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Rapidly Growing Locally Advanced Non-Small Cell Lung Cancer Treated with Definitive Chemoradiotherapy Using Adaptive Volumetric Modulated Arc Therapy Followed by Durvalumab Maintenance: A Case Report

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 43-year-old
Final Diagnosis: Lung cancer
Symptoms: —
Medication: —
Clinical Procedure: —
Specialty: Oncology • Radiology

Objective: Unusual or unexpected effect of treatment

Background: It is difficult to reduce lung toxicity in chemoradiotherapy for locally advanced lung cancer. Volume-modulated arc therapy (VMAT) is a useful lung dose-lowering radiation technique, but it is time-consuming because of its complexity. We present a case of a rapidly growing bulky lung cancer treated with VMAT and intensive adaptation to volume change.

Case Report: A 43-year-old man with chest pain was diagnosed with non-small cell lung cancer, cT4N3M0 stage IIIC (UICC 8th edition). Concurrent chemoradiotherapy with a VMAT of 60 Gy in 30 fractions and carboplatin/paclitaxel was performed. Despite initiating chemoradiation, monitoring with cone-beam computed tomography (CT) revealed tumor progression. The peak tumor volume was 1.5 times larger than that on CT simulation. The VMAT plan was recreated to cover the increased tumor size. After the irradiation field was enlarged, the tumor, on the contrary, shrank rapidly. Therefore, VMAT planning was performed again to further shrink the irradiation field. CT at the end of the treatment showed a good volume reduction response. Durvalumab therapy was continued for 1 year. After that, the patient was alive and showed no sign of progression. Only asymptomatic radiation pneumonitis was observed as a sub-acute adverse event.

Conclusions: We present a case in which proper adaptive VMAT and durvalumab for dramatically progressive non-small cell lung cancer were effective, resulting in 1-year progression-free survival. Even when rapid progression of bulky lung cancer is suggested, the combination of VMAT and adaptive radiotherapy with improved target coverage and reduced lung dose can be a treatment option.

Keywords: Chemoradiotherapy • Durvalumab • Lung Neoplasms • Radiation Oncology • Radiotherapy, Image-Guided • Radiotherapy, Intensity-Modulated

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Background

Definitive chemoradiotherapy is the standard of care for unresectable, locally advanced non-small cell lung cancer (NSCLC). Owing to the improved overall survival derived from durvalumab maintenance [1], the significance of radiotherapy as a local treatment is increasing. Radiation pneumonitis is a serious adverse event in chemoradiotherapy for lung cancer, and the incidence and severity of radiation pneumonitis depend on the volume of the irradiated normal lungs. Severe radiation pneumonitis not only causes accidental fatal situations but also causes interruptions in the maintenance of durvalumab, exacerbating the long-term outcome of lung cancer treatment. The volume of a normal lung receiving 20 Gy (lung V20) and the mean lung dose (MLD) represent dosimetric parameters used to identify the risk of radiation pneumonitis. To minimize the risk of radiation pneumonitis while using durvalumab, lung V20 or MLD should be reduced as much as possible [2].

One of the recent advances in radiotherapy for lung cancer is the introduction of intensity-modulated radiotherapy, including volumetric modulated arc therapy (VMAT), which can achieve better dose coverage for tumors and lower doses for organs at risk (OARs) than three-dimensional conformal radiotherapy (3DCRT) [3,4]. In the delivery of VMAT, image-guided radiotherapy, including daily image acquisition with cone-beam CT (CBCT), is a popular strategy for both patient position correction and recognition of anatomical changes [5,6]. The technique of modification of radiation treatment planning with the use of information obtained from these imaging devices is called adaptive radiotherapy [6-8]. Previous reports of adaptive radiotherapy focused on local shift and shrinkage of the radiation field, which reduced the dose to OARs [6,9].

Thus, VMAT has the advantage of improved dose coverage and reduced dose to OARs. However, it also has disadvantages. First, since planning and quality assurance (QA) for VMAT is time-consuming [10,11], most medical facilities take more than a few days from the acquisition of CT simulation to the start of VMAT. Thus, VMAT is often considered a contraindication when radiation oncologists predict a dramatic change in tumor shape or size. Second, the extension of the overall survival in patients with NSCLC by VMAT has not been proven to date [12,13]. Chemoradiotherapy for bulky lung cancer is a high-risk treatment for toxicity. However, at this time, it is believed that the best treatment for bulky stage III NSCLC is to try radical chemoradiation and introduce durvalumab as adjuvant therapy if the lung dose remains within acceptable limits. In such cases, VMAT is a very useful irradiation technique for reducing the dose of OARs, including the lung dose.

