

OncoLog

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MD Anderson Celebrates 70th Anniversary

By John H. McCool

Its first clinical facility was a converted Army barracks, its first headquarters was a renovated residential estate near downtown Houston, and its first cancer research was conducted by four scientists in a former horse stable.

It was a rather inauspicious beginning, to be sure, especially for an institution that now, 70 years later, anchors the vast Texas Medical Center with its main campus; has two additional research campuses and seven regional care cen-

ters, as well as numerous national and even international affiliations; and for the past 4 years has been ranked by *U.S. News & World Report* as the best hospital in the United States for cancer care.

The story of how The University of Texas MD Anderson Cancer Center rose from its state legislative creation in 1941 to its current status among the world's leading cancer centers cannot be told merely in terms of new building construction and expanding square footage. Neither was it a foregone conclusion that the name of its original benefactor, Monroe Dunaway Anderson—a successful cotton merchant and philanthropist—would become synonymous with life-saving cancer treatments and research aimed at transforming cancer, as historian James S. Olson put it, “from an acute to a chronic disease.”

One way to explain MD Anderson's evolution is to focus on three pillars that have long defined, supported, and animated the institution, namely translational research, multi-disciplinary patient care, and education.

Translational research

John Mendelsohn, M.D., the institution's president from 1996 to 2011, once said, “What is most unusual about MD Anderson, what we are acknowledged to lead the world in, is

From the late 1940s to 1954, patients at MD Anderson were treated and housed in 12 surplus army barracks.



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In 1942, MD Anderson opened its first research laboratory in a building that had once been a horse stable.

translating scientific discoveries into the clinic for the benefit of patients.” Indeed, within a decade of the institution’s founding, two MD Anderson fac-

ulty members—physician Gilbert H. Fletcher, M.D., and physicist Leonard G. Grimm, Ph.D.—designed and tested the world’s first cobalt-60 radia-

tion therapy unit. Later perfected by Dr. Fletcher himself, the revolutionary cobalt-60 unit provided a more effective and far less expensive means of delivering radiation therapy to cancer patients.

Examples abound of other translational research advances by MD Anderson faculty over the past 7 decades. Some of these include:

- introducing limb-sparing surgery using donor bones (and later metal prostheses) to save the arms and legs of patients with bone tumors and soft tissue sarcomas;
- documenting that combination chemotherapy was effective for children with rhabdomyosarcoma and osteosarcoma;
- determining appropriate techniques for mammograms and showing that such radiographic studies could detect minimal, highly curable breast tumors;
- developing the C-banding technique to precisely locate genes on various chromosomes;
- conducting countless clinical trials to investigate novel anticancer

Selected Research and Clinical Milestones at MD Anderson 1941–2011

1941

Texas Governor W. Lee “Pappy” O’Daniel signs legislation authorizing the creation of a cancer hospital as part of The University of Texas System.

1944

MD Anderson treats its first patient.

1950

Researchers design and test the first cobalt-60 radiation therapy unit.



Drs. Gilbert Fletcher (left) and Leonard Grimm (not shown) designed the world’s first cobalt-60 unit.

1951

Some of the world’s first psychological research and counseling programs for cancer patients begin at MD Anderson.

1956

The first issue of MD Anderson’s newsletter to physicians, now named *OncoLog*, is published.

1964

Vincristine becomes the first successful chemotherapy for children with inoperable Wilms tumors.

1966

Surgeons begin performing limb-sparing surgery for extremity tumors.

1966

MD Anderson is the first cancer hospital in the U.S. to install “life islands” to protect immunocompromised patients against infections.



MD Anderson was the first U.S. hospital to install “life islands,” which helped reduce infections among leukemia patients.

1970

C-banding enables scientists to pinpoint the precise location of genes on various chromosomes.

treatments, including early clinical trials of paclitaxel and the three-drug combination of 5-fluorouracil, doxorubicin, and cyclophosphamide—both of which proved highly effective against breast cancer;

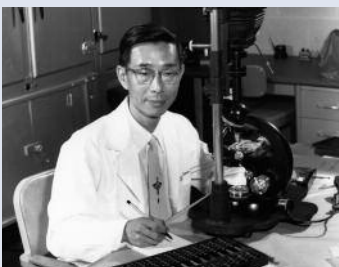
- pioneering the fields of chemoprevention and genetic therapy;
- advancing the use of microvascular tissue transfer to repair defects caused by the removal of cancers and introducing immediate reconstructive surgery following tumor excision;
- documenting a direct molecular link between cigarette smoking and lung cancer;
- revealing a possible hereditary component to nicotine addiction;
- and advancing radiation therapy once again by developing pencil-beam proton therapy, which enables a greater radiation dose to be delivered directly to the tumor and is particularly effective in treating tumors in children and complex tumors—like those in the prostate, brain, skull base, and eye—while leaving healthy tissue and critical structures unharmed.



