

## Intratumoral Therapies Offer Novel Cancer Treatment Approach

By Bryan Tutt

**Injecting cancer treatments such as vaccines and genetically modified bacteria and viruses directly into tumors may shrink or destroy the tumors and stimulate an immune response that attacks tumor cells. These treatments have shown promise in clinical trials, and newer trials are exploring whether such treatments can augment the effectiveness of immunotherapy in patients with metastatic or inoperable disease.**

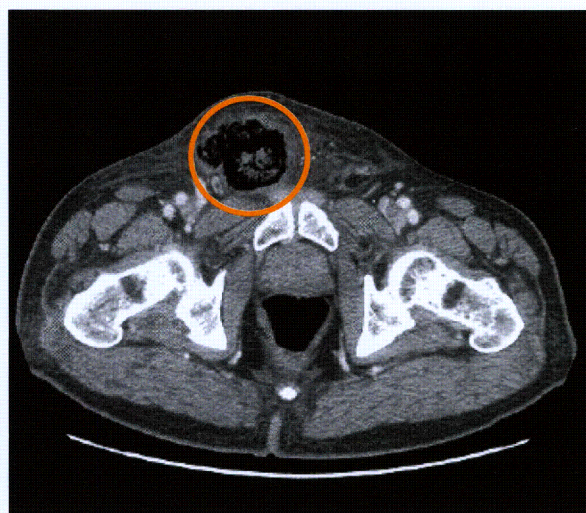
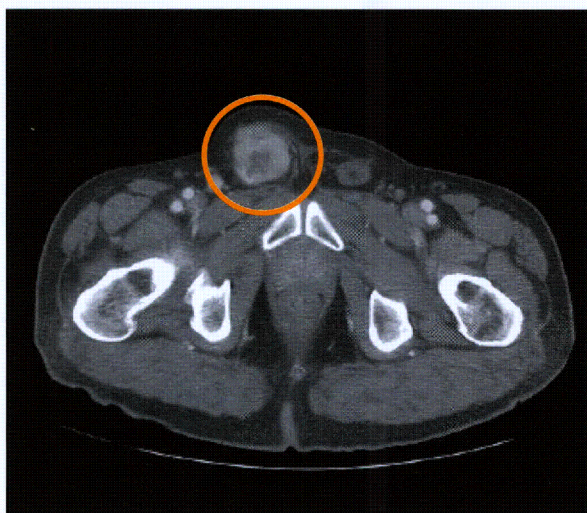
"I think we are poised to make a big difference for patients with unresectable or other difficult-to-treat tumors," said Vivek Subbiah, M.D., an assistant professor in the Department of Investigational Cancer Therapeutics at The University of Texas MD Anderson Cancer Center.

### **Intratumoral therapies**

#### *Dendritic cell vaccine*

Dr. Subbiah is the principal investigator of a phase I/II clinical trial (2013-0160) of a dendritic cell vaccine in patients with locally advanced or metastatic solid tumors. The personalized vaccine is made from each patient's dendritic cells and injected into that patient's tumor.

*A dedifferentiated liposarcoma (circles) is shown before (left) and 4 days after (right) intratumoral injection of Clostridium novyi-NT, a nontoxic bacterial strain. Images courtesy of Dr. Filip Janku.*

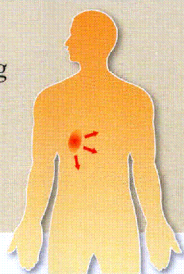


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## Intratumoral Therapies

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The phase I portion of the trial found no dose-limiting toxic effects. The main side effect was fever, which was manageable, although one patient experienced systemic inflammatory response syndrome necessitating emergency care.

Thus far, Dr. Subbiah said, analyses of tumors injected with the vaccine found increases in tumor-infiltrating lymphocytes. However, in the current trial, only one tumor per patient is injected, and patients with multiple tumors have had stable disease at best in their noninjected tumors.