To the best of our knowledge, no study has reported the achievement of local control of rapidly growing, locally advanced NSCLC using adaptive VMAT modulated multiple times to cope with the rapid growth and shrinkage of the tumor.

The present study reports a case of a rapidly growing, locally advanced NSCLC that continued to progress drastically even after the start of definitive chemoradiotherapy and shifted to rapid shrinkage after the peak time.

Case Report

A 43-year-old man presented with pain in the right chest, axilla, and shoulder region for approximately a month. On day -37, he visited his local doctor, and a chest computed tomography (CT) (**Figure 1A**) showed a 70.5×50.8 mm elliptical tumor in the S2 of the right lung, and enlarged hilar lymph nodes. The patient was suspected to have a malignant lung tumor. On day -34, he was referred to the Department of Respiratory Medicine at our hospital for close examination and treatment. His ECOG performance status was 1. No sputum or hemoptysis was observed. He had no particular medical history or occupational exposure to any risk factors. He had no regular medication. He was a current smoker (25 pack-years). There were no significant elevations in serum tumor markers. On day -18, contrast-enhanced CT showed a well-defined mass with a broad base bordering the pleural surface of the right upper lobe, which was suspicious of lung cancer, suggesting chest wall invasion (**Figure 1B**) with right supraclavicular fossa and right hilar lymph node metastasis. The primary tumor volume in this image was approximately 250 cm^3. PET/CT and brain MRI with contrast enhancement showed no distant metastases. Ultrasound-guided biopsy of the primary tumor led to a diagnosis of NSCLC with no specific differentiation tendency. PD-L1 expression by immunohistochemistry was low (TPS <1%). The result of molecular testing and immunostaining was as follows: EGFR mutation (-), ROS-1 fusion (-), ALK fusion (-), BRAF V600E mutation (-), CD56 (+-), TTF-1 (-), p40 (-), p63 (-), Napsin A (-), synaptophysin (+-), and chromogranin (-). The percentage of Ki-67 positive cells was approximately 95%. The cancer stage was evaluated as cT4N3M0 stage IIIC according to the Union for International Cancer Control (UICC) 8th edition, and definitive concurrent chemoradiotherapy followed by maintenance immune checkpoint inhibitor treatment was administered.

On day -4, the patient underwent CT simulation (**Figure 1C**), which revealed increment in the tumor size (102×75.4 mm) compared to the CT on day -18. The definitions of irradiated volume and procedures of initial VMAT were as follows: the clinical target volume for the primary tumor and the metastatic lymph node was constructed by adding a 0.5 cm margin to the gross tumor volume; the clinical target volume for the lymph node area included #1R, #2R, #4R, and #10R; the planning target volume was constructed by adding a 0.5 cm