In 2006, MD Anderson installed the world's first fully integrated intraoperative magnetic resonance imaging suite.

The past, it is often said, is prologue, and this is certainly true for translational research at MD Anderson. The institution is currently the single largest recip-

ient of both research grants and grant dollars from the National Cancer Institute, and MD Anderson researchers are involved in a wide range of studies,



Dr. T.C. Hsu and MD Anderson colleagues developed the C-banding technique to pinpoint the precise location of genes on various chromosomes.

1975

A clinical protocol for vinblastine and bleomycin becomes the first chemotherapy regimen to offer complete remission for patients with testicular cancer.

1976

MD Anderson opens the first Department of Dental Oncology in the U.S.

1976

Clinical studies demonstrate that lumpectomy followed by radiation therapy is as effective as radical mastectomy for breast cancer treatment.

1976

A clinical trial of the mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) regimen for treatment of pediatric patients with brain tumors begins.

1981

The Department of Urology establishes a Section of Sexual Rehabilitation—the first of its kind—to help patients maintain intimacy following cancer treatment.

1985

The first clinical use of liposomes to deliver targeted drug therapy is reported.

1987

Researchers adapt the polymerase chain reaction test to detect lymphoma cells in concentrations as low as 1 lymphoma cell per 1 million blood cells.

1988

MD Anderson opens the country's first operating room equipped with a linear accelerator to deliver intraoperative radiation therapy.

1988

A landmark study establishes the benefits of administering chemotherapy to shrink breast tumors before surgery and radiation therapy.

1993

Surgeons establish the benefit of surgical resection of multiple brain metastases in some patients.

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including the growing field of epigenetics, the testing of targeted therapies, the development of new anticancer drugs, and the increased understanding of metastasis and angiogenesis.

Multidisciplinary care

When MD Anderson opened its doors to its first patient on March 1, 1944, surgery—in many cases radical surgery—was the most common, and often the only, cancer treatment. However, guided by people such as R. Lee Clark, M.D., the institution's president from 1946 to 1978, MD Anderson established the multidisciplinary patient care model as one of its key distinguishing features. Under Dr. Clark's leadership, patients benefited from having close access not only to surgical oncologists, but to radiation oncologists, medical oncologists, and pathologists. This model evolved into today's team approach that includes oncological nurses, social workers, nutritionists, genetic counselors, and many other specialists.

Moreover, Dr. Clark's formation of the Physicians Referral Service in 1957, which pooled all physician income into a central fund and paid MD Anderson

physicians fixed salaries, eliminated competition for patients among the various disciplines and helped ensure that the only professional motivation was providing high-quality patient care. This system, Dr. Olson wrote, "became the economic foundation for multidisciplinary care."

Two prominent early practitioners of multidisciplinary patient care were the aforementioned radiation oncologist, Dr. Fletcher, and surgical oncologist William S. MacComb, M.D., who in 1959 came to MD Anderson to direct the Head and Neck Surgery Section. Cross-trained in radiation therapy, Dr. MacComb closely collaborated with Dr. Fletcher in treating head and neck malignancies. They later coauthored a seminal book titled *Cancer of the Head and Neck*, published in 1967, that became the standard text for decades to come.

Three years later, in 1970, MD Anderson had its "coming of age" moment when it hosted the 10th International Cancer Congress and some 6,000 visiting physicians and scientists. By then there had been a definite sea change in cancer treatment. Radical surgery,

of the kind once associated with Dr. William Stewart Halstead, had gradually but steadily been giving way to an understanding that many cancers required systemic treatment, such as combination chemotherapy, or even a combination of surgery, radiation therapy, and chemotherapy.

At the forefront of this trend toward a multidisciplinary approach to cancer care and a treat-to-cure culture, MD Anderson was named one of the first three comprehensive cancer centers upon passage of the 1971 National Cancer Act, of which Dr. Clark himself was an architect. This act infused hundreds of millions of federal dollars into the nation's declared "war on cancer" through the National Cancer Institute.