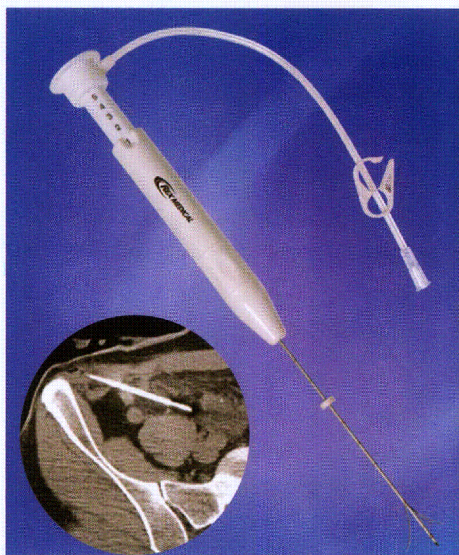
“Biopsies of noninjected tumors showed some distant effects, but these effects were weak,” said Ravi Murthy, M.D., a professor in the Department of Interventional Radiology, who performs the image-guided intratumoral injections for patients in the trial. “In the next study, we’ll inject multiple tumors—perhaps up to five sites—multiple times.”

Another strategy for future trials might be to combine an intratumoral vaccine with an inhibitor of an immune checkpoint such as programmed cell death protein 1 (PD-1) or the PD-1 ligand (PD-L1). Dr. Subbiah said that such combination therapy might create both local and systemic effects.

### Oncolytic bacteria

The concept of using bacteria to treat cancer may sound radical, but it is hardly new. In the 1890s, William B. Coley, a surgeon and pioneer of immunotherapy, observed that cancer patients with bacterial infections sometimes experienced tumor regression. But until recently the risks associated with bacterial infection outweighed the benefits of bacteria-based treatment for cancer patients.

A nontoxic strain of bacteria, *Clostridium novyi-NT*, was engineered to be capable of germinating only in a hypoxic environment such as that in some tumors. “*C. novyi-NT* is not capable of germinating in normal tissue because the oxygen levels are too high,” said Filip Janku, M.D., Ph.D., an assis-



*Intratumoral injections (other than those for brain tumors) can be performed using a multipronged array needle and a procedure similar to that used for image-guided biopsy. Inset: Computed tomography shows the injection of a therapeutic agent into a tumor. Images courtesy of Dr. Ravi Murthy.*

tant professor in the Department of Investigational Cancer Therapeutics. “But *C. novyi-NT* is capable of germinating in hypoxic cancer tissue and causing lysis—the destruction of the tumor.”

Hypoxic tumors historically have been difficult to treat. The limited blood supply to the tumors hampers the delivery of systemic agents. Also, the lack of molecular oxygen, which acts as a radiosensitizer, limits the efficacy of radiation therapy against hypoxic tumors. Bacteria that target such tumors could therefore be very useful.

In the first clinical trial of *C. novyi-NT*, which was not conducted at MD Anderson, the bacteria were injected intravenously. “The theory was that the bacteria would be selectively delivered to the tumor, which did occur; however, the problem was that some tumors were not accessible by surgery, which made adverse events difficult to manage,” Dr. Janku said. “It was felt that intratumoral injection would work better because we can select a lesion that is accessible so that we can control for potential collateral damage.”

*C. novyi-NT* is injected intratumorally in an ongoing multicenter trial (2013-0549) for which Dr. Janku is MD Anderson’s principal investigator. The *C. novyi-NT* injection is an outpatient procedure, but the study’s protocol requires patients to be hospitalized for 7 days after the injection so that immediate care can be given in case of adverse events. As a precaution, all patients receive oral doxycycline starting on the seventh day after *C. novyi-NT* injection.

Although preliminary data from the current trial are not yet available, Dr. Janku estimates that some level of local response is seen in about one-third of patients. Some of these responses have been dramatic, with complete destruction of the tumor in a few days.

Side effects of the treatment can be dramatic as well. For example, the first patient treated in the trial had a tumor surrounding the right humerus. The tumor was injected with *C. novyi-NT* and was destroyed, but the patient suffered a right humerus fracture 2 months later because the bone was too fragile without support from the large surrounding tumor. “We had a bad consequence of a good effect,” Dr. Janku said. Other patients had systemic inflammatory reactions that included fever, low blood pressure, and coagulopathy; these reactions were controlled by antibiotics and other supportive measures. “The reaction seems to be mediated by cytokines rather than bacteremia because we don’t see bacteremia in these patients,” Dr. Janku said.

Researchers think the bacteria works through two mechanisms. The first, direct lysis of the tumor, is very rapid. The second is the abscopal effect: the immune system is primed by the destruction of the tumor to recognize the cancer. “It’s still too early to tell, but some patients seem to have signals of a systemic response,” Dr. Janku said. “We see a slowdown in the growth of the tumors that were not injected, but that effect doesn’t last very long. Data suggest that this therapy can be even more effective when combined with some immune checkpoint inhibitors.”



