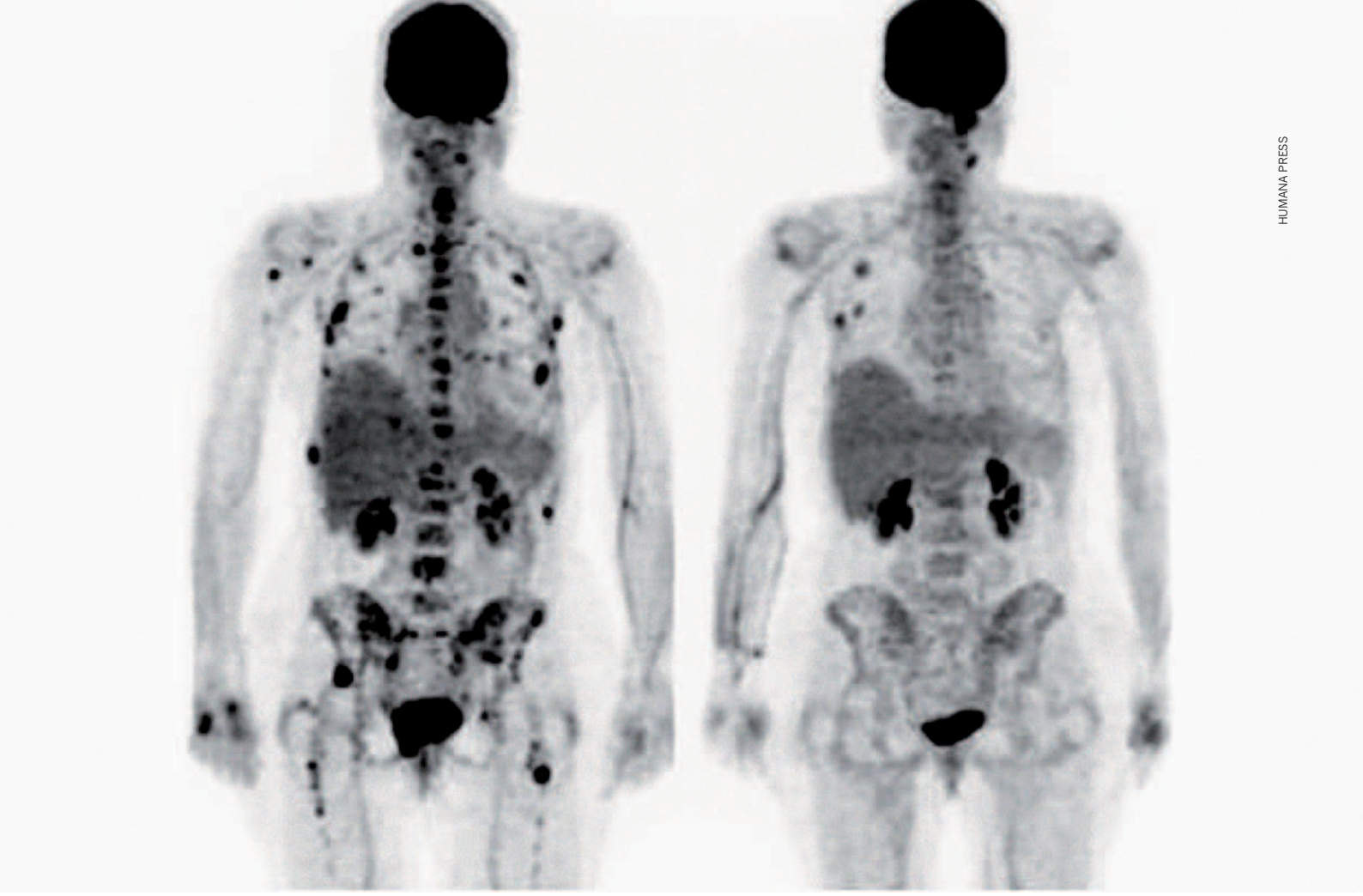


HUMANA PRESS

Better view: positron emission tomography can show how patients respond to treatment.

IMAGING

Seeing is believing

New technology to peer into the bones could help improve the treatment of multiple myeloma patients.

BY CASSANDRA WILLYARD

Noopur Raje first met Ben (not his real name) in 2006. Blood tests and a bone-marrow biopsy revealed that Ben had a type of multiple myeloma. But unlike most patients, who have cancerous lesions throughout their body, Ben had just one — a big one — on his rib. Raje, an oncologist at Massachusetts General Hospital in Boston, had seen cases like this before. She irradiated the cancer and began scanning Ben once a year, just in case.

