Stereotactic ablative radiotherapy with or without immunotherapy for early-stage or isolated lung parenchymal recurrent node-negative non-small-cell lung cancer: an open-label, randomised, phase 2 trial

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Lancet 2023 Sep 9;402(10405):871-881.
doi: 10.1016/S0140-6736(23)01384-3. Epub 2023 Jul 18.

Abstract

Background: Stereotactic ablative radiotherapy (SABR) is the standard treatment for medically inoperable early-stage non-small-cell lung cancer (NSCLC), but regional or distant relapses, or both, are common. Immunotherapy reduces recurrence and improves survival in people with stage III NSCLC after chemoradiotherapy, but its utility in stage I and II cases is unclear. We therefore conducted a randomised phase 2 trial of SABR alone compared with SABR with immunotherapy (I-SABR) for people with early-stage NSCLC.

Methods: We did an open-label, randomised, phase 2 trial comparing SABR to I-SABR, conducted at three different hospitals in TX, USA. People aged 18 years or older with histologically proven treatment-naive stage IA-IB (tumour size ≤4 cm, N0M0), stage IIA (tumour size ≤5 cm, N0M0), or stage IIB (tumour size >5 cm and ≤7 cm, N0M0) as per the American Joint Committee on Cancer version 8 staging system or isolated parenchymal recurrences (tumour size ≤7 cm) NSCLC ($T_{any}N_{any}M0$ before definitive surgery or chemoradiotherapy) were included in this trial. Participants were randomly assigned (1:1; using the Pocock & Simon method) to receive SABR with or without four cycles of nivolumab (480 mg, once every 4 weeks, with the first dose on the same day as, or within 36 h after, the first SABR fraction). This trial was unmasked. The primary endpoint was 4-year event-free survival (local, regional, or distant recurrence; second primary lung cancer; or death). Analyses were both intention to treat (ITT) and per protocol. This trial is registered with ClinicalTrials.gov (NCT03110978) and is closed to enrolment.

Findings: From June 30, 2017, to March 22, 2022, 156 participants were randomly assigned, and 141 participants received assigned therapy. At a median 33 months' follow-up, I-SABR significantly improved 4-year event-free survival from 53% (95% CI 42-67%) with SABR to 77% (66-91%; per-protocol population, hazard ratio [HR] 0·38; 95% CI 0·19-0·75; p=0·0056; ITT population, HR 0·42; 95% CI 0·22-0·80; p=0·0080). There were no grade 3 or higher adverse events associated with SABR. In the I-SABR group, ten participants (15%) had grade 3 immunologial adverse events related to nivolumab; none had grade 3 pneumonitis or grade 4 or higher toxicity.

Interpretation: Compared with SABR alone, I-SABR significantly improved event-free survival at 4 years in people with early-stage treatment-naive or lung parenchymal recurrent node-negative NSCLC, with tolerable toxicity. I-SABR could be a treatment option in these participants, but further confirmation from a number of currently accruing phase 3 trials is required.