*C. novyi-NT* will be combined with a PD-1 inhibitor in an upcoming trial at MD Anderson and other centers. Patients who have superficial masses or accessible masses that do not involve the bones or internal organs and who are not candidates for surgery may be candidates for the trial. It is hoped that the immune checkpoint inhibitor will enhance the systemic response to the bacteria.

“The key is to have enough bacterial germination for a maximal antitumor effect and at the same time to have a systemic reaction that is controllable and does not put patients at risk,” Dr. Janku said.

Dr. Janku said that systemic reactions to intratumoral *C. novyi-NT* treatment need to be better controlled before its use becomes widespread. “The treatment can be done safely at MD Anderson and other major cancer centers, but I don’t think it could be easily done at a local hospital,” he said. “On the other hand, I feel far more confident giving this treatment than I did when the trial started; we’ve learned a lot. If applied correctly, *C. novyi-NT* can be a very powerful tool.”

### Oncolytic viruses

As with bacterial infections, for many years there were case reports and other anecdotal evidence of patients whose cancer went into spontaneous remission after exposure to or vaccination against a virus. But studies done in the 1960s using adenoviruses to treat cancer showed limited efficacy and virus-related complications.

Little further research was done in this area until the 1990s, when it became possible to genetically manipulate a virus in the laboratory. It was then that Juan Fueyo, M.D., a professor in the Department of Neuro-Oncology, and Candelaria Gomez-Manzano, M.D., an associate professor in the Department of Neuro-Oncology, began working to develop an adenovirus that acts against cells that lack retinoblastoma tumor suppressor protein (Rb).

“We made a virus that cannot inac-

tivate Rb, which prevents the virus from replicating in a normal cell,” Dr. Fueyo said. “But when it infects a cancer cell, Rb is already gone, and the virus can replicate.” In vitro studies revealed that some cells were resistant to the virus, so Drs. Fueyo and Gomez-Manzano modified the virus with the Arg-Gly-Asp tripeptide (RGD) motif because RGD integrins are expressed at high levels on cancer cells but low levels on normal cells.

The resulting virus, Delta-24-RGD (also called DNX-2401), was recently investigated in a phase I dose escalation trial in which it was injected intratumorally in patients with recurrent glioblastoma. The trial’s principal investigator, Frederick F. Lang, M.D., a professor in the Department of Neurosurgery, said, “We escalated all the way up to the top dose, which is  $5 \times 10^{10}$  viral particles, with no dose-limiting toxic effects.” Among the 25 patients treated, the tumors disappeared completely in three and partially regressed in one.

“When a patient’s glioblastoma comes back, survival often is measured in weeks,” Dr. Lang said. “But these four patients lived more than 3 years after their treatment—and one patient lived 4 years—before their cancer recurred. Three of the patients are still alive.”

Drs. Fueyo and Gomez-Manzano theorize that Delta-24-RGD triggered

an immune response. “When you inject the virus, it replicates in the tumor for a short period, but after a while the immune system will identify the virus and destroy it,” Dr. Fueyo said. “But in a few patients—these three whose tumors regressed—we believe that the immune system shifted from targeting the virus to targeting the tumor cells.” Upcoming trials will test whether combining Delta-24-RGD with other immunotherapy drugs will improve patient outcomes.

A phase IB study (2014-0488) of intratumoral Delta-24-RGD with or without subsequent interferon-gamma is now enrolling patients with recurrent glioblastoma or gliosarcoma at MD Anderson and other centers. Another study is being planned that will combine Delta-24-RGD with a PD-1 inhibitor.

Another oncolytic virus, talimogene laherparepvec (T-VEC), which was recently approved for the treatment of advanced melanoma, also will be combined with an immune checkpoint inhibitor in an upcoming clinical trial. The trial is scheduled to begin enrolling patients with melanoma at MD Anderson and other centers later this year.

### Procedures for intratumoral injection

In addition to establishing the safety and feasibility of Delta-24-RGD treatment, the phase IB trial of the oncolytic virus helped perfect the procedure for injecting the virus into brain tumors. The resulting procedure uses magnetic resonance imaging (MRI)-guided stereotactic implantation of a new microinfusion cannula developed specifically for injecting therapeutics into the brain.

