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CASE REPORT

Spontaneous pneumothorax after stereotactic radiotherapy for non-small-cell lung cancer

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Abstract The report presented here describes a case of spontaneous pneumothorax observed after stereotactic radiotherapy (SRT) for non-small-cell lung cancer (NSCLC). An 84-year-old man with a Stage IIB, T3N0M0 NSCLC in the right upper lobe and a Stage IA NSCLC in the right lower lobe of the lung was treated with SRT for both tumors. He received SRT with a total dose of 60.0 Gy in 10 fractions delivered to the right upper lobe, and 48.0 Gy in 4 fractions delivered to the right lower lobe. Two months after completion of the treatment, he developed spontaneous pneumothorax. He was asymptomatic and recovered with conservative management. Spontaneous pneumothorax has occasionally been reported to occur following thoracic radiotherapy for malignancy. Almost all of the reported cases are patients who had received mantle irradiation for Hodgkin's disease. We have been unable to find any reports of spontaneous pneumothorax after SRT, which has recently been used for treating patients with early-stage NSCLC. Because a case of spontaneous pneumothorax after SRT was observed in our institution, its clinical course is described here along with a discussion of possible causes of spontaneous pneumothorax.

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Key words Spontaneous pneumothorax · Stereotactic radiotherapy (SRT) · Non-small-cell lung cancer (NSCLC)

Introduction

Spontaneous pneumothorax is a recognized complication of thoracic radiotherapy. The causes and mechanisms leading to spontaneous pneumothorax after radiotherapy have not yet been defined. However, it has been stated that radiation-induced pulmonary changes, apical pleural injury, and parenchymal injury may be responsible for the development of spontaneous pneumothorax. Almost of all the reported cases of spontaneous pneumothorax following thoracic radiotherapy occurred in patients who underwent mantle irradiation for Hodgkin's disease, which encompasses a relatively large amount of pleural surface area compared to other types of thoracic radiotherapy.[1–7]

Recently, spontaneous pneumothorax was observed after stereotactic radiotherapy (SRT) was applied to a patient with non-small-cell lung cancer (NSCLC). SRT can deliver a high total dose to a small lung volume with a short overall treatment time. In many studies, SRT has been shown to achieve excellent local control and survival rates for Stage I NSCLC.[8–11] Therefore, the number of patients with Stage I NSCLC who are being treated with SRT has been increasing rapidly, and although the rate of treatment-related toxicity is low, several reports have described serious complications.[12,13] Among the pulmonary complications, radiation pneumonitis is the most common and important. To our knowledge, spontaneous pneumothorax following SRT has not been reported in the literature. A case report is presented here describing spontaneous pneumothorax following SRT, along with a review of the literature and a discussion of the possible causes of spontaneous pneumothorax.

Case report

An 84-year-old man with no significant past medical history presented to our institution on September 21, 2004 with a 2-month history of right back pain. At the initial physical examination, the Karnofsky performance status (KPS) was 70. Laboratory data showed elevated squamous cell carcinoma-related antigen (SCC) and cytokeratin 19 fragments (CYFRA). The SCC value was 7.0 ng/ml (normal 0–1.5 ng/ml) and the CYFRA value was 14.5 ng/ml (normal 0–3.5 ng/ml). The other laboratory data were normal. Pulmonary function tests showed slight restriction, with no obstruction. An arterial blood gas analysis showed hemoglobin saturation of 96%, partial pressure of oxygen (PaO_2) at 83.6 mmHg, partial pressure of carbon dioxide ($PaCO_2$) at 45.5 mmHg, and pH 7.42.

A chest X-ray showed a mass of 5 cm (maximum diameter) in the apex of the right lung. A chest computed tomography (CT) scan showed a mass with third rib involvement in the right upper lobe and a nodule with pleural indentation in the right lower lobe. Cytology specimens confirmed the squamous cell carcinoma diagnosis. Further examinations—including brain CT scan, bone scintigraphy, and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) scan—showed no lymph node involvement or distant metastases. The patient was diagnosed as having Stage IIB, T3N0M0 NSCLC in the right upper lobe and Stage IA, T1N0M0 NSCLC in the right lower lobe (Fig. 1). Because the patient was not considered a candidate for surgery owing to his advanced age and poor performance status, it was decided to use SRT to treat both tumors.

With 10-MV X-rays using seven beams, SRT to the right upper lobe was started on October 10, 2004. A total dose of 60.0 Gy was delivered at 6.0 Gy per fraction over 15 days (Fig. 2). After completing the treatment, a CT-guided lung biopsy of a nodule in the right lower lobe was performed on November 9, 2004. It revealed squamous cell carcinoma. Pneumothorax following the CT-guided biopsy occurred and was treated with conservative management. The patient was subsequently started on SRT to the right lower lobe on November 25, 2004 when expansion of the right lower lobe was observed. A total dose of 48.0 Gy was delivered at 12.0 Gy per fraction over 6 days with 10-MV X-rays using seven beams (Fig. 3). The two courses of SRT were completed without any acute toxicity.

The patient was seen for a routine follow-up on January 31, 2005. He was completely asymptomatic, but a chest X-ray showed a right pneumothorax (Fig. 4). A chest CT scan also showed that the right lower lung was collapsed, and simultaneously, the tumor in the right upper lobe had adhered to the chest wall and

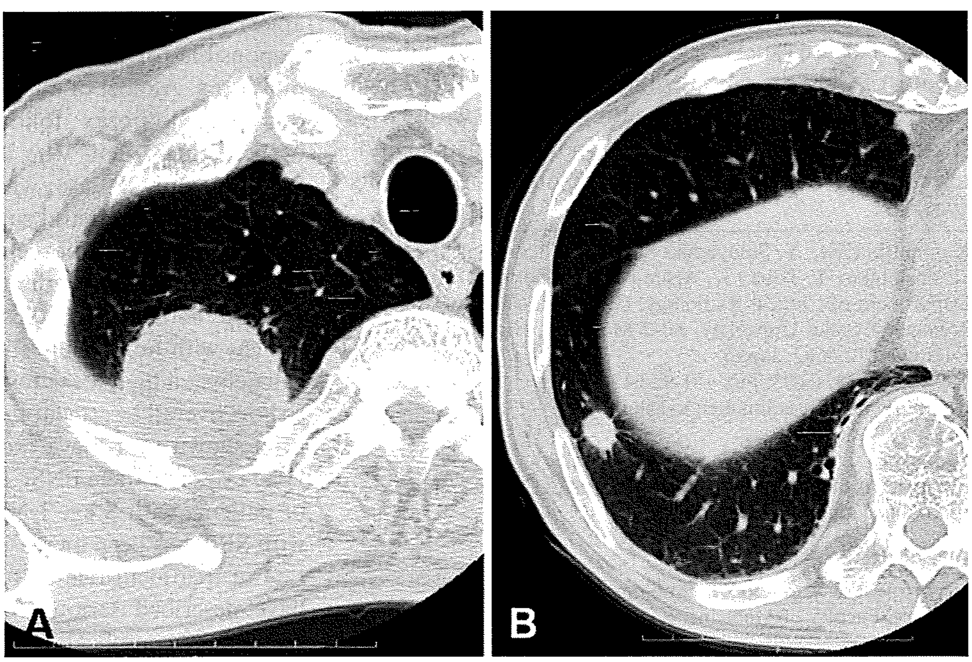


Fig. 1. Pretreatment high-resolution computed tomography (CT) scan. **A** There is a mass with third rib involvement in the right upper lobe. **B** Nodule with pleural indentation in the right lower lobe

