

## FEATURE STORY

# The New Sarcoma Story

BY BEVERLY A. CALEY

*Strategies for diagnosing and treating sarcomas shift to a more patient-specific approach.*

In August 2001, Erin Toole was a 19-year-old college student working part-time at a kayak rental business. She slipped on some algae and extended her right arm to break the fall. Tremendous pain followed. As an athlete, Toole, of Costa Mesa, California, had experienced sports injuries before and could distinguish between major and minor injuries. So after her first doctor dismissed the pain, she sought another opinion from a doctor who took an X-ray of the painful area. She remembers the “X-ray showed it as clear as day. The best way I can describe it was that it looked like a moth-eaten bone. You could see right through my bone in certain areas.” The doctor referred Toole to a sarcoma center, where a biopsy confirmed a bone cancer called osteosarcoma.

Sarcomas are a relatively rare group of cancers of connective or supportive tissue, such as bone, cartilage, fat, muscle, and blood vessels, that can occur in both the pediatric and adult populations. The two main kinds of sarcoma—soft tissue and bone—likely encompass more than 600 subtypes that can be hard to tell apart and have different prognoses and outcomes, says George Demetri, MD, director of the Center for Sarcoma and Bone Oncology at Dana-Farber Cancer Institute in Boston.

Based on the tricky and unique nature of sarcomas, doctors are using new tactics to diagnose and treat these tumors that’s more about the patient and less about the general type of sarcoma. And it’s starting to pay off.

View Illustration: Picking Apart Sarcoma

## The Initial Diagnosis

More than 9,000 cases of soft-tissue sarcoma are expected this year plus about 900 cases of bone sarcoma. Since benign lumps are common and sarcoma is uncommon, making a diagnosis of sarcoma can be difficult. The typical family doctor sees, on average, only two soft-tissue sarcomas during his or her career.

Given that they see hundreds of lumps, how can community doctors keep sarcoma on their mental list of potential diagnoses? “Many clues can indicate the presence of sarcoma, but they can be very subtle,” says Dr. Demetri. These clues include the size, firmness, and location of a lump, and its appearance on a CT

(computed tomography) scan.

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Margaret von Mehren, MD, director of the sarcoma program at Fox Chase Cancer Center in Philadelphia, says not all patients have the benefit of appropriate imaging prior to surgery. "One thing we see is that patients who have a lump or mass will have either no form of X-ray study or have an inadequate X-ray study, such as an ultrasound, before going for a surgical procedure. Many times, that is not adequate, and better imaging with at least a CT scan, if not an MRI, is indicated."

Last November, a CT scan revealed a 10-centimeter mass in Jim Foppiano's mediastinum (the area between the right and left lung that contains the heart). But when a needle biopsy came back indicating the mass was benign, there seemed to be no hurry for surgery. Just before Christmas, surgeons removed a grapefruit-sized mass and sent it to the lab. "A week later is when I actually got the news it was cancer," says Foppiano, 54, of St. Charles, Missouri.

Improvement in the initial diagnosis of sarcoma will ultimately have to come from education of community doctors, says Dr. Demetri. "When our colleagues in the community recognize that there are 600 different kinds of sarcoma, they'll begin to say, 'Why don't we send the patient to a referral center and then we can work together to tease apart the differences.' "

Pathologists at sarcoma centers "have tremendous expertise and very sophisticated tools to enable them to tell these tumors apart from one another—and probably most importantly, from look-alikes that may be benign," says Dr. Demetri. "We've seen people who have been given a death sentence, and they haven't even had sarcoma. And we've seen people who had a sarcoma managed as if it were another sort of cancer."

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—Peter Pisters, MD

Dr. Demetri envisions a partnership with community doctors where in some cases sarcoma experts provide detail on what they think should be done, but for the more complicated cases, explain why the treatment plan should be implemented at a sarcoma center. "That way, we maintain convenience for patients. Why should a patient drive six hours to get to us for a routine form of chemotherapy when they might be able to get the same care closer to home? However, deciding what

is the right form of therapy is the key component.”

## Surgical Shift

Recent advances in surgery have made it possible to avoid amputation for many patients who have sarcoma in their extremities. Peter Pisters, MD, chief of the sarcoma service in the Department of Surgical Oncology at M.D. Anderson Cancer Center in Houston, says the main advances are improved surgical techniques and increased ability to do more complex procedures that replace joints and blood vessels.