The scan Raje prescribed is really two scans in one. The first identifies areas of active cancer. The second uses X-rays to create a three-dimensional image of the body's interior. Together, the scans allowed Raje to track Ben's disease.

Ben's first scan showed that the treatment had worked: the cancer was gone. But two years later, in another scan, "he lit up like a Christmas tree", Raje says. The imaging showed that Ben's rib lesion had returned, and he also had new masses around his kidneys and adrenal glands. At the time, he felt fine and his blood tests were normal. Raje put him on an aggressive treatment regimen. He experienced an almost complete remission, and today he is in good health.

Ben's case illustrates the importance of imaging technologies in the treatment of multiple myeloma. New techniques, along with refinements to existing technologies, promise to give doctors more accurate information to help them spot myeloma, predict how fast and far it will spread, and tailor treatments based on the characteristics of the individual's disease.

IMAGING IN THE CLINIC

Cancerous skeletal lesions, which resemble pits in the bone, are a hallmark of multiple myeloma. A skeletal survey using an X-ray machine has long been the gold standard for spotting these lesions, and the International Myeloma Working Group still recommends that doctors conduct such a survey once the disease is suspected. Radiography machines are inexpensive and widely available, but the process can be slow and uncomfortable for patients. To ensure that the radiologist gets images of the entire skeleton, patients must reposition themselves frequently. "You have to lie on your side and then stand up — there's a huge amount of moving around," says Ciaran Healy, a radiologist at Mater Misericordiae University Hospital in Dublin, Ireland. For patients who are frail or already in pain, the process can be agonizing. And X-rays tend to miss small lesions.

A variety of newer, more sensitive imaging technologies are now used to examine patients with multiple myeloma, but researchers are still figuring out how best to use them. Healy's team has replaced the skeletal survey with low-dose computed tomography (CT), which combines several X-ray images to create a three-dimensional picture. One benefit is that CT scans are

quicker and detect more and smaller lesions than standard X-rays; another is that the patient can lie down throughout the scan.

Many medical centres, including Mater Misericordiae, also use magnetic resonance imaging (MRI) to spot multiple myeloma. X-rays and low-dose CT scans can find lesions in the bone, but MRI is better at detecting cancer in the soft marrow inside the bones. "It can identify not only very small lesions, but lesions which spread around the spinal cord," says Homer Macapinlac, chair of the nuclear-medicine department at the M. D. Anderson Cancer Center in Houston, Texas. Spotting these lesions is particularly important because they can press against the spinal cord and cause paralysis.

Studying MRI images can also help doctors decide where to biopsy. In some patients, cancer cells are concentrated in clusters, or hotspots, in the bone marrow. If the biopsy misses those lesions, "you might miss a diagnosis", says Ronald Walker, a radiologist and nuclear-medicine physician at the Vanderbilt-Ingram Cancer Center in Nashville, Tennessee. Also, because MRI relies on radio waves and strong magnets, radiation exposure is not a concern. However, MRI is more expensive and time consuming than CT scans. And because the conventional MRI is "optimized for the marrow", Walker says, scans may not detect cancer that has spread outside the bones into the surrounding soft tissue.

SEEING A RESPONSE

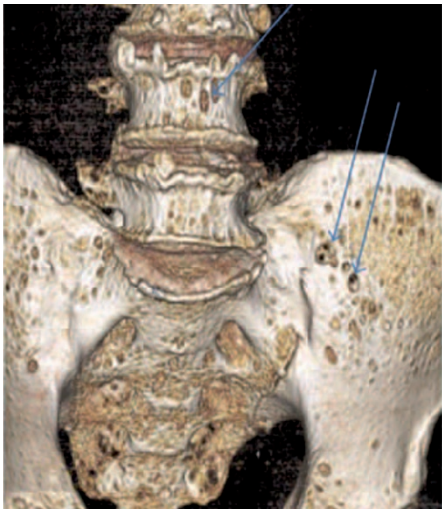
Imaging techniques have long been used to help diagnose patients and determine the stage of disease. They can now be used to investigate the response to treatment. New cancer is immediately evident in MRI scans, so it can catch a relapse, but the changes associated with a therapeutic response can take years to show up.

In the 1990s, oncologists working with multiple myeloma patients began combining CT with positron emission tomography (PET), which lets them visualize biological processes in the body. The radiologist injects a radioactive tracer and a scanner detects the gamma radiation it emits. The most widely used tracer, fluorodeoxyglucose (FDG), allows researchers to track the uptake of glucose. Cancer cells grow and divide faster than normal cells, so they usually use more glucose. Areas of high glucose uptake show up as bright spots on the PET image. Combining PET and CT locates these bright spots in the body. It was a PET–CT scan that alerted Raje to Ben's relapse.

