***Robust comprehensive dataset gives pause for thought; reply to Salem et al***

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As reported [1] we agree that some uncertainty remains around patient selection as one of the potential determinants of outcome. Nevertheless, the marked geographical variation in the relative use of the two main dose fractionation regimens suggests that the selection is not principally patient specific. In the cohorts reported (patients receiving radiotherapy with radical intent) deprivation index was not an independent prognostic factor and does not explain the regional differences.

The authors suggest, without providing evidence, that data completeness and data quality may have compromised the analysis. It is correct that the data collection was transferred from NATCANSAT to the National Cancer Registration and Analysis Service within Public Health England (PHE) in April 2016 and therefore approximately 22% of the data in the validation cohort was collected by PHE. There is no suggestion that either the amount of data captured, or the data quality were compromised in the period between April 2016 and December 2016 and no reason to believe that, if even that had been the case, it would have resulted in uneven distribution between the two principal fractionation cohorts.

In the list of possible confounders suggested by Salem et al. all, except for performance status and volume of disease, have been corrected for. We believe that comorbidity, as obtained from HES, is a reasonable but admittedly not a fool proof surrogate for performance status. The authors appropriately point out the potential higher normal tissue toxicity associated with the hypofractionation regimen. Patients with larger volume tumours would therefore be more likely to be offered conventional fractionation and this is particularly likely to be the case when a significant portion of the heart and lung were to receive high radiation doses. This selection would compromise the outcome in the conventional fractionation group and hence is likely to strengthen the conclusion.

In our previous publication [2] we reported that NSCLC population outcome (i.e. all patients potentially eligible for radical radiotherapy, of which 17.6 % received it) was related to the regional variation in radiotherapy utilisation and the independent prognostic factors included among others the deprivation index. The study showed that the best outcome was not associated with the highest utilisation such as would be enabled by the increasing use of IMRT, but that treating beyond the "optimum" proportion of eligible patients results in decline in the NSCLC population survival.

Hypofractionated radiotherapy for NSCLC has been introduced in the UK on empirical grounds without high level evidence to support its widespread use. This has not been mirrored by general acceptance in other countries. We welcome the suggestion that the challenging and unexpected data warrants a future randomised controlled trial. While some of the differences in survival may be a result of as yet unaccounted for prognostic factors, the magnitude of difference, well beyond that seen with adjuvant and concomitant chemotherapy, would indeed argue in favour of revisiting dose fractionation to offer the best treatment to patients with NSCLC requiring radical radiotherapy.

1. Brada M, Forbes H, Ashley S, Fenwick J. Improving Outcomes in NSCLC: Optimum Dose Fractionation in Radical Radiotherapy Matters. *J Thorac Oncol* 2022; **17**(4): 532-43.
2. Brada M, Ball C, Mitchell S, Forbes H, Ashley S. Improving outcomes in non-small cell lung cancer; population analysis of radical radiotherapy. *Radiother Oncol* 2019; **132**: 204-10.