Education

The criteria for earning the comprehensive cancer center designation were having fully developed programs in research, patient care, and education. Although affiliated with and under the jurisdiction of The University of Texas System, MD Anderson did not originally have an educational infrastructure. This

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Milestones 1941–2011

1997

Researchers pioneer the use of reduced chemotherapy doses for patients also requiring stem cell transplantation, resulting in lower mortality rates.

1997

A miniature multileaf collimator to more precisely shape radiation therapy beams is designed at MD Anderson.

2003

An epidermal growth factor receptor VIII peptide vaccine is developed to treat cerebral tumors.

2005

Researchers report initial clinical results of berubicin, the first blood-brain barrier-penetrating anthracycline for treatment of brain tumors, which was discovered and developed at MD Anderson.

2006

Researchers establish the effectiveness of dasatinib and nilotinib against imatinib-resistant chronic myelocytic leukemia.

2006

MD Anderson opens the largest proton therapy center in the U.S.

2007

Researchers demonstrate the efficacy of intensity-modulated radiation therapy against several types of cancer.

2007

A clinical trial of lenalidomide plus dexamethasone for patients with relapsed multiple myeloma leads to FDA approval of lenalidomide.

2008

Stereotactic body radiation therapy is shown to be an effective treatment for some lung cancer patients.

2009

Researchers report a successful phase III clinical trial of a therapeutic vaccine for follicular lymphoma.

2011

Results from BATTLE, a clinical trial of four drugs (each targeting a different signaling pathway), support the use of biomarkers and personalized therapy for lung cancer.

2011

A phase II study demonstrates that proton therapy with chemotherapy can reduce radiation-related toxicity compared with conventional photon treatment.

Compass

Quarterly discussion of cancer types for which there is no standard treatment or more than one standard treatment

Stage II or III Soft Tissue Sarcoma

Chemotherapy and radiation therapy before or after surgery benefit patients

By **Sunni Hosemann**

Overview

Soft tissue sarcomas can arise from virtually any connective tissue and can manifest as tumors at almost any anatomical site.

There are at least 50 different histological subtypes of soft tissue sarcoma. This great variety presents unique challenges for developing standard guidelines for treating these tumors.

Experts generally agree that surgical resection is the definitive treatment for soft tissue sarcoma, but surgery alone is not curative for some stage II and III tumors. For those tumors, some combination of additional treatment—chemotherapy and/or radiation therapy—must be considered. However, which additional treatments to use, and in what sequence, remains unclear.

About sarcoma

Sarcomas, which account for less than 1% of cancers in adults, are relatively rare. Only about 10,000 new diagnoses of sarcoma occur annually; of those, about two thirds arise from soft tissues and about one third from bone.

This discussion is limited to American Joint Committee on Cancer (AJCC) stage II or III soft tissue sarcomas that are resectable or potentially resectable. Kaposi sarcoma, desmoid tumors, and gastrointestinal stromal tumors are sarcomas with special characteristics and considerations and are not included in the AJCC staging system; therefore, they are not included in this discussion.

Sarcomas can affect almost any soft tissue—including fat, muscle, nerves, and vascular, lymphatic, and synovial tissues—and tumors are frequently named for the specific tissues they most closely resemble. More than half of soft tissue sarcomas

are found in the extremities, about 20% are found in the thorax, 15% are found in the abdomen, and 10% are found in the head and neck. Some soft tissue sarcomas are organ-specific; such tumors arise exclusively in the lungs, liver, kidneys, etc. The specific sarcoma subtype and anatomical site are important factors in treatment choice and outcome.

Soft tissue sarcomas exhibit a wide range of behavior in their patterns of growth and metastasis. Some soft tissue sarcomas tend to grow by spreading locally with microscopic extensions into the surrounding tissue, whereas others are visibly—macroscopically—infiltrative in nature.

Some soft tissue sarcomas are slow to metastasize or may never metastasize at all. For example, among patients with retroperitoneal and abdominal soft tissue sarcomas, fewer deaths are attributable to distant metastases than to uncontrolled local recurrence. However, other soft tissue sarcomas are rapidly aggressive in their dissemination.

Most soft tissue sarcomas metastasize hematogenously rather than via regional lymph nodes, as is often the case with carcinomas. The most common site of soft tissue sarcoma metastasis is the lung, but metastases can also appear in nerve, cutaneous, or fat tissue in some patients. Some soft tissue sarcoma metastases, called skip metastases, occur in the soft tissue of the same limb as the primary tumor but at locations that are not adjacent to the primary tumor. Also, the individual metastases themselves may differ in their aggressiveness.

