



Stereotactic ablative radiotherapy with CyberKnife for advanced thymic carcinoma: a case report

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ABSTRACT

Thymic carcinoma is a rare but lethal mediastinal cancer. The optimal treatment for advanced thymic carcinoma is not yet established. This report is the first known of stereotactic ablative radiotherapy (SABR) with CyberKnife (Accuray, Sunnyvale, CA, U.S.A.) as definitive therapy for thymic carcinoma.

The patient, a 70-year-old woman with thymic carcinoma, invasion into neighboring organs, and pleural metastases—underwent CyberKnife SABR at 40 Gy in 5 fractions for two lesions, one in the thymus and one in the right paraspinal pleura. After 61 months of observation, a partial response was observed in the irradiated fields. However, disease progression in the non-irradiated pleura was noted. The patient underwent salvage CyberKnife SABR for the four initially nonirradiated pleural lesions. Computed tomography images obtained 10 months after the salvage therapy revealed a partial response.

The patient is living, with progression-free irradiated lesions and no radiation-related toxicity. CyberKnife SABR is feasible for patients who are unable to undergo either surgery or conventionally fractionated radiation therapy.

Key Words Stereotactic ablative radiotherapy, CyberKnife, thymic carcinoma

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INTRODUCTION

Thymic carcinoma is a rare mediastinal neoplasm, differing clinically from thymoma by its aggressiveness and frequent metastasis¹⁻³. Most patients with thymic carcinoma are diagnosed with locally advanced or metastatic disease and have a median overall survival of 2 years⁴. The primary treatment for resectable thymic carcinoma is surgery, frequently followed by chemotherapy and radiation therapy⁵. Because surgery is refused or not suitable for patients with medically inoperable or unresectable tumours, noninvasive alternative treatment methods are needed.

The CyberKnife system (Accuray, Sunnyvale, CA, U.S.A.) delivers highly precise hypofractionated radiation therapy known as stereotactic radiosurgery or stereotactic ablative radiotherapy (SABR). The CyberKnife system consists of a 6-MV linear accelerator mounted on a robotic arm with two orthogonal radiographic imaging cameras that track the target. It was developed for cases that are difficult to treat using surgery or conventionally fractionated radiation therapy and chemotherapy. Here,

we present the first instance of CyberKnife SABR as definitive therapy for advanced thymic carcinoma, achieving long-term local control.

CASE DESCRIPTION

A 70-year-old woman presented with a 2-month intermittent cough and dyspnea since May 2008. Chest computed tomography (CT) demonstrated a lobulated soft-tissue mass measuring 9.4×7.8×4.0 cm in the prevascular space of the anterior mediastinum, involving the heart and great vessels [Figure 1(A)]. There were also a few small nodules in the subpleural regions of the right lung and a fusiform-shaped soft-tissue mass measuring 2.7×2.4×0.8 cm in the right paraspinal pleura [Figure 1(B)]. A CT-guided biopsy of the primary lesion was performed, and the diagnosis of squamous cell carcinoma was confirmed pathologically. According to the classification set out by Masaoka *et al.*⁶, the clinical stage was IVA.

Because of multiple pleural metastases and patient preference, our patient underwent 3 cycles of cisplatin 50 mg/m², doxorubicin 40 mg/m², vincristine 0.6 mg/m²,

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and cyclophosphamide 700 mg/m² intravenously (ADOC regimen) at 4-week intervals between 24 July and 25 September 2008. However, CT at 1 month after chemotherapy showed no significant change in the tumours, and CyberKnife SABR was selected as the next mode of treatment.

CyberKnife SABR was administered between 3 and 16 December 2008. The thymic lesion and largest pleural metastasis in the right paraspinal pleura were treated with 40 Gy in 5 fractions for the gross tumour volume. Radiation was delivered to a prescription isodose line of 70% for both lesions (Figure 1). For the thymic lesion, 102 beams were used to treat the prescription volume of 173.3 cm³, with 82.3% target volume coverage. For the right pleural lesion, 134 beams were used to treat the prescription volume of 4.8 cm³, with 95.4% target volume coverage. The new conformity index was 1.65 in the thymic lesion and 1.97 in the right pleural lesion. Abdominal compression and real-time imaging were used to ensure submillimeter accuracy during treatment.