Although whole-body MRI is better than PET–CT at picking up active cancer[1], PET–CT is more effective at determining whether a patient is responding to therapy. If treatment works, the cells stop proliferating, use less glucose and become dimmer on the image. The largest and most comprehensive study of the use of imaging to detect treatment response in multiple myeloma found that the number and intensity of active cancer spots on a PET–CT scan was predictive of how patients respond to therapy[2]. "The higher the number of hotspots and the greater their intensity, the poorer the outcome," says Bart Barlogie, director of the Myeloma Institute for Research and Therapy at the University of Arkansas for Medical Sciences in Little Rock. Barlogie now relies on PET–CT scans to individualize treatment. "We do the scanning sometimes on a weekly basis," he says. "And if the lights don't dim in a week, we know the drug is not active and we change course."

TRACING THE FUTURE

Researchers are working to develop imaging techniques that will make it easier to detect and treat myeloma. One approach used with MRI involves introducing a chelated form of gadolinium, which acts as a contrast agent to help researchers quantify blood flow in the bone marrow. Jens Hillengass, a haematologist at the University of Heidelberg in Germany, has been investigating this technique — called dynamic contrast-enhanced MRI (DCE-MRI) — for more than a decade.



A reconstruction of the lumbar spine and pelvis reveals 'punched out' lesions caused by myeloma.

First, a pump intravenously injects the agent, which travels through the blood vessels. Multiple scans allow physicians to track the agent and quantify blood flow and vessel density in the bone marrow. The technique also helps doctors measure the leakiness of blood vessels, which is usually higher in areas of malignancy. This measurement could enable DCE-MRI to spot signs of progression in patients with 'smouldering myeloma' — an early form of the disease — sooner than other imaging techniques. "We are hoping that this would help to define patients at risk of going on to symptomatic myeloma," Hillengass says.

Hillengass's group is also investigating another version of MRI, called diffusion-weighted imaging (DWI), which measures the diffusion of water molecules through tissue. In regions of the body with a low density of cells, water can travel farther than in areas where cells are packed tightly together, such as malignant areas of the bone marrow. Hillengass suspects that DWI could help doctors track the progression of early stage myeloma.

Another promising direction involves new tracers to identify lesions in PET imaging. "A lot of the lesions in myeloma do not have increased glucose uptake," says Ola Landgren, head of the multiple myeloma section at the National Cancer Institute in Bethesda, Maryland. A tracer known as 18F-FLT measures the rate of DNA synthesis, rather than glucose uptake. Because cancer cells cycle more rapidly than normal cells, they synthesize more DNA. However, the rate of DNA synthesis is also high in normal bone-marrow cells, minimizing the difference between cancer cells and normal bone-marrow cells. "It's like trying to identify chocolate chips in a chocolate cupcake," Macapinlac says. "They kind of all blend in." But 18F-FLT can detect a patient's response sooner than FDG. "You don't have to wait for several cycles of therapy," he says.

Scientists are also investigating a PET tracer that is preferentially taken up by bone-forming cells. This tracer, 18F-sodium fluoride (NaF), was approved in the 1970s but was not widely adopted because for many years PET scanners were expensive and scarce. Now they are widely available, researchers are investigating how the NaF tracer can help myeloma patients. There is evidence from a South Korean PET study that NaF is better than FDG at spotting bone lesions. Doctors used to think that "once you have a hole in the bone, it's not ever going to heal", says Raje. But new therapies that promote bone formation are challenging that wisdom. And tracers such as NaF might enable physicians to observe this healing process in real time.

A machine that combines PET imaging with MRI could offer the most complete picture of multiple myeloma. The US Food and Drug Administration approved the first such system, manufactured by Siemens Medical Solutions of Malvern, Pennsylania, in June 2011. It could provide all the benefits of PET–CT without exposure to radiation. This is especially useful for younger patients, who have a greater risk of developing CT-related cancers, Macapinlac says. Researchers are working to optimize the algorithms needed to reconstruct the PET images and to make it quicker to do scans, he adds.

New imaging techniques could improve the care for myeloma patients and lead to a greater understanding of cancer biology. "One of the problems whenever people do bench work is they remove a tumour from the milieu of the human host," says Walker. Cancer cells can act differently outside the body. Imaging that allows researchers to track tumours in their natural habitat could lead to insights and drive the development of new treatments — and help patients like Ben stay cancer free. ■

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2. Bartel, T. B. *et al. Blood* **114,** 2068–2076 (2009).