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FDG PET/CT in Clinical Oncology

Case Based Approach
with Teaching Points

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Foreword

To my son, Aleks, whom I love and appreciate and who has enriched my life despite the time I spend away with patients, medical research and writing this book; and to my parents, Milos and Ljubica who have brought joy and love to my life.

Special appreciation and gratitude to my mentor and friend, Professor Dr. Ljubomir Stefanovic, who passed away while this volume was being assembled. Professor Ljubomir Stefanovic created me and supported me throughout my adult life, both professionally and during personal challenges.

And to Stanley Goldsmith who gave me the idea of writing this book in the first place.

Jasna Mihailovic

To my mother, Angela, and my late father, John: thank you for affording me every opportunity a person could want in life.

And to Stanley Goldsmith: thank you for inspiring me and mentoring me in all things molecular and otherwise.

Ronan Patrick Killeen

To my wife, Miriam, and our family who have sacrificed much so that I can continue to pursue my dreams.

Stanley J. Goldsmith

Collectively, the editors express appreciation and gratitude to their colleagues and patients who have taught us so much and continue to teach us daily in our practice of nuclear medicine.

Jasna Mihailovic, Ronan Patrick Killeen, and Stanley J. Goldsmith

Foreword

Stanley J. Goldsmith, M.D.
Jasna Milosavljevic, M.D., Ph.D.
Ronald Kline, M.D.

This volume presents a variety of nuclear oncology FDG PET/CT cases which can serve as an introductory text for radiologists and nuclear medicine physicians initially confronting the practice of PET/CT. It is likely that it will also serve medical oncologists who order these procedures and even medical students studying the diagnosis and management of patients with malignancies.

This volume evolved from an experience that the editors had working together in the PET/CT component of a clinical nuclear medicine department in a large academic medical center. Most of the cases included in this collection were accumulated during a 2-month period. Since the majority of clinical referrals are for various indications involving oncology patients, it was decided to limit this collection to that application of FDG PET/CT. The cases illustrate the diverse nature of the clinical issues that confront a nuclear medicine physician in daily practice. They are presented in a clinical context with the limited information provided by referring clinicians. While obviously less than ideal in some instances, the setting illustrates what nuclear medicine physicians have to deal with. To demonstrate another point, the cases are organized according to the variety of clinical indications within nuclear oncology for FDG PET/CT studies. First among these indications is "diagnosis" when the primary malignancy is unknown or when a tumor is identified incidentally in a study requested for another reason. This demonstrates that even though most cases are accompanied by a clinical diagnosis, the nuclear medicine physician has to be mindful of alternative diagnoses. Most often, however, FDG PET/CT is requested to determine the "extent of disease" which determines staging and often defines a course of therapy. The efficacy of FDG PET/CT for this application depends on the sensitivity of this technique which in turn depends on the technical quality of the study, the amount of FDG accumulated, the size and location of the lesion – although in this regard, PET/CT imaging is generally at an advantage compared to SPECT imaging as PET images are created by coincidence imaging and are corrected for attenuation and therefore are less influenced by distance from the detectors. Use of PET/CT for confirmation of the "response to treatment" depends also on sensitivity for detection but also requires knowledge of the natural history of the disease and the physiologic responses associated with tumoricidal therapies. The role of FDG PET/CT in the "follow-up" of the patient who has initially responded to therapy is dependant on sensitivity of the technique as well as the specificity of the technique which differentiates between residual fibrous tissue at sites of tumor that has been successfully treated and would remain detectable on CT alone from recurrent tumor, the metabolic activity of which is detectable only with FDG PET.

FDG PET/CT of brain tumors is different enough from body imaging to merit a separate section. Consistent with the usual practice in our institution, correlation of the FDG PET/CT with MRI images is provided. MRI images are an essential component of the information necessary for PET/CT interpretation of these problems.

Each case presentation begins with a brief historical setting. In general, the whole body maximum intensity projection [MIP] image is provided separately from the specific sections that most illustrate the significant finding or findings. The most frequently presented are the transaxial sections of the FDG PET distribution alone, the corresponding CT image, and

the fusion image with the metabolic FDG data superimposed on the CT anatomic map. When followed up, similar sections, transaxial or other, are presented in succession.