“We put a frame around the patient’s head, which gives us an XYZ coordinate system, and then we do an MRI with that frame in place to provide points of reference,” Dr. Lang explained. With the patient under local anesthesia with conscious sedation, a hole is drilled in the skull through which, with MRI guidance, Dr. Lang passes the cannula (which is less than

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**“When a patient’s glioblastoma comes back, survival often is measured in weeks. But these four patients lived more than 3 years after their [Delta-24-RGD] treatment.”**

**– Dr. Frederick F. Lang**



## Intratumoral Therapies

[Continued from page 3]

2 mm in diameter) into the brain using an arc-shaped stereotactic device that sits on the frame. “We use this stereotactic system to precisely position our cannula within the tumor,” he said.

Once the cannula is in place, Dr. Lang infuses gadolinium contrast medium to allow him to monitor the virus’s distribution as it pushes the medium along. Then the 1-mL dose of Delta-24-RGD virus is infused at a slow rate (0.9 mL/h) using a microinfusion pump. “The idea of this controlled slow infusion, called convection-enhanced delivery, is that it opens up the interstitial spaces within the tumor by creating a continuous, very slow pressure gradient, and the fluid and virus can move through that interstitial space,” Dr. Lang said.

Compared with the infusion of the oncolytic virus into brain tumors, the injection of *C. novyi-NT* or dendritic cell vaccine into tumors in other parts of the body is a straightforward procedure. “The technique is a natural extension of the technology we use every day for image-guided biopsies, but instead of just taking tissue, we’re injecting therapy,” Dr. Murthy said.

The location, size, and characteristics of the tumor determine whether ultrasonography, computed tomography, or (rarely) MRI is used to guide the injection. The type and size of the needle are determined by the tumor’s size and location and the type of therapy to be injected. For example, Dr. Murthy said, “For *C. novyi-NT* we use a multipronged array needle to ensure even distribution. Because tumors are heterogeneous, we don’t know the best area to target. So we spread the bacteria evenly within the tumor because we think this will give the bacteria the best chance of germinating. The procedure is simple—it just needs to be done right.”

### Future directions

Because dendritic cell vaccine, *C. novyi-NT*, and Delta-24-RGD are either known or theorized to stimulate the immune system, combining them

**“I think we are poised to make a big difference for patients with unresectable or other difficult-to-treat tumors.”**

– Dr. Vivek Subbiah

with immunotherapy drugs was the next logical step in their clinical development.

Dr. Subbiah hopes that combining an intratumoral vaccine and an immune checkpoint inhibitor will enhance the efficacy of both drugs. “Checkpoint inhibitors have changed the landscape of immunotherapy for many cancers,” he said. “But some patients do not respond to these drugs, and others develop resistance. The lack of response may be due to a lack of pre-existing immune response in these patients. We all know that dendritic cells are needed for induction of an adaptive tumor response, which is one reason I think the intratumoral dendritic cell vaccine has the potential to augment checkpoint inhibitors.”

In addition to combining Delta-24-RGD with an immune checkpoint inhibitor, Drs. Gomez-Manzano and Fueyo, along with Carlo Toniatti, M.D., Ph.D., executive director of the Oncology Research for Biologics and Immunotherapy Translation platform in MD Anderson’s Institute for Applied Cancer Science, and Laura Bover, Ph.D., an associate professor in the Department of Genomic Medicine, hope to go one step further. “We are trying to make a virus that itself will express a positive regulator of the checkpoints,” Dr. Fueyo said. The new virus, Delta-24-RGDOX, expresses the ligand for OX40 (also called tumor necrosis factor receptor superfamily member 4), which is expressed on

tumor-specific T cells. Delta-24-RGDOX has shown promise in preclinical studies. “We are at the interface between virotherapy and immunotherapy,” Dr. Fueyo said.

In addition to its use for delivering vaccines and oncolytic viruses and bacteria, intratumoral injection may provide the answer in areas of immunotherapy research that seem to have stalled. “Many of the treatments we give to stimulate the immune system, such as toll-like receptor antagonists, never actually make it into the tumor and are too toxic when given systemically,” Dr. Murthy said. Indeed, a trial of an intratumorally injected toll-like receptor antagonist is in the planning stage.

