History of Contemporary Medicine in Iran

Professor Abass Alavi, Distinguished Medical Scientist

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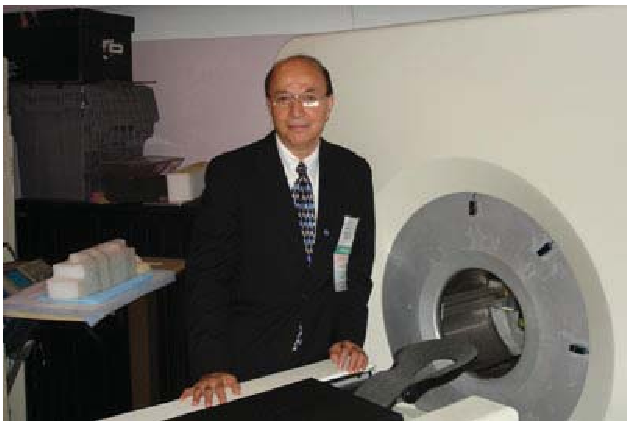

Professor Abass Alavi, Distinguished Medical Scientist

Dr. Abass Alavi was born on March 15, 1938 in Tabriz, a city in Eastern Azerbaijan, north west province of Iran. After graduating from high school in 1957, he moved to Tehran and enrolled at Tehran University of Medical Sciences. Following graduation from the medical school in 1964, and as part of the military obligation, he served in small communities in the outskirts of Tehran. In 1966, he traveled to the United States to further his medical education by pursuing advanced degrees in medicine. Abass Alavi holds the position of Professor of Radiology and Neurology at the Hospital of the University of Pennsylvania (HUP) Department of Radiology. In the US, he received training in internal medicine, hematology, diagnostic radiology, and nuclear medicine (molecular Imaging). As a nuclear medicine fellow at the University of Pennsylvania (PENN) in the early 1970s, Dr. Alavi worked on pioneering research in tomographic imaging of brain tumors and lymphoma. During this period, he collaborated with Drs. David Kuhl and Martin Reivich in the development of [^{18}F] fluorodeoxyglucose (FDG), which has come to be the most widely utilized PET radiotracer in both research and clinical settings. In 1976, Dr. Alavi became the first to administer FDG to human and in 1980, he and Dr. Jane Alavi were among the first to investigate the ability of this novel modality to grade primary brain tumors and predict clinical outcomes.

Starting in the 1990's, whole body imaging with PET became available as an experimental tool in several centers, and received external funding from the National Institute of Health (NIH) and other agencies. Dr. Alavi was among the early investigators to apply FDG-PET imaging to examine non-neurological malignancies. He was funded by the Department of Defense to conduct a large study comparing FDG PET to conventional imaging techniques in patients with breast cancer. These studies showed that PET was more sensitive in assessing the extent of disease in soft tissues and bony skeleton. Most research for patients with head and neck cancer, lung cancer, melanoma, sarcoma, and several other malignancies also showed PET to be superior in evaluating the primary tumor, staging and response to therapy. Dr. Alavi has studied pediatric brain tumors, showing that PET scan results are diagnostic of tumor grade and biology. He also evaluated neurofibromatosis and its malignant transformation in children and adults. He has determined the efficacy of ultrasonic ablation of metastatic liver lesions in colon cancer patients. In skin lymphoma (mycosis fungoides and Sezary syndrome) he was the first to introduce PET technology for correlation of metabolic activity with other markers.

Convincing results from the studies that were performed at PENN and other centers in the 90's, eventually led to a change in clinical practice of medical, surgical, and radiation oncology. As such, PET scans were employed alone or in combination with structural imaging techniques in assessing many malignancies. This trend convinced CMS (Medicare) to reimburse for PET imaging in cancer in 1999 (twenty-three years after Dr. Alavi performed the first human scan at PENN). In recent years the payment has been expanded to cover scan expenses related to almost all malignancies. The introduction of PET-CT in 2001 and PET-MRI in recent years has further enhanced the role of FDG-PET imaging in cancer management.