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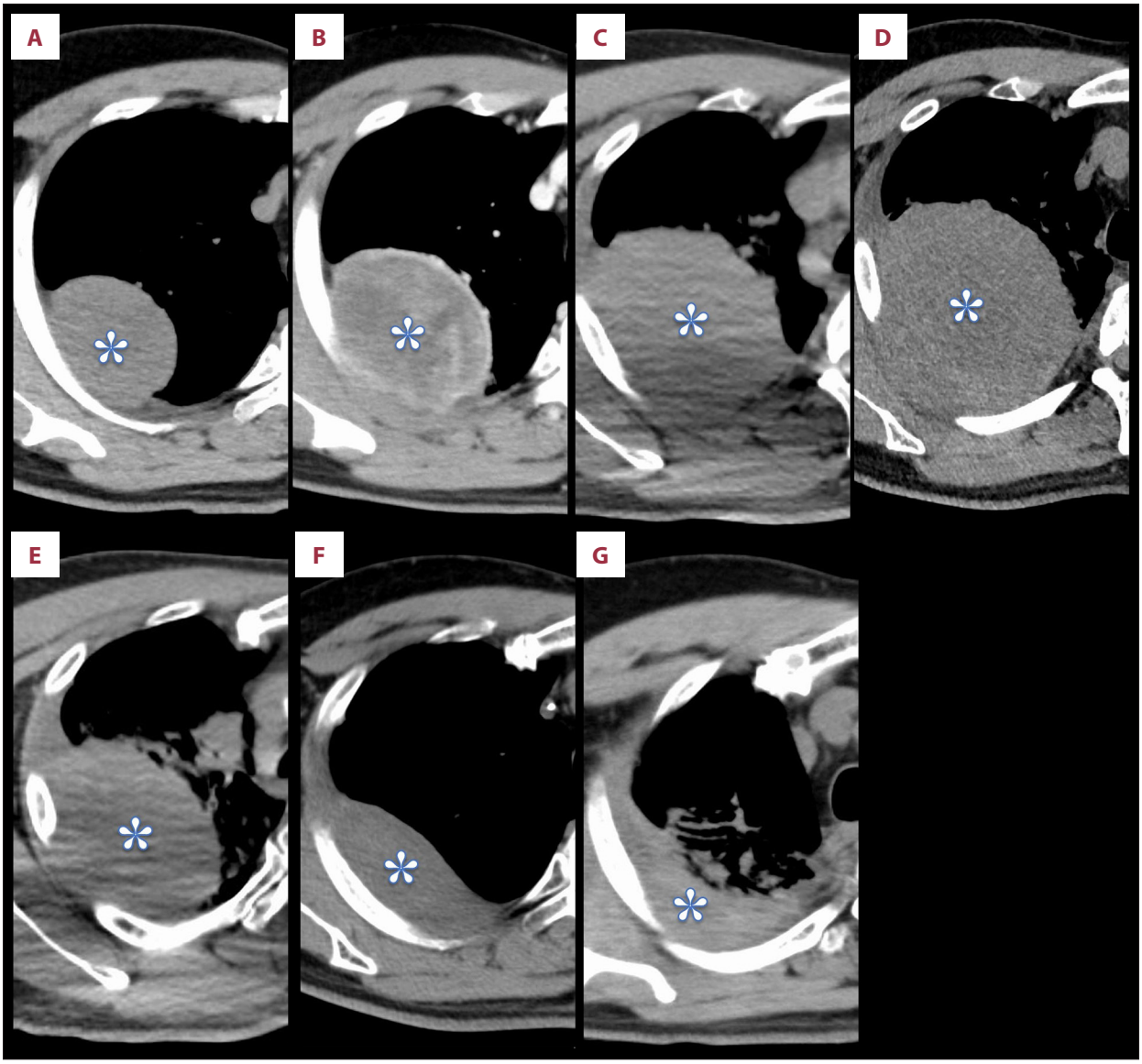

Figure 1. CT axial images before and during the treatment. A (Day -37), B (Day -18), C (Day -4), D (Day 11), E (Day 29), F (Day 51), G (Day 282). A, B, images before treatment; C-F, images during chemoradiotherapy; G: follow-up CT image taken during durvalumab maintenance. The asterisk indicates a primary tumor.

margin to the clinical target volume; the VMAT plans consisted of 2 full-rotation arcs for decreasing the dose to the lungs, and 10-MV energy x-rays; the dose of 60 Gy in 30 fractions was prescribed as the mean dose to the planning target volume; the lung V20 was 21.1%, and the lung volume receiving at least 5 Gy (lung V5) was 39.9% (Figure 2A-2C). We performed distribution verification using a diode array dosimeter and dose verification using an ionization chamber as the QA. VMAT was started on day 1, and concurrent carboplatin and paclitaxel chemotherapy was started on day 4. Daily CBCT monitoring revealed further increase in the primary tumor volume in the first week of treatment. On day 11, a diagnostic CT (Figure 1D) also showed an increasing trend in the tumor without necrosis or infection. The primary tumor volume reached a peak of approximately 650 cm^3. The daily CBCT imaging showed that the tumor growth approached the edges of the target volume, and we decided to adapt the irradiation plan for tumor growth. We performed a second CT simulation on day 16. After confirming that the tumor shrinkage was not observed, we decided to create a new VMAT plan for adaptation to the increase in tumor size (Figure 2D-2F). Treatment with the new VMAT plan was commenced on day 22, and from day 25, the daily CBCT showed a reduction in tumor volume in response to the treatment. As the tumor size decreased, pain improved significantly. After performing the third CT simulation (Figure 1E) on day 29, the final boost VMAT plan adapting to