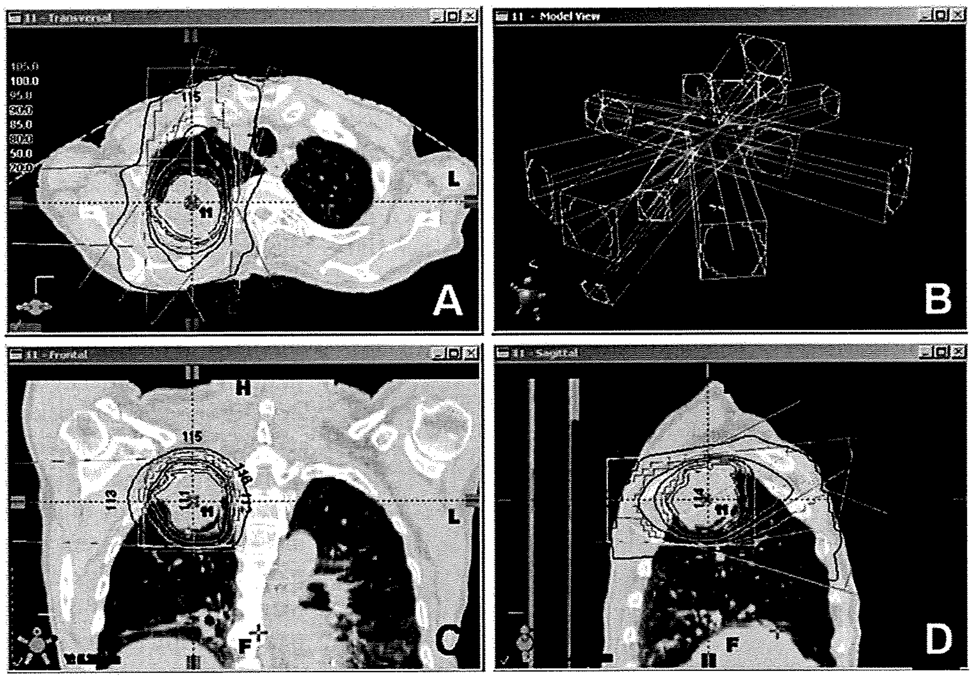


Fig. 2. Stereotactic radiotherapy (SRT) treatment planning for the right upper lobe. **A** Isodose curves on an axial image through the isocenter. **B** Three-dimensional image shows all radiotherapy beams. **C** Isodose curves on a coronal image through the isocenter. **D** Isodose curves on a sagittal image through the isocenter

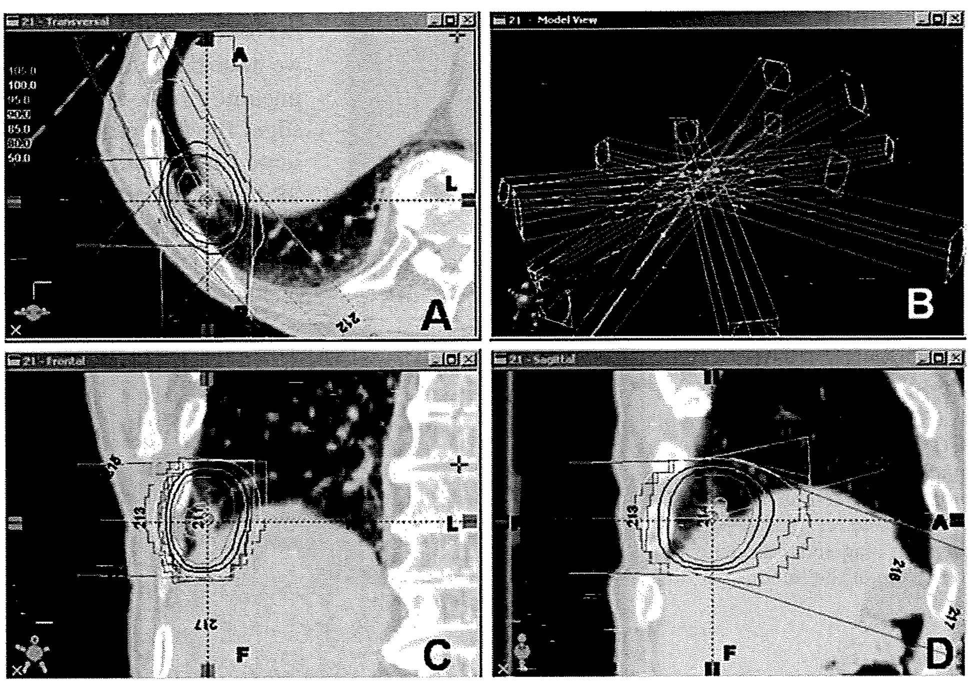


Fig. 3. SRT treatment planning for the right lower lobe. **A** Isodose curves on an axial image through the isocenter. **B** Three-dimensional image shows all radiotherapy beams. **C** Isodose curves on a coronal image through the isocenter. **D** Isodose curves on a sagittal image through the isocenter

been slightly decreasing in size (Fig. 5A). Therefore, he was admitted to our institution and was under observation, during which time we performed repeat chest radiography. Because the chest radiographs showed that the right lung was expanding gradually, he was discharged on February 14, 2004. Since then, complete reexpansion of the right lung was shown on a chest radiograph, and he was doing well at the last follow-up in April 2005. A follow-up chest CT scan at that time showed that both of the tumors had been decreasing in size (Fig. 5B).

Discussion

Spontaneous pneumothorax can occur without preceding trauma or obvious precipitating causes.[14–16] Spontaneous pneumothorax is classified as primary or secondary.

Primary spontaneous pneumothorax occurs without underlying lung disease, whereas secondary pneumothorax occurs in the presence of coexisting lung disease. Every lung disease has been reported to be associated with secondary spontaneous pneumothorax, but chronic obstructive pulmonary disease (COPD) is the most common underlying disease.[17] Among those with COPD, spontaneous pneumothorax occurs in 26 cases per 100 000 population per year.[18]

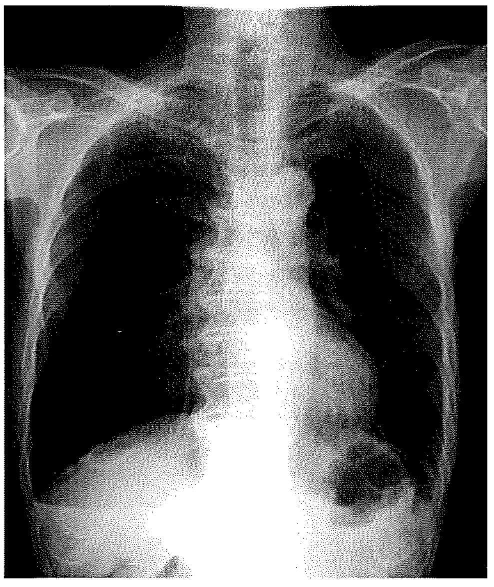
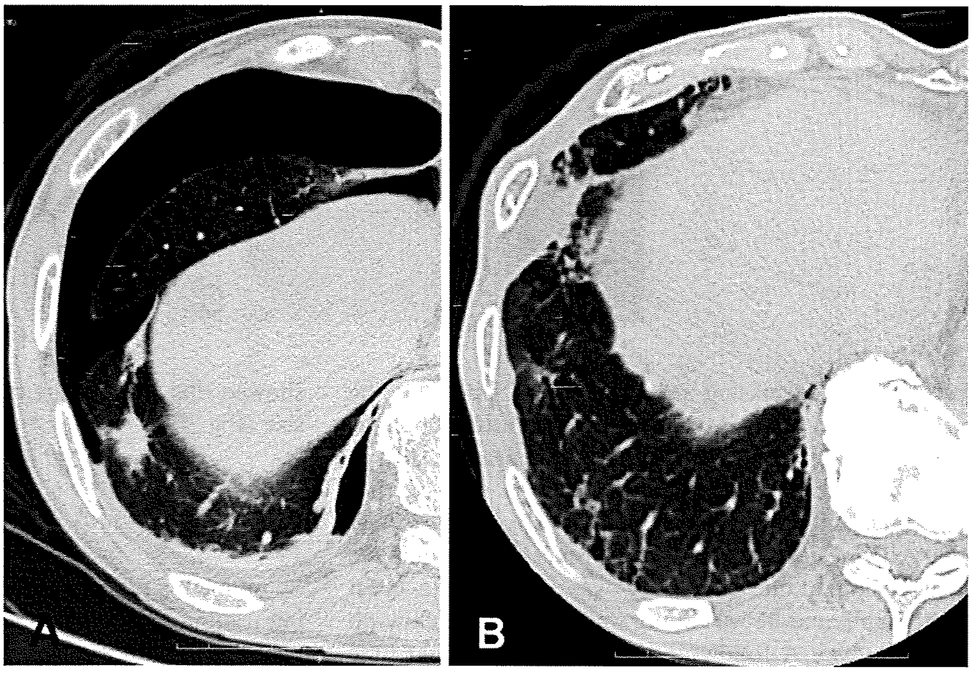