Of note is the work that Dr. Alavi carried out on PET-based response assessment of radiotherapy in patients with lung, head, and neck cancers. This paved the way for the routine use of PET scans in treatment planning by radiation oncologists in both malignancies. This innovative research by him and his radiotherapy colleagues resulted in securing funding by the American College of Radiology Imaging Network to conduct a multi-center trial of

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the role of PET in assessing response to radiation therapy in lung cancer. This study collected data from more than 250 patients and provided evidence for the efficacy of PET. This novel research approach is currently employed to assess response to proton therapy and global inflammatory complications following radiation treatment with great success.

Over the past forty-five years, Dr. Alavi has been a major contributor to neurosciences and clinical applications of PET in neuropsychiatric disorders. His research has included molecular imaging techniques with conventional radiopharmaceuticals and novel positron labeled preparations such as FDG. He has examined dementing illnesses, cerebrovascular disorders, head injuries, brain malignancies, and seizures. His work in Alzheimer's disease and other cognitive impairments has been heavily employed for assessing the rapidly aging population. Also, Dr. Alavi's research in head injury has become a main focus for assessing implications of car accidents and sports medicine, particularly those related to American football and boxing. He has contributed immensely to the better understanding of molecular and structural abnormalities that are associated with diverse maladies, and their underlying molecular bases. He was the first to demonstrate the effects of pain and acupuncture on brain structures and, therefore, provided evidence for the validity of this therapy. Dr. Alavi was also encouraged by the Dalai Lama to study the effects of meditation on brain function when he visited PENN to learn about ongoing functional imaging activities in Dr. Alavi's laboratory.

Dr. Alavi has also been instrumental in investigating novel technologies. These include animal studies on gene therapy with radiolabeled ganciclovir, hypoxia in tumors using agents EF1 and EF5 as well as tumor visualization with radiolabeled monoclonal antibodies. He was one of the early investigators in imaging radiolabeled antibodies in various cancers in collaboration with scientists at the Wistar Institute. His work was carried out in the early 1980s. In the 1990s, Dr. Alavi was among the first to image the antigens CD 20 and CD 22 in the lymph nodes of patients with lymphomas, demonstrating the poor prognosis that accompanied discrepancies in tumor burden on FDG-PET and antibody-based imaging. His work with antibodies led to the use of anti-CEA antibody imaging and treatment for patients with colon, breast, and lung cancers. Dr. Alavi has been interested in cell kinetics and was the first to examine dynamics of a variety of inflammatory and immune cells in humans and in experimental animals including Tall 104 Killer Cells as the basis for their efficacy in treating cancer and other diseases. This technology is now being employed for immunotherapy in human beings at PENN and elsewhere around the world. Furthermore, he introduced a methodology for imaging lymph nodes, phytate labeled with Tc-99m, which is now widely used for sentinel node imaging in breast cancer and melanoma. He was also the first to suggest and study the role of sentinel node imaging with Tc-labeled colloids, changing the way that breast cancer patients are staged. He was a pioneer in the assessment of lymphatics in cancer patients with lymphedema.

Thyroid cancer is another area of interest in which Dr. Alavi demonstrated the role of combined structural and molecular imaging techniques. Most notably, he was the first to introduce Iodine-123 as an agent for diagnostic imaging, which significantly reduced radiation exposure (by 100 – 200 times) compared to the previously favored Iodine-131, and produced images of higher quality. This approach has now been adopted worldwide.

In the field of endocrinology, Dr. Alavi was among the first to employ I-123 labeled MIBG to assess pheochromocytoma, which revolutionized the management of this malignancy. Moreover, he investigated the treatment of pediatric neuroblastoma patients with I-131 MIBG and the detection of neonatal hyperinsulinism secondary to pancreatic islet cell hyperplasia using 18-F FDOPA. The use of these technologies has eliminated the need for X-ray based interventions and substantially reduced the radiation exposure in these children. Furthermore, the test appears to be more sensitive and specific than the previous radiologic studies, with improving outcome.