Another upcoming trial will test intratumoral injection of avidin followed by an intravenous injection of radioactive biotin, which binds irreversibly and with an extreme affinity to avidin. This trial is being planned by Drs. Murthy and Subbiah along with Gregory Ravizzini, M.D., an assistant professor in the Department of Nuclear Medicine. Still more trials of intratumoral oncolytic treatments are expected to follow.

“These intratumoral treatments are blossoming,” Dr. Murthy said. “It’s an exciting time to be involved in this area of clinical research.”

Dr. Janku agreed. He said, “These treatments are making their way into the standard of care.” ■

### FOR MORE INFORMATION

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# High-Risk Acute Lymphoblastic Leukemia Subtype Targeted in Upcoming Clinical Trial

By Katelyn Werner

**Early T cell precursor acute lymphoblastic leukemia (ETP-ALL), an uncommon subtype of T cell acute lymphoblastic leukemia (T-ALL), carries a poor prognosis and low response rate to traditional chemotherapy drugs. But a clinical trial of a targeted agent that shows promise against ETP-ALL will soon be enrolling patients at The University of Texas MD Anderson Cancer Center.**

Few connections have been made between the biological features of T-ALL (which also presents as T cell lymphoblastic lymphoma) and patients' clinical outcomes. The World Health Organization classifies T-ALL cases into subtypes based on leukemic cell biomarkers that correspond to four stages of T cell maturity: pre-thymic, pro-thymic, thymic, and mature. In practice, many researchers began combining the pro-thymic and pre-thymic stages into one class, "early." But neither classification system nor any subtypes of T-ALL have demonstrated prognostic or predictive value—until the discovery of ETP-ALL.

## A clinically relevant T-ALL subtype

ETP-ALL was first described in a 2009 study of pediatric T-ALL. By flow cytometry, the leukemic cells of some patients had an expression profile reminiscent of recent arrivals in the thymus from the bone marrow. These cells had a unique biomarker signature: the key immunophenotypic features of immature leukemic T cells—the absence of antigens CD1a, CD8, and CD5—along with the expression of one or more stem cell or myeloid antigens. Clinical assessment of the pediatric patients in that study showed that those with this

subtype of T-ALL responded poorly to conventional T-ALL treatments.

Subsequent studies reported ETP-ALL in 11%–12% of childhood and 7%–8% of adult T-ALL cases and confirmed that children with ETP-ALL have significantly worse clinical outcomes. However, studies of clinical outcomes in adults were largely inconclusive until a recent study by Joseph Khoury, M.D., an associate professor in the Department of Hematopathology; Nitin Jain, M.D., an assistant professor in the Department of Leukemia; and colleagues.

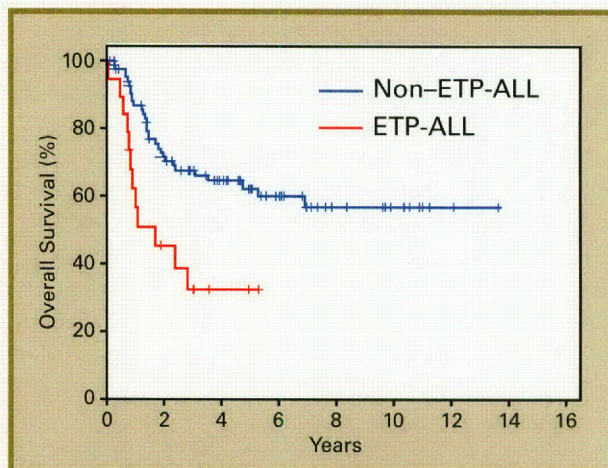
The researchers retrospectively analyzed the records of 111 patients newly diagnosed with T-ALL at MD Anderson between 2000 and 2014. All patients had received frontline chemotherapy with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) or an augmented Berlin-Frankfurt-Münster regimen. Reassessment of the patients' flow cytometry data identified 19 pa-

tients who met the criteria for ETP-ALL, and these patients experienced a significantly lower complete remission rate (73%) than did patients with non-ETP-ALL (91%). In fact, a multivariate analysis of 11 potential prognostic markers found only two to be significant: age and the ETP-ALL subtype.

