Perspective

Role of PET/CT for precision medicine in lung cancer: perspective of the Society of Nuclear Medicine and Molecular Imaging

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Abstract: This article discusses the role of PET/CT in contributing to precision medicine in lung cancer, and provides the perspective of the Society of Nuclear Medicine and Molecular Imaging (SNMMI) on this process. The mission and vision of SNMMI are listed, along with the guidance provided by SNMMI to promote best practice in precision medicine. Basic principles of PET/CT are presented. An overview of the use of PET/CT imaging in lung cancer is discussed. In lung cancer patients, PET/CT is vitally important for optimal patient management. PET/CT is essential in determining staging and re-staging of disease, detecting recurrent or residual disease, evaluating response to therapy, and providing prognostic information. PET/CT is also critically important in radiation therapy planning by determining the extent of active disease, including an assessment of functional tumor volume. The current approach in tumor imaging is a significant advance over conventional imaging. However, recent advances suggest that therapeutic response criteria in the near future will be based on metabolic characteristics and will include the evaluation of biologic characteristics of tumors to further enhance the effectiveness of precision medicine in lung cancer, producing improved patient outcomes with less morbidity.

Keywords: Lung cancer; precision medicine; PET/CT; Society of Nuclear Medicine and Molecular Imaging (SNMMI); tumor imaging

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Role of nuclear medicine in medicine overall

Most nuclear medicine (NM) studies are diagnostic. The major reasons in oncology are: to make a diagnosis, determine staging/re-staging or extent of disease, detect recurrence or residual disease, assess response to therapy and provide prognostic information.

There are some therapeutic procedures in NM. In thyroid disease, we can treat hyperthyroidism and thyroid cancer. In the 1980s, we began to use radionuclides to provide palliation of bone pain for osseous metastatic disease, with substantial success. In the last few years, we have begun to treat malignancies with various radionuclides that are beta-emitters, and more recently, alpha-emitters, to actually improve outcomes. In the near future, I expect to see major success in using radionuclides to treat various malignancies, with much better outcomes and far less morbidity.

Mission and vision of the Society of Nuclear Medicine and Molecular Imaging (SNMMI)

Mission: to improve human health by advancing nuclear medicine, molecular imaging, and radionuclide therapy.

Vision: SNMMI is the recognized leader in promoting the value of nuclear medicine, molecular imaging and radionuclide therapy, globally.

SNMMI can accomplish its mission and vision in part by providing guidance that promotes best practice, including procedure guidelines and quality measures regarding lung cancer and other malignant diseases and by providing appropriate use criteria to assist referring physicians in managing their patients by ordering the appropriate studies

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for diagnosis and therapy. SNMMI provides guidance in dosimetry and dose optimization. SNMMI also provides guidance in quality of practice in a number of avenues, including journal articles, webinars, educational and review presentations at the annual meeting, and statements regarding physician credentialing for various studies.

Basic principles of PET/CT

PET imaging in oncology uses short-lived positron-emitting radio-isotopes (radionuclides). The most commonly used radionuclide is fluorine-18, which is used to label glucose, resulting in F-18 fluorodeoxyglucose (F-18 FDG). Fluorine-18 emits positrons. These positrons after emission combine with electrons. Both are annihilated, and this annihilation process produces photons (also known as gamma rays) of equal energy (511 keV) that travel in almost exactly opposite directions. The PET camera detects the gamma rays emitted from this process, which is referred to as annihilation coincidence detection. The PET camera detects coincident gamma rays at approximately 180 degrees apart. If these equal and opposite gamma rays are detected within the coincidence timing window, which is generally 6 to 12 nanoseconds, the event is recorded for the production of an image that maps the distribution of these events. The tomographic images are reconstructed from the raw data. The images can be viewed in axial, coronal and sagittal projections. The images are therefore a recording of the distribution of the tracer in the body. The images are quantitative, and are more accurate when corrected for scatter and random events, as well as other physical effects. PET imaging is now combined with CT, as the PET camera provides high sensitivity for the distribution of the tracer, and the CT provided precise anatomic localization and attenuation correction. The combination makes PET/CT the most sensitive and accurate modality to evaluate most malignancies (1,2).

Most malignancies have increased glycolysis (known as the Warburg effect) and are therefore hypermetabolic. We can take advantage of this characteristic of these malignancies to image them with a glucose analog, F-18 fluorodeoxyglucose. F-18 FDG is transported into cells (to a greater degree by most malignant cells) by glucose transporter molecules, which are upregulated in malignancy. F-18 FDG, like glucose, is initially phosphorylated by hexokinase, but it cannot be metabolized further so it becomes trapped within the cell. These malignant cells can therefore be detected by PET/CT as abnormally increased uptake of F-18 FDG (1).