Fig. 4. A Chest radiograph 2 months after SRT shows a right pneumothorax

Spontaneous pneumothorax with malignancies is classified as secondary. It is seen with primary or metastatic lung lesions, which are occasionally the preceding event.[1] The most common malignancies associated with spontaneous pneumothorax are sarcomas. Spontaneous pneumothorax is also associated with nonsarcomatous tumors including Hodgkin's disease, non-Hodgkin's disease, and primary lung cancers.

Spontaneous pneumothorax secondary to thoracic radiotherapy (RT) for malignancies has rarely been reported. Almost of all the reported cases occurred in patients who underwent mantle irradiation for Hodgkin's disease.[1–7] The risk of spontaneous pneumothorax in lymphoma patients following RT far exceeds the incidence in the general population.[19] Pezner et al. reported that the frequency of spontaneous pneumothorax in the absence of concurrent pulmonary diseas e was 2.2% for patients with Hodgkin's disease who were treated with mantle irradiation.[5] Shapiro et al. reported that 2 of 13 patients with Hodgkin's disease developed asymptomatic pneumothorax after mantle irradiation.[6] In patients with NSCLC, several cases of spontaneous pneumothorax following thoracic RT have been reported.[20] However, we have been unable to find any reports of spontaneous pneumothorax after SRT for NSCLC. To our knowledge, the first case of pneumothorax after SRT is presented here, and another case of pneumothorax after SRT was recently observed. At our institution, 113 patients were treated with SRT from April 2003 to December 2006; and among them, 2 patients developed pneumothorax. The frequency of pneumothorax after

Fig. 5. CT changes after SRT, which delivered 48.0 Gy in four fractions. **A** CT scan at the time of pneumothorax. **B** CT scan 5 months after completion of SRT showed reexpansion of the right lung and a decrease in the size of the tumor



SRT was thus at least 1.8%, which is higher than what is seen in the general population.

A number of factors may contribute to the development of spontaneous pneumothorax following thoracic RT. However, there is no apparent risk factor for spontaneous pneumothorax in our review of the 20 reported cases with lymphoma.[1–5] No correlation was found with age, sex, physique, or smoking history. No radiation dose–response effect has been obvious, although spontaneous pneumothorax was not observed in patients who received less than 3000 cGy.[5,7] Chemotherapy also does not appear to correlate with the occurrence of pneumothorax. However, spontaneous pneumothorax in patients with concurrent pulmonary disease, such as chemotherapy-induced interstitial fibrosis and pneumonia, tended to be severe, bilateral, and/or recurrent.[5] In the case described here, the patient was treated with radiotherapy alone. SRT seems most likely to be related to the occurrence of pneumothorax, although the irradiated volume of the lung and pleura was small compared to the mantle field for lymphoma. Another possible factor in this case is thought to be the CT-guided lung biopsy: If the damage to the pulmonary tissue had not persisted after the biopsy, it might not have contributed to the extent of the development of pneumothorax.

Various mechanisms to explain the development of spontaneous pneumothorax associated with malignancies have been suggested. When small airways are restricted by an invasive cancer, they can act as valves, causing air to be trapped, the dilation of distal alveolar spaces, and eventual rupture.[21] Bronchopleural fistulas can be caused by direct tumor invasion, or they can develop secondarily after necrosis of a peripheral tumor following an effective treatment or from spontaneous vascular occlusion within the tumor itself.[22] The rupture of small subpleural blebs is also thought to be related to pneumothorax. In one study, the surgical findings in patients with pneumothorax who underwent exploratory thoracotomy after radiotherapy showed the presence of subpleural apical blebs and/or dense pleural fibrosis. Dense pulmonary and/or pleural fibrosis caused by radiotherapy may increase the chance of forming and rupturing subpleural blebs, with the subsequent development of pneumothorax.[5] In our case, a tumor with a pleural indentation existed in the peripheral part of the right lower lung, and subpleural blebs around the tumor were seen in a pretreatment high-resolution CT scan. This CT finding suggests that traction may be a result of radiation-induced changes and shrinkage of the tumor following SRT, ultimately leading to the rupture of subpleural blebs.

Although this is a limited review, the number of patients treated with SRT for early stage NSCLC has been increasing. A tumor in the peripheral part of the lung is thought to be a good indication for SRT, as there are no critical organs such as the trachea or great vessels to create problems. In general, spontaneous pneumothorax is not a serious complication. However, spontaneous pneumothorax should be recognized as one of the possible adverse effects related to SRT for NSCLC.

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Corrugated Fiberboard as a Positioning Insert for Patients Undergoing Radiotherapy

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Triple-wall corrugated fiberboard/Carbon-fiber base plate/Patient-positioning insert/Body immobilization device.

We have developed a new body fixation system for single patient use, which consists of a vacuum cushion, a thermoplastic fixation sheet which is used to suppress involuntary and voluntary patient movement, and a triple-wall corrugated fiberboard base plate to which both the vacuum cushion and the thermoplastic sheet are affixed. To evaluate the characteristics of the fiberboard as a patient-positioning insert, the photon beam attenuation of a fiberboard base plate, a carbon-fiber base plate, and a vacuum–formed cushion were compared. The strength of the fiberboard was also evaluated. The attenuation for the carbon-fiber base plate was 3.7% and 2.6% in 4 MV and 10 MV photon beams, respectively, while the results were less for the fiberboard base plate, i.e. 1.9% and 1.6%. The vacuum–formed cushion had a minimal effect on transmission. None of the materials subsided under the weight loading of 20 g/cm^2. There was no difference between the thicknesses of the fiberboard before and after a 50 times daily load with the 60 kg weight of a volunteer. Corrugated fiberboard is a robust and low attenuating material that functions well as a patient-positioning insert.

INTRODUCTION

For the adoption of precise radiotherapy, including intensity-modulated radiotherapy or stereotactic radiotherapy, high precision in patient positioning is essential.[1)] In addition, many radiation oncologists recognize the need for patient immobilization during treatment, especially because the treatment time for precise radiotherapy has become longer than that generally required for conventional radiation techniques. As for the head and neck fixation, traditional methods have been replaced by modern materials such as carbon-fiber support plates, a vacuum cushion, and thermoplastic materials.[2)] A body immobilization system such as a fixation system based on double-vacuum technology[3)] or a body cast system using a carbon fiber base plate[4)] has also been developed, but these devices have been found to be complicated and expensive.

Corrugated fiberboard is a paper-based construction consisting of corrugated "medium" sandwiched between layers of flat linerboard. In particular, triple-wall corrugated fiberboard is a stronger structure than conventional single- or double-wall corrugated board. Accordingly, triple-wall corrugated fiberboard has been used in a broad range of industries for its strength, flexibility, and environmental friendliness. However, it has rarely been reported as a material for patient fixation devices.