These variations influence and present considerable challenges to the staging of soft tissue sarcomas. For example, because sarcomas generally metastasize hematogenously rather than to regional lymph nodes, the node (N) status has a different significance for sarcomas than it does for carcinomas. According to Raphael Pollock, M.D., Ph.D., a professor in and head of the Division of Surgery at The University of Texas MD Anderson Cancer Center and chair of the AJCC Sarcoma Staging Committee, “An N1 sarcoma may be less ominous than an N1 carcinoma and is a stage III rather than stage IV tumor.”

At least two staging systems for soft tissue sarcoma are in common clinical use. The Musculoskeletal Tumor Society

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staging system classifies sarcoma according to the tumor grade, extent of tumor spread beyond its anatomical compartment, and presence of metastases. The AJCC stages soft tissue sarcoma using tumor size and grade, lymph node involvement, and presence of distant metastases; tumor depth in relation to tissue fascia is also used to characterize these tumors.

The fact that more than one staging system for sarcomas is in common use highlights the difficulties in categorizing these very diverse tumors. According to Dr. Pollock, MD Anderson physicians have found that considering histology when classifying sarcoma may provide more robust prognostic information than grade alone. He also said that a need exists for continued refinements in staging approaches to identify additional prognostic factors that can guide treatment decisions.

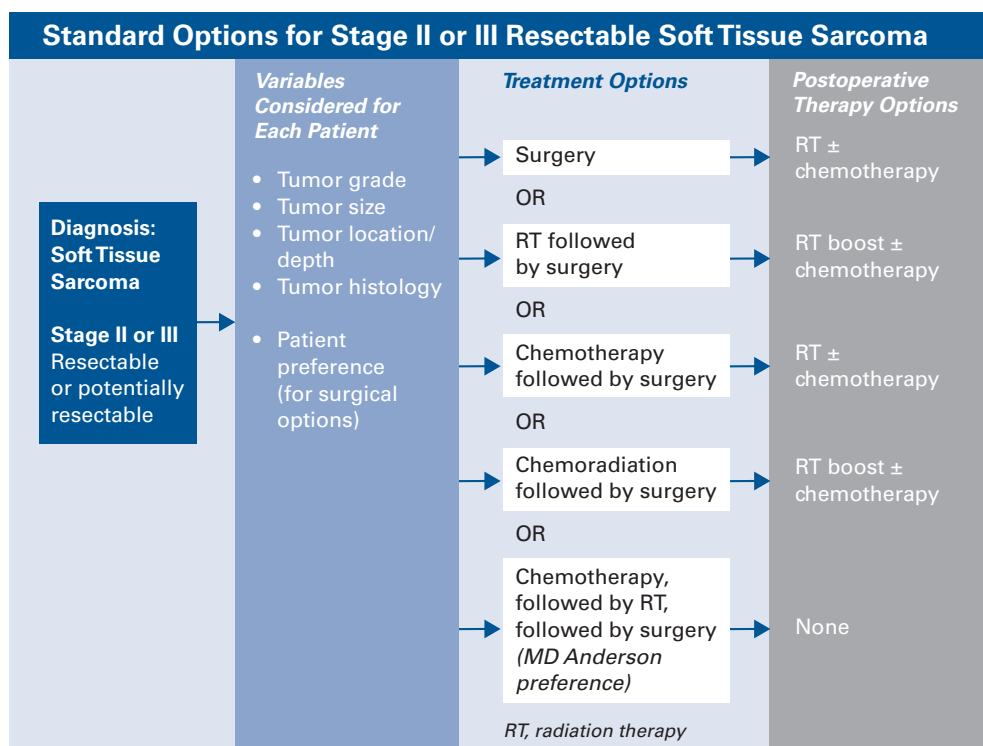
Refinements in the staging of soft tissue sarcomas have been limited by the paucity of large data sets for these rare tumors. An initiative of the National Cancer Institute aimed at addressing this concern is The Cancer Genome Atlas, a tissue procurement program that links tissue specimens with clinical data regarding treatment responses, disease progression, and survival. Upon completion of this project in several years, it is hoped that the National Cancer Institute will make The Cancer Genome Atlas data freely available to researchers and clinicians throughout the world.

