



## **The Clinical Case for Individualized Use of Proton Beam Therapy**

According to physicians and researchers who use proton beam therapy, the technology is a long-needed, excellent alternative to use of conventional x-ray (photon) radiation for selected patients. In tumors that are too close to critical organs, the benefit of precisely targeting protons only on the target tumor produces fewer side effects than x-ray's broader and deeper shaft of radiation. While x-rays travel through the body in a straight line without stopping, protons are targeted to the precise location of the tumor and do not exit out the other side. In that way, proton beam therapy substantially limits collateral damage to organs and tissue, and offers the possibility of using higher doses of radiation for more beneficial outcomes.

"Having the ability to use proton beam therapy will allow Mayo Clinic to match each cancer patient to the radiation treatment that best fits that individual. We now offer our patients all forms of radiation therapy — one of the few cancer centers worldwide that can do so," said Sameer R. Keole, M.D., a radiation oncologist at Mayo Clinic in Arizona.

The caveat to use of proton therapy, of course, is cost, points out Dr. Keole, who is anticipating the spring 2016 opening of what will be Mayo's second proton beam facility.

Because building the proton machines, encased in concrete vaults, and setting up the space age instrumentation is costly, proton beam therapy is generally more expensive than even the most advanced form of x-ray treatment, intensity modulated radiation therapy (IMRT).

Between the proton beam facility that opens on the Mayo Clinic campus in Rochester, Minnesota, in June, 2015, and the Arizona campus facility opening soon, Mayo Clinic invested \$368 million.

Because these funds came from the capital budget for Mayo Clinic, which is non-profit, and millions of dollars from generous donors — no taxpayer dollars and no venture capital were used — and because proton beam treatment will clearly be advantageous to a subset of cancer patients, Mayo Clinic's standard fee for proton therapy delivery will be the same as for delivery of IMRT, says Robert L. Foote, M.D., the chair of Radiation Oncology at Mayo in Minnesota, and the director of Mayo's Proton Beam Therapy Program.

"We want, as much as is possible, to be able to offer proton beam therapy to those patients who would benefit from it, without cost being the prohibitive factor," he says.

### ***Use of proton beam therapy should be selective***

With its three campuses in Minnesota, Arizona, and Florida, Mayo Clinic treats more than 122,000 patients for cancer each year. (Mayo Clinic is the only National Cancer Institute (NCI) designated cancer center in the country with a multi-site presence.)

But the fact is that not all cancer patients need radiation treatment, and fewer still would benefit best from proton therapy. Many cancer patients needing radiotherapy have cancers

that respond well to other forms of radiation such as Intensity Modulated Radiation Therapy (IMRT) and brachytherapy.

When fully operational in 2021, Mayo Clinic's proton beam therapy program is expected to serve 2,400 cancer patients annually.

While Mayo can only offer proton therapy to a small subset of its patients, most cancer patients in the country will have much less access to proton beam therapy. There are relatively few proton beam facilities in the U.S., and many of these are for-profit facilities.

So researchers at Mayo and other academic medical centers around the world that can offer proton beam therapy are actively researching the best use of the treatment — which patients benefit the most.

“Proton beam therapy offers no benefit in blood cancers or in cancers that have metastasized. But research has shown us that younger patients likely benefit more from the treatment, compared to older patients, because proton beam therapy reduces the occurrence of second cancers caused by radiation. It takes years for those cancers to develop, so younger patients should be protected,” says Dr. Foote.

And patients who have cancers near the eyes, in the brain or central nervous system can also be good candidates for proton beam therapy, he says. “But in other cancers, individualized patient factors make the difference in which radiotherapy we would choose.”

“For example, if a patient's heart is going to be exposed to radiation, we need to know if their heart is healthy or diseased? Do patients have coronary artery disease; have they been smokers; do they have hypertension, diabetes mellitus or a family history of heart disease? A woman with breast cancer and heart disease would fare better with proton beam therapy, because her ailing heart would not be affected by radiation, which it might be with x-rays,” says Dr. Foote. “Evidence suggests that there is no safe dose of radiation therapy to the heart.”

To explain how proton beam therapy spares prostate cancer patients excess radiation, compared to use of x-ray, Dr. Keole uses the example of a common dental x-ray. “The reduction in exposure to the bladder and rectum using proton beam therapy is equivalent to 450,000 dental x-rays.”

While children, young adults and healthy older patients with solid tumors located next to sensitive critical organs will likely be given the highest priority in Mayo's proton beam therapy program, other patients will also benefit, says Dr. Foote.

“Use of proton therapy is going to be a very individualized, highly selective process that weighs many factors,” Dr. Foote says. “Unfortunately, it cannot be offered to all patients. There are not enough facilities. And even if there were, use of them for the majority of cancer patients — with more than 1.7 million new cancer diagnoses annually — would be very costly to society.”