While F-18 FDG is a "non-specific" tracer, it is a useful tracer in many malignancies because most malignancies are hypermetabolic. F-18 FDG has become the main tracer currently to evaluate many malignancies for detection, identification, staging and re-staging, detecting recurrence or residual disease, monitoring response to therapy and prognosis.

Overview of PET in lung cancer

PET/CT is a valuable modality in the evaluation of lung cancer (NSCLC and also small cell lung cancer). One of the important indications is in the evaluation of a solitary pulmonary nodule (less than or equal to 3 cm in diameter). These can be detected incidentally on chest radiographs or chest CT scans. However, pulmonary nodules cannot be completely evaluated for malignancy by chest CT since anatomic findings are often non-specific. PET/CT has much greater sensitivity to detect the metabolic changes seen in malignancy, often before structural changes can be identified, and particularly before structural changes specific for malignancy can be seen.

False-negative studies are uncommon, and can be seen in small nodules, generally less than 8–10 mm in diameter. False negative results can also be seen with low-grade malignancies, such as bronchoalveolar carcinoma (now reclassified into various lung cancer types mainly by invasiveness and growth characteristics) or carcinoid. These also include mucinous adenocarcinomas, tumors which have relative large amounts of mucin and a relatively small amount of cells (3).

Solid pulmonary nodules greater than 8–10 mm in diameter which show lack of uptake for F-18 FDG is much more likely to be benign.

False positive results can be seen with infections, particularly tuberculosis and granulomatous infections. Non-infectious inflammatory conditions, especially sarcoid, can also cause false-positive results. The degree of hypermetabolism in these infectious or non-infectious inflammatory conditions can be similar to that of high-grade malignancies.

PET/CT has been shown to be highly cost-effective in evaluating solitary pulmonary nodules. This is particularly true when the pre-test probability is discordant with CT scan findings (3).

PET/CT with F-18 FDG is clearly important in the characterization of a solitary lung mass (greater than 3 cm

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in diameter). PET/CT has high sensitivity and specificity in evaluating a pulmonary mass. The likelihood of malignancy is greater when the standard uptake value (SUV) is greater than 2.5, and increasing SUVs suggest a more unfavorable prognosis. In situations where a pulmonary mass is present, and the PET/CT demonstrates hilar and mediastinal involvement, futile thoracotomy can be avoided. In situations of a large pulmonary mass with no hilar or mediastinal involvement, a thoracotomy would provide a favorable prognosis.

Accurate staging of non-small cell lung cancer is critically important for determining the optimal management of these patients. FDG PET/CT is the single most sensitive and accurate modality to detect hilar and mediastinal nodal involvement. It is also the most sensitive and accurate modality in detecting metastatic disease, including local, regional or distant metastases (except in the brain, where MRI is more sensitive). False negative results can be seen with lesions too small to detect, or low-grade malignancies, with too low a degree of hypermetabolism. PET/CT has changed management in NSCLC in 30–40% of cases (3).

Some investigators have studied dual time-point imaging with PET/CT, since malignancies have increasing uptake over 2–6 hours, while inflammatory conditions generally show a stable level of uptake beyond 60 minutes post injection. However, not all studies have confirmed the usefulness of this technique (3).

Evaluation of treatment response is vitally important for optimal management. PET/CT has been valuable in assessing response to treatment, including chemotherapy, radiation therapy or in combination. The improved sensitivity in using metabolic criteria instead of anatomic criteria makes PET/CT an important modality in evaluating treatment response. PET/CT is superior to CT alone, especially due to anatomic changes from atelectasis, inflammatory changes and postradiation fibrosis, each of which makes CT interpretation difficult.

In monitoring therapy, PET/CT can guide continuation of chemotherapy, or changes in chemotherapy, based on imaging results.

PET/CT is critically important in radiation therapy planning. PET/CT provides staging information and can detect previously unknown metastasis, which can determine which patients can receive definitive (i.e., potentially curative) radiotherapy and which patients should receive palliative therapy. PET/CT can provide accurate delineation of extent of disease, so that definitive radiotherapy has a better chance of success. PET/CT can accurately delineate gross tumor volume and functional tumor volume, which are critically important to guide radiotherapy. The degree of uptake by of the tumor of F-18 FDG can predict response to radiotherapy as well as outcome. Higher uptake (increased SUV) suggests decreased survival. PET/CT is also useful in predicting radiation pneumonitis (3).