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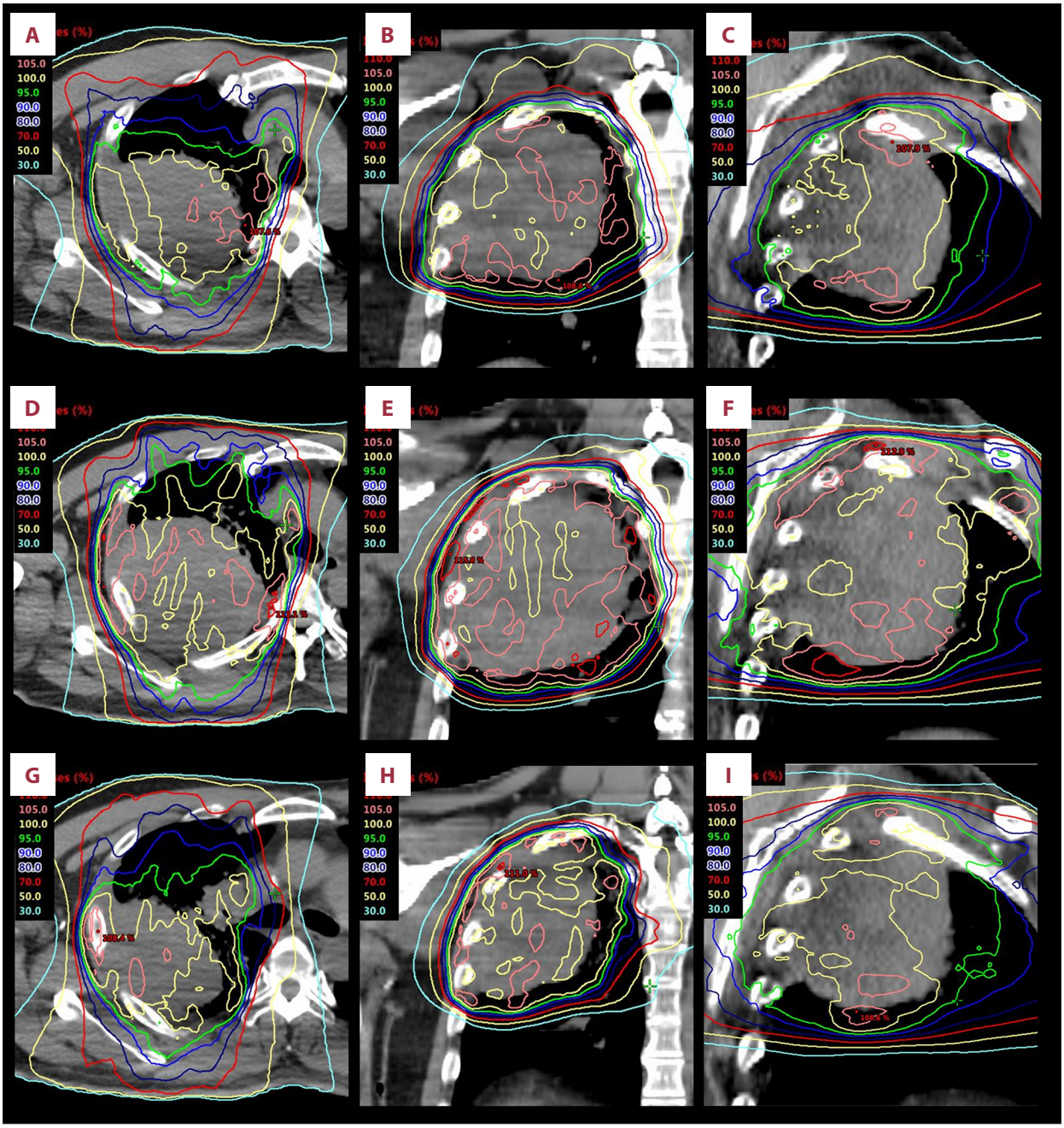

