

## Fewer Side Effects From Proton Therapy in NSCLC

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LONDON – Proton beam therapy for non–small cell lung cancer is associated with fewer radiation-induced side effects than are conventional radiotherapy methods when combined with chemotherapy, according to preliminary data from two retrospective studies conducted at the University of Texas M.D. Anderson Cancer Center in Houston.

Significantly less esophagitis, pneumonitis, and bone marrow toxicity were observed with proton beam therapy (PBT) than with intensity-modulated radiotherapy (IMRT), Dr. Ritsuko Komaki reported May 10, at the European Society for Therapeutic Radiation Oncology (ESTRO) Anniversary Conference.



Photo credit: M.D. Anderson Cancer Center

**The Proton Therapy Center at M.D. Anderson Cancer Center in Houston is one of the few particle-beam radiation facilities at U.S. hospitals. It houses the technology for generating the beam, three patient-care areas for delivering the beam to the patient, clinical areas, and diagnostic areas.**

Proton beam therapy also significantly reduced the incidence of esophagitis when compared with IMRT and three-dimensional conformal radiotherapy (3D-CRT). A mean esophageal dose of 40 Gy or higher was identified as the cut-off point for high-grade esophagitis occurring with any method.

"Radiation dose escalation improves local control but increases toxicity, especially when combined with concurrent chemotherapy for non–small cell lung cancer [NSCLC] or even small cell lung cancer," said Dr. Komaki, a professor of radiation oncology at M.D. Anderson, which opened its 94,000-square-foot [Proton Therapy Center](#) in 2006. As such, "radiation chemotherapy is a double-edged sword," she observed. "It will kill cancer cells, but it also kills normal tissues, and more targeted treatment is needed."

"One of the most important benefits of PBT is that there is no exit dose," Dr. Komaki added in an interview with Elsevier Global Medical News. "The protons stop after

penetrating the tumor, and there is no dose of radiation beyond it."

This has the potential to spare surrounding cells and organs from damage, she observed. Normal tissues that might be affected by radiation therapy for NSCLC include the lungs, esophagus, heart, and bone marrow, which cannot always be avoided by the use of 3D-CRT or even IMRT.

An expensive new technology that delivers highly targeted radiation with electrically charged particles, proton beam therapy is promising but unproven, according to a 2009 review commissioned by the [Agency for Healthcare Research and Quality](#) (AHRQ). The authors found few comparative studies to establish effectiveness or safety for the technology, which is housed in a small but growing number of proton beam centers that can cost \$100 million to \$225 million to build ([Ann. Intern. Med. 2009;151:556-65](#)).

Dr. Komaki and her associates are recruiting patients into the first, [prospective randomized trial](#) to directly compare proton beam therapy with IMRT in unresectable stage II /III NSCLC. The phase II trial is supported by a grant from the National Cancer Institute, and involves treatment with 74 Gy proton beam therapy or IMRT with concurrent carboplatin and paclitaxel. To date, 107 of the planned 168 patients have been enrolled in the study at the Texas institution and at the Massachusetts General Hospital in Boston, the other participating center, she said.

A recent report from the M.D. Anderson showed that higher doses of proton radiation could be delivered to lung tumors with a lower risk of esophagitis and pneumonitis than either IMRT or 3D-CRT (Cancer 2011;[doi.org/10.1002/cncr.25848](https://doi.org/10.1002/cncr.25848)).

The new data presented by Dr. Komaki showed significantly reduced rates of grade 2 or higher esophagitis ( $P$  less than .0001), pneumonitis ( $P$  less than .002), hematologic toxicities ( $P$  less than .0001 for neutrophil toxicity and  $P$  less than .001 for hemoglobin and white blood cell toxicities), and fatigue ( $P$  less than .0001) in 60 patients treated with proton beam therapy compared with 75 patients treated with IMRT (Radiother. Oncol. 2011;99:S89-90, abstract 233).