Finally, the material is supplemented with "Teaching Points" as if after image interpretation, the case is presented in a clinical conference setting and discussed by a senior nuclear medicine physician.

Stanley J. Goldsmith, M.D.
Jasna Mihailovic, M.D., Ph.D.
Ronan Kileen, M.D.

This volume presents a variety of nuclear oncology PET/CT cases which can serve as an introductory text for radiologists and nuclear medicine physicians initially confronting the practice of PET/CT. In this study, it will also serve as a useful reference for nuclear oncologists who order these procedures and even medical students studying the diagnosis and management of patients with malignancies.

The volume evolved from an experience that the editor had working together in the PET/CT component of a clinical nuclear medicine department in a large academic medical center. Most of the cases included in this collection were accumulated during a 2-month period. Since the majority of clinical nuclear oncology PET/CT cases involve oncology patients, it was decided to first list the cases in this collection by their clinical presentation. The cases illustrate the diverse nature of the clinical issues that confront a nuclear medicine physician in daily practice. They are presented in a clinical context with the limited information provided by referring clinicians. While obviously not that ideal in some instances, the reader will appreciate what nuclear medicine physicians have to deal with. To determine another part, the cases are organized according to the variety of clinical indications within nuclear oncology for PET/CT studies. First among these indications is "diagnosis" when the primary malignancy is unknown or when a tumor is identified incidentally in a study requested for another reason. This demonstrates that even though most cases are accompanied by a clinical diagnosis, the nuclear oncologist must be able to be mindful of alternative diagnoses. Most often, however, PET/CT is requested to determine the extent of disease, which determines staged and often defines a course of therapy. The efficacy of FDG PET/CT for this application depends on the sensitivity of the technique which in turn depends on the technical quality of the study. The sensitivity of PET/CT is related to the size and location of the lesion - although in this regard, PET/CT enjoys a generally stated advantage compared to SPECT imaging as PET images are created by coincidence counting and are corrected for attenuation and therefore are less influenced by distance from the detector. Use of PET/CT for confirmation of the response to treatment depends also on sensitivity for detection but also requires knowledge of the natural history of the disease and the physiologic responses associated with tumoricidal therapies. The use of PET/CT in the follow-up of the patient who has initially responded to therapy is dependent on sensitivity of the technique as well as the specificity of the technique when differentiating between residual fibrous tissue at sites of tumor that has been successfully treated and viable tumor detectable on CT alone from recurrent tumor. The metabolic activity of which is detectable only with FDG PET.

FDG PET/CT of brain tumors is different enough from body imaging to merit a separate section. Consistent with the usual practice in our institution, inclusion of the FDG PET/CT with MRI images is provided. MRI images are an essential component of the information necessary for PET/CT interpretation of these problems.

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Introduction

Without doubt, presently, ^{18}F -fluorodeoxyglucose [FDG] PET/CT is the most frequently performed positron emission tomography [PET] clinical application used in medicine.

The role of glucose in accelerated tumor metabolism of tumors was initially described by Warburg in the 1920s when he observed the increased anaerobic metabolism of neoplasms. FDG acts as a glucose analog in which one of the hydroxyl groups (molecular weight of 17 and a single negative charge) is replaced by ^{18}F (atomic weight of 18 and as the fluoride ion also with a single negative charge). Since a hydroxyl group is removed (deoxy) and replaced by a fluorine, the molecule is "fluorodeoxyglucose"; its molecular weight and electronegativity is sufficiently close to the glucose molecule to be acceptable to the glucose transport mechanisms of most tissues and tumors. Hence, it is carried into the intracellular environment by the glucose transport mechanism and undergoes enzymatic phosphorylation to fluorodeoxyglucose-6-phosphate. Fortunately, the enzyme in the next step of glucose metabolism, glucose 1-6 phosphate transferase, does not efficiently recognize the fluorinated deoxyglucose-6-phosphate, which remains in that form with minimal conversion to anything else, nor is it eliminated from the cell until it eventually undergoes breakdown. Hence, the FDG serves as a soluble microsphere and is trapped in the cell. The amount of FDG accumulated, however, serves as a marker of the degree of anaerobic glucose metabolism and hence is useful to identify and characterize tumors.