We have developed a new body fixation system, which consists of a vacuum cushion, a thermoplastic fixation sheet which is used to suppress involuntary and voluntary patient movement, and a triple-wall corrugated fiberboard base plate to which both the vacuum cushion and the thermoplastic sheet are affixed. The aim of this study is to investigate the characteristics of the fiberboard base plate as a patient-positioning insert in external radiotherapy.

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MATERIALS AND METHODS

Fiberboard base plate

A home-made fiberboard base plate was evaluated. The base plate was composed of two-ply triple-wall corrugated fiberboard (HiPLE-ACE, Oji Interpack, Tokyo, Japan) to increase its strength (Fig. 1).

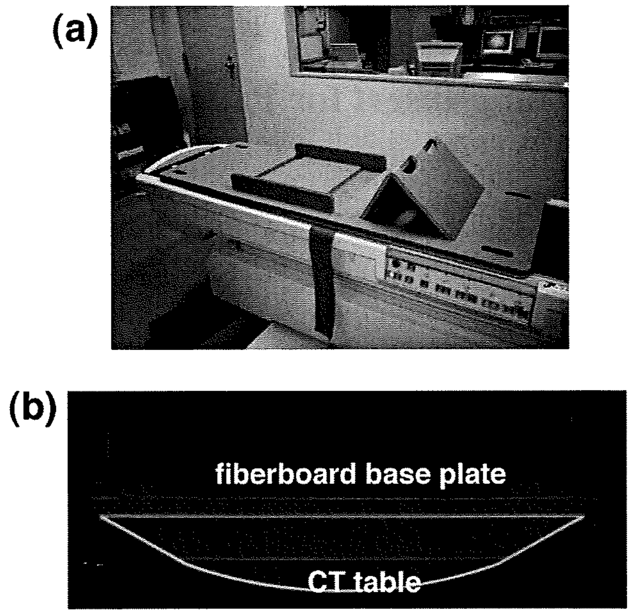

Fig. 1. A home-made fiberboard base plate characteristics: a view (a) and a CT image (b).

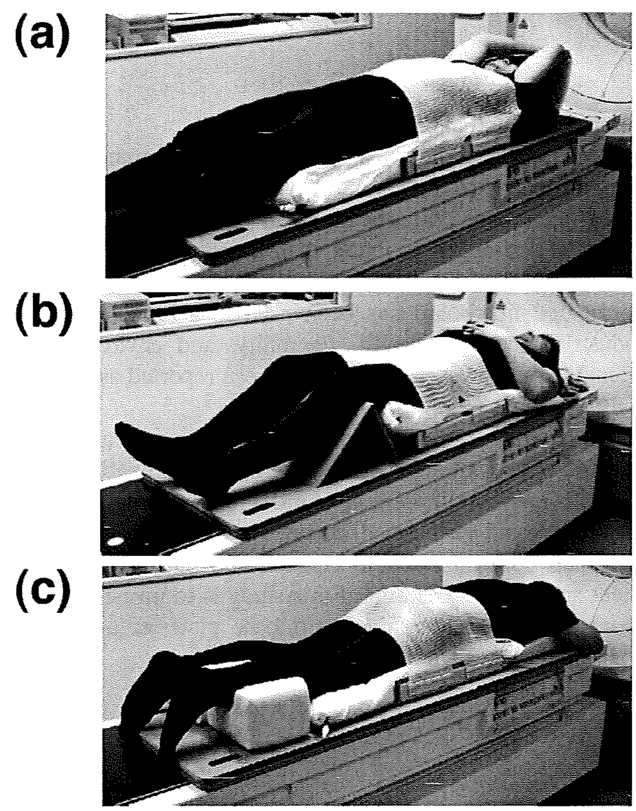

Fig. 2. Examples of the fixation using the fiberboard base plate: chest fixation using an arm support (a), pelvic fixation in the supine position using a knee support (b), and pelvic fixation in the prone position using a chest and leg support (c).

Table 1. Characteristics of the materials used in the study.

Materials	Thickness (cm)	Density (g/cm^3)
Fiberboard base plate	3.2	0.131
Carbon-fiber base plate	3.0	0.339
Vacuum-formed cushion	5.0	0.027

The vacuum-formed cushion was examined after a vacuum pressure of 300 mmHg for five minutes was applied. Densities were calculated from the relation between the material's real weight and its volume.

Patients can be positioned in a vacuum–formed cushion on the plate. A thermoplastic fixation sheet can also be attached using a hook and loop fastener system. Using an arm support or a knee support, the system can be utilized in the treatment of chest or pelvic lesions (Fig. 2).

To compare the characteristics of materials as an insert between the treatment tabletop and the patient, carbon-fiber base plate (ESN-1800, Engineering system, Matsumoto, Japan), and vacuum–formed cushion (ESF-19D, Engineering system, Matsumoto, Japan) were also evaluated in this study (Table 1).

Attenuation measurement

All attenuation measurements were made with an ionizing chamber (PTW30013, PTW, Frieburg, Germany) in a solid water phantom on a linear accelerator (Mevatron KD2 Primus, Siemens, Germany) using photon energies of 4 and 10 MV. A standard geometry of 10 × 10-cm fields, an SAD = 100 cm, was used for all measurements. The material was placed in direct contact with the surface of the phantom. The angle of the beam was perpendicular to the material. The chamber was placed at a depth of 10 cm directly under the part to be measured using the room lasers for alignment. A total of 100 monitor units were delivered. The attenuation was calculated as one minus the ratio of the ionization measured at the reference depth with and without the material on the surface of the phantom.

Measurement of the strength of the materials under weight loading

To evaluate the strength of the material under weight loading, changes in the position of the solid water phantom (35 × 35 × 20 cm^3) on the material were measured using a commercially available high-speed machine vision system (CV-3000, Keyence, Osaka, Japan).[5,6] This machine vision system was composed of a 2,000,000-pixel color CCD camera and computerized control systems. The CCD camera was positioned 1.5 m from the phantom on the materials (Fig. 3a). External fiducials were placed on the phantom, and the image data obtained from the fiducials were captured onto the CCD, converted to digital data within the camera

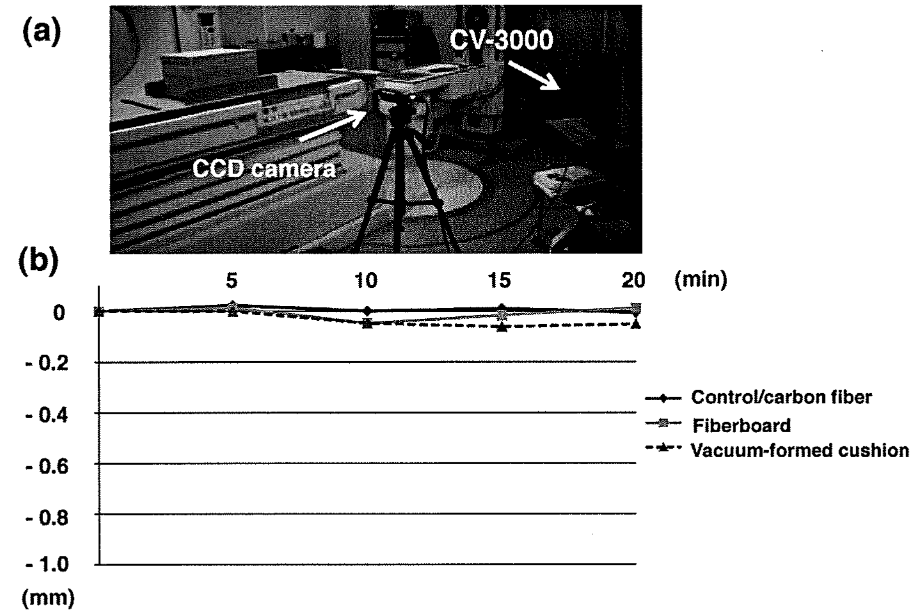

Fig. 3. Experimental setup for measurement of the strength of the materials (a), and the changes in position of the solid water phantom (b).

unit, and transferred to the controller, after which the position of the fiducials was calculated to an accuracy of < 0.1 mm.[5,6] The positions of the fiducials (i.e., the position of the phantom) were calculated at 0, 5, 10, 15, and 20 min after loading weight of the phantom. The measurement was repeated 3 times and average values were taken.