The patient tolerated the treatment well and did not receive further chemotherapy or surgery. During follow-up, CT imaging showed a persistent partial response in the irradiated fields (Figure 2). The thymic lesion shrank to 52.2 cm³ from 173.3 cm³, and the right pleural lesion shrank to 3.6 cm³ from 4.8 cm³. However, disease progression in the nonirradiated pleura was noted.

At 61 months after the initial SABR, the patient had a right chest tube inserted for massive pleural effusion. Between 22 January and 21 February 2014, she underwent salvage CyberKnife SABR for the four initially nonirradiated but progressed right pleural lesions [45 Gy in 5 fractions for two lesions, and 40 Gy in 5 fractions for two lesions; Figure 3(A)]. After the salvage therapy, the chest tube was removed, and CT images obtained on 23 December 2014 revealed a partial response [Figure 3(B)]. The right inferior, right superior, right lateral, and right posterior

pleural metastases shrank in size to 18.1 cm³ from 68.9 cm³, to 11.2 cm³ from 46.7 cm³, to 2.2 cm³ from 9.9 cm³, and to 2.3 cm³ from 7.1 cm³ respectively. At 72 months' follow-up, the patient is living and has no radiation-related toxicity.

DISCUSSION

Owing to a paucity of experience with locally advanced and metastatic thymic carcinoma, the optimal treatment is not well established. In general, aggressive multimodal treatment comprising surgery, radiation therapy, and chemotherapy is warranted. Definitive radiation therapy or chemotherapy, or both, are used for patients who are not candidates for surgery because of extent of disease or comorbid medical conditions.

Patients with thymic carcinoma can receive external-beam radiation therapy delivered as three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, or SABR. After SABR for central lung tumours, the risk of grade 3 or 4 toxicities is increased⁷, and therefore, to prevent toxicity, SABR requires a highly conformal technique to deliver high-dose radiation in 5 or fewer treatment fractions. The CyberKnife system provides real-time image guidance to verify organ position throughout treatment⁸. A total dose of 60–70 Gy (1.8–2 Gy per fraction per day) is recommended for patients with unresectable thymic carcinoma⁵. Using an α/β ratio in the linear quadratic model of 10 Gy for thymic carcinoma, the dose equivalent to 40 Gy delivered in 5 fractions was calculated to be 60 Gy if delivered at 2 Gy per fraction. In that setting, long-term local control was achieved without significant toxicity. That no acute or late toxicity was seen could be a reflection of the location of tumour in the anterior mediastinum (prevascular space) and of the fact that the total dose delivered was lower than the dose recommended for primary lung cancers or thymic carcinoma.

