Positron Emission Tomography with ^{18}Fluorodeoxyglucose in Radiation Treatment Planning for Non-small Cell Lung Cancer

A Systematic Review

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Introduction: This article summarizes the available evidence on the role of ^{18}fluorodeoxy-D-glucose positron emission tomography (PET) and PET-computed tomography in radiation treatment (RT) planning for non-small cell lung cancer.

Methods: Relevant studies were identified through a systematic review of the medical literature between January 1996 and May 2010. Medline, EMBASE, and the Cochrane databases were searched.

Results: Twenty-eight nonrandomized prospective and retrospective studies and one randomized trial reported in abstract form were identified. There were no guidelines, systematic reviews, or meta-analyses found in the search. There are no data available that demonstrate an impact of PET-based RT planning on survival or local recurrence rates. Nineteen studies reported changes in gross tumor volume, and 11 studies reported changes in planning target volume. The limited data suggest that PET in RT planning is more likely to decrease the dose to the esophagus, but the data on the dose to lung tissue are mixed. In two studies that evaluated the effect of PET on total RT dose administered to patients, the RT dose increased by approximately 15 Gy and tumor control probability increased by 8.6% and 17.7% ($p = 0.026$). In 12 studies, PET detected distant metastases in 8 to 25% of patients and resulted in a change from curative to palliative RT intent in 8 to 41% of patients.

Conclusions: The inclusion of PET imaging in the planning process produces modifications in RT planning that may be beneficial. These changes include a change in treatment intent from radical to palliative and substantial modifications of the gross tumor volume and planning target volume. It is not certain that these changes result in better clinical outcomes, but ongoing evaluation of PET for this purpose is warranted.

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Lung cancer is the leading cause of cancer-related deaths in both men and women in Canada.[1] Radiation treatment (RT) is indicated for use in approximately 60% of all patients with lung cancer and is used for a variety of intents, including curative, adjuvant, neoadjuvant, and palliative.[2] RT is most commonly applied in stage III non-small cell lung cancer (NSCLC), where it is estimated that it might be indicated for as many as 84% of patients.[2]

External beam radiotherapy (i.e., teletherapy) is the most common form of RT and involves the targeting of high-energy photons (i.e., x-rays) at cancerous tissues to promote malignant cell death. Although healthy cells are better able to repair damage from radiation, RT can kill healthy tissues at sufficient dosage, and epithelial tissues are particularly vulnerable. Tissue scarring can result from radiation exposure and lead to reduced elasticity. This is especially relevant in lung cancer, where critical organs such as the heart, spinal cord, esophagus, and the remainder of the normal lung are often in the vicinity of tumor tissues (i.e., organs at risk [OARs]) and damage to these can be detrimental to the patient. Because of the possibility for significant adverse effects from radiation, radiation oncologists are continually seeking methods to target RT more precisely. The use of positron emission tomography (PET) with radiolabeled [^{18}F]-2-fluorodeoxy-D-glucose (^{18}FDG) PET imaging information is being evaluated as a possible means to improve current RT practices.

RT dosage in lung cancer is generally provided to patients in daily fractions, and a typical dose for a solid epithelial tumor ranges from 60 to 70 Gy, with a fractionation schedule for adults of 1.8 to 2.0 Gy per day. Radiation dosage exposures are commonly described in terms of the percentage of the organ receiving a particular total dose of radiation. For example, V_{20} lung indicates the percentage of the lungs,

excluding the planning target volume (PTV), that received a dose of 20 Gy or more during the course of treatment. The extent to which RT has achieved its objective in killing tumor cells is conveyed by the concept of tumor control probability (TCP). Imaging technologies, specifically planning computed tomography (CT), are used in the RT planning process to delineate tumors and adjacent healthy structures. Traditionally, specialized CT scanners are combined with planning software to virtually simulate the tumor and accurately place x-ray beams. Newer approaches, such as three-dimensional conformal radiotherapy or intensity-modulated RT are expected to further enhance these efforts.

