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# The Safety and Efficacy of Cyberknife for Thymic Malignancy

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## Abstract

**Purpose:** To evaluate the safety and efficacy of Cyberknife (CK) for the treatment of primary or recurring thymic tumors.

**Materials and Methods:** We retrospectively reviewed 12 patients (16 tumor lesions) with primary or recurring thymic tumors who were treated with CK between March 2008 and October 2017. Their data was stored in prospectively collected database. Kaplan-Meier method was used to calculate survival curves.

**Results:** 5 patients (41.7%) who had inoperable disease or refused surgery were treated with CK initially, and 7 patients (58.3%) were treated with CK when they had recurrence diseases. The disease sites treated with CK were primary tumor site (5), regional lymph nodes (4), tumor bed (3), chest wall (2), pleura (1), and bone (1). The median target volume was 43.8 $cm^3$ (range, 13.1 $cm^3$ to 302.5 $cm^3$) for the 16 tumor lesions. The median follow-up time was 69.3 months (range, 9.7 months to 124.8 months). The median survival time was 48.2 months, and the 5-year and 10-year OS rates were 68.2% and 45.5%, respectively. A high response rate for the tumor lesions irradiated with CK was obtained. Only one patient (8%) experienced in-field recurrence, and the 5-year local recurrence free survival was 90.9%. A case indicated that CK may induce the abscopal effect, which provides the potential to combine CK and immunotherapy. No severe radiation related toxicities were observed, and no treatment related death occurred.

**Conclusion:** CK treatment resulted in good outcomes, particularly local control, with minimal side effects, in highly selected patients with primary and recurring thymic tumors. More studies with larger sample are needed.

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## Introduction

Thymic epithelial malignancies originate in the thymus, including thymoma and thymic carcinoma, which are rare disease in the anterior mediastinum. Although thymoma can spread loco-regionally, it is much less aggressive [1], and has much better survival, compared with thymic carcinoma. 5-year Overall Survival (OS) rate for thymoma is up to 90% [2-4]. Whereas, it is less than 55% for thymic carcinoma [5-7]. Surgery remains the key modality for patients with operable thymoma and thymic carcinoma who can tolerate surgery [8-10]. Complete resection is the most important predictor of outcomes [2,5,10]. However, even after complete resection, up to 80% patients with advanced stage can experience recurrence [11,12].

Radiation therapy is routinely used for patients with inoperable or recurring diseases, and those who cannot tolerate surgery, often in combination with systemic chemotherapy. Radiation techniques have achieved the giant advances in the past several decades, such as Intensity Modulated Radiation Therapy (IMRT), image-guided radiation therapy (IGRT), proton therapy, etc. CyberKnife (CK), one of the modern radiation techniques, is a robotic with image guided radiosurgery system that enables the delivery of a focused dose concentration to tumors while allowing a steep decrease in dose to nearby organs at risk (OARs) [13-16]. This dosimetry is due to CK's ability to deliver high dose per fraction, short course radiotherapy, and real-time tracking [17,18]. Thus, CK may be appropriate for limited volume diseases, given the relatively resistant nature to Conventional Fractioned Radiation (CFRT) of thymic tumors, and it may have the potential to subvert the traditional theory of radio-sensitivity, accordingly, to improve local control and OS. However, there is no high level evidence to support the utility of CK for thymic tumors so far. Thus, this study aims to determine the safety and efficacy of CK for inoperable or recurring thymic tumors.

