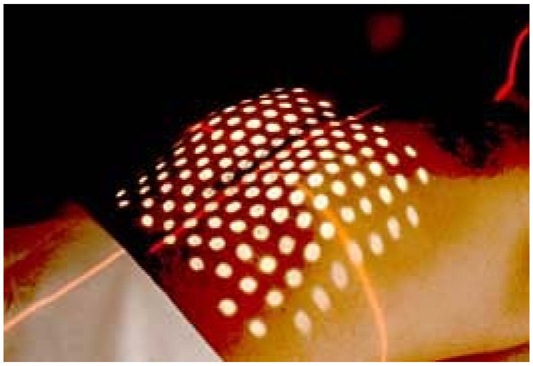
Going for the GRID:

Last-Chance Radiation Therapy Gives Patients New Hope



The spongy mass of aberrant cells kept growing unchecked, and now covered the entire right side of Matthew's face. The cancer was making a pincer movement around Matthew's right eye and, deeper, was gnawing away—centimeter by centimeter—his mandible, jaw and cheekbone.

Matthew had been told by his most recent doctors that they'd done all they could—traditional radiation therapy was essentially powerless against such a colossal tumor. He fully understood the unstated consequence of this pronouncement. The tumor would win.

But then in the summer of 1998, he was referred to Dr. Mohammed Mohiuddin, who chairs the Department of Radiation Medicine in the University of Kentucky College of Medicine. Mohiuddin at that time was building a reputation for being able to successfully treat large advanced tumors by using spatially fractionated radiation therapy (commonly referred to as GRID therapy), a technique he developed 13 years ago. The UK Chandler Medical Center is the only institution in the United States where patients can receive this treatment.

"The concept of GRID therapy has been around for a long time," says Mohiuddin, who is originally from Hyderabad, India. "During my residency at Royal Marsden Hospital in London in the early '70s, we would routinely use GRID therapy for very large tumors at the end of a traditional treatment, and I saw some very, very impressive responses."

GRID therapy was used widely in the 1950s as a way to reach tumors deep in the body. The ability of the human body to tolerate radiation is dependent on the size of the area that is exposed to radiation. The larger the area of tissue, the smaller the dose that can be given because radiation damage is just like any other tissue injury: the larger the wound, the more difficult the healing process. But if the radiation is limited to very small areas, much higher radiation doses can be safely used.

Mohiuddin has been "updating" GRID treatment by using it in combination with high-energy X-rays. The grid used by UK radiation technicians is a block of lead alloy about seven centimeters thick through which 250 holes have been drilled. The one-centimeter holes are equidistantly spaced so that the radiation can get through the lead as separate beams. In this way, six to 18 million X-ray volts can be directed at a large tumor on or below the skin. "Instead of using one beam of radiation, we use many smaller beams," Mohiuddin says.


"Breaking radiation up spatially is outside of the mainstream experience here. The medical establishment doesn't embrace whatever they conceive of as 'radical ideas' very easily."—Mohiuddin

Such an approach became feasible in the '70s, he explains, when new technology could generate high-energy X-rays. In the 1940s and '50s, X-rays could be given safely only in the kilowatt range—100 to 400 kilovolts—with the result that most of the radiation was absorbed by the skin; it couldn't reach deep-seated tumors. "The GRID technique was used to give very high doses to the skin where much of the radiation was absorbed but some of it could get through, and a reasonable dose could reach the deeper tissues," Mohiuddin says. When machines in the '70s could generate energies of a million volts and this concentrated energy could easily reach deep into the body, the skin was no longer a barrier. "So GRID-like therapy went out of favor," Mohiuddin says. "No one thought it was valuable any longer.

For the past quarter of a century, small tumors have been treated successfully by high-energy radiation—training two or more tightly focused beams from different entry points on a tumor. Still, the problem of how to treat large tumors, especially those lodged deep in the body, remained.

"I was trying to figure out a way to get more radiation doses into bigger tumors," Mohiuddin says. "In a traditional treatment, radiation is delivered in increments of two Gray (a Gray is a standard unit of radiation), every day, five days a week for an extended period of time, usually five to seven weeks. This technique is called dose/time fractionation—the radiation dose is broken up into small daily doses spread out over time." In contrast, GRID radiation is called spatially fractionated radiation therapy because the radiation is broken up in space—250 points of entry—rather than time. GRID therapy attacks the tumor with non-confluent, pencil-sized beams, separated from each other.

"Each small area gets a very high dose and the areas in between get little or no radiation," Mohiuddin explains. "Using this approach we can give anywhere from 15 to 20 Gray of radiation in a single treatment so the patient gets seven to 10 times the normal daily dose." He adds that because each radiation area is relatively small, the patient can tolerate these high doses without problematical side effects.

The areas untouched by radiation were originally a matter of concern, Mohiuddin says, because surely some of them, if not most, sheltered cancer cells. "We were concerned about this, but at the same time we were seeing that this procedure was working, and in most cases working very well. When we discovered what was happening in these non-radiated areas, it was a very happy surprise."