### ***“The evidence matters ....”***

Mayo Clinic spent six years, from 2004-2010, researching use of proton beam therapy. “We performed an in depth study of the 20-year modern history, from 1990-2010, of proton beam therapy, including review of hundreds of manuscripts reporting the results of thousands of patients treated with proton beam therapy worldwide,” Dr. Foote says.

“The evidence matters. We need to identify patients in which proton beam therapy results in real clinical benefit and a higher cure rate,” he says.

To contribute to that knowledge base, once the proton beam facilities are up and running, clinical outcomes for all Mayo patients will be entered into one central database to improve care models and services for cancer patients. And researchers at the Mayo Clinic Proton Beam Therapy Program will conduct joint prospective clinical studies as a unified program across all Mayo locations.

Mayo Clinic Cancer Center has also joined with other academic medical centers, including Massachusetts General Hospital, the University of Pennsylvania, the University of Florida and the University of Texas M D Anderson Cancer Center, to develop and conduct phase III clinical trials comparing proton therapy to x-ray treatment.

### ***Testing the effectiveness of proton therapy***

Many clinical trials have already offered valuable information on the benefit of proton beam therapy in certain cancer types. Among them are:

#### ***Liver cancer:***

Liver cancers are difficult to treat with radiation therapy since the liver cannot tolerate a high dose of radiation therapy and other sensitive organs are close by including the bowel, kidney, and spinal cord. And many patients with liver cancer have sick livers, says Dr. Foote. Proton beam therapy can treat the liver cancer while sparing the rest of the liver and other organs resulting in prolonged survival and a lower rate of complications, he says.

- A systematic review and meta-analysis of 70 observational studies (5,204 patients) found that survival rates were significantly higher in liver cancer patients treated with proton beam therapy, compared to patients who received x-ray treatment. Toxicity was also lower in proton beam patients. (*Radiotherapy & Oncology*, published online December 9, 2014)

#### ***Lung cancer:***

Lung cancer remains the most common cause of death from cancer in the U.S. About 75 percent of patients are diagnosed when their lung cancer is too advanced to be surgically removed. The challenge with inoperable non-small cell lung cancer is administering a high enough dose of chemotherapy and radiation therapy to cure the patient without causing severe damage to the heart, lung, and esophagus.

- Researchers at MD Anderson Cancer Center have shown that physicians can increase the dose with protons, resulting in longer survival and a lower risk of lung and esophagus complications.
- In one study, 44 patients with stage III lung cancer that could not be surgically removed were treated with a higher dose of protons along with weekly chemotherapy. No patient experienced serious side effects and the median survival time of 29.4 months was longer than normally expected. (*Cancer*, October 15, 2011)

“We know that proton beam therapy can decrease the risk of significant complications in treatment of lung cancer by as much as 80 percent,” says Dr. Keole.

#### ***Head and neck cancers:***

“The challenge with nasal cavity and paranasal sinus cancers — tumors that arise from the nose or the sinuses — is that we are limited in the amount of radiation therapy that we can safely give because the eyes, optic nerves, brain, brain stem, and spinal cord are so close to the tumor,” says Dr. Foote. “This results in a high recurrence rate. With protons, a higher dose can produce longer survival and fewer recurrences without causing more harm.”

- Dr. Foote participated with a team of Mayo Clinic researchers who conducted a systematic review of nasal cavity and paranasal sinus cavity cancer. In their evaluation of 41 observational studies, they compared the outcomes from 286 patients treated with proton beam therapy and 1,186 patients given IMRT treatment. The researchers found that patients treated with protons had significantly longer disease free survival five years after treatment — 72 percent versus 50 percent — and fewer cancer recurrences — 81 percent of the proton treated group were cancer free versus 64 percent of patients treated with IMRT. (*Lancet Oncology*, published online June 27, 2014). “Many researchers feel this systematic review offers strong evidence for the use of proton beam therapy in these cancers,” Dr. Foote says.

#### ***Prostate cancer:***

Thousands of patients with localized prostate cancer have been treated with proton beam therapy as this is an excellent treatment option for these tumors, says Dr. Keole. However, the treatment may be overused, he adds. “The critics could argue that low-risk patients probably didn’t need any treatment at all, and I think that is a fair argument. But to have a 99 percent five-year survival and a 1 percent or lower severe complication rate for the intermediate risk patients is phenomenal,” Dr. Keole says.

These findings come from a study, published in 2014, conducted by the University of Florida.

- Researchers analyzed 211 patients and found that five years after having proton beam radiotherapy for early- and intermediate-risk prostate cancer, 99 percent of men were living cancer-free and with excellent quality of life. The five-year freedom from biochemical and clinical progression rates were 99 percent, 99 percent, and 76 percent for low-risk, intermediate-risk, and high-risk patients, respectively. There was also low severe complication rate using proton beam therapy — .5 to 1 percent. (*Radiation Oncology Biology Physics*, 2014).

“This study proves that proton beam therapy is safe and effective for prostate cancer with outcomes that are better than what has been published for IMRT,” says Dr. Keole.