Dr. Alavi was the first to point out that metastases to osseous structures are due to spread of cancer cells to red marrow rather than to the bone. This observation was based on the pattern of FDG uptake in the skeletal system, which is primarily in locations where red marrow resides. In other words, metastases most commonly affect the axial skeleton and are less common in the extremities. This concept further emphasizes the critical role of FDG PET imaging in the accurate staging of malignancies, and obviates the need to perform additional imaging with either radiologic or nuclear medicine techniques to detect cancer in the osseous structures.

His work has shown that the accuracy of FDG-PET imaging is far superior to alternative modalities. Dr. Alavi has conducted innovative and novel research in hematological disorders including bone marrow abnormalities such as bone marrow expansion in hemolytic anemia, the effects of aging on bone marrow distribution as well as bone marrow involvement in multiple myeloma and other cancers. The results of such investigative work are relevant to various hematologic malignancies and solid tumors.

Dr. Alavi has had an interest in the study of inflammation and infection in both benign and malignant disorders. He was among the first to use radiolabeled WBCs to detect infection in patients with cancer, orthopedic complications, and diabetic foot. Over the past twenty years, he has pioneered the use of FDG–PET imaging in the detection of infection and inflammation in both animal experiments and human studies. These in vivo imaging research applications of FDG followed extensive in vitro studies. This technology is revolutionizing the management of patients with infectious disease, orthopedic complications, auto-immune disease, and cancer. Dr. Alavi has published extensively on the application technique in prosthesis, osteomyelitis, and other infections. He has also conducted similar work in sarcoidosis, inflammatory bowel disease, osteoarthritis and rheumatoid arthritis.

His interest in inflammation has led him to investigate vascular inflammation, introducing a novel quantitative approach to the early detection of atherosclerosis in normal aging as well as its association with inflammatory disorders such as psoriasis, HIV-AIDS and rheumatoid arthritis. The methodologies that Dr. Alavi has introduced allow early detection of plaques in the major arteries and assess response to treatment. Furthermore, Dr. Alavi was the first to demonstrate the accurate measurement of calcification in the coronary arteries in the heart as well as major vessels as a global response to advancing inflammatory reactions. This research has resulted in a paradigm shift in the understanding of atherosclerosis. Particularly, with the rising incidences of obesity and diabetes, this research has enormous implications for managing the patients in the future.

In recent years, the presence and degree of inflammatory cells in cancer tissue have been implicated in the poor prognosis of various malignancies, and their presence has become important in the application of immunotherapy. Current imaging modalities are incapable of detecting inflammatory cells in cancer in vivo. However, animal studies carried out by Dr. Alavi suggest that radiolabeled nanoparticles may permit the detection of these cells in tumor tissues in vivo. Dr. Alavi has also been interested in the detection of thrombosis, and become the first to employ radiolabeled monoclonal antibodies to detect clots in patients with peripheral venous thrombosis. In recent years, Dr. Alavi has employed FDG-PET imaging to detect clots in the venous system without known predisposing factors or in patients with various malignancies including multiple myeloma. This may prove to be an important tool in detecting the serious complication in patients with cancer and preventing fatal pulmonary embolism in the population. Following this work, he served as a lead investigator in a national multicenter trial of pulmonary embolism assessment (PIOPED), funded by the NIH.

In the field of gastroenterology, Dr. Alavi discovered a method for detecting gastrointestinal bleeding using radiolabeled compounds, a test which has changed the management of patients and replaced invasive arteriographic techniques over the past several decades. This test is significantly more sensitive than arteriography and can be repeated as needed, preventing systemic consequences such as organ damage. He was a pioneer in developing gastric emptying procedures, which are now considered the standard.

Dr. Alavi has been very interested in methodologies related to quantification with novel molecular imaging techniques. He was the first to demonstrate that the time course of the uptake of radiotracers, particularly that of FDG, differs significantly between cancer lesions and inflammatory cells. This discovery has been extremely helpful in differentiating benign from malignant cells and improving the specificity of FDG-PET in cancer tissues. Dr. Alavi has utilized this finding in the assessment of tumor biology, demonstrating that high grade tumors take up FDG rapidly in an exponential pattern and retain it, compared to the slow uptake by low grade tumors. This appears to be of prognostic value. Dr. Alavi was also the first to demonstrate tumor heterogeneity at the primary and metastatic sites in the same patient.