The study was notable for its use of a single, large patient population, Dr. Khoury said. "The prognostic significance of this subtype is demonstrated now within a relatively well-controlled cohort of patients who received the same fundamental types of treatment," he said. "We confirmed that clinical outcomes of adult ETP-ALL patients mirror those of pediatric ETP-ALL patients," Dr. Jain said. "When treated uniformly with chemotherapy, patients with ETP-ALL have poor long-term outcomes."

## Targeting the ETP-ALL subtype

"Traditionally, patients with T-ALL are grouped within a single category from a therapeutic standpoint," Dr. Khoury said. Whereas the more com-



A retrospective analysis of 111 patients with T cell acute lymphoblastic leukemia revealed that those with the early T cell precursor (ETP-ALL) subtype ( $n = 19$ ) had lower rates of overall survival than did patients with other subtypes ( $p = .008$ ) after standard chemotherapy regimens. Adapted from Jain N, et al. *Blood*. 2016;127:1863–1869.



## High-Risk Acute Lymphoblastic Leukemia Subtype

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mon B cell ALL cases are treated differently based on genetic markers such as the Philadelphia chromosome, all T-ALL cases are typically treated with the same chemotherapy regimens. “Based on our findings,” Dr. Khoury said, “patients with ETP-ALL need a different approach than those with non-ETP-ALL.”

“ETP-ALL affects a relatively small group of patients,” Dr. Jain said, “but these patients have a largely unmet medical need.” Drs. Jain and Khoury and their team are investigating how to address that need. One drug target they’ve recognized as promising is the apoptosis regulator Bcl-2. In recent years, studies by Marina Konopleva, M.D., Ph.D., a professor in the Department of Leukemia, and others have noted that T-ALL cells—and especially ETP-ALL cells—express high levels of Bcl-2. An oral inhibitor of Bcl-2, venetoclax (formerly called ABT-199), has demonstrated activity against chronic lymphocytic leukemia in clinical trials, and preclinical studies suggest that venetoclax may be effective against ETP-ALL. “ETP-ALL cells are preferentially sensitive to Bcl-2 antagonism in vitro and in mouse models,” Dr. Jain said, adding that he and others are optimistic about this strategy’s potential for patients with ETP-ALL.

In the next 3–5 months, Dr. Jain and researchers from the Departments of Leukemia and Hematopathology plan to open a single-arm, phase IB multiple ascending dose trial evaluating the safety of venetoclax in patients with ALL. Eligible patients must have untreated ALL (of any type), be over 50 years of age, have good organ function, and not be currently receiving treatment for other cancers. This will be the first trial of venetoclax in patients with ALL.

The trial, as planned, will pair venetoclax with a low-intensity chemotherapy regimen that the team calls “mini-hyper-CVD,” which is similar to hyper-CVAD but omits doxorubicin and uses much smaller doses of the other agents. Dr. Jain said the low-intensity chemotherapy regimen was designed to minimize the risks of tumor lysis syndrome and neutropenia, both

### CLINICAL TRIALS: T-ALL

**A phase IB/randomized phase II study to evaluate LY3039478 in combination with dexamethasone in T cell lymphoblastic leukemia (T-ALL) or T cell lymphoblastic lymphoma (T-LBL) patients (2015-0020).** Principal investigator (PI): Dr. Gautam Borthakur. The goals of the study are to determine the recommended dose of Notch inhibitor LY3039478 plus dexamethasone in patients with relapsed/refractory T-ALL and to compare remission rates of patients who receive dexamethasone plus LY3039478 to those who receive dexamethasone plus placebo. Preclinical studies have shown mutations in *NOTCH* genes in T-ALL leukemic cells.

**Phase II study of hyper-CVAD plus nelarabine in previously untreated T-ALL and lymphoblastic lymphoma (2006-0328).** PI: Dr. Farhad Ravandi-Kashani. The goal of this study is to determine the complete remission rate and progression-free survival durations following treatment with hyper-CVAD in combination with nelarabine in patients with previously untreated T-ALL.

**A pharmacokinetic and pharmacodynamic study to evaluate the safety and feasibility of continuous infusion nelarabine in patients with relapsed/refractory lymphoid malignancies (2009-0717).** PI: Dr. Tapan Kadia. The goal of the study is to determine the recommended dose of nelarabine in patients with relapsed/refractory T-ALL. ■

#### FOR MORE INFORMATION

Visit [www.clinicaltrials.org](http://www.clinicaltrials.org).



of which have been associated with venetoclax treatment.