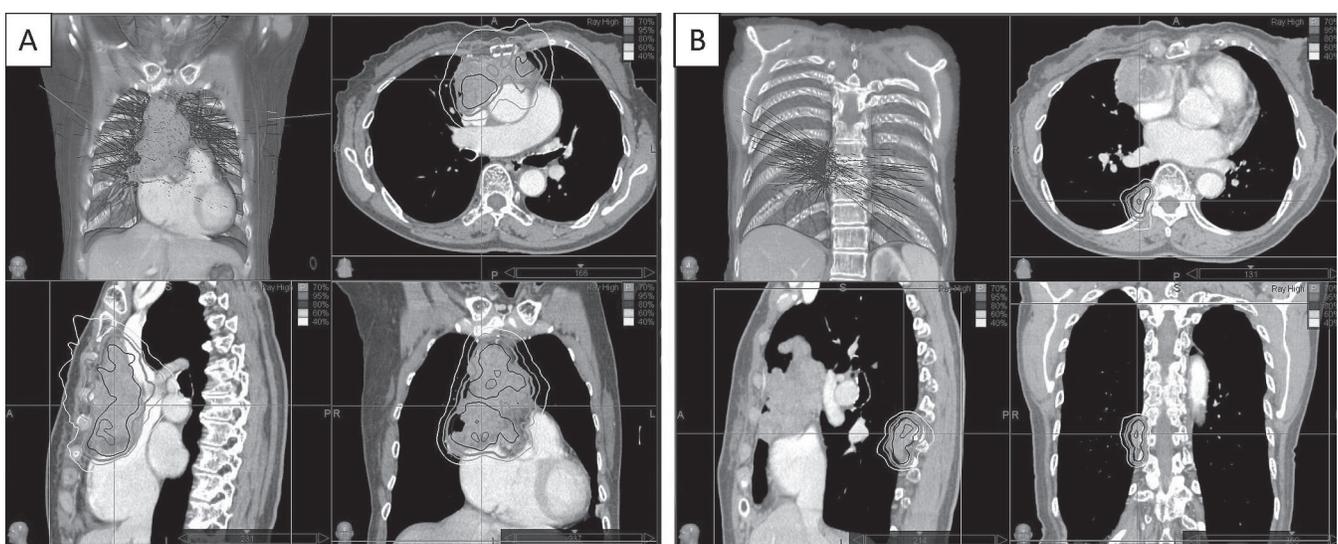


FIGURE 1 Treatment planning and rendering for lesions at (A) the thymus and (B) the right paraspinal pleura to be treated using CyberKnife (Accuray, Sunnyvale, CA, U.S.A.). The primary tumour is located in the prevascular space of the anterior mediastinum, with involvement of the heart and great vessels. The metastatic pleural lesion is a fusiform-shaped soft-tissue mass in the right paraspinal pleura. Radiation (40 Gy) was to be delivered to a prescription isodose line of 70%.

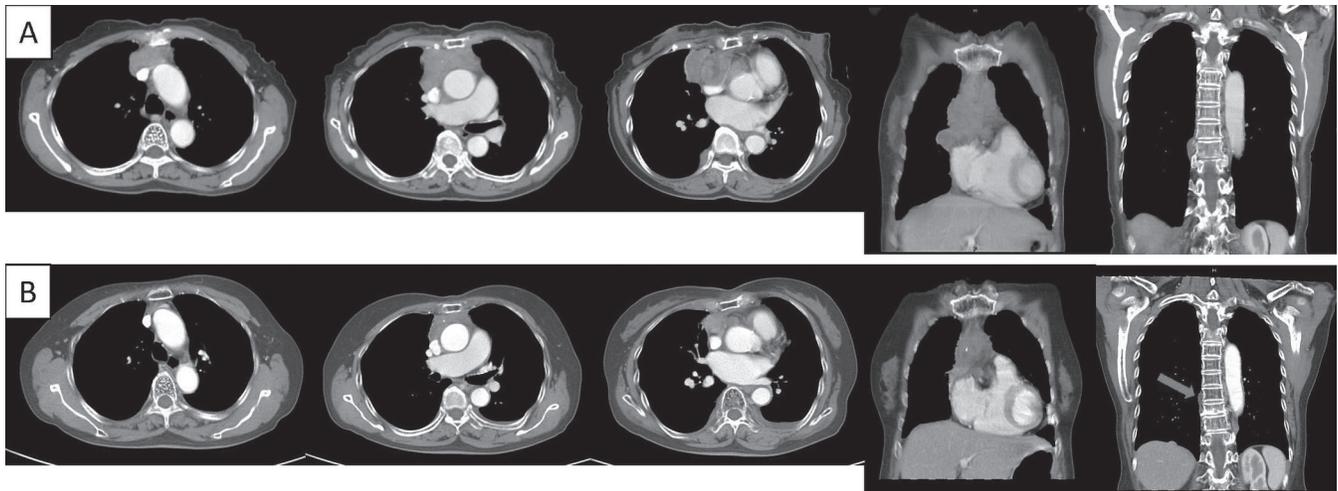


FIGURE 2 Computed tomography (CT) imaging (A) on 26 November 2008 before treatment with CyberKnife (Accuray, Sunnyvale, CA, U.S.A.), and (B) on 26 October 2010 after treatment. Post-treatment imaging revealed a persistent partial response of the thymic lesion and the right paraspinal pleural lesion (arrow).