RT planning requires precise definition of the region of the diseased part of the body that is the target of the radiation dose. In current practice, this region or "volume" is defined three dimensionally in accordance with principles articulated by the International Commission on Radiation Units and Measurements. The gross tumor volume (GTV) and clinical target volume (CTV) are clinical-anatomic concepts and refer to the physical space occupied by disease. The GTV is "the gross, palpable, visible or clinically demonstrable location and extent of the malignant growth" and is generally defined by all gross disease identified in scans (e.g., CT, PET, and fused) and through other clinical information.[3] The GTV includes the primary tumor and metastatic lymphadenopathy. The CTV contains the GTV and areas where there is a high probability of subclinical malignant disease and typically includes a volumetric extension of the GTV (e.g., a 0.6–0.8 cm margin and/or inclusion of draining lymph node regions).[4–6] Unlike GTV and CTV, the PTV is geometric definition that is used directly in targeting a radiation beam. The PTV contains the CTV and margins to account for variability due to internal motion such as respiration in patient setup ("setup margin") or position of the target for lung tumors ("internal margin").[7] Several algorithms have been proposed to aid in the determination of the PTV, but ultimately it is a clinical judgment that takes into account adjacent topology, specifically the OARs for radiation toxicity.

CT has traditionally been the primary source of anatomic imaging information for target volume selection and delineation in oncology. Nevertheless, CT is limited by the fact that it has diminished resolution for normal soft tissue structures and tumor extent. A number of studies have reported significant variations in the delineations of GTV based on CT data.[8,9] There is reason to believe that the tumor metabolic information provided by PET would be valuable in RT planning. Tumor tissues generally exhibit more rapid glycolysis than normal tissues, and the ^{18}FDG tracer allows for the metabolic imaging of this tissue. A number of studies have compared the accuracy of PET in comparison with CT for the purposes of diagnosis and staging in lung cancer.

PET has greater sensitivity and marginally greater specificity relative to CT in specific instances.[10–14] This has implications for RT planning in lung cancer. For instance, the systematic review found PET to be superior to CT for mediastinal staging in NSCLC.[10] The greater sensitivity of PET is believed to improve the detection of metastatic lymph nodes that CT would have missed. PET may be better able to detect distant metastases and allow for the exclusion of patients from unnecessary radical RT. Conversely, PET may result in the downstaging of CT-false-positive nodes and the exclusion of nonmalignant tissues from the PTV. The benefit of this for patients could be substantial: Graham et al.[15] have argued that a reduction of V_{20} lung by 5 to 17% would reduce the incidence of grade 2 or greater pneumonitis occurring within 24 months of treatment by up to 23%.

Despite this strong theoretical rationale for using PET in RT planning, it is not yet clear that the addition of PET imaging data has a clinically significant impact on planning. Furthermore, assuming there is a benefit to including PET data in planning, the optimal approach to using PET data is not yet established. At present, PET tumor contouring remains unsatisfactory, and there is little standardization in its use. For instance, the delineation of tumor volumes based on a metabolic activity threshold in PET has been shown to vary both by tumor size and the background-to-tumor ^{18}FDG uptake ratio.[16] Some clinicians include an area of lower uptake, which some term as the "anatomic-biologic halo," in the GTV, and one study has shown that including this halo improves coverage of the PTV,[17] although, again, the practice is not yet standard.

This systematic review was initiated because of the increasing use and potential importance of PET in this area. This systematic review will provide an evidence-based perspective as to whether planning based on PET and PET-CT imaging data represents an improvement over planning based on CT data alone and inform guidance on its role in RT planning in the lung cancer setting.

PET is an imaging technique that gives high-resolution images based on the use of biologically active compounds, substrates, ligands, or drugs labeled with positron emitters. These radiolabeled agents are processed in vivo in a manner virtually identical to their nonradioactive counterpart, thereby producing images and quantitative indexes of blood flow, glucose metabolism, amino acid transport, protein metabolism, oxygen consumption, and even cell division.

Traditional radiologic imaging (e.g., CT scan and magnetic resonance imaging) is based on structural information and defines disease states based on gross anatomic changes, whereas PET imaging is based on biochemical processes that often precede any gross anatomic distortion. PET imaging is now used primarily in oncological imaging due to the successful application of ^{18}F-FDG. This systematic review will only evaluate the role of ^{18}FDG-PET.

Imaging by PET is based on the detection of 511 keV annihilation photons that are the result of positron, in this case emitted from ^{18}F, colliding with an electron. Photons that are in coincidence are detected by two detectors at 180-degree angle from each other. These photons are considered to have originated from a point source along that axis. All the collected information is then processed into the final image in a two-dimensional or three-dimensional representation that reflects the concentration and distribution of the radioisotope. This creates the image of FDG localization.