Measurement of the thickness of the fiberboard base plate after iterative weight loading

The thickness of the fiberboard base plate was evaluated before and after a 50 times daily load of approximately 10 minutes with the 60 kg weight of a volunteer. Because the volunteer was positioned in a vacuum–formed cushion, the body weight was considered to be distributed evenly on the plate. The board thicknesses were measured on the CT images by using a digital ruler in a treatment planning system (XiO, CMS, St. Louis, MO). The images acquired had a pixel size of 0.9 mm × 0.9 mm, and the ruler had a resolution of 0.1 mm. The measurements were repeated at five different points at the center, the right periphery, and the left periphery of the board, and average values were taken.

RESULTS AND DISCUSSION

The attenuation properties of the different materials are shown in Table 2. The attenuation values for the carbon-fiber base plate were 3.7% and 2.6% in 4 MV and 10 MV photon beams respectively, while the results were less for the fiberboard base plate, i.e. 1.9% and 1.6%. The vacuum–formed cushion had a minimal effect on transmission.

The changes in position of the solid water phantom on the materials are shown in Fig. 3(b). None of the materials examined subsided under the weight loading of 20 g/cm^2, which is almost equal to the weight loading of the body with a thickness of 20 cm.

The changes in thickness of the fiberboard before and after a 50 times daily load with the 60 kg weight of a volunteer are shown in Table 3. There was no difference between the thicknesses of the board before and after iterative weight loading.

For optimum daily use in the treatment room, an immobilization system should be (a) accurate but simple, (b)

Table 2. 4 MV or 10 MV X-ray attenuation results for various materials.

	4 MV	10 MV
Fiberboard base plate	1.9%	1.6%
Carbon-fiber base plate	3.7%	2.6%
Vacuum-formed cushion	0.2%	0.1%

Table 3. The thickness of the fiberboard base plate before and after iterative weight loading.

Thickness	Before weight loading (cm)	After weight loading (cm)
Center	3.2	3.2
Right periphery	3.3	3.3
Left periphery	3.2	3.3

portable and light-weight, (c) adaptable for the treatment of many lesions, (d) comfortable, (e) inexpensive, and (f) radiolucent. The fiberboard immobilization system described here meets these criteria. In addition, fiberboard is easy to handle and is an environmentally friendly solution.

The high strength and low density of triple-wall corrugated fiberboard suggest an excellent material with minimal attenuation for a support plate on a treatment table. Using triple-wall corrugated fiberboard, we have created a body fixation system (Fig. 2). Unlike other body immobilization devices, this system consists not only of a vacuum cushion, but also of a thermoplastic fixation sheet which is used to suppress involuntary and voluntary patient movement, and a fiberboard base plate to which both the vacuum cushion and the thermoplastic sheet are affixed. This system may be applicable to the treatment of lesions in various sites, because all components of this system consist of low attenuating materials as shown in Table 2. However, it should be noted that the transmission depends on beam angle. We recommend that the transmission through this system should be accounted for, for example, incorporating this system directly into the planning process.

Compared to the rigid fixation system using carbon fiber,[4] the fiberboard base plate may be less durable and less rigid. Because the permanence of this board has not been proven, we consider this system to be appropriate for single patient use. Although this non-rigid system may potentially reduce reproducibility compared with the system using a carbon-fiber base plate, if a careful analysis of patient positional reproducibility is performed using image-guided radiation techniques, we can use it easily and effectively on our patients. Although it is not well known that the fixation system incorporating a body compression element influences intrafraction or interfraction motion of the target,[7] we believe that suppression of involuntary and voluntary patient movement is essential in precise radiotherapy. This subject is under investigation.

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Predictive Factors of Esophageal Stenosis Associated with Tumor Regression in Radiation Therapy for Locally Advanced Esophageal Cancer

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Esophageal stenosis/Radiation therapy/Esophageal cancer/Chemoradiation.

The purpose of this retrospective study was to clarify the predictive factors correlated with esophageal stenosis within three months after radiation therapy for locally advanced esophageal cancer. We enrolled 47 patients with advanced esophageal cancer with T2–4 and stageII–III who were treated with definitive radiation therapy and achieving complete response of primary lesion at Kyushu University Hospital between January 1998 and December 2005. Esophagography was performed for all patients before treatment and within three months after completion of the radiation therapy, the esophageal stenotic ratio was evaluated. The stenotic ratio was used to define four levels of stenosis: stenosis level 1, stenotic ratio of 0–25%; 2, 25–50%; 3,50–75%; 4,75–100%. We then estimated the correlation between the esophageal stenosis level after radiation therapy and each of numerous factors. The numbers and total percentages of patients at each stenosis level were as follows: level 1: n = 14 (30%); level 2: 8 (17%); level 3: 14 (30%); and level 4: 11 (23%). Esophageal stenosis in the case of full circumference involvement tended to be more severe and more frequent. Increases in wall thickness tended to be associated with increases in esophageal stenosis severity and frequency. The extent of involved circumference and wall thickness of tumor region were significantly correlated with esophageal stenosis associated with tumor regression in radiation therapy ($p = 0.0006$, $p = 0.005$). For predicting the possibility of esophageal stenosis with tumor regression within three months in radiation therapy, the extent of involved circumference and esophageal wall thickness of the tumor region may be useful.

INTRODUCTION

Among solid-tumor type cancers, esophageal cancer has one of the highest mortality rates. Advanced esophageal cancer is treated with a multidisciplinary approach: surgery, radiation therapy and chemotherapy. Surgery has been accepted as a standard treatment for resectable locally advanced esophageal cancer, while radiation therapy has been accepted as the standard therapy for unresectable or inoperable locally advanced esophageal cancer. Recently, with the development of chemoradiation, some reports have indicated that definitive chemoradiation has a curative potential for locally advanced esophageal cancer and may be considered equivalent to surgery in terms of its survival benefit.[1–7)]

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In some cases, however, the esophageal stenosis worsens during the course of radiation therapy, despite the reduction in tumor size. If the esophageal stenosis increases the patients may experience dysphagia and oral intake disorders, which can substantially decrease their quality of life (QOL). There have been several reports on the risk factors or mechanism of esophageal stenosis after radiation therapy for locally advanced esophageal cancer. However, there has been no study examining the frequency or degree of esophageal stenosis in such cases.

The purpose of this retrospective study was to clarify the factors correlated with esophageal stenosis within three months after radiation therapy for locally advanced esophageal cancer. The "esophageal stenosis" used in this study dose not mean a late toxicity but stenotic change which sometimes occurred with tumor shrinkage responded to radiation therapy.

MATERIALS AND METHODS

Patients

We enrolled 47 patients (43 males and 4 females) with advanced esophageal cancer with T2–4 and stageII–III treated with definitive radiation therapy with/without concurrent chemotherapy achieving complete response of primary lesion at Kyushu University Hospital between January 1998 and December 2005. The characteristics of the patients are shown in Table 1. The patients' ages ranged from 50 to 87 years (mean: 70 years). In all patients, pathological examination of the specimen obtained by biopsy revealed squamous call carcinoma (SCC). Written informed consent was obtained from all patients enrolled in this retrospective study.