Figure 2. A-C, dose distribution of the initial plan; **D-F**, dose distribution of the second plan adapted to tumor progression; **G-I**, dose distribution of the third plan adapted to tumor shrinkage. The colored lines indicate isodoses.

the volume reduction of the tumor was started from day 33. The lung V20 of the combined plans was 23.4% (**Figure 2G-2I**). Concurrent chemoradiotherapy was completed on day 43 without suspension of treatment. During chemoradiotherapy, no acute adverse events occurred other than grade 2 hematological toxicity (CTCAE Version5.0). A diagnostic CT scan (**Figure 1F**) on day 46 showed drastic reduction in the tumor volume (approximately 100 cm^3). The change in the primary tumor volume in the course of treatment is shown in **Figure 3**. Maintenance therapy with durvalumab was started on day 51 and continued for 1 year. Diagnostic CT evaluation was performed every 3 months, and the latest CT scan was taken on day 282 (**Figure 1G**). The tumor volume continued to shrink during durvalumab maintenance therapy. The opioid analgesic medication was continually tapered without recurrence of the pain. Asymptomatic radiation pneumonitis was observed, but it did not require any specific treatment. The patient was alive without tumor progression at 1 year after chemoradiotherapy.

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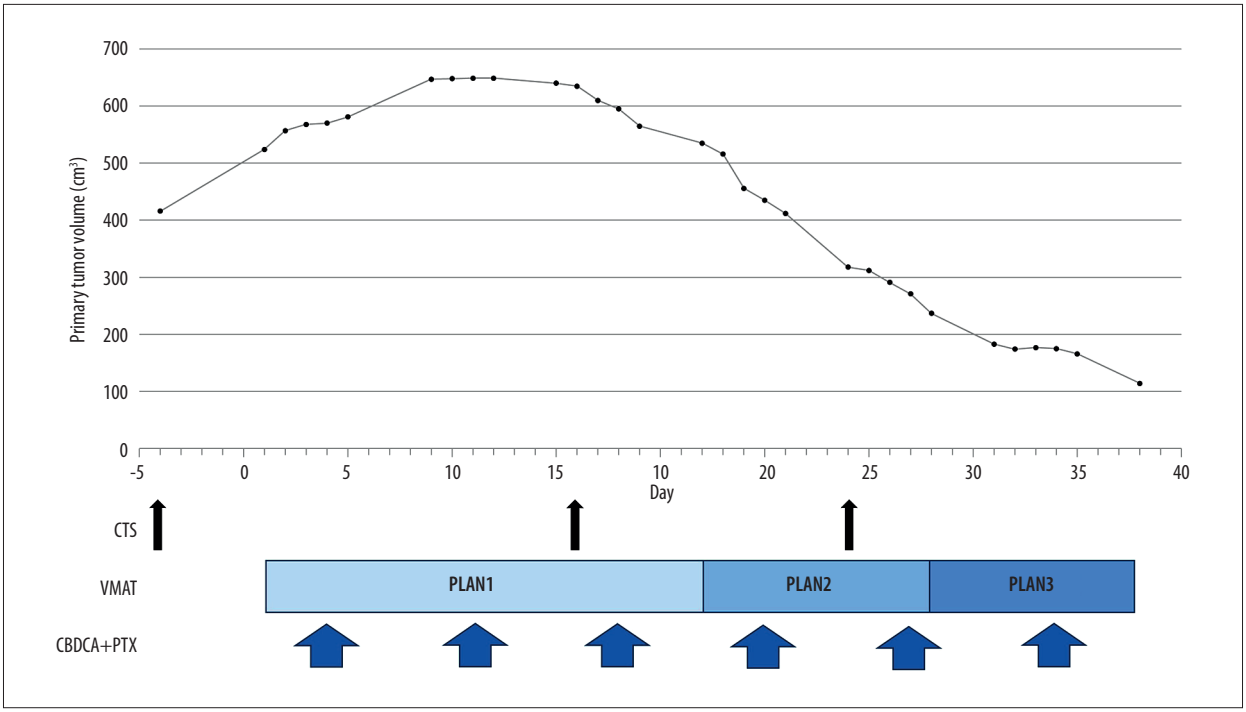

Figure 3. Treatment schedule compared to the change in primary tumor volume. Thin black arrows indicate the date of planning CT. Bold blue arrows indicate the date of chemotherapy administration. CTS – computed tomography simulation; VMAT – volumetric modulated arc therapy; CBDCA – Carboplatin; PTX – Paclitaxel.