Another promising strategy against ETP-ALL is to target the Janus kinase (JAK) signaling pathway. Like Bcl-2 levels, JAK levels are especially high in ETP-ALL cells, suggesting that inhibitors of JAK may also be effective against this subtype. And in preclinical studies, the JAK1/JAK2 inhibitor ruxolitinib has shown activity against T-ALL cells. Dr. Jain said, “Ruxolitinib may be a future option for treating patients with T-ALL, including patients with the ETP-ALL subtype.” Drs. Jain and Khoury, along with other researchers from the Departments of Hematopathology and Leukemia, are studying the feasibility of JAK inhibition in experimental models.

#### Identifying ETP-ALL

Identifying the ETP-ALL subtype is a practical way to anticipate a poor response to traditional T-ALL treatment, Dr. Khoury said. Screening requires only flow cytometry, a standard diagnostic procedure already used in

most clinical workups. Patients who screen positive for ETP-ALL may respond better to more intensive treatments or to chemotherapy using nonstandard agents.

Dr. Khoury and his team are calling for awareness of this subtype in research centers to find new treatments and in clinics for oncologists and patients to make informed treatment decisions. “It is important for oncologists to be aware that patients whose T-ALL is subtyped ETP-ALL will likely need a different approach,” he said. ■

#### FOR MORE INFORMATION

Dr. Nitin Jain.....713-745-6080

Dr. Joseph Khoury.....713-745-2387

#### FURTHER READING

Jain N, Lamb A, O'Brien S, et al. Early T-cell precursor acute lymphoblastic leukemia/lymphoma (ETP-ALL/LBL) in adolescents and adults: a high-risk subtype. *Blood*. 2016;127:1863–1869.





# What Is Metastasis?

## Understanding the spread of cancer

**Metastasis is the spread of cancer from where it began to other places in the body.** Because metastasis affects treatment options and possible outcomes, understanding the process of metastasis can help patients and their families communicate with their health care providers.

### The process of metastasis

Metastasis usually begins when cancer cells break away from a tumor and move into nearby tissue; this step is called invasion. The cancer cells then enter the bloodstream or the lymphatic system (the network of lymph vessels and lymph nodes that are part of the immune system) to circulate throughout the body.

Most cancer cells in the blood or lymph are identified and destroyed by the immune system. Any cells that go undetected may stay suspended in the blood or lymph and never settle down, or they may become stuck to vessel walls. Occasionally, cells that have become stuck will move into nearby tissues and begin to multiply, creating a new tumor. This new tumor is called a metastasis, a metastatic lesion, or a secondary tumor.

Cancer cells in the lymphatic system are likely to settle in a lymph node near the primary tumor, an occurrence called

regional lymph node metastasis; other cancer cells may move to distant parts of the body and form distant metastases.

While metastasis can occur in almost any type of cancer, the process of metastasis can be shorter in some cancers—such as leukemia and lymphoma—in which cancer cells are already circulating through the body.

Some types of cancer tend to metastasize to particular places. When breast cancer spreads, it often moves to the lungs, liver, bones, or brain. In contrast, metastatic melanoma occurs in the bones and brain more frequently than it does in other organs.

No matter where the metastatic tumors develop, they are still named for the primary cancer, not the locations of metastases. For example, if lung cancer metastasizes to the brain, the brain tumors will be called metastatic lung cancer.

### Metastasis in cancer staging

Metastasis is one factor doctors use to determine cancer stage, which guides treatment. A cancer that has spread to nearby organs or lymph nodes is usually called locally advanced cancer and is typically classified as stage III, but such a cancer might be stage II depending on factors such as the cancer type and the

tumor size. Cancer that has spread to distant parts of the body is said to be stage IV.

Metastatic cancer can be difficult to identify. Occasionally, the metastatic tumor is diagnosed before the primary tumor. But in most cases, the primary cancer is identified first, prompting doctors to look for metastases.

Metastases can be found by multiple methods. A physical examination may identify unusual lumps that could be tumors. Imaging techniques like x-ray, computed tomography, and magnetic resonance imaging can locate and measure tumors inside the body. Additionally, if surgery is performed to examine or remove a primary tumor, doctors may examine nearby lymph nodes and organs for signs of metastasis.