Regardless of whether a normal subject or a patient with a malignancy is imaged, the FDG PET scan will identify normal organ and tissue utilization of glucose. At rest, the brain, principally the gray matter, is the dominant site of glucose utilization. PET imaging of the brain is sufficiently sensitive to identify the differences in the visual cortex utilization of glucose when the eyes are open or shut, staring at a blank wall versus a checkered pattern or a complex scene. Similar differences in the auditory cortex can be characterized depending on the complexity of the sound stimulation.

Since the heart, particularly the left ventricle, is always consuming energy, the left ventricle may be identified, although in the truly fasting state the left ventricle and the remainder of the myocardium utilizes free fatty acid. After meals, however, or other sources of glucose and subsequent insulin release, plasma free fatty acids decrease dramatically and the myocardium switches to glucose metabolism. In PET evaluation of myocardial viability, differences in fatty acid and glucose utilization is useful to identify viable hibernating myocardium. Bowel peristalsis will also consume more glucose and consequently accumulate FDG.

Glucose appears in the glomerular filtrate. The enzyme-mediated tubular reabsorption of glucose, however, does not handle FDG as a substrate. As a consequence, FDG appears in the urine. In fact, the relatively rapid renal excretion of FDG augments the contrast between the tumor or normal organ glucose accumulation and the background.

It is clear from the above brief review that since tumor uptake of FDG is not insulin dependant, FDG PET imaging is augmented in the fasting state. Likewise, a nonfasting metabolic state results in an increased fraction of the FDG entering the liver and muscles. Even if the blood glucose level is normalized by physiologic or pharmacologic insulin, a greater fraction of FDG will enter these other sites, making less FDG available for tumor uptake and adversely affecting the tumor to background ratio.

Lastly, physicians utilizing FDG PET/CT must be aware of other causes of FDG accumulation. Inflammation, either sterile or infectious, is of most concern. In addition to unrelated infections, the inflammatory response to therapy, particularly radiation therapy, will be associated with increased FDG accumulation, thus complicating evaluation of the tumor response to therapy.

In oncology, a routine ^{18}F -FDG acquisition protocol consists of several steps. Blood glucose level should be determined prior to FDG administration. Clinical history as to whether or not the patient has diabetes and the medication used to control blood glucose should be reviewed prior to scheduling. Diabetic patients require special preparation which often has to be individualized so as to maintain the blood glucose below (or near) 200 mg/dL without insulin administration within 1–2 h preceding the FDG administration. In many centers, the dose of FDG is based on patient body weight (approximately 5 MBq/kg), whereas in other centers, a 370–555 MBq (10–15 mCi) is used in adults with PET scanners utilizing BGO crystals. Recent advances in PET scanner design and engineering have substituted BGO with more sensitive crystals. In this circumstance, satisfactory images can be obtained with doses below 370 MBq for an adult of 70 kg or more.

Patients should relax and avoid any unnecessary movement for at least 45 min to prevent muscular uptake which results in artifacts and possible misinterpretation. The patient should be told not to engage in conversation or chewing particularly if the area of interest involves the head and neck region. Depending on the area of interest, oral contrast may be administered prior to FDG injection as an aid in identifying bowel loops and differentiating bowel from masses, lymph nodes, or blood vessels. In some centers, and again depending upon the organs or regions of interest, IV contrast CT may be obtained. In these cases, the IV contrast is usually administered after initially obtaining a CT without contrast to be used for attenuation correction of the PET image data which also is obtained prior to the administration of the IV contrast. The typical image acquisition for body imaging involves scanning from the base of the skull to mid thigh. Of course, brain and head and neck FDG PET/CT involves imaging this area (a single-bed position) usually for a longer PET acquisition period than for body PET acquisitions. FDG PET/CT for evaluation of patients with either multiple myeloma or malignant melanoma should include head-to-toe imaging.