“There’s an increased focus on quality-of-life issues, which are really important. We try to make sure that the surgery keeps these patients as functional as possible. That’s something we do much more consistently now than we’ve done in the past,” says Dr. Pisters.

Experts agree poorly planned sarcoma surgery can contaminate the anatomical area where the tumor is located, possibly causing the sarcoma to spread and necessitating additional surgeries to remove a larger area.

Amputation may still represent the best option for patients who have tumors in places where it would be difficult or impossible to obtain clean margins—in other words, getting all the cancer—or who may be at excessive risk for major complications from radiation therapy. In some sarcoma cases below the knee, prosthesis may be a better option than a leg severely damaged by surgery and radiation.

For Foppiano, surgeons were unable to get a clean margin, so he received 33 rounds of radiation that ended in March. Foppiano is now cancer-free.

Adding radiation to surgery has not improved overall survival in most clinical trials, but it does reduce the risk of local recurrence. This is an important benefit, says Dr. Pisters, because local recurrence generally requires more treatment.

Current research focused on the proper combination and sequence of radiation with surgery shows factors like tumor location and size have an important impact on treatment sequencing decisions. So a person with a tumor in the arm might be better off with radiation treatment prior to surgery, whereas a patient with a leg tumor might have more complications with the same treatment sequence. Researchers are also looking for factors that predict which patients do fine with surgery alone in order to spare patients the side effects of radiation therapy.

## Drug Options

Chemotherapy has a clear role in some types of sarcoma to reduce the size of the tumor to make surgery easier and increase the likelihood of removing the entire tumor.

Doctors planned to treat Toole’s osteosarcoma with a four-drug chemotherapy regimen prior to surgery, beginning with methotrexate. But after two treatments, Toole reacted badly to it.

“My tumor was growing and my arm was in much more pain than it was even before I started treatment,” Toole says. She responded better to ifosfamide with relatively mild side effects before receiving a combination of Adriamycin (doxorubicin) and cisplatin. Toole then underwent surgery to remove most of her right humerus, including the shoulder section. A metal rod now rests in its place anchored into the remaining part of her humerus and attached to the shoulder. Toole received additional chemotherapy after surgery.

Controversy surrounds the role of chemotherapy before and after surgery for sarcoma. Dr. Demetri says data from the American Society of Clinical Oncology meeting earlier this year suggests “old-style chemotherapy does not add much” in the treatment of most non-GIST (gastrointestinal stromal tumor) sarcomas, except for patients with osteosarcoma, rhabdomyosarcoma, and Ewing’s sarcoma, following optimal surgery.

“As sad as that is,” he says, “it really is important that we figure that out, so we can move beyond it, and develop other, smarter drugs that will have an impact in improving patient outcomes.”

Charles Forscher, MD, however, notes not all doctors believe the recent data are definitive. “There were some problems with that trial in general,” says Dr. Forscher, medical director of the Cedars- Sinai Sarcoma Center in Los Angeles. “The sarcomas that are treated with chemotherapy tend to be the intermediate- to high-grade tumors, and that study included some smaller tumors and low-grade tumors as well. That may have been part of the issue of why that trial did not show a benefit. But it does raise important issues.”

Drug therapy for sarcoma is on a path to be driven more by what the sarcoma looks like under a microscope than by the body location or the type of tissue in which it arose. Identification of biological attributes of sarcoma can help researchers discover new targets for treatment, some of which already include proteins known as c-Kit and mTOR (mammalian target of rapamycin).

“Our understanding of the biology of these tumors is increasing, really quite dramatically,” says Dr. von Mehren. “We need to try to sort out the biologically relevant and unique thing about each one of these tumors, and determine if that relevant factor can be targeted to make the tumors respond better. I think the most exciting thing we’re seeing in sarcoma clinical trials is that you’ll find trials that are specifically addressed to specific types of sarcoma.”

Case in point: Avastin (bevacizumab), a drug Dr. von Mehren’s institution is now studying in angiosarcoma. “This is a tumor of abnormal blood vessels, and here’s a drug that prevents the binding of a growth factor that’s known to be important in the development of blood vessels. That’s an example of taking a piece of what’s unique about this tumor, thinking about its biology, and then applying it to a drug that works on that.”