Dr. Alavi's most significant contributions have been his description of the partial volume effect and global disease assessment. The partial volume effect is an imaging phenomenon that results in the under-estimation of disease activity, particularly in small lesions. This is a major source of error in the characterization and assessment of response to treatment using PET. Dr. Alavi has introduced methods for correcting for the error in order to arrive at a more accurate measure of tumor activity. Global disease assessment is a measure of total metabolic activity, which is calculated by multiplying the partial volume-corrected activity in each lesion by its volume and summing the products. This provides a single value per patient that can be compared at different stages of disease. The practitioners in the field of molecular imaging are now shifting to use this method to quantify overall disease burden and avoid confusing the referring physicians with multiple values as has been the standard practice in the past.

Over the past four decades, Dr. Alavi has closely collaborated with the Physics and Instrumentation group in the Division of Nuclear Medicine in developing novel instruments for both SPECT and PET imaging. In particular, the use of three-dimensional imaging by his team has made it possible to acquire images faster, and has resulted in the modification of the design of modern PET instruments. Dr. Alavi has also been involved in hybrid imaging that combines structural (such as CT) and molecular techniques (such as PET and SPECT) since these technologies were first devised and introduced in the 1970s and 1980s. He was also involved in designing and testing a specialized PET instrument for breast and brain imaging. Most of his research over the past four decades has been based on combined modalities.

Dr. Alavi has published extensively, amassing over 1000 papers, numerous book chapters, and more than fifty books and periodicals. He is the consulting editor of PET Clinics, which publishes state of the art applications of this powerful imaging technique, and also serves as an editorial member of several scientific journals. After four decades of work, he has become one of the most cited physician-scientists in the country as well as the most cited faculty member at the University of Pennsylvania. In addition to serving as an editorial board member and associate editor of many journals, he has edited several editions of the Seminars in Nuclear Medicine. He has given countless lectures throughout the world. His overall citations now exceed 42,000, more than 14,500 since 2010, giving him an H-index of 104.

For the past forty-five years, Dr. Alavi's extensive research in cancer and other disorders have been heavily funded by the NIH, Department of Energy, Department of Defense, and other funding agencies. Such funds have been utilized for both conducting human and animal research as well as building innovative PET machines, and purchasing state-of-the-art instruments to conduct forefront research at PENN. Furthermore, he has been invited to participate in multiple study sections at the NIH and other research organizations. He has been a member and chairman of these sections at the American Cancer Society as well as the NIH. He has been invited by the NCI to join its Subcommittee F, Institutional Training and Education study section. He also serves as a reviewer for PET-related grants for many European countries including Germany, France, Finland, Austria, and England.

Dr. Alavi has received the highest recognition by his peers. He was awarded an honorary Doctorate of Medicine and Surgery from the University of Bologna,[1] Italy as well as an honorary Doctorate of Science from the University of the Sciences, in Philadelphia.[2] In 2004, he was honored by the Society of Nuclear Medicine with the Charles de Hevesy Nuclear Pioneer Award,[3] for outstanding contributions to the field of nuclear medicine. In 2012, the Society awarded him the Benedict Cassen Prize,[4] given to a scientist whose work has led to major advances in nuclear medicine.

Overall, contributions made by Dr. Alavi and his collaborators at PENN have brought about a major revolution in medicine which have energized molecular imaging as a very powerful methodology for both research and clinical purposes. The impact of PET imaging goes far beyond what has been achieved in oncology, and covers almost every domain in medicine. This includes developing more effective treatment modalities and personalizing therapeutic interventions in each patient. In addition, PET is quite cost effective and its widespread use will substantially reduce healthcare costs in the future.

References

1. Honorary Doctoral Degree in Medicine and Surgery by University of Bologna, Italy, 2007.
2. Honorary Doctoral of Science Degree by the University of Sciences in Philadelphia, 2008.
3. George de Hevesey Award by Society of Nuclear Medicine, 2004.
4. Cassen Prize by Society of Nuclear medicine, 2012, this is considered as the Nobel Prize of the specialty.