Discussion

This is the first report on definitive chemoradiotherapy using adaptive VMAT for drastically progressive NSCLC, resulting in the completion of durvalumab maintenance therapy and achievement of 1-year local control after chemoradiotherapy. To discuss the indication of adaptive VMAT for rapidly growing NSCLC, the following 3 points are taken into consideration: first, the growing importance to further reduce the lung dose in the era of immune checkpoint inhibitors; secondly, the shortening of the planning and QA procedures of VMAT, and lastly, the time lag between the day treatment is commenced and the day the reduction in tumor volume is first observed.

In the present case, the patient completed durvalumab maintenance therapy without developing grade 2 or higher pneumonia. The development of radiation pneumonitis interferes with the completion of durvalumab maintenance therapy and may lead to worse clinical outcomes. Thus, it is desirable to reduce the dose to the lungs as much as possible. As in previous reports [3,4], VMAT can achieve better dose coverage to the tumor than 3DCRT, especially in the case of tumors with distorted shapes; at the same time, the dose to the lungs can be kept low. In the present case, the clinical adaptive VMAT plans were able to lower the lung V20 compared to the referential 3DCRT plan (VMAT vs 3DCRT: lung V20 23.4% vs 25.7% and MLD 13.7% vs 14.7%, respectively). Two replans of the VMAT played an important role in reducing the lung dose while ensuring dose to tumors whose size varied widely during treatment.

The main concern when applying VMAT to rapidly growing tumors is that VMAT has a longer delay between the date of simulation CT and the start of treatment compared to 3DCRT. If the tumor continues to grow after the onset of treatment, a situation may arise where it is inappropriate to continue the original treatment plan. The worst-case scenario could be that the growth rate during the delay was too fast, so that even the newly made VMAT plan is already inappropriate at the starting time. On the other hand, even for rapidly shrinking tumors, it is important to change the VMAT plan promptly, and a long delay before changing the plan can be a factor in increasing the dose to the normal tissues surrounding the tumor. These concerns are at the root of avoiding VMAT for tumors that rapidly change in volume and shape. However, in recent years, the two-or-three-dimensional array detector has replaced the role of validation with radiographic film, and the time required for QA procedures is getting shorter [14]. Moreover, further simplification of the QA procedure has been attempted in some research [10,11]. The shorter the time for completing the planning of VMAT, the greater the chance of using adaptive VMAT. Owing to the development of QA tools, the combination of VMAT and adaptive RT can be an option for the treatment of rapidly growing tumors.

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In the present case, the tumor volume changed significantly during treatment. The tumor grew in size for 2 weeks after the start of treatment, and then suddenly began to shrink. In experimental tumors, it has been observed that there is a delay between the start of irradiation and the start of tumor shrinkage, even if the tumor is eventually controlled [15,16]. Even in clinical cases, it is presumed that this delay may actually occur in tumors with rapid growth. Thus, continued tumor progression in the early stages of treatment does not necessarily mean abandonment of the first definitive chemoradiotherapy. In the present case, adaptive VMAT and adjuvant durvalumab therapy were effective for rapidly growing NSCLC. Continuation of chemoradiation therapy for locally advanced NSCLC with adaptive VMAT may be effective even if the growth trend continues after the start of treatment.

Conclusions

In this report, we present a case in which proper adaptive VMAT and durvalumab maintenance therapy for dramatically progressive NSCLC was effective, resulting in 1-year progression-free survival. Even when rapid tumor progression is suggested, the combination of VMAT and adaptive RT may be an option to achieve control of locally advanced lung cancer by providing good coverage of the growing PTV. Conversely, when the tumor has shrunk with treatment, VMAT can be adapted to reduce the lung dose and the risk of radiation pneumonitis. For rapidly growing locally advanced lung cancers, chemoradiotherapy with multiple adaptations of VMAT has shown good results by both providing good PTV coverage and reducing the OAR dose. Although adaptive VMAT may need modulation multiple times to cope with the changes in tumor volume, drastic tumor growth after the start of chemoradiotherapy does not necessarily mean that adaptive VMAT is not indicated.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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