**Table 1:** Patients and treatment characteristics before cyber knife treatment.

| Pt | Age (years) | Sex | ECOG score | Masaoka stage | WHO histology | Treatment modalities | Recurrence | Free Recurrence time |
|---|---|---|---|---|---|---|---|---|
| 1 | 34 | Male | 0 | II | Type C | S | Yes | |
| 2 | 37 | Male | 1 | IVB | Type C | S+bonemets RT | Yes | 25 months |
| 3 | 41 | Female | 1 | III | Type B1 | CK | | |
| 4 | 43 | Male | 1 | III | Type B2 | CK | | |
| 5 | 59 | Male | 0 | III | Type C | S+RT+CT | Yes | 9.5 months |
| 6 | 66 | Male | 1 | II | Type C | CK | | |
| 7 | 51 | Female | 1 | IVA | Type C | CT+RT | Yes | 60 months |
| 8 | 37 | Female | 1 | II | Type AB | S | Yes | 43.5 months |
| 9 | 59 | Female | 1 | IVB | Type C | CT+CK | | |
| 10 | 57 | Male | 1 | IVB | Type C | CT+CK | | |
| 11 | 61 | Female | 1 | IVB | Type C | S+CT | Yes | 60 months |
| 12 | 48 | Female | 0 | IVA | Type B2 | S+RT+CT | Yes | 58 months |

**Abbreviations:** Pt: Patient; S: Surgery; RT: Radiation; CK: Cyberknife; CT: Chemotherapy

**Table 2:** Cyber knife treatment characteristics and clinical outcomes.

| Pt | Initial treatment | CK time | CK sites | TV ($cm^3$) | RT dose | BED | LR | LRfree time (months) | RR | RR free time (months) | DM | DMfree time (months) | Survive | Survival time (months) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | No | 3/11/2008 | Tumor bed | 62.3 | 45Gy/5f | 85.5 | No | 124.8 | No | 124.8 | No | 124.8 | alive | 124.8 |
| 2 | No | 6/22/2009 | Tumor bed | 51.3 | 45Gy/5f | 85.5 | No | 57.9 | Yes | 21.9 | Yes | 21.9 | dead | 57.9 |
| 3 | Yes | 7/22/2010 | Primary site | 63.6 | 40Gy/5f | 72 | No | 96.5 | No | 96.5 | No | 96.5 | alive | 96.5 |
| 4 | Yes | 9/3/2012 | Primary site | 47.3 | 45Gy/5f | 85.5 | No | 71 | No | 71 | No | 71 | alive | 71 |
| 5 | No | 12/17/2012 | Tumor bed | 43.3 | 40Gy/5f | 72 | No | 67.6 | No | 67.6 | Yes | 53.5 | alive | 67.6 |
| 6 | Yes | 3/11/2013 | Primary site | 30.5 | 50Gy/5f | 100 | Yes | 10.3 | Yes | 17.3 | Yes | 10.4 | dead | 17.3 |
| 7 | No | 7/31/2014 | Lymph node | 19.1 | 48Gy/8f | 76.8 | No | 48.2 | No | 48.2 | No | 48.2 | alive | 48.2 |
| 8 | No | 11/4/2014 | Pleura | 13.1 | 45Gy/5f | 85.5 | No | 45 | Yes | 42.1 | No | 45 | alive | 45 |
| 9 | Yes | 12/8/2014 | Primary site | 34.3 | 45Gy/5f | 85.5 | No | 11.8 | Yes | 1.8 | Yes | 1.8 | dead | 11.8 |
| 10 | Yes | 3/16/2015 | Primary site | 302.5 | 45Gy/10f | 65.25 | No | 39 | No | 39 | No | 39 | alive | 39 |
| 11 | No | 10/13/2017 | Bone metastasis and lymph nodes | 44.2, 60.7, 38.8 | 49Gy/7f, 49Gy/7f, 49Gy/7f | 83.3, 83.3, 83.3 | No | 9.7 | No | 9.7 | No | 9.7 | alive | 9.7 |
| 12 | No | 10/25/2010, 11/10/2014, 2/9/2015 | Chest wall, Lymph node, Chest wall | 20.7, 77.2, 15.9 | 40Gy/5f, 45Gy/5f, 45Gy/5f | 72, 85.5, 85.5 | No | 80.3 | Yes | 74.4 | Yes | 74.4 | dead | 80.3 |

**Abbreviations:** CK: Cyberknife; RT: Radiation; BED: Biological Equivalent Dose; Pt: Patient; LR: Local Recurrence; RR: Regional Recurrence; DM: Distant Metastasis; TV: Target Volume

## Materials and Methods

### Patients

We retrospectively analyzed 12 patients (16 tumor lesion) with primary or recurring thymic tumors, who were treated with CK between March 2008 and October 2017. Five patients who had inoperable disease or refused surgery were treated with CK initially. Among 7 patients with recurrence diseases who were treated with CK, 4 patients initially received CFRT prior to CK, in the form of intensity-modulated radiotherapy and 3D conformal radiotherapy. According to ITMIG definitions, the relapse of thymoma is defined as a strong clinical suspicion of thymoma recurrence, without a specific requirement of pathological proof. The time of recurrence should be recorded as the time when a strong suspicion first exists. One oncologist and two radiologists diagnosed patients with recurrence according to clinical symptoms and the results of CT scan and MRI when needed. Biopsy is not mandatory.

