Original Article

Pulmonary aspergillosis as a late complication after surgery for locally advanced non-small cell lung cancer treated with induction chemoradiotherapy

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Abstract

Purpose: Some long-term survivors after surgery for locally advanced non-small cell lung cancer (NSCLC) treated with induction chemoradiotherapy (trimodality treatment) develop chronic pulmonary aspergillosis (CPA). The aim of our study was to assess the characteristics and outcomes of CPA that develops after trimodality treatment.

Methods: We retrospectively reviewed the data of 187 NSCLC patients who underwent trimodality treatment between 1999 and 2018.

Results: Six male ever-smoker patients developed CPA. All 6 patients had undergone extended resection for NSCLC and had a history of either adjuvant chemotherapy (n=3) or radiation pneumonitis (n=4). Among the 4 patients with CPA localized in a single lung, 3 patients were treated surgically (completion pneumonectomy or cavernostomy) and 1 patient was treated with antifungal therapy alone. Both treatments led to the improved control of CPA. In contrast, patients with CPA in both lungs were not candidates for surgery, and died of CPA. The survival rates after trimodality treatment in the CPA group and the group without CPA were comparable (10-year survival rate, 50.0% vs. 57.6%, *P*=0.59).

Conclusion: The early diagnosis of CPA localized in a single lung after NSCLC surgery is critical to improving control and survival in patients with CPA.

Keywords: lung cancer; aspergillosis; surgery; radiation; chemotherapy

Introduction

Chronic pulmonary aspergillosis (CPA), including simple aspergilloma and chronic cavitary pulmonary aspergillosis, sometimes develops in non-immunocompromised patients with prior or current lung disease [1]. Risk factors for CPA include chemotherapy [2], radiotherapy, thoracic surgery, and lung cancer [3-6], which are inevitable in patients who have undergone induction chemoradiotherapy followed by surgery for non-small cell lung cancer (NSCLC). Induction chemoradiotherapy followed by surgery has been shown to be a feasible therapeutic option for patients with locally advanced NSCLC [7], and this trimodality therapy for NSCLC has been shown to provide favorable long-term results [8], which have led to an increase in survivors of NSCLC. Thus, long-term survivors may develop CPA due to risk factors for CPA that are involved in trimodality therapy, despite the irradiated lung containing the NSCLC being resected at surgery. Furthermore, the risk of CPA may be increased by chronic obstructive lung disease, which is a common comorbidity of ever-smoker NSCLC patients as well as by prolonged corticosteroid therapy for radiation pneumonitis, which sometimes develops as a complication after chemoradiotherapy [1, 6, 9]. Although evidence has accumulated on the treatment of NSCLC by induction chemoradiotherapy followed by surgery [10], little information is available in relation to CPA after the trimodality therapy. The aim of our study was to assess the characteristics and outcomes of CPA after surgery for locally advanced NSCLC treated by induction chemoradiotherapy.

Methods

Patients

Trimodality therapy has been performed to treat NSCLC patients with mediastinal nodal

metastasis. It has also been selectively applied to the treatment of localized N3 or T3-4N0-1M0 and, at the physician's discretion, to patients with large or invasive tumors, such as bulky N1 tumors with chest wall invasion, or T4 involvement, as a means of achieving complete resection with a pathologic safety margin [11, 12]. This study was a retrospective review of cases of locally advanced NSCLC treated by induction chemoradiotherapy and surgery at Okayama University Hospital between January 1999 and December 2018. A total of 187 patients were included in this study. The inclusion criteria were an Eastern Cooperative Oncology Group performance status of 0 to 1 and adequate functional reserves of the major organs, as previously described [13]. Staging was performed according to the International Association for the Study of Lung Cancer TNM Staging System for NSCLC, eighth edition [14]. The study protocol (No. 1055) was approved by the Institutional Review Board of Okayama University Hospital. The requirement for patient consent was waived due to the retrospective nature of the study and the patients were informed of their right to opt out.