Pretreatment evaluation

The extent of disease in each patient was evaluated by physical examination, esophagography, esophagoscopy and computed tomography (CT) of the neck, chest and abdomen. Bronchoscopy was performed when tracheobronchial involvement was suspected. Endoscopic ultrasound (EUS) was applied when the transducer could pass through the tumor. Assignment of clinical staging and tumor finding type was performed according to the criteria of the International Union against Cancer (UICC, 1997).[8] The tumor finding type was evaluated by the criteria of the Japanese Society for Esophageal Diseases, which were based on the findings from esophagograms and esophagoscopy.[9] The extent of involved circumference and the tumor length were evaluated with esophagography and esophagoscopy, and wall thickness was evaluated with contrasted enhanced CT images before radiation therapy by measuring the thickness of the thickest portion of the tumor. The degree of stenosis before treatment was also evaluated with esophagography by the method described below. These characteristics of are summarized in Table 1.

Treatments

In all patients, radiation therapy was performed using an external beam and delivered at a daily dose of 1.8–2 Gy, five times per week with a Varian 21EX (Varian Medical Systems, Palo Alto, CA) linear accelerator. The regional RT was delivered through antero-posterior portals using 4, 6 or 10 MV photon beams with a T- shape field including the bilateral supraclavicular, mediastinal and abdominal regional lymph nodes or I-shape field including mediastinal and abdominal regional lymphnode to 40–41.4 Gy, and the boost was delivered through parallel opposed oblique portals avoiding spinal cord using 10 MV photon beams. The total dose ranged from 50.4 to 76 Gy (median 65 Gy). 39 patients were treated with radiation and concurrent chemotherapy and 8 were treated with radiation alone (Table 1). The concurrent chemotherapy regimen consisted of cisplatin or carboplatin plus 5-fluorourasil. No patients was performed a procedure like balloon dilatation or insertion of esophageal stent against esophageal stenosis before radiotherapy.

Response evaluation

The response was determined within three month following the completion of treatment by using esophagography and esophagoscopy. The response of the primary tumor was evaluated by the criteria of the Japanese Society for Esophageal Diseases, which were based on the findings from esophagograms and esophagoscopy.[9] CR was defined based on findings from esophagograms and esophagoscopy as disappearance of the tumor lesion and disappearance of ulceration.

Table 1. Characteristics of patients and treatment

Characteristic	
Age	
median	70 years
ranges	50–87 years
Gender	
Male	43
Female	4
Pathology	
SCC	47
Finding Type	
1	3
2	34
3	9
4	1
Portion	
Ce	4
Ut	15
Mt	24
Lt	3
Ae	1
T stage	
T2	16
T3	20
T4	11
Extent of involved circumference	
full	20
non full	27
Tumor length	
median	55 mm
ranges	10–110 mm
Wall thickness of tumor region	
median	13 mm
ranges	2–55 mm
Stenosis level before treatment	
1–2	18
3–4	29
Radiation therapy total dose	
median	65 Gy
ranges	50.4–76 Gy
Concurrent chemotherapy	
done	39
undone	8

Abbreviations: SCC = squamous cell carcinoma; Ce = cervical esophagus; Ut = upper thoracic esophagus; Mt = middle thoracic esophagus; Lt = lower thoracic esophagus; Ae = abdominal esophagus

Evaluation of esophageal stenosis

We evaluated the stenotic ratio using the image of esophagography before and within three months after the completion of radiation therapy by the method shown in Fig. 1. Using an image in which stenotic change was mostly reflected among the esophagography series, we measured the lumen diameter at the narrowest part of (b) and the widest part of the oral side of the (a) of the primary site after radiation therapy. The esophageal stenotic ratio (c) (expressed as a percentage) was calculated as c = (a – b) / a*100. The definition of stenosis levels was shown in Table 2; the stenotic ratio was used to define four stenosis levels: stenosis level 1, stenotic ratio of 0–24%; 2, 25–49%; 3, 50–74%; 4, 75–100%.

Statistical analysis

We estimated the correlation between the esophageal stenosis level after radiation therapy and each of numerous factors about tumors and therapy; age, gender, T stage, extent of involved circumference, length and wall thickness of the tumor region, stenosis level before treatment, total dose of radiation therapy and with/without concurrent chemotherapy. For univariate analysis, a chi-square test was performed to compare the distribution of the characteristics of patients and treatments among the stenosis levels. For multivariate analysis, logistic regression analysis was performed. Differences were considered statistically significant when $p < 0.05$.

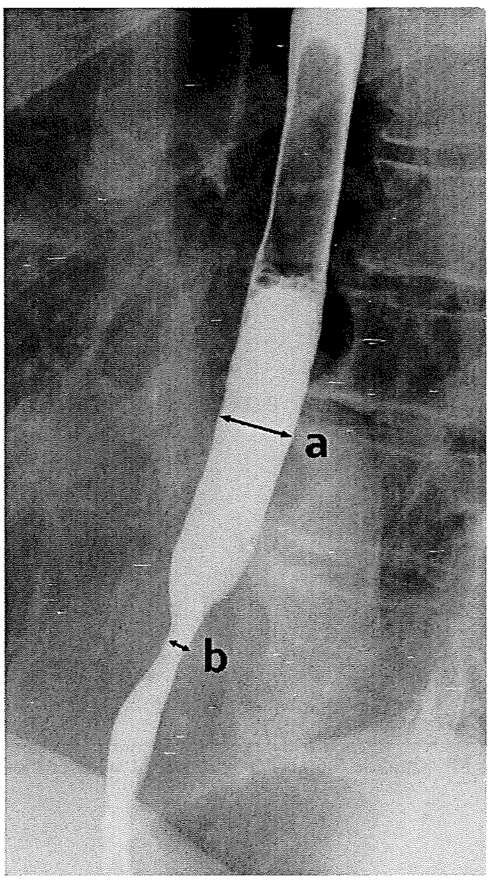

Fig. 1. Esophagography image. We measured the lumen diameter of the narrowest part (b) and the widest part of the oral side (a) of the primary site after radiation therapy. The esophageal stenotic ratio (c) (presented as a percentage) was calculated as c = (a – b) / a*100.

RESULTS

The number and percentage of patients with each level of stenosis is shown in Table 2: stenosis level 1: n = 14 patients (30%); level 2: 8 (17%);, level 3:14 (30%); and level 4:11 (23%). The summary of correlation between each factors and the proportion of patients with each stenosis level was shown in Table 3. In regard to the extent of involved circumference, the proportion of patients with level 4 stenosis were 8% and 45% of the case of non-full and full circumference involvement. Esophageal stenosis in the cases of full circumference involvement tended to be more severe and more frequent than that in the cases of non-full circumference involvement. Among cases with a tumor thickness of less than 10 mm, more than 10 mm, the proportions of patients with level 4 stenosis were 0% and 38%, respectively. Increases in wall thickness tended to be associated with increases in esophageal stenosis severity and frequency.

The results of the statistical analysis are summarized in Table 3. In the univariate analysis, significant differences appeared for T stage, the wall thickness of tumor region, the extent of involved circumference and stenosis level before treatment ($p <$ 0.05), and significant associations were not seen for age, gender, tumor length, radiation total dose and concurrent chemotherapy. In the multivariate analysis, significant differences appeared for the wall thickness of tumor region and the extent of involved circumference (p = 0.005, p = 0.0006). The extent of involved circumference and wall thickness of tumor region were significantly correlated with esophageal stenosis associated with tumor regression in radiation therapy.

