Japan Academy Prize to:

Hiroki Shirato
Professor, Graduate School of Medicine,
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Distinguished Professor, Hokkaido University

for "Biomedical and Engineering Research on Real-time Tumor Tracking Radiotherapy/Particle Beam Therapy against Cancer"

Outline of the work:

In cancer radiotherapy, it is critical to focus the radiation dose on the tumor while reducing the irradiation to the surrounding normal tissue. In the early 1990s, Dr. Hiroki Shirato demonstrated the biomedical appropriateness of the hypothesis in which precise small volume irradiation can deliver much higher doses than conventional radiotherapy through theoretical modeling for the radiation-induced damage in small animals and a retrospective analysis of human late skin necrosis.

Dr. Shirato developed stereotactic irradiation (STI) apparatus that improved the spatial accuracy of X-ray therapy to ±1.0 mm and demonstrated its safety and effectiveness for small intracranial tumors in the late 1990s, and in the early 2000s, he also conducted a multi-institutional randomized controlled study of treatment with STI with and without the entire brain irradiation for metastatic brain tumors. The results are still being used in international clinical guidelines as of the end of September 2021.

In the late 1990s, there was debate about the possibility of achieving the same accuracy for tumors in organs that move with respiration or bowel movements. Dr. Shirato overcame the problems by implanting a 2.0-mm fiducial gold marker near the tumor with the relationship between the tumor and fiducial marker recorded using computed tomography. In this method, a pattern recognition algorithm, which incorporates machine learning, is used to calculate the three-dimensional position of the marker 30 times per second, automatically, using two sets of fluoroscopes installed in the treatment room. Furthermore, therapeutic X-rays are gated and irradiate the tumor only when the gold marker is within 1.0–2.0 mm of the planned position. The technique was termed and become known as "real-time tumor tracking radiation therapy" (RTRT); it was developed in 1999 by a Japanese vendor, and it can reduce the unnecessarily irradiated volume of normal tissue to one third or one fourth for small tumors in organs that move with respiration or bowel movements. At the end of September 2021, 1,473 patients with cancers of the lungs, liver, prostate, or other organs with RTRT had been treated at Hokkaido University. Many new findings of tumor motion and excellent outcomes with reduced adverse reactions have been reported using RTRT. The RTRT system has been refined and improved several times, and currently (September 2021), it is used in 15 university hospitals and cancer centers in Japan. In the late 1990s, Dr. Shirato described general radiotherapy that improves temporal accuracy and spatial accuracy as four-dimensional radiotherapy (4DRT). Since then, the number of biomedical and engineering papers dealing with organ motion, real-time tracking, and 4DRT has increased rapidly worldwide.

In the late 2000s, spot-scanning proton therapy can produce better dose distributions than X-ray therapy for large static tumors, but the technology was not suitable for tumors in moving organs because of the difficulty of maintaining the localization accuracy. Dr. Shirato proposed combining real-time tumor tracking technology with spot-scanning proton therapy to treat larger tumors in moving organs. This fusion resulted in miniaturization and cost reductions in the equipment compared with conventional passive-scattering proton therapy systems. The proposal was refined by collaborators, developed with a Japanese vendor, and named real-time-image gated proton therapy (RGPT) in the FIRST project, which was supported by national grant-in-aid funds. In the 2010s, RGPT was safe and effective for a range of cancers, including large liver cancers and it is approved for reimbursement in the national health care system in Japan. The RGPT system has been installed in high-end university hospitals and cancer centers globally, including Johns Hopkins University Hospital, the National Singapore Cancer Centre, Navarra University Hospital Madrid, Kyoto Prefectural University Hospital, and the MD Anderson Cancer Center. Dr. Shirato proposed guidelines for the safe integration and operation of adaptive external-beam radiotherapy systems for real-time adaptive radiotherapy to the International Electrotechnical Commission (IEC), which were approved as Technical Report 62926 in 2019.

Developing and training young researchers in addition to providing the equipment to ensure the sustainable development of new science and technology is essential. Dr. Shirato helped establish the Graduate School of Biomedical Science and Engineering at Hokkaido University to develop young researchers in biomedical science and engineering who have backgrounds in science or engineering and who can conduct research and development of radiation-related medical equipment in the future. Since 2017, distinguished researchers from Stanford University and other institutions have supported and cooperated with Dr. Shirato's initiatives.

In the last 20 years, Dr. Shirato has published numerous scientific papers, with eight papers receiving top 1% citations and 68 papers receiving the top 10% citations in clinical medicine (Web of Science, as of September 14, 2022). Dr. Shirato has contributed to the development of new ideas for real-time tumor tracking radiotherapy/particle beam therapy against cancer, as well as collaborative research, translational research, proposals for international guidelines, and the development of young researchers in the biomedical and engineering field.

List of Main Publications

Monograph

Shirato, H, Onimaru, R., Fujino, M., Onishi, H.: Stereotactic Radiotherapy and Gated Therapy, pp. 435–446. In *Advances in Radiation Oncology in Lung Cancer* (Ed. Jeremic, B.) Springer-Verlag Berlin Heidelberg New York 2005.

Research Articles

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3. Shirato, H, Mizuta, M, and Miyasaka, K: A mathematical model of the volume effect which postulates cell migration from unirradiated tissues. ***Radiother. Oncol.*** 35; 227–231, 1995.
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11. Aoyama, H, Shirato, H, Tago, M, Nakagawa, K, Toyoda, T, Hatano, K, Kenjyo, M, Oya, N, Hirota, S, Shioura, H, Kunieda, E, Inomata, T, Hayakawa, K, Katoh, N, and Kobashi, G: Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. ***JAMA*** 295; 2483–2491, 2006.
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