Induction chemoradiotherapy followed by surgery

The details of trimodality treatment as initial therapy targeting a primary NSCLC tumor have been described previously [8, 11, 15]. Briefly, most patients received cisplatin and docetaxel as induction chemotherapy, and some patients received alternative chemotherapy regimens. On the first day of chemotherapy, radiotherapy was initiated with a planned total radiation dose of 40–46 Gy. Dose escalation up to 60 Gy was allowed when tumors responded poorly. The surgical procedure after induction chemoradiotherapy was decided on the basis of the disease extent before the start of induction therapy. Although the preferred procedure was pulmonary lobectomy with

complete ipsilateral mediastinal and subcarinal nodal dissection, bilobectomy or pneumonectomy was performed to achieve complete resection when necessary. The patients received postoperative adjuvant therapy at the physician's discretion. After the completion of trimodality treatment, the patients were followed up in accordance with our follow-up regimen [8].

Management of pulmonary aspergillosis

The diagnosis of CPA during the follow-up period was confirmed on the basis of the clinical, laboratory, and radiographic findings, including testing for 1,3-beta-D-glucan and galactomannan antigen, cultures, bronchoscopy, chest X-ray, and chest computed tomography. After confirming the diagnosis of CPA, the patients were initially treated with antifungal agents. In accordance with the guidelines for the treatment of CPA published by the European Respiratory Society [1], after a careful risk assessment, surgery was considered for improved disease control in patients whose CPA was refractory to medical management.

Statistical analysis

All statistical analyses were performed using the GraphPad Prism 7.03 software program (San Diego, CA, USA). Overall survival was defined as the interval between the start of induction therapy and the date of death or the last follow-up examination. The survival rates were analyzed by the Kaplan–Meier method, and the log-rank test was used to compare the differences between groups. P values of <0.05 were considered to indicate statistical significance.

Results

Patient characteristics

As shown in Table 1, six patients developed CPA after trimodality treatment for NSCLC. All 6 patients were male ever-smokers and had been histologically diagnosed with adenocarcinoma. All 6 patients underwent extended resection: combined resection in 4 patients, N3 nodal dissection in one patient (Case 4), and bilobectomy in one patient (Case 6). The total number of resected lung segments was ≥4 in 5 patients. After surgery, 3 patients received adjuvant chemotherapy, and 4 patients developed radiation pneumonitis.

Table 2 summarizes the details with regard to CPA. Five patients had cough and fever, and 3 patients had hemosputum. The intervals between the initial therapy for NSCLC and the diagnosis of CPA ranged from 1.3 years to 9.9 years. Testing for 1,3-beta-D-glucan and galactomannan antigen was positive in two patients each. *Aspergillus fumigatus* was detected in 4 patients, and *Pseudomonas aeruginosa* was detected in the sputum culture of one patient (Case 2). It is noteworthy that in each patient computed tomography showed consolidation in the single remaining lung or both lungs as well as a cavity at the resection site. A fungus ball was demonstrated in 4 patients, and a bronchopleural fistula was diagnosed in the other 2 patients, who were diagnosed with empyema (Case 1 and 2). Cavernostomy with fenestration was initially performed in the 2 empyema cases, and one patient (Case 1) subsequently underwent completion pneumonectomy. Completion pneumonectomy was performed as the initial surgery in the patient (Case 3) who had no comorbidities (Fig. 1). A prompt diagnosis of CPA was achieved in Case 4 during close follow-up of glucocorticoid tapering for radiation pneumonitis, and CPA was subsequently successful controlled with antifungal agents (Fig.

2). The 2 patients with bilateral CPA lesions (Fig. 3) were not considered to be candidates for surgery and died of CPA. The 4 patients with a unilateral CPA lesion are still alive. The overall survival rate of the CPA group was similar to that of the group without CPA after trimodality treatment for NSCLC (*P*=0.59). It is noteworthy that no cancer recurrence or death was observed among the NSCLC patients who developed CPA, which is an indication of the importance of CPA control in improving the outcomes of trimodality treatment.

