Doctopic: Analysis and Interpretation
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Less is more? Imaging-based target volume reduction

We congratulate Ursula Nestle and colleagues on the PET-Plan trial[1] for their work on reducing target volumes for chemoradiotherapy of patients with locally advanced non-small-cell lung cancer (NSCLC). The authors compared involved-field irradiation informed by ^{18}F-fluorodeoxyglucose (FDG)-PET with and without elective nodal irradiation. [A: OK?] Radiation dose was prescribed with an isotoxic escalation strategy (60–74 Gy). The non-inferiority of involved-field irradiation informed by ^{18}F-FDG-PET was shown and, more surprisingly, better locoregional control was seen, without a higher rate of out-of-field progression. These results could establish involved-field irradiation informed by ^{18}F-FDG-PET as the new standard of care.

The safety and efficacy of involved-field irradiation informed by ^{18}F-FDG-PET and elective nodal irradiation [A: OK?] for NSCLC has been previously studied.[2,3] In a retrospective cohort of 524 patients treated with involved-field irradiation,[2] 60% had pretreatment ^{18}F-FDG-PET, and omission of elective nodal irradiation was a safe strategy (only 6·1% of elective node failure). Findings of a randomised controlled study[3] showed better 5-year locoregional control (51% *vs* 36%; p=0·032) in patients assigned involved-field irradiation (68–74 Gy) compared with those assigned elective nodal irradiation (60–64 Gy).

Nestle and colleagues suggest that better locoregional control with involved-field irradiation informed by ^{18}F-FDG-PET [A: OK?] might be attributable to the ability to deliver increased doses (because of smaller volumes) and advocate for involved-field irradiation with higher doses. [A: correct?] We question the supposed benefit of radiation dose escalation.

First, despite better locoregional control, no benefit in survival was seen with involved-field irradiation informed by ^{18}F-FDG-PET (hazard ratio [HR] 1·21, 95% CI 0·79–1·84), compared with conventional targeting with ^{18}F-FDG-PET and elective nodal irradiation [A: OK?], which might be partly accounted for by more treatment-related deaths among patients assigned involved-field irradiation informed by ^{18}F-FDG-PET (13 *vs* seven in the conventional targeting group). Second, no data were available to show a possible correlation between locoregional control and dose. Third, analyses of Radiation Therapy Oncology Group (RTOG) trial 0617 (60 Gy *vs* 74 Gy)[4] showed lower survival in the high-dose arm (HR 1·35, 95% CI 1·08–1·69) and, counterintuitively, lower progression-free survival (HR 1·22, 95% CI 1·00–1·51) with less locoregional control. Elective nodal irradiation was not permitted in RTOG-0617, suggesting that involved-field irradiation with high doses might be neither efficient nor safe.

As greater thoracic vertebral and cardiopulmonary volumes spared are known to mitigate lymphopenia, we submit the hypothesis that improved locoregional control seen in patients assigned involved-field irradiation informed by ^{18}F-FDG-PET [A: correct?] in the study by Nestle and colleagues might be a result of less treatment-related lymphopenia because of lower volumes irradiated.[5] If this hypothesis proves correct, limiting irradiation of adjacent thoracic organs with restrictions of target volumes based on ^{18}F-FDG-PET and use of standard radiation dose would be of utmost importance in the era of adjuvant immunotherapy.

We declare no competing interests.

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1 Nestle U, Schimek-Jasch T, Kremp S, et al. Imaging-based target volume reduction in chemoradiotherapy for locally advanced non-small-cell lung cancer (PET-Plan): a multicentre, open-label, randomised, controlled trial. *Lancet Oncol* 2020; **21:** 581–92.

2 Rosenzweig KE, Sura S, Jackson A, Yorke E. Involved-field radiation therapy for inoperable non-small-cell lung cancer. *J Clin Oncol* 2007; **25:** 5557–61.

3 Yuan S, Sun X, Li M, et al. A randomized study of involved-field irradiation versus elective nodal irradiation in combination with concurrent chemotherapy for inoperable stage III nonsmall cell lung cancer. *Am J Clin Oncol* 2007; **30:** 239–44.

4 Bradley JD, Hu C, Komaki RR, et al. Long-term results of NRG Oncology RTOG 0617: standard- versus high-dose chemoradiotherapy with or without cetuximab for unresectable stage III non–small-cell lung cancer. *J Clin Oncol* 2020; **38:** 706–14.

5 Tang C, Liao Z, Gomez D, et al. Lymphopenia association with gross tumor volume and lung V5 and its effects on non-small cell lung cancer patient outcomes. *Int J Radiat Oncol Biol Phys* 2014; **89:** 1084–91.