Table 2. The number and proportion of each stenosis levels after treatment

stenotis level	stenotic ratio	number of patients	%
1	0–24%	14	30
2	25–49%	8	17
3	50–74%	14	30
4	75–100%	11	23

DISCUSSION

For esophageal cancer, surgical resection has been widely accepted as the standard treatment.[10–11)] This treatment has been associated with subsequent mortality, high complication rates and quality of life deterioration.[12–14)] Long-term survival after resection of esophageal cancer is generally poor, with a 20–42.4% 5-year survival rate.[15–18)] Both radiation therapy and surgery have been shown to be useful therapies for locally advanced esophageal cancer. The histological type of most esophageal cancers is SCC,

Table 3. Correlation between each factors and the patients with each stenosis level (%)

Characteristics	N	the proportion of patients with each stenosis level (%)				*p*-value	
		1	2	3	4	univariate	multivariate
Age							
< 70 years	21	24	14	38	24	0.68	0.34
70 years ≦	26	25	19	23	23		
Gender							
male	43	33	16	30	21	0.49	0.61
female	4	0	25	25	50		
T stage							
T2	16	56	19	6	19	0.011*	0.90
T3	20	15	25	40	20		
T4	11	18	0	45	36		
Extent of involved circumference							
full	20	5	10	40	45	0.0004*	0.0006*
non full	27	48	22	22	8		
Tumor length							
< 60 mm	24	42	13	25	21	0.67	0.56
60 mm ≦	23	17	22	35	26		
Wall thickness of tumor region							
< 10 mm	18	52	21	26	0	0.0006*	0.005*
10 mm ≦	29	14	14	32	38		
Stenosis level before treatment							
1–2	18	61	22	6	11	0.0002*	0.09
3–4	29	10	14	45	31		
Radiation therapy total dose							
< 65 Gy	14	27	20	26	27	0.94	0.97
65 Gy ≦	33	31	16	31	22		
Concurrent chemotherapy							
done	39	36	18	23	23	0.08	0.06
undone	8	0	13	62	25		

Abbreviations: Ce = cervical esophagus; Ut = upper thoracic esophagus; Mt = middle thoracic esophagus; Lt = lower thoracic esophagus; Ae = abdominal esophagus

which is considered to have high radiosensitivity. Some reports on chemoradiation have indicated various advantages of this modality for managing esophageal cancer.[1–4),19–22)] Oncologists advocate that a nonsurgical approach with definitive chemoradiotherapy may be the standard for this disease.[23–26)] Recently, some reports have suggested that chemoradiation may be considered equivalent to surgery in terms of survival.[5–7)] It may thus be necessary to select among surgery, definitive chemoradiotherapy, and chemoradiation on an individual patient basis.

Dysphagia due to esophageal stenosis is often observed after radiation therapy, and esophageal stenosis decreases QOL of patients after radiation therapy, and can often lead to dysphagia.

After completion of the radiation therapy, in some cases the tumor size was reduced and esophageal narrowing was improved, but in other cases the esophageal stenosis worsened despite the reduction in tumor size. If the esophageal stenosis increases, patients will experience dysphagia, and oral intake may become difficult for them. If oral intake becomes impossible, intervention is immediately needed to decrease the stenosis.

As palliative procedures against esophageal stenosis, balloon dilatation, endoscopic placement of esophageal stents, and bypass operations have been performed. Simple balloon dilatation is considered safe, but the probability of re-stenosis is high. Endoscopic placement of esophageal stents is the most widely used palliative treatment for patients with esophageal stenosis or fistula, but some reports have suggested that it has a high rate of severe complications (perforation, fistula, bleeding, etc.) that can lead immediately to death, especially when esophageal intuvation is combined with radiation therapy and the patients with complications took food for shorter periods than those who had no complication.[27–33] A bypass operation is considered very risky. Therefore, although there are numerous palliative, procedures against esophageal stenosis, their outcome are not yet satisfactory.

It is considered that esophageal stenosis after radiation therapy may be caused by fibrosis or ischemic change of the process of tumor reduction, but the details have not been clarified yet. Nonetheless, a few reports have proposed possible mechanisms or frequencies for esophageal stenosis after radiation therapy.[34–37] These reports have suggested that patients with dysphagia after radiation therapy to the chest and neck show histologic evidence of fibrosis of the submucosa and hyalinization of the smooth muscle layers of the esophagus,[34] and these processes include the accumulation of macrophages and increased local levels of pro-inflammatory cytokines,[35,36] producing edema and fibrosis that may secondarily affect the underlying muscles.[37]

In this study, in order to predict the possibility of esophageal stenosis after radiation therapy, the extent of involved circumference and the wall thickness of tumor region may be useful. If we could predict the degree of esophageal stenosis after radiation therapy, this would be useful in various contexts—e.g., for the selection of therapy (definitive chemoradiation or surgical resection) or for obtaining informed consent for the patient before radiation therapy. Additionally, in operable cases, if we could predict that severe esophageal stenosis will occur after radiation therapy, it would be possible to prevent or avoid the stenosis and reduce patients' concerns over this very problematic side effect.

In conclusion, for predicting the possibility of esophageal stenosis associated with tumor regression within three months in radiation therapy, the extent of involved circumference and esophageal wall thickness of the tumor region may be useful.

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CASES JOURNAL

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Case report

Effective palliative radiotherapy in primary malignant melanoma of the esophagus: a case report

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Abstract

Introduction: Primary malignant melanoma of the esophagus is a rare but highly aggressive tumor with poor prognosis. Surgical resection is the treatment of choice. However, some cases may be diagnosed with advanced inoperable disease. Palliative radiotherapy may be used to relieve symptoms caused by the esophageal tumor.

Case presentation: We report on a case of advanced inoperable primary malignant melanoma of the esophagus treated with palliative radiotherapy. The patient's dysphagia resolved with radiotherapy.

Conclusion: Malignant melanoma of the esophagus is rare. Patients with advanced inoperable malignant melanomas of the esophagus benefit from radiation therapy. Radiation therapy is effective for palliation.

Introduction

Primary malignant melanoma of the esophagus is an uncommon disease accounting for only 0.1 % to 0.5 % of all esophageal carcinomas [1-3]. It has a highly aggressive tumor behavior with a median survival of about 10 months [4]. Some patients are inoperable at presentation. Radiation therapy has been used to relieve symptoms. Malignant melanomas are generally considered radioresistant, requiring higher dose per fraction. We report on a case of primary malignant melanoma of the esophagus treated with palliative radiotherapy.

Case presentation

A 71-year-old male subject presented to us in very poor general condition (Eastern Cooperative Oncology Group performance status 3) with a history of hoarseness

(3 months) and dysphagia (1 month). Clinically, the left supraclavicular lymph node (3 × 3 cms) was palpable. Computed tomography (CT) scan of the chest and abdomen demonstrated extensive swelling of the mediastinal lymph nodes extending from 4 cm above the level of the upper margin of the sternum to 2 cm below the carina, the esophagus was compressed and trachea shifted to the right of the midline. Primary esophageal tumor was not separately identifiable from the mediastinal lymph nodes. Lymph nodes in the superior and middle mediastinum measured approximately 12 × 7.7 × 6.0 cm (Figure 1A). Left supraclavicular (3.3 × 3.0 cm) and abdominal node (1.9 × 1.5 cm) metastases were also observed (Figure 1B, 1C). Esophagoscopy demonstrated a 10 mm pigmented polypoidal lesion (25 cm from the inscisor) and multiple pigmented flat lesions (Figure 2). Esophageal narrowing due to extrinsic compression was seen from 19 cm to 24 cm. Histopathology of the biopsy specimen from the esophagus showed diffuse proliferation of atypical polygonal cells with hyperchromatic oval to round nuclei, eosinophilic cytoplasm, and prominent nucleoli, accompanied by various amounts of melanin pigments and immunohistochemically - positive for S-100 protein. These findings were all compatible with malignant melanoma of the esophagus. A final diagnosis malignant melanoma of the esophagus T4N1M1a, stage IVa (UICC-TNM classification [5]) was made.

Due to the fact that PS was 3, palliative radiotherapy was offered for palliation of dysphagia and tracheal compression and chemotherapy was not administrated. He received radiation therapy for primary tumor and mediastinal and left supraclavicular lymph nodes in a dose of 45 Gy (gray) in 15 fractions over 3weeks at 5 fractions per week, using anteroposterior and posteroanterior field with10-MV photon. Patient tolerated the radiotherapy well. The patient's dysphagia resolved completely shortly after radiotherapy. 1 week after radiotherapy there was a marked decrease in the size of the mediastinal lymph nodes and subject improved symptomatically. The axial dimensions of the lymph node were maximal around the level of the aortic arch where it measured approximately 4.5 × 3.5 cm 1 week following completion of radiotherapy (Figure 3). Patient had sustained palliation i.e, continuous relief of dysphagia for 4 months after radiotherapy.