Discussion

In this study we elucidated the characteristics of CPA that developed in patients who had undergone surgery for locally advanced NSCLC after induction chemoradiotherapy and the outcomes of patients with CPA after trimodality treatment. All patients who subsequently developed CPA had undergone extended resection for NSCLC and had a history of either adjuvant chemotherapy or radiation pneumonitis. CPA developed at the resection site of all 6 patients, and the 4 patients whose CPA was localized in a remaining lobe in a single lung at the time of the diagnosis were considered to be candidates for surgery, which resulted in improved CPA control and long-term survival. To the best of our knowledge, this is the first report describing CPA after trimodality treatment.

Trimodality treatment for NSCLC, which consists of chemotherapy, radiotherapy, and surgery, may itself be a risk factor for CPA [2-6]. Adjuvant chemotherapy may further increase the risk of developing CPA [2], and radiation pneumonitis may contribute to the development of a destroyed lung, which is susceptible to aspergillus infection. In addition, extended lung resection may lead to the compensatory overexpansion of the remaining lobes, especially in the emphysematous lungs of ever-smokers, as was observed in this

study, and contribute to cavity formation in the pulmonary parenchyma. Furthermore, treatment of lung infections and second primary cancer may prolong patient survival after trimodality treatment for NSCLC [16]. In view of these factors, physicians should be aware of CPA as a possible late complication after trimodality treatment for NSCLC.

The diagnosis of CPA requires a consistent appearance on computed tomography, such as a cavity and fungus ball, which are direct evidence of *Aspergillus* infection, or evidence of an immunological response to *Aspergillus* species and the exclusion of other diagnoses [1]. No *Aspergillus* species were detected in 2 of our patients (Cases 2 and 4). Because an antagonistic relationship has been shown to exist between *Aspergillus fumigatus* and *Pseudomonas aeruginosa* [17], in Case 2, in which a fungal infection was histologically diagnosed based on the examination of the surgical specimen, the pseudomonal infection may have resulted in a false-negative *Aspergillus* culture. In Case 4, the presence of a fungus ball and a positive galactomannan antigen test contributed to the early diagnosis of CPA. An early diagnosis of CPA is required for effective treatment to prevent the spread of CPA from one lung to the contralateral lung.

The localization of CPA in a single lung after NSCLC surgery at the time of the diagnosis may be a key to the improved control of CPA after trimodality treatment for NSCLC. Three patients with CPA in a single lung after NSCLC surgery underwent successful surgery, including completion pneumonectomy. Another patient, whose CPA remains well controlled with antifungal agents, would still be a candidate for surgery, even if their condition deteriorated. Because pneumonectomy has been shown to provide favorable results as a treatment for complex aspergilloma [18], completion pneumonectomy may be a therapeutic option for operable CPA patients after trimodality treatment for NSCLC. Survivors of NSCLC after trimodality treatment who have risk

factors for CPA might benefit from prophylactic antifungal therapy, which is routinely administered to lung transplant recipients [19]. The further accumulation of cases of CPA after trimodality treatment will be necessary for a more detailed evaluation.

In conclusion, careful follow-up is necessary to detect CPA as a late complication after surgery for locally advanced NSCLC treated with induction chemoradiotherapy, especially in ever-smoker patients who have undergone extended resection and have a history of either adjuvant chemotherapy or radiation pneumonitis. The early detection and diagnosis of CPA localized in a single lung after NSCLC surgery is critical to improving the control of CPA with antifungal agents and surgery as well as long-term survival after trimodality treatment.

Compliance with ethical standards

Conflict of interest: Shinichi Toyooka received research grants from Astellas Pharma Inc., Chugai Pharmaceutical Co., Ltd., and Taiho Pharmaceutical Co., Ltd. Katsuyuki Kiura received research grants from Bristol-Myers Squibb K. K., Chugai Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., and Ono Pharmaceutical Co., Ltd. The other authors declare no conflicts of interest in association with the present study.