Technological advances have helped as well: high-throughput molecular analysis and tissue microarrays have enabled researchers to rapidly evaluate large collections of specimens for many hundreds of molecular markers. Dr. Pollock believes these advances will yield valuable genetic and molecular prognostic information that could be integrated with clinical information to better stratify and stage sarcomas, which in turn could lead to better-informed treatment recommendations for individual patients.

Treatment options and decisions

Surgery alone is curative for many soft tissue sarcomas that can be resected en bloc with microscopically negative margins. The possibility of such optimal resection is determined by the size and location of the tumor; however, tumor histology and grade also yield prognostic information about the risk of recurrence and metastasis.

Type of surgery is an additional concern when planning optimal treatment for soft tissue sarcoma. When a sarcoma is located in an extremity, the surgeon must decide whether



to perform limb-sparing surgery or amputation. Limb-sparing surgery should be considered if complete resection of the tumor can be performed without seriously compromising the function of the limb. The surgical expertise needed to perform limb-sparing surgery is a limiting factor that affects the rate of amputations for sarcoma, which varies from 3% to 10% at most hospitals but is 0.1% at MD Anderson and other major sarcoma centers.

However, even when limb-sparing surgery is possible, patient preferences play a role in determining the type of surgery to be performed. Because the recovery and rehabilitation period after some limb-sparing procedures can be substantially longer than that after amputation, some patients opt for amputation as a shorter, simpler form of surgery. For example, in some patients, radiation therapy would be required with limb-sparing surgery—and thus prolong treatment—but not with amputation. The location and extent of limb loss, prosthetic possibilities, and lifestyle issues all play a part in this very individualized decision.

In most patients with stage II or III soft tissue sarcoma, surgery alone is not sufficient, and radiation therapy and/or chemotherapy are also employed. The grade and size of the tumor, in addition to its location in relation to the deep fascia, are considered when determining the need for additional, nonsurgical therapies. Shreyaskumar Patel, M.D., a professor in the Department of Sarcoma Medical Oncology, said, “Tumors that are high-grade, deep, and large are all bad actors that are likely to require additional therapy.”

According to Gunar Zagars, M.D., a professor in the Department of Radiation Oncology, radiation therapy is considered a standard adjuvant therapy for sarcomas when surgery

alone is believed to be insufficient. Targeting radiation to sarcomas can be challenging because of their wide variation in anatomical locations and depths in the body. However, Dr. Zagars said that precise radiation delivery systems such as intensity-modulated radiation therapy and proton therapy make it possible to treat soft tissue sarcomas that cannot be treated with conventional external-beam radiation therapy. Given these options, Dr. Zagars said, “It is exceedingly rare today to see a tumor that I can’t access to treat.”

The addition of chemotherapy as an adjuvant to surgery for soft tissue sarcoma is less well accepted by clinicians worldwide. “The standard of care has been surgery with or without radiation therapy,” Dr. Patel said, “but this is clearly inadequate because we know that up to half of patients with stage III soft tissue sarcoma will have a recurrence and will die of the disease within 3–5 years.” However, given the rarity of soft tissue sarcomas, not enough large, randomized clinical trials have been conducted in homogeneous populations to provide the evidence needed to establish firm guidelines for the use of chemotherapy in these patients.

Still, said Dr. Patel, a number of smaller studies support the addition of chemotherapy for patients at a high risk of recurrence, even if such therapy does not necessarily result in a cure. For example, a 1997 meta-analysis of 14 trials that were conducted in the 1970s and 1980s concluded that the addition of doxorubicin-based therapy, while not conferring a statistically significant overall survival advantage, did increase local control rates and relapse-free intervals. In the subset of extremity soft tissue sarcomas, however, there was a survival advantage. An update in 2008 that included four newer trials found that the modern combination of doxorubicin and ifosfamide offered an overall survival benefit for the entire population of soft tissue sarcoma patients. And a prospective study conducted by the Italian Sarcoma Group found a 19% increase in the 5-year overall survival rate following aggressive therapy with anthracycline, ifosfamide, and growth factor support in patients with extremity and superficial trunk tumors that had a high risk of recurring. However, with follow-up beyond 7 years, the overall survival benefit lost its statistical significance owing to late recurrences.

“It’s important to note that overall survival is not the only measure we should consider,” Dr. Patel said. “Longer disease-free intervals—lengthening the time to relapse—are important for patients.” The short- and long-term toxicities associated with chemotherapy and radiation therapy must also be considered when adding these therapies to a patient’s treatment plan.

