**What is the Benefit of Positron Emission Tomography with 18 Fluorodeoxyglucose in Radiation Treatment Planning for Non-Small Cell Lung Cancer?**

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Lung cancer is the most common cancer in Canada, accounting for 14% of all cancers.1 In Ontario, there were 10,072 new cases reported in 2012 and despite an overall decrease in mortality, lung cancer continues to be the leading cause of cancer-related death.2

Non-Small Cell Lung Cancer (NSCLC) is the most common type of lung cancer (70.9%).2 Radiotherapy (RT) plays an integral role in the management of NSCLC in both curative and palliative settings. Roughly one-third of NSCLC patients will have unresectable disease that is amenable to curative intent chemoradiation. The utilization of RT in the management of early stage (Stage I ) NSCLC is rapidly increasing with the advent of Stereotactic Ablative Radiotherapy as the treatment of choice in medically inoperable patients.34

[18F]-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) scanning is now considered standard of care in the staging evaluation of patients with NSCLC who are being considered for curative-intent treatment. The use of FDG-PET as a staging tool for NSCLC improves the sensitivity of detection of both locoregional and distant metastases, 5,67 and can significantly impact the selection of patients for curative treatment. 8 91011 Inclusion of PET in the staging workup improves the apparent survival of patients treated with radical intent chemoradiotherapy by excluding incurable patients.12 In a prospective study investigating the benefit of FDG-PET staging in candidates for curative radiotherapy with unresectable NSCLC, 30% of patients received palliative treatments due to FDG-PET detected distant metastases or extensive locoregional disease. 11 PET data such as standard uptake value (SUV) or derivations of this measurement have also been shown to correlate with clinical outcomes including local recurrence, survival and distant relapse.131415

Radiotherapy planning volumes are delineated on CT scans, which provide only anatomical data on tumour extent. In recent years, numerous studies have investigated the hypothesis that the incorporation of FDG-PET into CT-based planning of radiotherapy using a combined CT-PET acquisition for NSCLC may be of significant value in optimizing radiotherapy planning, with the potential to improve patient outcomes. The addition of metabolic data from FDG-PET is thought to permit more accurate delineation of tumor from atelectasis and identify occult nodal disease or other lesions not apparent on CT or MRI, with the potential to improve tumour control and reduce toxicity to normal tissues. A systematic review by Ung et al. of 29 studies found that the incorporation of FDG-PET into the radiotherapy planning process reliably identified PET positive tissue that was missed on the planning CT (lymph nodes and primary tumour), permitted escalation of dose and improved tumour control probability, and reduced the dose to esophageal and lung tissue. 16 Furthermore, the variation in delineation of treatment volumes among different radiation oncologists is significantly reduced with FDG-PET. 171819

The incorporation of FDG-PET into RT planning can alter the intent of treatment in a substantial proportion of patients. A recent systematic review by Hallqvist et al., which included data from 36 original trials, reported that approximately 40% of patients had a significant change in target volume definition and approximately 20% would have been inappropriately treated with radical intent chemoradiotherapy due to the finding of new M1 metastatic disease at the time of the radiation planning FDG-PET. These proportions were similar regardless of whether patients had a prior staging PET.20

Delays between staging FDG-PET and the radiation planning FDG-PET as short as 3-4 weeks appear to have a significant impact on target definition and intent of treatment. A study by Geiger et al. showed that 26% of patients progressed to the point of incurability between scans and 17% of patients showed stage progression within an interval 20 days.21 Similar findings have been reported in elsewhere, and the authors highlight the importance of avoiding delays in the workup of NSCLC patients that could result in inferior clinical outcomes.20 Single-institution reports from two Ontario cancer centres reported that roughly 50% of patients with stage III NSCLC lose eligibility for curative intent treatments due to delays that occur during the diagnostic journey. The causes of these delays are multifactorial, and are due in large part to time-dependent variables such as deterioration in performance status, weight loss or tumour progression, and support the notion that FDG-PET should be performed as close possible to the initiation of radiotherapy. 2223

Whether improvements in target delineation with PET/CT translate to improved local control, survival, reduced toxicity or improved quality of life is the subject of ongoing investigation, as listed in clinicaltrials.gov. The PET-START trial is the only randomized controlled trial to compare clinical outcomes in patients planned with FDG-PET-Computed Tomography (CT) planning vs. standard CT planning in stage III NSCLC patients. Preliminary results, published only in abstract form, suggest that the use of a radiation planning PET-CT results in fewer patients receiving curative radiotherapy and improves overall survival by as much as 20-30%.24 The PET-BOOST trial is a prospective randomized phase II trial to further investigate the benefit of dose escalation to PET-defined tumour sub-volumes in locally advanced NSCLC, based on emerging data that suggesting a local control benefit with dose escalation to metabolically active tumour volumes. The primary outcome measure is local control; secondary outcome measures include overall survival, progression free survival and quality of life. The study is presently accruing patients in Ontario25.

Recommendations as to how PET-CT should be incorporated into the radiation planning process for NSCLC are detailed in the 2014 International Atomic Energy Agency (IAEA) Consensus Report.26 Significant differences in patient positioning between the planning CT (typically performed on a flat-top couch, with arms immobilized above the head, and the diagnostic PET images (typically performed on a curved couch top, with arms down) can make anatomical registration between the two image sets difficult, leading to potential misinterpretation and inaccurate tumour volume delineation. Coregistration or fusion of the two images sets using deformable or elastic registration can partially correct for positional differences but these methods have not been consistently validated and the authors do not recommend these approaches. The accumulated data are considered robust enough that several clinical societies (IAEA, EORTC, and NCCN) recommend that the best available option is to acquire a PET/CT scan exclusively for radiation treatment planning, whereby radiotherapy planning volumes are delineated on a FDG-PET CT-simulation scan performed in the treatment position. 262728

In summary, the available evidence demonstrates substantial benefits for the use PET-CT for radiotherapy dose planning in NSCLC. These include improvements target volume delineation, patient selection, and change in treatment intent from radical to palliative in a significant proportion of patients. Further studies investigating the impact of these changes on clinical outcomes are ongoing; however, the existing data are presently convincing enough that many international clinical guidelines recommend radiotherapy planning using FDG-PET CT-simulation as the ideal standard.

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