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Table 1. Patient characteristics

No.	Age at the diagnosis of CPA (years)	Sex	Smoking history	Histology	Tumor location	c-Stage	Chemotherapy	Radiation (Gy)	Thoracotomy	Pulmonary resection	Combined resection	Lymph node dissection	Total number of resected lung segments	Pathological evaluation	Adjuvant chemotherapy	Comorbidities
1	47	Male	Ever	AD	Rt. S1	IVA, T4N2M1b(rib)	VNR	60	MS, T	RUL	Rt. clavicle, SVC, pherenic nerve, wedge of rt. S6	N2 level	3	Minor	Yes	Radiation pneumonitis
2	55	Male	Ever	AD	Lt. S1+2	IIIB, T4N2M0	CDDP+DOC	46	MS	LUL	Wedge of lt. S6	N2 level	5 or more	Major	Yes	Alcoholic chirrhosis, Diabetes mellitus, Right pneumothorax
3	52	Male	Ever	AD	Lt. S6	IIB, T3N0M0	CDDP+DOC	46	PL	LLL	Wedge of lt. S1+2, chest wall	N2 level	4 or more	Complete	No	Radiation pneumonitis
4	73	Male	Ever	AD	Lt. S1+2	IIIA, T1cN2M0	CDDP+DOC	46	MS, T	LUL	None	N3 level	5	Complete	No	Radiation pneumonitis treated with glucocorticoid, Pulmonary venous thrombus
5	57	Male	Ever	AD	Lt. S1+2	IIB, T2aN1M0	CDDP+DOC	46	PL	LUL	Pulmonary artery	N2 level	5	Major	Yes	Left adrenal metastasis treated with surgery and chemotherapy 9 months after initial therapy
6	56	Male	Ever	AD	Rt. S4	IIIB, T3N2M0	CDDP+DOC	46	PL	RML, RLL	None	N2 level	7	Major	No	Radiation pneumonitis

AD adenocarcinoma, *CDDP* cisplatin, *LLL* left lower lobe, *Lt* left, *LUL* left upper lobe, *MS* median sternotomy, *PL* posterolateral thoracotomy, *RLL* right lowe lobe, *RML* right middle lobe, *Rt* right, *RUL* right upper lobe, *S* segment of the lung, *SVC* superior vena cava, *T* transverse thoracotomy, *VNR* vinorelbine

Table 2. Summary of chronic pulmonary aspergillosis

No.	Symptoms			Interval between initial therapy for NSCLC and the diagnosis of CPA (years)	Laboratory findings			Aspergillus species	Culture specimen	CT findings				Antifungal agents	Operative procedure	Histology	Outcome (years after initial therapy for NSCLC)
	Fever	Cough	Sputum		1,3-beta-D-glucan (pg/mL)	GM	CRP (mg/dL)			Consolidation	Cavity in the resection site	Fungus ball	Empyema with broncho-pleural fistula				
1	Yes	Yes	None	9.9	24.8	Negative 0.2	15.76	Aspergillus fumigatus	Pleural effusion	Unilateral	Yes	No	Yes	ITCZ, VRCZ, MCFG	Cavernostomy with fenestration followed by completion pneumonectomy	Fungus infection	Alive (13.3)
2	Yes	Yes	Purulent	9.4	＜6.0	Positive 4.5	1.67	Negative	Sputum, BAL	Unilateral	Yes	No	Yes	ITCZ, VRCZ, CPFG	Cavernostomy with fenestration followed by muscle plombage	Fungus infection	Alive (12.2)
3	Yes	Yes	None	4.2	7.9	N/A	6.74	Aspergillus fumigatus	Sputum	Unilateral	Yes	Yes	No	ITCZ, VRCZ	Completion pneumonectomy with thoracoplasty	Fungus infection	Alive (5.0)
4	No	No	Bloody	1.3	＜6.0	Positive 1.1	0.75	Negative	Sputum	Unilateral	Yes	Yes	No	ITCZ, VRCZ, MCFG	None	None	Alive (5.6)
5	Yes	Yes	Bloody	6.3	＜6.0	Negative 0.1	16.76	Aspergillus fumigatus	BAL	Bilateral	Yes	Yes	No	VRCZ, MCFG	None	None	Dead (6.3)
6	Yes	Yes	Bloody	3.6	＜6.0	Negative 0.3	2.94	Aspergillus fumigatus	Sputum	Bilateral	Yes	Yes	No	VRCZ, L-AMB	None	None	Dead (9.8)