Treatment sequence

Soft tissue sarcomas are best treated by collaborative multidisciplinary teams in comprehensive cancer centers. However, treatment strategies at such centers vary considerably in terms of whether radiation therapy, chemotherapy, or both should precede or follow surgery. At MD Anderson, preoperative therapies are preferred.

“In cases where all three modalities are brought to bear, radiation therapy and chemotherapy are oriented toward achieving a successful surgery,” said Dr. Zagars. “Treatment hinges on realizing that surgery is necessary and building around that.”

At MD Anderson, the preferred sequence begins with chemotherapy followed by radiation therapy and then surgery. This treatment sequence has notable advantages. For example, when chemotherapy is delivered preoperatively, its effect on the tumor can be observed directly when the tumor is resected. In contrast, the effectiveness of chemotherapy given after surgery cannot be gauged by direct observation. “When chemotherapy is delivered postoperatively, we are only guessing about its benefit for an individual patient,” Dr. Patel said. “But we can actually see the effect of preoperative chemotherapy and thus stop treatment for patients who are not benefiting.”

Giving radiation therapy before surgery also has advantages. For example, preoperative radiation therapy uses a lower dose of radiation than does postoperative therapy. Also, the radiation field is usually smaller for preoperative radiation therapy than for postoperative radiation therapy, in which the radiation field would have to encompass the entire surgical field to control the tumor’s microscopic extensions into surrounding tissue.

According to Dr. Zagars, radiation oncologists at MD Anderson do not routinely employ postoperative radiation boosts because the required time lapse between the last preoperative radiation treatment and the boost renders the boosts less effective.

Despite the advantages of preoperative radiation therapy in patients with soft tissue sarcomas, the potential for complications can limit its use. When radiation precedes surgery, postoperative wound healing is delayed, and the potential for wound complications is higher. Therefore, Dr. Zagars said, preoperative radiation therapy requires close collaboration and a high degree of trust between medical, surgical, and radiation oncologists. “Complications from preoperative radiation therapy heal faster than those resulting from postoperative radiation therapy,” he said. “But the surgeon and patient have to be comfortable with the risk of complications and agree to it.”

In the absence of universally accepted treatment guidelines for stage II and III soft tissue sarcomas, a multidisciplinary approach can help determine which combination of surgery, radiation therapy, and chemotherapy will benefit each individual patient. ■

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“lack of an academic venue,” Dr. Clark believed, “would hamper recruitment of top-quality scientists and clinicians.” Thus, in 1948, The University of Texas Postgraduate School of Medicine was formed as part of MD Anderson. But even though the institution could now offer residencies and fellowships, it could not yet offer academic degrees. That changed in 1963 with the establishment of The University of Texas Graduate School of Biomedical Sciences (GSBS), which was staffed by faculty from MD Anderson and offered graduate degrees in physics, biochemistry, and biology. Faculty from the newly created The University of Texas Health Science Center at Houston joined in the early 1970s. Not until the turn of the 21st century, however, did GSBS master’s and doctoral degrees officially bear the MD Anderson name. And in 2006, the new MD Anderson School of Health Professions began offering bachelor’s degrees in eight allied health disciplines, replacing the certificate programs the institution previously offered.

Throughout the institution’s 70-year history, continuing medical education has been an important part of MD Anderson’s educational mission, from the offering of short courses and in-service training for physicians to the presentation of seminars, grand rounds, conferences, lectures, and workshops. In the past year alone, nearly 7,000 physicians, scientists, nurses, and other health professionals have taken part in educational programs at MD Anderson, and thousands more participate annually

in continuing education and distance-learning opportunities.

In addition to providing educational opportunities for the medical community, MD Anderson has produced educational programs and materials for the general public—particularly in the area of cancer prevention. Cancer prevention has long been an important adjunct to MD Anderson’s educational programs, and in many ways it is supported by the other two institutional pillars, translational research and multidisciplinary care. A charge originally taken up by Charles A. LeMaistre, M.D., MD Anderson’s president from 1978 to 1996, cancer prevention is a clinical and research initiative with an educational component, and this initiative directly benefits not only patients but also healthy individuals, those at risk of developing cancer, survivors, and caregivers.

Dr. LeMaistre once said, “Most cancers are avoidable and most cancers are preventable ... but curative medicine, despite its remarkable achievements, will not single-handedly lead us to significant control of cancer.” By successfully integrating translational research, multidisciplinary patient care, education, and cancer prevention efforts, MD Anderson continues its stated mission “to eliminate cancer in Texas, the nation, and the world.” ■

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