Following the completion of the CT scan, PET emission scanning is performed in the caudocranial direction, starting at the pelvis region. With BGO crystal scanners, depending on the axial range and the individual bed position acquisition time, scanning, including transmission and emission scans, can be completed in 30–45 min. Newer instruments with faster crystals and electronics can reduce this to 20 min or less.

The clinical utilization of FDG PET imaging was initially limited to brain imaging as the diameter of the early PET scanner openings could not accommodate larger body parts. Although all tumors did not vigorously concentrate the FDG tracer, Giovanni Di Chiro at the National Institutes of Health in the United States noted the relationship between the “tumor avidity” for FDG and tumor aggressiveness. This observation provided a basis for the stratification of the aggressiveness of therapeutic intervention. Nevertheless, initially between the cost of the instrumentation, the difficulty in obtaining FDG, and the limited application for patient management, utilization of FDG PET was limited to only a few centers with access to cyclotrons and PET radiochemistry laboratories.

All of that has changed so that, at the present time, FDG PET/CT plays a role in several aspects of management of the patient with a malignant tumor – in some cases, even in assisting in the original diagnosis, in almost every case contributing to the assessment of the extent of disease, confirming response to therapy, playing an essential role in the monitoring of the patient after therapy for early detection of recurrence of disease, and more recently (and still under development) predicting response to the current course of chemotherapy (and to a limited extent, radiotherapy) early in the course of therapy. In the future, when this latter application is better understood, it is possible that some of the current prolonged therapeutic regimen can be terminated earlier. Certainly, in the event that it can be demonstrated that despite a transient clinical response to therapy during the regular administration of chemotherapy (or irradiation), if it is possible to predict early relapse, alternative therapeutic options can be considered.

To progress from the early days of limited availability and application of FDG PET to the now widely available and utilized status of FDG PET/CT, many components had to be brought together. In retrospect, it is remarkable that such a complex and costly procedure has grown so fast and spread so far. There are probably several versions of the sequence of historical growth of this procedure. From the perspective of the editors, the following sequence seems to be a reasonable reconstruction of the events involved:

- Realization that there might be applications of FDG PET imaging in areas of the body other than limited to the brain.
- Commercial development of instrumentation that allowed imaging of other body parts (head and neck, thorax, abdomen, pelvis, extremities).
- Imaging of these areas and demonstration of tumor utilization of FDG.
- Realization by commercial interests of the potential wider demand for cyclotron-produced ^{18}F and FDG synthesis, hence increased availability of FDG (although FDG was still quite expensive).
- Simultaneous academic-industrial development and exploitation of whole body scanning accompanied by growth in computer capabilities that permitted storage of large amounts of data representing the reconstructed transaxial images which could be stored with reconstruction of additional views, that is, coronal and sagittal sections or slices as well as a volume display, currently called maximal intensity projection [MIP].
- Even prior to the combination of PET and computed tomography [CT], the MIP and coronal images provided sufficient anatomical detail so as to improve the anatomic placement of observations. The imaging community beyond nuclear medicine began to appreciate the images which heretofore had been accessible to a limited group of dedicated physicians interested and supportive of this technique.
- Further increase in the availability of FDG. With increased utilization, competition among commercial suppliers resulted in decreasing costs of unit doses, further increasing utilization.
- Finally, the marriage of PET and CT resulted in widespread application and further assessment of the clinical merit of the technique.

At the same time, on the other side of the patient is the issue of costs. Increased utilization and demand for FDG brought about competition among suppliers and decreased cost for unit doses of FDG, from perhaps \$800 per dose initially to less than \$150 in some areas. This is still expensive but competitive with costs of contrast agents in general. Equipment costs have not declined as dramatically, in part because the technology employed continues to grow more sophisticated, with faster acquisition times, faster image reconstruction, extraction of more complex data, and most recently, the combination of PET and MRI – a technology with a new set of advantages and challenges.