BAL bronchoalveolar lavage, *CPA* chronic pulmonary aspergillosis, *CPFG* caspofungin, *CRP* C-reactive protein, *CT* computed tomography, *GM* galactomannan, *ITCZ* itraconazole, *L-AMB* liposomal amphotericin B, *MCFG* micafungin, *NSCLC* non-small cell lung cancer, *VRCZ* voriconazole

Figure legends

Fig. 1 Representative diagnostic images of surgical cases of chronic pulmonary aspergillosis in a single lung after trimodality treatment (Case 3). A preoperative chest X-ray film (a) and computed tomography scan (b) showed a cavity and fungus ball in the remaining left upper lobe. A postoperative chest X-ray film showed fluid accumulation in the left post-pneumonectomy space (c).

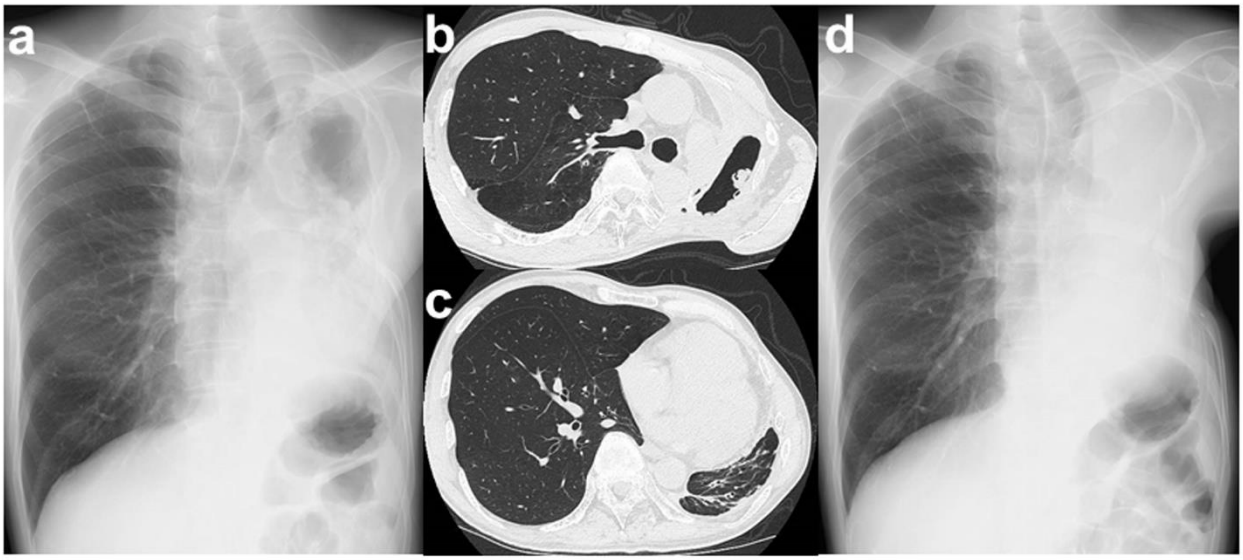

Fig. 2 A case of successful medical management of chronic pulmonary aspergillosis in a single lung after trimodality treatment (Case 4). A chest X-ray film (a) and computed tomography scan (b) revealed a cavity and fungus ball (arrow) in the left lower lobe remnant. A chest X-ray film (c) and computed tomography scan (d) after antifungal therapy showed that the fungus ball had shrunk.

