Editorial

A promising result of locoregional tumor control with biologically adaptive radiotherapy in patients with locally advanced non-small cell lung cancer

Yukinori Matsuo

Department of Radiation Oncology and Image-applied Therapy, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Correspondence to: Yukinori Matsuo. Department of Radiation Oncology and Image-applied Therapy, Graduate School of Medicine, Kyoto University, Kyoto, Japan. Email: ymatsuo@kuhp.kyoto-u.ac.jp.

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Concurrent chemoradiotherapy (CCRT) is the standard treatment option for unresectable locally advanced non-small cell lung cancer (LA-NSCLC) (1). Radiotherapy with a dose of 60–66 Gy and platinum-based doublet chemotherapy are commonly used in CCRT. However, outcomes with the standard treatment are not satisfying with a median survival of approximately 20 months. Both locoregional tumor recurrence and distant metastasis are potential obstacles in the treatment of LA-NSCLC.

Recently published data from the PACIFIC study indicated that durvalumab will become a game-changer in the treatment of LA-NSCLC (2). The study randomized 713 patients to receive CCRT with durvalumab for consolidation therapy or CCRT with a placebo. The durvalumab group showed significantly better progression-free survival than the placebo (16.8 versus 5.6 months in median). The better progression-free survival was mainly due to a lower rate of distant metastasis with durvalumab treatment. Median metastasis-free survival time was 23.2 months among those in the durvalumab group and 14.6 months among those in the placebo group. Distant metastasis in LA-NSCLC treatment might be overcame after the PACIFIC study. Exact data on locoregional failure were not provided for the PACIFIC study. It seems like quite a few patients in both groups developed locoregional failure when considering that the difference between progression-free survival and the metastasis-free survival corresponds to the locoregional failure.

Radiotherapy plays a main role in locoregional tumor control (LRTC) in the treatment of LA-NSCLC. Radiation oncologists previously believed that a higher dose of radiotherapy would result in better LRTC and better survival. The Radiation Therapy Oncology Group (RTOG) 0617 trial was conducted based on this belief (3). That was a randomized two-by-two factorial phase 3 study that compared two factors in CCRT for LA-NSCLC: the radiotherapy dose (standard dose of 60 Gy *vs.* high dose of 74 Gy) and the use of cetuximab. The use of cetuximab had no significant effect on survival outcomes. Regarding the radiotherapy dose, contrary to the expectation, overall survival was significantly worse in the high-dose group than in the standard-dose group (median survival time of 20.3 and 28.7 months, respectively; P=0.004). More surprisingly, the cumulative incidence of local failure was higher in the high-dose group (39.0% and 30.4% at 2 years for the high- and low-dose groups, respectively; P=0.19). The exact reasons for such inferior outcomes with the high-dose group are still unclear. The RTOG trial suggested that uniform dose escalation over all lesions in 2-Gy fractions might not contribute to improvement of outcomes in CCRT for LA-NSCLC.

This editorial introduces a paper based on a phase 2 trial of biologically adaptive radiotherapy (ART) for LA-NSCLC based on mid-treatment ^{18}F-fluorodeoxyglucose-positron

emission tomography/computed tomography (FDG-PET/CT) published in *JAMA Oncology* in 2017 (4). The phase 2 trial was conducted by Kong *et al.* at two academic medical centers with 42 patients who had inoperable or unresectable stage II to stage III NSCLC. Radiotherapy was delivered in 30 daily fractions of 2.1–5.0 Gy. At the initial phase of the treatment, fractional doses of 2.1–2.85 Gy were administered for a total of approximately 50 Gy. During the treatment, a FDG-PET scan was taken to identify FDG-avid lesions. Then, escalated doses of 2.85–5.0 Gy per fraction were delivered to the FDG-avid tumor in the adaptive phase. The total physical dose was limited to 86 Gy, which kept the normal lung tissue complication probability (NTCP) lower than 17.2%. This novel treatment approach achieved a high in-field LRTC of 82%. Radiation pneumonitis of grade 2 or worse was observed in 7 patients (16.6%) as expected from the pre-determined NTCP of the lung. Median survival was 25 months, and the 2-year overall survival was 52%. The trial by Kong *et al.* had two noteworthy aspects. First, radiotherapy dose escalation was implemented without prolongation of the overall treatment time, and second, biologically ART was used. This editorial focuses on the latter aspect.

ART is a technique that adjusts the radiotherapy plan according to the anatomical change of the tumor and surrounding normal tissues during the treatment course. The ART approach allows us to reduce normal tissue doses and to escalate the radiotherapy dose to the tumor if necessary. The concept of ART partially overlaps with image-guided radiotherapy (IGRT). The ART would be classified into the following 3 categories according to its level of adaptation: (I) point adaptation; (II) volumetric adaptation; and (III) biological adaptation. The point-based adaptation is associated with the IGRT concept. Differences in the patient's position throughout the treatment plan are measured based on an arbitrary point (bony structure or tumor itself) at each treatment fraction using imaging modalities including stereo fluoroscopy, cone-beam CT, and magnetic resonance imaging (MRI). Then, the positional difference (= setup error) is corrected based on the arbitrary measurement. The IGRT can reduce margins that are required to compensate the setup error and to help to make radiotherapy highly conformal to the tumor. This is a key component of stereotactic body radiotherapy. The volumetric ART adapts the radiotherapy plan to morphological changes, which occur during the treatment course; these changes are assessed according to mid-treatment CT scans. The volumetric ART helps us to reduce doses to surrounding normal tissues when the tumor shrinks, or to ensure the tumor dose is efficient if the tumor enlarges during the treatment. Ramella *et al.* reported results from the LARTIA trial which was a prospective trial evaluating volumetric ART for LA-NSCLC (5). Patients underwent weekly chest-CT during CRT for their LA-NSCLC. When target reduction was observed, replanning was performed. Replanning was applied to 50 patients from a total of 217 patients. In the 50 patients, the severe pulmonary toxicity rate was reported to be as low as 4%. Local failure did not increase with this strategy (20% and 4% for in-field and out-field local failure, respectively). Low application rate of the replanning (50 of 217 patients) should be noted as a limitation of CT-based ART. The volumetric ART considers only morphological changes of the tumor and normal tissues. However, during treatment, biological changes occurred earlier than the morphological changes. Functional imaging such as FDG-PET (6) and diffusion-weighted MRI (7) can be used to detect the biological changes. The biologically ART allows us to modify the radiotherapy plan keeping high doses to highly active tumor regions. Kong *et al.* applied the biologically ART to LA-NSCLC treatment to escalate radiotherapeutic doses to biologically active tumors while keeping normal tissue doses within a certain level of NTCP. To the best of my knowledge, Kong *et al.*'s trial is the first phase 2 trial evaluating biologically ART for LA-NSCLC.

Kong *et al.*'s biological ART trial achieved an excellent in-field LRTC of 82%. However, 13 of the 42 enrolled patients developed local-regional failure, including three patients with isolated nodal failure. As a result, the overall LRTC was reported to be 62%, which was similar to the result in the standard arm of RTOG 0617. Regarding survival, the median survival of 25 months was also similar to that in the standard arm of RTOG 0617. The true value of this biological ART approach should be validated in a large scale clinical trial. The results of the RTOG 1106—a phase 2 trial—that compared the PET-based ART proposed by Kong *et al.* with the standard CCRT of 60 Gy, are yet to be determined; however, promising results are expected.

LRTC will be a key aspect in the treatment of LA-NSCLC in the era of immune checkpoint inhibitors. The biologically ART approach might contribute to better locoregional control.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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