Editorial

Precision radiotherapy for patients with locally advanced non-small cell lung cancer in the era of immunotherapy and precision medicine

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A report by Roswit *et al.* published in 1960 showing that radiotherapy extended the survival of patients, compared with no treatment, is the oldest finding demonstrating the significance of radiotherapy for the treatment of lung cancer (1). In the 1970s, a randomized trial (Radiation Therapy Oncology Group, RTOG 7301) was conducted to select the optimum dose from 40 to 60 Gy (2), and 60 Gy was established as the subsequent standard dose. Since then, thoracic radiotherapy has played an important role in treatment strategies for non-small cell lung cancer (NSCLC).

In 1995, a meta-analysis including multiple trials of chest radiotherapy alone and a chest chemoradiotherapy comparative trial was reported (3). As a result, the significance of adding chemotherapy as a systemic therapy in addition to treatment centered on local treatment, such as chest radiotherapy and surgery, was shown. However, even when radical chemoradiotherapy is performed, distant metastasis such as metastasis to the brain, bone, liver can occur at sites of exacerbation and recurrence for a considerable time. In recent reports, about 60% of lung cancer patients eventually experience in distant metastasis (4-8). Therefore, the reinforcement of systemic treatment is an important issue. The drugs used for chemoradiotherapy have changed with progress in anticancer drugs for the treatment of advanced NSCLC. Randomized trials of traditional regimens such as MVP therapy (mitomycin C, vindesine and cisplatin) and cisplatin + etoposide and new drugs (carboplatin, paclitaxel, docetaxel, vinorelbine and pemetrexed) have been conducted (4,5). In the PROCLAIM study, the superiority of cisplatin plus pemetrexed to cisplatin plus etoposide was examined (8). Cisplatin plus pemetrexed, which showed great results for stage IV NSCLC, was expected to achieve favorable results in patients with locally advanced NSCLC. Unfortunately, the results were negative, and pemetrexed did not exceed etoposide in terms of efficacy. Although the superiority of the new regimen to the old regimen was not shown, the safety advantages of the new regimen have been confirmed, and new regimens are now being introduced in clinical settings.

Recently, a huge paradigm shift in medical treatment for patients with locally advanced NSCLC has occurred. Basic research findings have shown that PD-L1 is expressed after radiation treatment, suggesting that the ability of immune cells to attack cancer cells is suppressed (9). Based on this finding, an immune checkpoint inhibitor that had been successfully used for the treatment of advanced disease was also used in patients with locally advanced NSCLC (PACIFIC) (10). As a result, a clear prolongation of the progression-free survival (PFS) period was confirmed for the group in which durvalumab was used as a consolidation therapy after radical chemoradiotherapy. The median PFS after the beginning of consolidation therapy was 5.6 months in the control group and 16.8 months in the group that received durvalumab after chemoradiotherapy. Promising results are expected also for the overall survival period,

which will be reported in the near future.

Furthermore, precision medicine has begun to attract attention as a treatment strategy for stage IV NSCLC to improve systemic treatment. In response to this movement, clinical trials to examine the significance of molecular targeted drugs and immunotherapy for stage III NSCLC have been progressing. Epidermal growth factor receptor (EGFR) is considered to be important for tumor growth, invasion and metastasis. Attempts have been made to introduce antibody therapy for EGFR into locally advanced NSCLC. The RTOG0617 trial sought to verify the significance of adding the anti-EGFR antibody cetuximab to standard chemoradiotherapy (11). Unfortunately, a survival extension was not obtained. Currently, two clinical trials [RTOG1306 (NCT01822496) and LOGIK1105 (UMIN000005086)] involving the use of an EGFR tyrosine kinase inhibitor (TKI) as an introduction therapy for chemoradiotherapy in patients with stage III NSCLC harboring an *EGFR* mutation are underway. In addition, two clinical trials [RTOG1306 (NCT01822496) and SAKULA (UMIN000017906)] using ALK-TKI as an induction therapy before local therapy (chemoradiotherapy and/or surgery) for patients with stage III NSCLC harboring and *ALK* fusion are being conducted.

How about radiotherapy? In 2004, a phase I trial was conducted by Socinski *et al.* to explore extensive dose escalation (12). The study concluded that high dose chest radiotherapy up to 90 Gy can be performed safely with concurrent chemotherapy. However, patient selection to suppress the occurrence of adverse events was necessary, thus, high doses of up to 90 Gy could only be implemented in a very limited number of cases. Indeed, the Phase III trial (RTOG0617) based on the results of this study selected 74 Gy as the dose for the study treatment rather than a high dose of above 78 Gy. The RTOG0617 trial aimed to improve the outcome of locally advanced NSCLC treatment by improving local control. Standard 60 Gy chest radiation was compared with 74 Gy high-dose chest radiotherapy (11). Unexpectedly, the survival time (28.7 months) of the standard radiotherapy group exceeded the survival period (19.5 months) of the high-dose group, and the significance of high-dose chemoradiotherapy was not confirmed. The study suggested that radiotherapy quality control, radiation toxicity (especially cardiotoxicity and pulmonary toxicity) might have affected the test results.

Thoracic radiotherapy using proton has gained attention, while the reinforcement of radiotherapy using photon has reached a certain limit. After entering the body, proton do not emit energy near the surface and instead releases energy just before it coming to a stop (Bragg peak). The Bragg peak delivers a large dose of energy to the target tissue, which is an important feature of proton therapy. Adjusting the Bragg peak according to the position and size of the lesion can increase the therapeutic effect while suppressing adverse events. To verify the significance of proton therapy for the treatment of locally advanced lung cancer, a randomized trial [RTOG 1308 (NCT 01993810)] is being implemented.

Another method that is under consideration for simultaneously improving treatment results by strengthening radiotherapy and reducing toxicity is irradiation field setting using PET. This technique is called FDG-PET/CT-guided adaptive radiation (PART), and the results of a phase II study have been reported for the first time (13). The primary endpoint was local-regional tumor control (LRTC) at 2 years. The LRTC was 82%, which achieved a primary endpoint and was substantially better than the LRTC (54–69%) in the RTOG 0617 and PROCLAIM trials. A strategy to improve effectiveness while suppressing toxicity by adjusting the irradiation field according to PET/CT findings during radiotherapy is currently being studied in a phase III trial [RTOG1106 (NCT01507428)].

The further innovation of multidisciplinary therapy (medical treatment, radiotherapy and surgery) is indispensable for improvement in the treatment outcome of stage III NSCLC. Immunotherapy (PACIFIC) has opened up a new era in medical treatment. In addition, the introduction of precision medicine, such as EGFR- and ALK-targeted therapies, is progressing. Precision radiotherapy using proton (PART) is expected to become the next big wave in treatment.

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Footnote

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