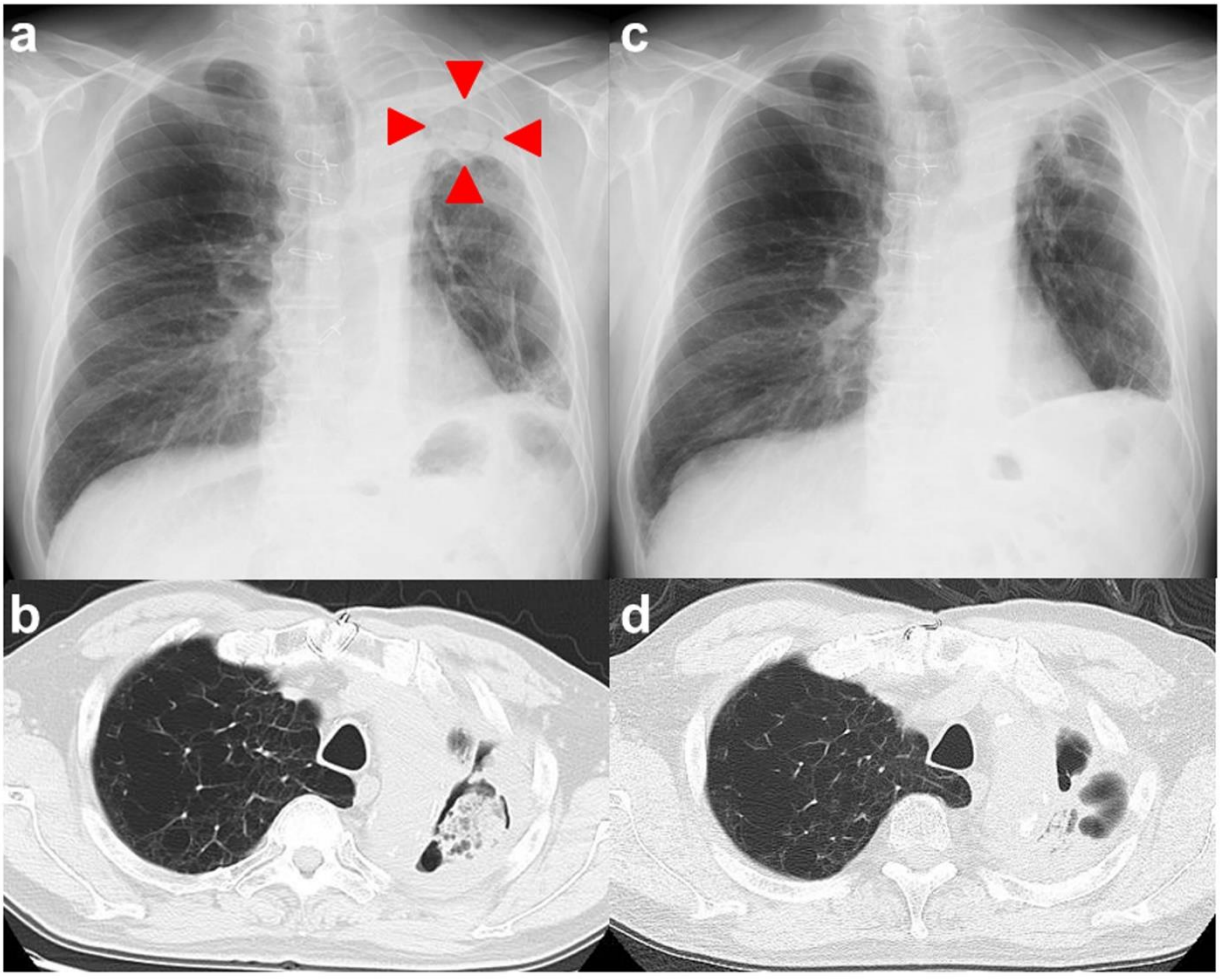

Fig. 3 Representative diagnostic images of chronic pulmonary aspergillosis in both lungs (Case 5). A chest X-ray film (a) and computed tomography scans showed a cavity with a thickened wall in the remaining lower lobe of the left lung (b) and consolidation in both lungs (b, c).

