Letter to the Editor

Increasing PET Use in Small Cell Lung Cancer

Re: Hong JC, Boyer MJ, Spiegel DY, et al. Increasing PET Use in Small Cell Lung Cancer: Survival Improvement and Stage Migration in the VA Central Cancer Registry. *J Natl Compr Canc Netw* 2019; 17(2):127–139.

We read with interest the study by Hong et al¹ on stage migration in small cell lung cancer (SCLC) after increased FDG-PET use. The authors postulate that this led to improved survival because appropriate treatment was delivered due to accurate staging provided by FDG-PET.

The authors should be commended for reporting data from a large retrospective cohort. However, as they acknowledged, there are many confounders and selection biases in this study that limit the ability to draw firm conclusions. For this reason, their findings do not provide sufficient evidence to support the routine clinical use of FDG-PET/CT in SCLC. The survival improvement reported over the course of the study could be due to improvements in supportive care or chemoradiotherapy delivery techniques, both unaccounted for in their analysis.

Hong et al compare their outcomes to those of the CONVERT trial,² in which 57% of patients were staged with FDG-PET/CT in addition to conventional imaging (thorax/abdomen CT, brain imaging $\pm$ bone scintigraphy). We would like to note our recently published secondary CONVERT trial analysis that investigated the impact of

FDG-PET/CT in limited-stage (LS) SCLC.³ Although patient characteristics were significantly imbalanced in favor of the FDG-PET/CT–staged group, we report that survival outcomes were not significantly different between patients staged with or without FDG-PET/CT, in contradiction to the findings by Hong et al.

Landmark trials that established chemoradiotherapy as standard treatment in LS SCLC were conducted before the FDG-PET/CT era.⁴ Furthermore, the CONVERT trial did not mandate FDG-PET/CT staging.² Data from the CONVERT FDG-PET/CT secondary analysis support that patients with SCLC without metastatic disease detected on CT may benefit from curative-intent chemoradiotherapy. Arguably, a proportion of these patients had low-burden metastatic disease undetected on CT. Caution is therefore required in the interpretation of the findings by Hong et al, because the routine use of FDG-PET/CT could deny these patients appropriate, evidence-based therapies.

Unfortunately, both the study by Hong et al and the CONVERT FDG-PET/CT secondary analysis do not provide level 1 evidence to support the use or omission of FDG-PET/CT for treatment selection in SCLC. A randomized controlled trial is required to settle this debate. However, in our view, there is little interest in conducting such a trial among the oncology and imaging communities. We encourage continued

debate and reflection of published data regarding the impact of imaging on improving outcomes of patients with SCLC.

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Authors' Reply

We thank Manoharan et al for their interest in our recent publication.¹ Further, their recent analysis detailing the impact of FDG-PET/CT on outcomes of patients with limited-stage small cell lung cancer (LS-SCLC) in the context of the CONVERT trial (evaluating the utility of once- vs twice-daily radiation) is a helpful contribution to

the literature.² We agree that, for a number of reasons, level 1 evidence supporting the use of FDG-PET/CT in staging for SCLC is unlikely, and therefore, retrospective and longitudinal data such as our analyses are likely the best data sources.

Overall, we recommend that patients be staged as comprehensively as possible

at diagnosis and that available resources be maximized to allow for the best treatment decisions for individual patients. Our analysis of a mandatory audited database of the largest integrated US health system suggests that all patients with SCLC may benefit from PET staging. In their analysis of patients enrolled on

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the CONVERT trial, Manoharan et al were unable to identify a significant survival difference based on FDG-PET/CT in a small cohort of patients with good performance status. It is worth noting that their study may have been underpowered to identify this difference. As they point out, retrospective studies such as theirs and ours are subject to a number of sources of bias. We note that several important factors that could contribute to bias were accounted for in our analysis as much as possible, with multivariate adjustment and multiple iterations of propensity matching. Our most stringent match included the use of treating facility in addition to year and time-based factors in an attempt to minimize bias.

Importantly in the CONVERT trial, patients staged with FDG-PET/CT had additional benefits, including lower radiation doses to critical tissues such as the lung, heart, and esophagus, which may offer alternative avenues to improved overall survival with further data maturation. Radiation doses delivered to these critical structures, particularly the heart, impacted survival

outcomes in patients with non-small cell lung cancer in the landmark RTOG 0617 study.³ Manoharan et al additionally point out that a proportion of patients with low-burden metastatic disease not detected on CT but identified on FDG-PET/CT may benefit from curative intent thoracic chemoradiation. However, this contrasts with the findings of RTOG 0937, which randomized patients with extracranial oligometastatic extensive-stage SCLC to prophylactic cranial irradiation (PCI) alone versus PCI plus consolidative radiation therapy to intrathoracic and extracranial metastases after response to chemotherapy.⁴ This study crossed the futility boundary for survival. These patients were staged with either CT or PET/CT.

We thank Manoharan et al for their contribution and insights. We additionally anticipate the results of CALGB 30610 (ClinicalTrials.gov identifier: NCT00632853), another phase III trial randomizing patients with LS-SCLC to once- versus twice-daily radiation treatments and which encourages use of PET/CT for staging, to further contribute to this literature.

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