What he and his colleagues, Mansoor Ahmed and Ali Meigooni in radiation medicine, found was that when the cells received high doses of radiation, the dying cells activated cell death genes that produced reactive protein byproducts and other substances called cytokines. One of these, well known to scientists, is called the Tumor Necrosis Factor, which in high enough concentrations can kill cancer cells by itself. "This phenomenon is getting quite a lot of attention now in experimental biology," Mohiuddin says. "It's called the 'bystander effect'— high-dose radiation causes the cancer cells to manufacture substances to kill those cells untouched by radiation."

In a study headed up by Mohiuddin and published a year ago in the International Journal of Radiation Oncology, 92 percent of the 70 patients treated with GRID therapy responded well to the procedure. In many cases the treatment eased pain or helped shrink the tumor so that surgery could then be performed, Mohiuddin says. "We're up to 300 patients now," he says, "and we've seen some incredible responses. We're hoping this approach will translate into saving the lives of some patients who come in with horrendous cancers."

Mohiuddin recalls one patient, Beth Adkins, who was referred to UK's Gynecologic Oncology Program. Adkins, 18, from Hamlin, West Virginia, was diagnosed with a rare form of ovarian cancer in May of 1998. "As the tumor grew," Mohiuddin says, "it finally filled her entire abdomen. She couldn't eat or drink. The cancer caused her to lose around 30 pounds and it continued to grow." Traditional radiation treatments—surgery and chemotherapy—hadn't helped.

After four treatments using GRID therapy radiation, Beth no longer had trouble eating. In an article that appeared in the Lexington Herald-Leader in October of 1999, she was quoted as saying, "It was a lot better than chemotherapy; it's not making me sick. I feel totally normal, and I've been eating like a pig."

"Although Beth died six months later from the metastasis of cancer, she had six quality months of life she wouldn't have had otherwise," Mohiuddin says.

Another patient referred to UK had a tumor the size of a small inner tube around her neck. Traditional radiation techniques had proved nearly useless.

"This woman was at the point where she could barely breathe because of the cancer," says Mohiuddin. "Her doctors had given up on her. She thought she was going to die."

But then she agreed to try GRID therapy, and the tumor began to shrink. By the end of the second week after GRID radiation her tumor was less than half of its original size. She received additional conventional radiation over the next four weeks, and by the end of her treatments the tumor in her neck had totally disappeared. She remained well for almost a year but then died because the cancer has spread to other organs.

There are some limitations on the use of this therapy. GRID hasn't been used over the spinal cord, the eyes or the brain because Mohiuddin and his group are unsure of the tolerance level of tissue in these areas. Since they have no data on how easily these organs repair radiation damage, these areas are, for now, off limits.

Mohiuddin stresses that this treatment was designed to treat the incurable patient, to help patients that can't be helped any other way. "We're taking patients at the end stage of their disease. We're not looking for 'the cure,' so to speak, though as we treat more patients with this method, expectation levels are getting higher and higher," he says. Mohiuddin adds that because of the successes, in the years to come the UK group is excited about looking at long-term survival of patients in earlier stages of disease. Optimism has to be tempered somewhat, he admits, by the fact that in so many patients with large, advanced tumors, the cancer may have already spread to other organs.

Asked why UK is the only institution in the United States offering GRID therapy, Mohiuddin says that by the time high-energy radiation was possible in the 1970s, very few people knew about the historical background of GRID therapy. "Breaking radiation up spatially is outside of the mainstream experience here. The medical establishment doesn't embrace whatever they conceive of as 'radical ideas' very easily."

Mohiuddin, however, believes that this type of treatment will become common in many medical institutions in the next decade or so. In London, England, doctors are now beginning to treat patients with GRID therapy, and in the United States there are nearly a dozen centers anxious to get started with GRID. "Once people see the results, they're going to realize how helpful this can be to patients," he says.

"It's really dramatic to see this method reduce and kill bulky tumors," says William Regine, vice chairman of the Department of Radiation Medicine. "Dr. Mohiuddin is looked at nationally and internationally as a leader in using radiation to treat cancer."

Alfred Cohen, the new director and CEO of UK's Markey Cancer Center, agrees. "Dr. Mohiuddin has been a pioneer in three strategies to increase the effectiveness in radiation treatment of large malignant tumors. First, he demonstrated that in patients with large rectal cancers, radiation given prior to an operation could dramatically shrink the tumors, maximize local eradication, and allow sophisticated surgical resection that avoided the need for a permanent colostomy bag in most patients.

"He has also studied the integration of chemotherapy with radiation in rectal cancer. And in this current, highly innovative program using spatially fractionated radiation, Dr. Mohiuddin has provided yet another strategy to effectively treat large tumors," says Cohen, who was formerly the director of the gastrointestinal cancer management team at Memorial Sloan-Kettering Cancer Center in New York City.

Jeff Worley

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