In the USA, approval of reimbursement for the procedure by government and third-party insurance was necessary because of the considerable cost per examination. The extent of procedures approved proceeded slowly but gradually as the merit of each application was demonstrated in peer-reviewed medical reports. Ultimately, a national review body, the NOPR (National Oncology Procedure Registry), was formed to collate data on the contribution of PET/CT in oncology to improved patient management and outcome. Analysis of the data accumulated during the first year of the NOPR was published in the *Journal of Clinical Oncology* several years ago. It demonstrated that in over two-thirds of the cases, FDG PET/CT had a significant impact on patient management. The monitoring of FDG PET/CT continues, but FDG PET/CT is available for most oncology applications. Throughout Europe, Japan, the Middle East, other Asian countries, South America, and most recently, parts of Africa, FDG PET/CT has become increasingly available and reimbursable.

It is likely that in the near future additional PET tracers will become available. ^{18}F -choline which is a measure of cell membrane synthesis can serve as a tumor marker because of the incremental rate of tumor cell division and hence would be more tumor specific than FDG as it would differentiate between tumor proliferation and inflammation. Other tracers that

characterize protein synthesis, RNA replication, or tissue oxygenation are being evaluated and developed for more widespread application.

In developing countries, financial resources are very limited. In a country like Serbia, there are only two PET/CT centers for the entire country with a population of 7.5 million people. FDG is imported from neighboring nations and currently costs approximately 540 euros per dose. The charge for the entire examination is 700 euros. There is a plan for the central government to build a cyclotron and PET radiochemistry facility within Serbia. Nevertheless, other problems remain: insufficient physician awareness of the value of FDG PET/CT in the management of patients, particularly oncology patients, and limited financial resources to support access and the costs that would be associated with expansion of utilization of this valuable procedure.

By contrast, in New York City, in the borough of Manhattan alone, there are more than 15 PET/CT scanners and 2 cyclotrons and PET radiochemistry facilities within medical centers. In addition, the area is supplied with FDG by 3-5 competing commercial radiopharmacies.

Hopefully, in the near future, the costs of the various components of the examination, particularly the FDG dose, will be further reduced and the merits of FDG PET/CT in the management of the oncology patient will be appreciated by referring physicians, government, and third-party payers so as to make this essential tool more widely available.

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Chapter 1

Solitary Pulmonary Nodule (SPN), Chest Mass

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Case 1

88-Year-Old Female with a Mass in the Right Upper Lobe and Enlarged Hilar Lymph Nodes

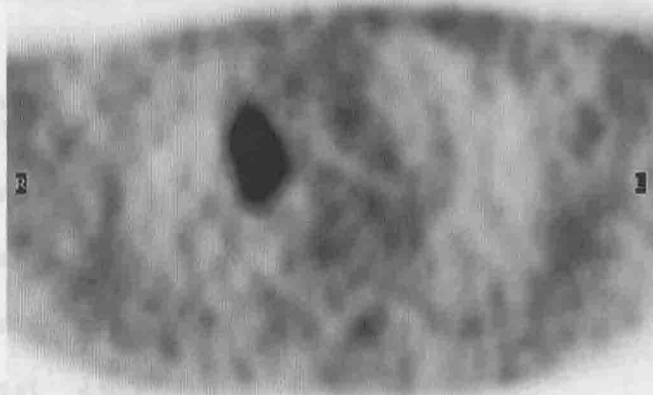
History: The patient was admitted to the hospital 1 month ago for pacemaker placement. Several days before, she complained of intermittent chest pains, weakness, and dyspnea which were felt to be due to AV block. The patient's post pacemaker procedure included chest x-ray that was notable for a collapsed right upper lobe. Review of pre-placement x-ray showed right upper increased density and prominent right hilum. CT confirmed collapse of the superomedial aspect of the right upper lobe secondary to a right suprahilar mass.

Findings:

a



■ Fig. 1.1 (a) The MIP image demonstrates hypermetabolic mass in the right paramediastinal region with small area of focal uptake in the subcarinal region



■ Fig. 1.1 (b) Hypermetabolic right upper lobe mass, 4.0×2.6 cm, SUVmax 10.2, which abuts the superior mediastinum and compressed the right upper lobe bronchus (not shown)