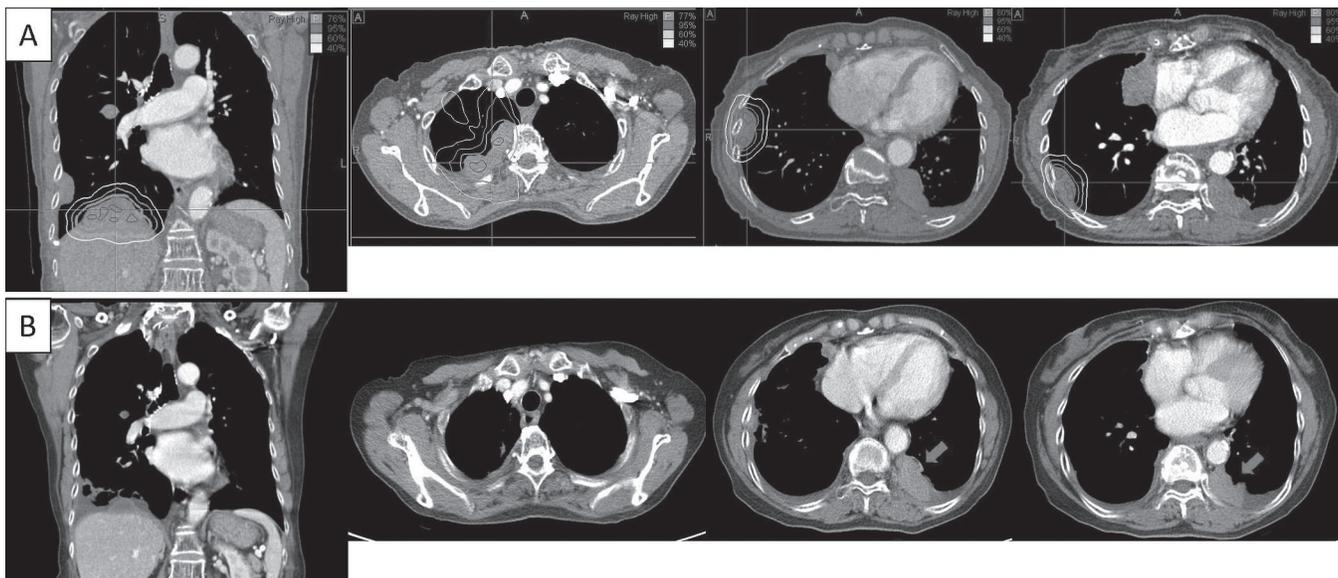


FIGURE 3 (A) Treatment planning and rendering on 15 January 2014 for the four right pleural lesions to receive salvage therapy using CyberKnife (Accuray, Sunnyvale, CA, U.S.A.). The two leftmost images show lesions in the inferior and superior right pleura that received 45 Gy in 5 fractions. The two rightmost images show the lesions in the right lateral and right posterior pleura that received 40 Gy in 5 fractions. (B) Computed tomography imaging on 23 December 2014 after salvage treatment. Imaging revealed a partial response in the irradiated fields, but persistent disease in the nonirradiated left pleural metastasis (arrow). Small bilateral pleural effusions were noted, with no obvious pulmonary fibrosis.

The outcome of patients with unresectable locally advanced or metastatic thymic carcinoma is poor. Even after conventionally fractionated definitive radiation therapy (with or without chemotherapy), median survival is 11–28 months^{9–11}. Until recently, few data about the effect of SABR on thymic carcinoma have been available. Fan *et al.*¹² reported a retrospective series of 45 patients with advanced thymic carcinoma. Compared with patients who underwent conventionally fractionated radiation therapy, 5 patients who underwent SABR (65–70 Gy in 8–10 fractions delivered using a traditional accelerator) experienced a longer median survival duration (54 months vs. 44 months). To our knowledge, no report in the English literature has

described a patient with thymic carcinoma receiving SABR delivered using CyberKnife as definitive therapy. Our patient experienced good local control in the irradiated field, resulting in long-term survival.

Theoretically, induction chemotherapy can not only eradicate micrometastases, but also decrease tumour size. Neoadjuvant chemotherapy with or without radiation therapy is known to improve the complete surgical rate^{13,14}. Although thymic carcinomas respond poorly to chemotherapy, the use of platinum-based chemotherapy was found to have some encouraging results in several studies^{15–17}. Still, the optimal chemotherapy regimen for advanced thymic carcinoma remains uncertain. Currently,

carboplatin–paclitaxel is recommended and has been found to be as effective as, and less toxic than, the ADOC regimen^{5,16}. Meanwhile, some researchers have reported successful treatment with targeted therapy using sorafenib or sunitinib in patients with chemotherapy-resistant advanced thymic carcinoma^{18,19}. An updated treatment strategy using three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, or CyberKnife SABR combined with targeted therapy might be useful in patients with advanced thymic carcinomas who do not respond to induction chemotherapy.

CONCLUSIONS

Thymic carcinoma is a rare malignancy with a poor prognosis. Aggressive multimodal treatments including surgery, radiation therapy, and chemotherapy are recommended for advanced thymic carcinomas. As an alternative treatment method, we used SABR delivered using CyberKnife, which was safe and effective for a patient with unresectable thymic carcinoma. This approach could be considered for patients who are unable to undergo surgery or conventionally fractionated radiation therapy.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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