“Current studies are evaluating the safety and efficacy of reducing the number of treatments from 40-44 to 26-28 or less to make it more convenient and less costly.”

#### ***Cancer of the esophagus:***

The use of chemotherapy combined with radiotherapy for esophageal cancer is linked to high rates of acute and chronic toxicity, including radiation exposure to the heart and lungs in the case of thoracic tumors.

- An MD Anderson Cancer Center study showed that in 444 patients with esophageal cancer, proton beam therapy, compared to x-ray therapy, was associated with a significant reduction in major lung complications and reduced hospital length of stay. (*International Journal of Radiation Oncology Biology Physics*, 2013)
- These results have been confirmed in a pooled analysis of 582 patients with esophageal cancer treated at M D Anderson Cancer Center, Mayo Clinic, or the University of Maryland between 2007 and 2013 (data presented at the May, 2015 annual meeting of the Particle Therapy Co-Operative Group).

#### ***Breast Cancer:***

Adjuvant radiotherapy improves survival in breast cancer patients, suggesting that the treatment reduces the risk of developing recurrence and metastases. But targeting regional lymph nodes results in lung and heart doses associated with increased cardiac toxicity, cardiac death, lung cancer, and lung cancer death.

- Proton therapy improves targeted radiation of affected regional lymph nodes while significantly reducing radiation doses to the lung and heart. (*Journal of Clinical Oncology*, 2013)
- Best evidence suggests proton beam therapy in breast cancer patients is associated with a clinically significant (more than 10 percent) reduction in the rate of major coronary events compared with x-ray irradiation in patients. (*New England Journal of Medicine*, 2013)
- A prospective phase II clinical study of 100 breast cancer patients found that proton beam therapy for partial breast irradiation produced excellent recurrence-free survival with minimal toxicity. The treatment proved to be adaptable to all breast sizes and lumpectomy configurations. Cosmetic results were also excellent and unchanged five years following treatment. (*International Journal of Radiation Oncology Biology Physics*, 2014)

### ***Pediatric cancers:***

The kind of finely targeted radiation that proton therapy offers is especially beneficial for children, who are most likely to suffer the greatest long-term harmful effects from conventional radiotherapy, says Dr. Keole, a specialist in treatment of these cancers.

“Pediatric cancers are considered by many as the ideal indication for proton beam therapy,” he says. “This is because developing tissues — brain, bones, and muscles — are exquisitely sensitive to the effects of radiation therapy, as compared to adults.”

Protons have been used in nearly every solid tumor radiation therapy indication in the body, including, but not limited to, brain tumors and sarcomas. For pediatric patients requiring radiation therapy for a brain tumor, there is strong evidence that proton beam therapy can mitigate the risk of neurological effects, says Dr. Keole. With sarcomas, depending upon the treatment site, side effects can be lowered without any compromise in the cure rates, he adds.

“And because proton beam therapy can spare healthy tissue from radiation exposure, as compared to the best x-ray techniques, it is widely believed that this will yield to a lower risk of radiation-induced cancers,” he says. “Some estimates are that proton beam radiation can decrease the risk of a radiation-induced cancer by as much as 10-fold.”

- For example, a 2014 study found that childhood gliomas in 32 patients treated with proton therapy found good clinical outcome after a follow up of more than seven years. (*International Journal of Radiation Oncology Biology Physics*, August 1, 2014)
- Another study also looked at second malignancies in 86 children diagnosed with retinoblastoma either treated with x-ray or proton beam radiotherapy. Radiation is curative in this disorder, but its use is often avoided due to fear of inducing new cancers. The study, led by investigators at Massachusetts General Hospital, found only one of 55 proton beam radiotherapy patients developed a second malignancy, compared to four of patients treated with x-ray radiation. [*Cancer*, 2014]

“There is little controversy about use of proton therapy with children,” says Dr. Foote. “Almost everyone agrees that proton therapy is the better choice.”

### **Second Cancers:**

Second cancers caused by radiation used to treat and cure a primary cancer have long been a concern. But radiation risk models have pointed to proton beam therapy as a treatment that will likely cause very few new malignancies, due to the smaller area of normal tissue and organs exposed to a lower dose of proton beam radiotherapy, compared to other radiation techniques.

- Clinical reports are now substantiating the risk model predictions. One study that compared the incidence of second cancers in 558 patients treated with proton beam radiotherapy compared to 558 patients treated with x-ray therapy, including IMRT. Researchers led by investigators at Boston University and Harvard Medical School found proton beam radiotherapy was not associated with an increased risk of second malignancy. In fact, the risk was reduced by 50%. (*Radiation Oncology*, 2013).
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“There are real benefits to proton beam therapy,” says Dr. Foote. “With it we can improve the cure rate of some cancers; people are living longer and with fewer side effects and complications,” he says. “And because we are able to do it at a lower cost at Mayo, it is a win-win for everybody.”

“We believe in this technology,” says Dr. Keole. “We really feel it is important that we are able to offer all the benefits of proton beam therapy to our patients.”