repeated the studies of xenogeneic graft-versus-host reaction. In vivo tests were done by giving the rats fraction 3 and cyclophosphamide injections. As expected, cyclophosphamide suppressed the animals' immune system, but fraction 3 restored it to the extent that the animals rejected normal donor grafts completely.

The researchers' third step was to add fraction 3 to experimental interleukin-2 (IL-2) treatments. The development of IL-2 has generated much interest in cancer research, but its antitumor effect is mitigated by its often extreme toxicity at the high doses needed. Blood cells contain precursors for lymphokine-activated killer cells, called LAK cells, that are generated when the blood is incubated with IL-2. When the LAK cells are applied to tumor cells in vitro, the LAK cells destroy the tumor cells. The higher the dose of IL-2, the greater the activity of the killer cells; but in a clinical setting, the higher the dose, the greater the toxicity as well.

Mavligit and Chu wanted to see if using fraction 3 in concert with lower doses of IL-2 would achieve the same level of LAK-cell activity as higher doses of IL-2 given alone. They found that adding fraction 3 of Astragalus potentiated IL-2 so that only one-tenth of the dose was needed to achieve the same LAK-cell activity in vitro. They also found that they were able to reduce the ratio of LAK cells to tumor cells needed to achieve the same result.

"We still don't know if fraction 3 also potentiates the toxicity of IL-2," said Mavligit. "We know that we can potentiate the biologic activity of IL-2 with fraction 3, but the Chinese herbs are far from being an FDA-approved drug. So now we are looking for another biological response modifier that is already available for clinical studies to do the same thing," he said.

Physicians who desire additional information may write Giora Mavligit, M.D., Department of Clinical Immunology and Biological Therapy, Box 41, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, 1515 Holcombe Boulevard, Houston, Texas 77030.
THE FIVE PRINCIPLES OF CANCER TREATMENT

The Chinese experience in the treatment of cancers dates back more than two thousand years and has evolved into the five principles of herbal medication related to cancer treatment today. (There is no direct correlation between the principles of traditional Chinese medicine and Western medicine; therefore, it is impossible to translate the Chinese concepts completely into English.) These drugs are given by prescription, under medical supervision. The physician selects the types and quantities of herbs needed by each patient.

扶正祛邪

Fu Zheng Qu Xie—Literally means promoting or enhancing the natural host defense mechanism to eliminate the external or internal pathogenic factors and products.

活血化瘀

Qu Yu Huo Xue—Literally means eliminating the stasis and activating the blood. Chinese medicine uses blood-activating and sludge-eliminating drugs to dissolve stagnant blood and maintain the circulation.

清热解毒

Qing Re Jie Du—Literally means dissipating heat and detoxifying. This is the therapeutic method of treating various carbuncles, cellulitis, sores, furuncles, and nameless swellings and toxins (including cancer) with heat-clearing and toxin-eliminating drugs.

软坚散结

Ruan Jian San Jie—Literally means softening and dissolution of hard masses. This includes phlegm-eliminating, sludge-dissolving, hardness-softening, and mass-dispersing drugs, and it is used to treat swelling and masses formed by accumulations of fluids, as in lymphadenopathy, goiter, abdominal masses, and so forth. The principle sounds strange from the viewpoint of Western medicine, but it benefits some patients, including patients with cancer.

以毒攻毒

Yi Du Gong Du—Literally is the use of poisons as antidotes to treat diseases such as leprosy, pyogenic infection, and tumor.
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therapy only for the ones who later show evidence of visceral metastasis.

Patients presenting with advanced regional metastasis (> 10 cm retroperitoneal mass; stage IIa) or visceral metastasis (stage III) are treated initially with systemic chemotherapy. As stated previously, we have achieved an 89% continuous disease-free survival rate using cyclic CISCA/V1 chemotherapy. Although the acute toxicity of this therapy is formidable, only one patient died as a result of chemotherapy, and the long-term toxicity appears less than that of other currently used regimens.

Conclusion

Therapy for patients with germ cell tumors of the testis is undergoing major changes, brought about by the availability of an ever-increasing number of curative chemotherapy programs. The goal is no longer merely cure, but rather maintaining the high cure rates now obtainable while at the same time limiting therapy and reducing both acute and long-term sequelae. Oncologists can be applauded for many of the recent gains made against testicular cancers. However, we need more awareness among young men and their physicians of the signs and symptoms of disease, and we need to encourage greater practice of testicular self-examination, especially by those who are between 18 and 34 years old—those who are at the greatest risk for developing testicular cancer. In this way, the disease can be detected at an earlier stage, requiring less extensive therapy.

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"Yes, you can get burnout," said Croy. "But I see a lot of progress. I've been in oncology since 1973 and I've seen progress in techniques. This has reduced the side effects of treatment and in certain circumstances led to better cure rates. One problem I see is that the technical staff members, who focus on the actual button-pushing and setting the patient up, don't have the immediate rewards of seeing the people come back for follow-up visits—unless the patients go down to the unit to say hello, which they often do."

Next Step

To improve the cure rate dramatically in GI cancer, Rich said, the next focus has to be on disseminated disease. "But we should not lose sight of the fact that, as more advances are made in treating and curing patients with disseminated disease, the more important is it to provide a high quality of care in treating the patient's local disease."

A strong message in radiotherapy in the last decade, he said, has been to use conservative surgical and radiotherapeutic techniques so that patients can maintain a normal lifestyle. As has been done in conservative breast cancer treatment, the GI oncologists are developing new techniques of conservative rectal cancer treatment to save patients from having permanent colostomies.

"This will be an advance for GI radiotherapy," Rich said. "I believe those things are ignored when one looks at survival curves. Our goal is not only to improve survival but to provide better and more acceptable local therapy. This we are learning to do."

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