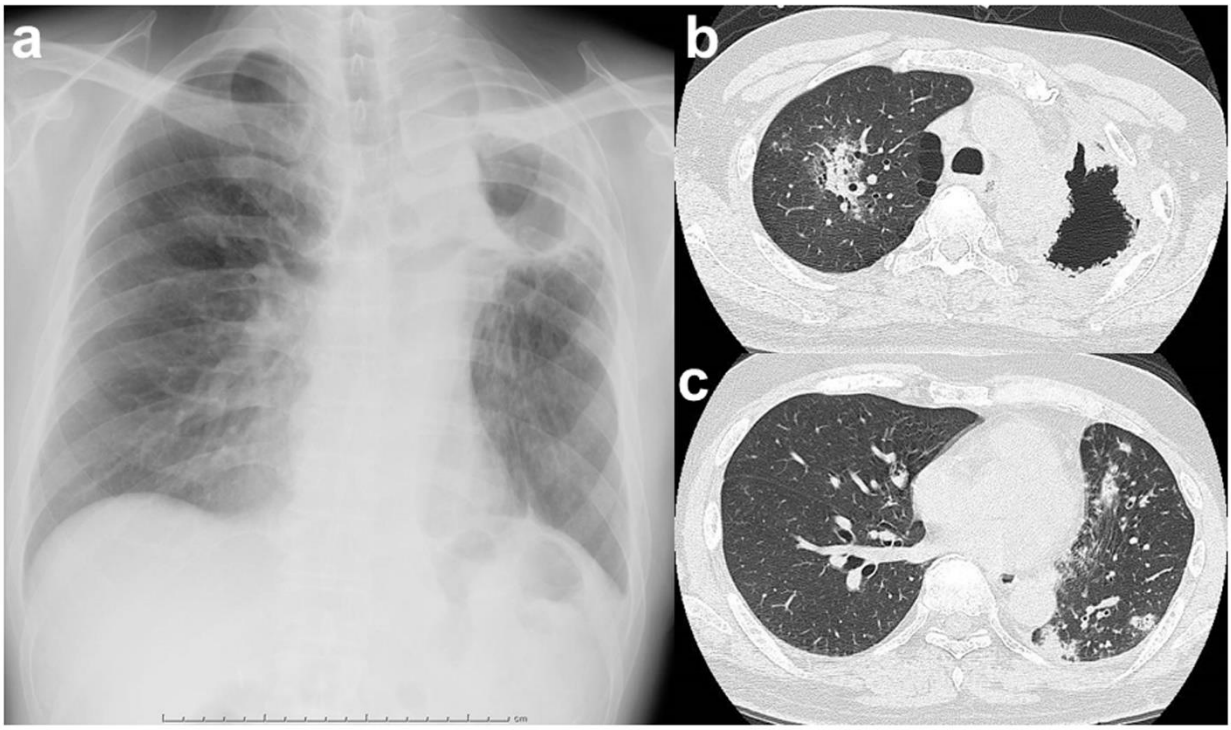

Fig. 4 Survival of patients who developed chronic pulmonary aspergillosis (CPA) and those who did not develop CPA after trimodality treatment for locally advanced non-small cell lung cancer. The survival rates of the CPA and non-CPA groups were comparable (10-year survival rate, 50.0% vs. 57.6%, respectively, *P*=0.59).