Serial PET/CT studies with F-18 FDG can be useful in detecting residual or recurrent disease. The sensitivity, specificity and accuracy are very high in detecting recurrent disease, in the 90% range. The level of SUV in these lesions can be predictive of survival, as higher SUV levels indicate a poorer survival rate (3).

Small cell lung cancer generally accounts for 15–20% of all lung cancers. Small cell lung cancers are generally very aggressive, and are considered metastatic at time of diagnosis. These cancers are initially very radiosensitive and also very sensitive to chemotherapy. However, responses to therapy are usually short-lived, and overall survival is poor (3). F-18 FDG PET/CT can accurately stage these cancers. Also in these tumors, PET/CT is less sensitive in detecting brain metastases than MRI. Also in small cell lung cancer, higher SUVs predict poorer outcomes. PET/CT is also useful for radiation therapy planning (3).

F-18 sodium fluoride (F-18 NaF) PET/CT has been used to evaluate bone metastases in lung cancer. In comparison to conventional bone scanning for metastatic disease in lung cancer with Tc-99m MDP, F-18 NaF was more accurate than Tc-99m MDP. Combining F-18 NaF with F-18 FDG is more sensitive and more accurate than Tc-99m MDP in detecting osteolytic bone metastases (4).

In addition to F-18 NaF, other novel PET tracers are being studies to evaluate other features of lung cancers, including proliferation (DNA synthesis), apoptosis, and hypoxia. Some of these agents, such as F-18 fluorothymidine (F-18 FLT) for evaluation of proliferation status (i.e., DNA synthesis), are in clinical trials. PET agents that can detect hypoxia may become important, as hypoxic tumors are more difficult to treat. At least one of the hypoxia agents can also function as an efficient hypoxic radiosensitizer. It remains to be seen if these agents for proliferation, hypoxia and other features of malignant cells will be clinically useful.

Future prospects

The current approach in tumor imaging includes screening, diagnosis, staging/re-staging, monitoring response to therapy, detecting residual or recurrent disease (including surveillance) and evaluating prognosis. In the near

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future, the preferred approach will more likely include (I) evaluating patients based on biologic characteristics of the primary tumor and metastases, which will enhance personalized, precision medicine, (II) evaluating prognostic and predictive markers, (III) evaluating therapeutic response, and (IV) focused surveillance/screening (personal communication, Lalitha Shankar, MD, PhD, NCI).

It is clear that therapeutic response criteria will be based on metabolic characteristics, rather than size alone (i.e., PERCIST rather than RECIST) (5).

In the more distant future, but probably within 10 years, I believe we will be able to image a number of cell functions, including transcription, translation, signal transduction, transport, enzyme function, and cell surface or intracellular receptor binding.

Future characterization of tumors will be based on the eight hallmarks of cancer, delineated by Hanahan and Weinberg (6):

- Self-sufficiency in growth signals;
- Evading growth suppressors;
- Evading apoptosis;
- Enabling replicative immortality;
- Sustained angiogenesis;
- Tissue invasion and metastasis;
- Reprogramming of energy metabolism;
- Evading immune destruction.

Also critically important to consider are evaluation of surrounding inflammation of the tumor mass and the tumor microenvironment.

Therefore, future characterization of tumors could include:

- Evaluation of the tumor microenvironment and surrounding inflammation;
- Evaluation of glucose metabolism with F-18 FDG;
- Evaluation of proliferation (DNA synthesis);
- Evaluation of amino acid synthesis and transport;
- Evaluation of cell surface receptors;
- Evaluation of angiogenesis, perfusion and hypoxia;
- Evaluation of lipid metabolism;
- Evaluation of other characteristics (e.g., osteoclastic activity);
- Evaluation of metastases (including clonal variation).

I predict this precise characterization of tumor cells will assist in the development of theranostic agents, useful for imaging and therapy. SNMMI supports the research in the development of new tracers for diagnosis and new theranostic agents and efforts to establish FDA approval and reasonable reimbursement for these agents. Radionuclide therapy will be precisely targeted and personalized, attacking various enzymatic pathways, cell surface and intracellular receptors and using dosimetry, possibly even intralesional dosimetry, to obtain more successful therapy, with better long-term outcomes and much fewer side effects.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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