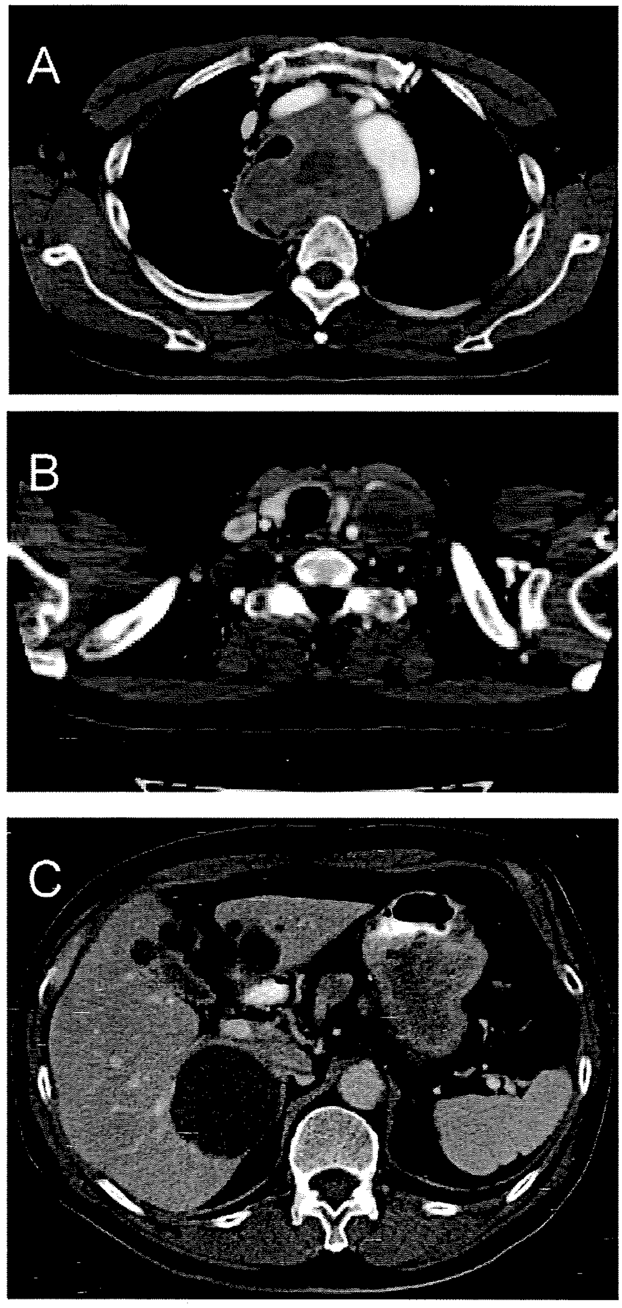

Figure 1. Contrast enhanced CT showed 7.7 cms mediastinal lymph nodes compressing the esophagus and trachea at the level of the aortic arch **(A)**, 3.3 × 3.0 cms left supraclavicular **(B)** and 1.9 × 1.5 cms abdominal lymph nodes **(C)**.

Discussion

Primary malignant melanoma affecting the esophagus is a rare and fatal disease with a poor prognosis. Sabanathan *et al.* documented that approximately 50% of patients have metastatic disease at presentation and long-term survival is extremely rare [6]. The clinical presentation of primary malignant melanoma of the esophagus is similar to the common forms of primary esophageal malignancies. The tumor most commonly occurs in the 6th and 7th decade, and the male to female ratio is 2:1. Subtotal esophagectomy is recommended as the treatment of first choice for primary malignant melanoma of the esophagus. Sabanathan *et al.* reported a median survival of between 7 and 12 months in patients who underwent radical

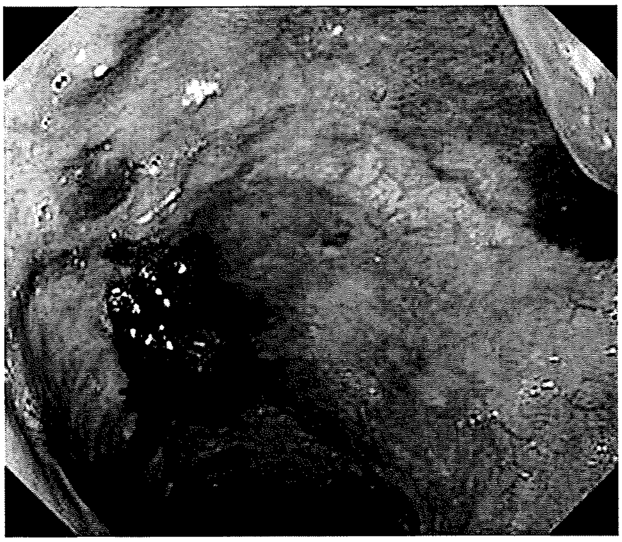

Figure 2. Endoscopic view of a dark gray polypoidal tumor of the esophagus at presentation.

resection and a 5 year survival of 4.2 % [7]. Chalkiadakis *et al.* reported, in a series of 110 patients, a mean survival of 13 months [8]. However, at the time of diagnosis, some cases may be diagnosed as having inoperable carcinoma. Chemotherapy is one of the treatment options for malignant melanoma. However, it is difficult to use chemotherapy to elderly or poor performance status patients. Paul *et al.* reported that the response rate for dacarbazine alone was 16.9 % and was 21.5% for dacarbazine plus immunotherapy [9]. Although radiotherapy may have a palliative role if surgery is not possible, malignant melanoma has been considered radioresistant [10]. At the time of diagnosis of the present case, multiple lymph node metastases were observed and the performance status was 3. Therefore, radical surgery and chemotherapy were not considered. There have been several case reports of effective palliation with photon radiotherapy [11,12]. Forgarty *et al.* reported that a patient with malignant melanoma of the esophagus received 36 Gy with a photon beam in six fractions given twice weekly, and CT after 4 months following completion of radiotherapy showed no residual mass [11]. In the present case, palliative radiotherapy using a once-daily fractionation of 3.0 Gy was offered, and the tumor markedly decreased in size and partial response was achieved.

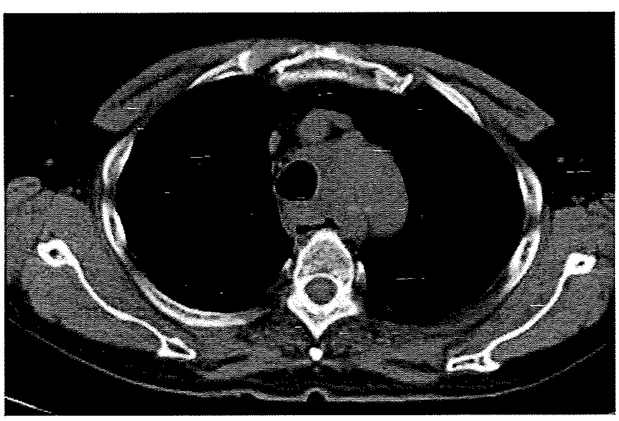

Figure 3. Mediastinal lymph node decreased in size on plain CT 1 week following completion of radiotherapy at the level of the aortic arch.

Conclusion

Malignant melanoma of the esophagus is rare. Patients with advanced inoperable melanomas of the esophagus benefit from radiation therapy. Radiation therapy is effective for palliation.

Consent

Written informed consent was obtained from the daughter of the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors contributed to acquisition of the case details and the analysis and interpretation of those details. All authors read and approved the final manuscript.

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