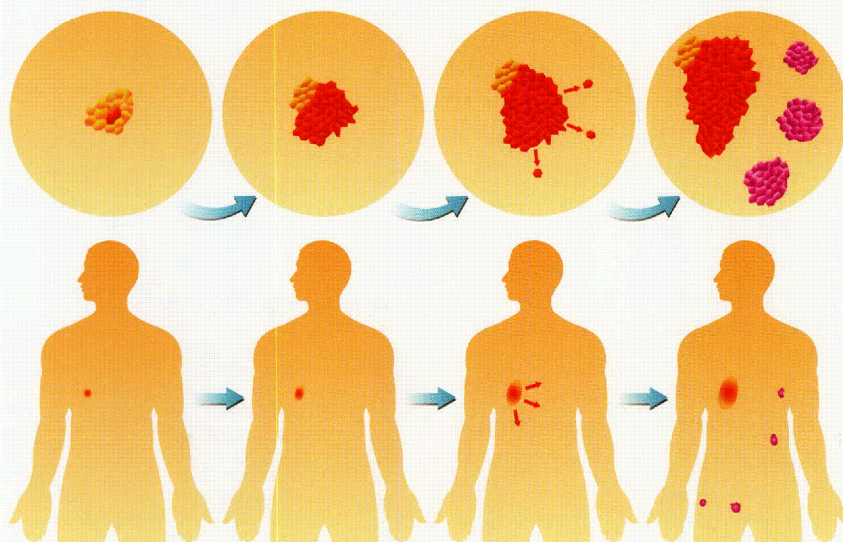
### Prognosis and treatment

For many types of cancer, the most effective way to prevent metastasis is finding the primary cancer early, before cancer cells invade the bloodstream, and removing the primary tumor completely. The risk of metastasis may also be reduced by radiation and chemotherapy. If the primary cancer is successfully treated and there is no sign of local or distant spread, the possibility of such spreading requires regular follow-up examinations so that if metastases do occur, they can be found and treated.

Once cancer has metastasized, treatment can become more difficult. However, new techniques and therapies have made it possible to treat metastases that were not treatable 5 or 10 years ago in some types of cancer.

Metastasis is a serious development, but surveillance and treatment can help patients fight the battle against cancer on all fronts. ■

—K. Werner



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## IN BRIEF

### New Staging System Proposed for HPV-Related Oropharyngeal Cancer

A new staging system for oropharyngeal carcinoma—one that more accurately predicts outcomes for patients with human papillomavirus (HPV)-related disease—has been proposed by researchers at The University of Texas MD Anderson Cancer Center.

Although HPV status is a strong prognostic factor in patients with oropharyngeal carcinoma, the current TNM guidelines for cancer staging (*AJCC Cancer Staging Manual*, seventh edition) do not adequately account for biological and clinical differences between HPV-positive and HPV-negative oropharyngeal carcinoma.

The researchers evaluated the prognostic value of the current staging system by reviewing the records of 661 patients with HPV-positive oropharyngeal carcinoma treated at MD Anderson from January 2003 through December 2012 and found no differences in overall survival among groups of patients stratified by disease stage.

Next, the researchers analyzed the current TNM categories individually as predictive factors for survival in the same patient population. The T category was the strongest predictive factor, whereas the N category appeared to have no predictive value.

Whereas the current N category criteria for oropharyngeal carcinoma are similar to those for head and neck cancers that are not associated with a viral infection, the N category criteria for nasopharyngeal carcinoma—which is associated with Epstein-Barr virus infection—include not only the number and laterality of positive lymph nodes but also whether supraclavicular nodes are involved. The researchers therefore adapted the N category criteria for nasopharyngeal carcinoma and repeated their analysis.

With the revised criteria, the N category became a significant predictor of survival. On the basis of their findings, the researchers developed a new staging system for HPV-positive oropharyngeal carcinoma that combined the current oropharyngeal carcinoma T category and nasopharyngeal carcinoma N category criteria. When the new system was applied to the cohort of 661 patients with HPV-positive oropharyngeal cancer, the risk of death increased with each disease stage.

“The revised staging system has greater predictive power than the current system, which has been shown to be insufficient for HPV-positive oropharyngeal carcinoma,” said Erich Sturgis, M.D., a professor in the Department of Head and Neck Surgery and the corresponding author of the study’s report, which was published in February in the *Journal of Clinical Oncology*. However, Dr. Sturgis added that the study’s findings need to be confirmed in cohorts of patients treated elsewhere. ■

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