Other research from the M.D. Anderson team focused on esophagitis, and examined dosimetric and clinical factors that could lead to this side effect following proton beam therapy, IMRT, or 3D-CRT for definitive NSCLC treatment (Radiother. Oncol. 2011;99[Suppl.1]:S210, abstract 518).

Dr. Daniel Gomez, a radiation oncologist at M.D. Anderson, presented data on 678 patients treated at the institution between 1999 and 2008. Dr. Gomez explained that the type of radiation therapy received had altered over the years, with 463 patients treated with 3D-CRT between 1999 and 2005, 122 with IMRT between 2005 and 2007, and 94 patients treated with proton beam therapy between 2006 and 2008.

"Esophagitis is a common toxicity in the treatment of NSCLC with definitive radiation," Dr. Gomez observed. Although studies have looked at what factors might predict this life-limiting side effect, conflicting results have been obtained.

Data show, for example, that the presence of acute toxicity is a predictor of late toxicity ([Int. J. Radiat. Oncol. Biol. Phys. 2005,61:335-47](#)), but a variety of dosimetric parameters have been noted and there does not appear to be a single threshold at which a toxic effect is or is not likely to be observed ([Int. J.](#)

[Radiat. Oncol. Biol. Phys. 2010;76:S86-93](#)).

Data presented by Dr. Gomez, however, suggest that a mean delivered esophageal dose of above 40 Gy may be predictive of high-grade inflammation regardless of whether proton beams, IMRT or 3D-CRT is used. This research might eventually help develop dosing guides for clinicians to use in routine practice, he suggested.

"Patients receiving IMRT had a higher rate of esophagitis in all grades, including grade 3," Dr. Gomez said. In contrast, "patients receiving proton therapy had lower rates of esophagitis at all grades." The incidence of grade 3 or higher esophagitis was 14% (n = 65) for 3D-CRT, 27% (n = 33) for IMRT, and 6% (n = 6) for proton beam therapy.

Dr. Gomez also reported that grade 3 or higher esophagitis was more likely in patients who received concurrent chemotherapy than in those who did not (18.4% vs. 7.4%, *P* less than .001). The mean esophageal dose of radiation delivered to patients given concurrent chemotherapy also was, significantly higher (32.2 Gy vs. 15.8 Gy, *P* less than .001), however.

The M.D. Anderson investigators said they have just finished (May 12) recruiting patients into a phase III trial ([Radiation Therapy Oncology Group](#) [RTOG] 0617) that will compare conventional (60 Gy in 6 weeks) vs. high dose (74 Gy in 7.5 weeks) radiation therapy in combination with paclitaxel and carboplatin, with or without the addition of cetuximab (Erbix) in 500 patients with NSCLC.

Although the trial is not directly comparing the type of radiation treatment used, it should still be possible to retrospectively analyze the results to determine the individual effects of the radiation modalities used at each participating center, Dr. Komaki noted.

"When we started this trial, it was not acquiring patients because some of the radiation and medical oncologists said that it was obvious that patients given 60 Gy would do worse compared to 74 Gy," she added in the interview. "When we included cetuximab based on the results of the RTOG 0324 trial, however, recruitment started to rocket." The RTOG 0324 trial showed the feasibility of combining cetuximab with chemoradiation in NSCLC ([J. Clin. Oncol. 2011 May 9](#) [Epub ahead of print, doi: 10.1200/JCO.2010.31.7875]).

Discussing the downsides of proton beam therapy vs. IMRT, Dr. Komaki conceded that the newer method involved a lot more sophisticated planning and was more expensive. There is also concern that the sharp drop-off of radiation received with proton beam therapy might mean that important areas of the tumor are missed – although this may explain the lower rate of side effects seen with PBT to date. "There is no give," Dr. Komaki said.

As relatively few proton beam facilities are in operation, large cooperative trials are difficult to perform. The prospective phase II trial comparing proton beam therapy and IMRT now being conducted at M.D. Anderson and the Massachusetts General Hospital will be the proof that such trials are possible, and provide valuable information on the comparative safety and efficacy of the two procedures.

Dr. Komaki and Dr. Gomez said they had no financial conflicts of interest.

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