Another agent in clinical testing with a unique method of action is Yondelis (trabectedin). It works by binding with DNA in such a way that the DNA changes its shape. Researchers have discovered Yondelis is especially effective in treating myxoid liposarcoma.

A family of drugs called tyrosine kinase inhibitors is also showing promise for

treatment of sarcoma. Gleevec (imatinib), a targeted agent used to treat chronic myeloid leukemia, is now standard treatment for some GIST tumors, and Sutent (sunitinib), an agent used to treat kidney cancer, is now FDA-approved for Gleevec-resistant GIST.

Dr. von Mehren and colleagues are conducting research with a new tyrosine kinase inhibitor called Tasigna (nilotinib). She says initial studies in specific types of sarcoma suggest the drug is well tolerated and prolongs the time to disease progression.

The mTOR inhibitors comprise another class of drugs being investigated for sarcoma. Deforolimus (AP23573) has shown promise in treating several types of sarcoma and is now entering phase III testing.

## Research Roadblocks

“There hasn’t really been a lot of hard evidence of good quality to guide our practice” in treating sarcoma, says Dr. Demetri. The exceptions, he says, are in sarcomas found most commonly in children and teenagers (osteosarcoma, rhabdomyosarcoma, and Ewing’s sarcoma) and for the new GIST targeted agents. For those diseases, he says physicians routinely placed their patients from all over the world in research trials, and they managed them in systematic ways that generated useful information. By doing this, they learned from each individual patient, resulting in increased knowledge of these tumors that led to more successful treatment strategies.

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The lessons learned are now being applied in many sarcomas through international collaborations. Indeed, Dr. Demetri says the mTOR inhibitor deforolimus will be the subject of a global study.

The current state of scientific knowledge about the diversity of sarcoma must be taken into account in clinical testing, says Dr. Demetri. So, if a drug that looks promising for a subset of sarcomas were to be empirically tested in every type of sarcoma, “that could make a very good drug look bad,” he says. “That’s what we learned from a lot of the ‘smart’ drugs that are around. We’re not going to make the old mistakes twice. In general, we are trying to avoid this hodgepodge one-size-fits-all kind of clinical trial [and instead design trials for] specific, molecularly defined subsets of sarcomas.”

Another clinical trial hurdle comes in the form of funding. Because of its relatively simple genetics, sarcoma is a good model for studying other cancers, and in the past it was studied at a rate larger than the proportion of cancer

patients who have sarcoma. Recently, however, the reverse has been true.

“Just when the country stands most poised to take advantage of 50 years of biomedical research, the funding for cancer research generally is decreasing in real terms, and the funding for sarcoma has been disproportionately hit,” Dr. Demetri says. Although the funding cuts are dispiriting, Dr. Demetri is encouraged by the fundraising efforts of the sarcoma community. “We are blessed with patients and caregivers who recognize that there is a lack at the federal level and are stimulating philanthropy to try to fund our field. Bake sales help,” he says.

An example of that “bake sale” activism is Willow Crest Winery’s Sunflower Series wines. Marny Tobin, interviewed for a 2004 *CURE* article, died of sarcoma in November 2006, and in her memory, the Sarcoma Foundation of America receives half the proceeds of each wine sale. Tobin’s husband, Tom, is a lifelong friend of the owner of the winery.

Twenty-year liposarcoma survivor Rose Burt, 70, is also doing her part by managing the Association of Cancer Online Resources sarcoma support group. And although still early in his recovery, Foppiano is motivated to help other survivors. “I hope I can provide somebody else some hope or ideas about how they can better manage treatment of their specific sarcoma,” he says.

Now a third-year medical student, Toole is making an impact on sarcoma awareness early in her career. Through the University of California-Irvine and Children’s Hospital of Orange County, she is assisting with a research project that focuses on young adults and adolescents with cancer. Through the research project, she is developing a curriculum to make medical students aware that young people get cancer too.

“Yes, it’s rare,” she says, “but if you just write them off, that can result in horror stories. I was very lucky because I was adamant in getting a second opinion.” Toole says she’s determined to be the kind of doctor who listens to her patients.