### Treatment schedule

The CK Robotic Radiosurgery System, which is a 6-MV X-band linear accelerator mounted on a completely articulated robotic arm that is capable of rotational and translational movements to target tumors without rigid external fixation, was used to deliver the radiosurgical treatments. A proprietary inverse treatment planning system (MultiPlan®, Accuray) was used to determine the number, direction, diameter, and duration of treatment beams. All patients received tumor tracking by Synchrony® Respiratory Tracking System.

All patients adopted linac-based CK. Patients were immobilized supine in a vacuum mattress. A contrast-enhanced CT scans with 1.5-mm slice thickness and covering the 15-cm distance anterior and posterior the target. Then we define Gross Target Volume (GTV) in the CT image. The Planning Target Volume (PTV) expanded 3 mm to 5 mm on the basis of GTV. The dose was prescribed to the 66% to 81% isodose line (median, 75%) to obtain adequate PTV coverage.

PTV was 3.88 $cm^3$ to 302.4 $cm^3$ (median, 43.7 $cm^3$). A total dose of 40 Gy to 50 Gy (median, 45 Gy), in 5 fractions to 10 fractions (median, 5) of successive radiation. We outlined vital structures, such as lungs, heart, and cord etc.

### Follow up and observation end point

All patients received evaluation of safety and efficacy one month after CK treatment. Then every 3 months for the following two years, every 6 months for 3 years to 5 years, and one year afterwards. The follow-up time was measured from the date of initial CK. The observation end point is local control and OS. Local control was defined as stable or decreased area of treated diseases on follow up scans. The primary endpoint was local control rate. Secondary endpoints were Local Recurrence-Free Survival (LRFS), Regional Recurrence-Free Survival (RRFS), Distant Metastasis Free Survival (DMFS), and Overall Survival (OS). LRFS was calculated from the beginning of CK to the time when the tumor became locally progression-free. RRFS was calculated from the beginning of CK to the time when patients have intrathoracic recurrence, but except for the recurrence of irradiated sites or lungs. DMFS was calculated from the beginning of CK to the time when patients have lung recurrence or extrathoracic recurrence. OS was calculated from the beginning of CK to the time when the patient died or lost follow-up.

### Statistical analysis

The Kaplan–Meier method was used to calculate the survival rates. A P-value less than 0.05 indicated statistical significance. Statistical analysis was performed using SPSS 23.0 software (IBM, Armonk, NY, USA).

## Results

The baseline characteristics and initial treatment modalities of patients 12 consecutive patients including 16 target lesions who were treated with CK were analyzed in this study. The baseline characteristics and initial treatment modalities of all patients were shown in Table 1. The median age of the patients was 49 years (range, 34 years to 66 years), and 6 of these patients were male. 66.7% of the patients were thymic carcinoma, and a half was classified into stage IVA or IVB. None of our patients with thymic tumors had an associated immunologic disorder such as Myastheniagravis (MG).

### The Cyberknife characteristics of patients

Five patients (41.7%) were treated with CK initially, and 7 patients (58.3%) were treated with CK when they had recurrence diseases. All the patients completed CK. The CK treatment characteristics of patients were shown in Table 2. The disease sites treated with CK were primary tumor site (5), regional lymph nodes (4), tumor bed (3), chest wall (2), pleura (1), and bone (1). The median target volume was 43.8 $cm^3$ (range, 13.1 $cm^3$ to 302.5 $cm^3$) for the 16 tumor lesions.

### Survival

The median follow-up time was 69.3 months (range, 9.7 months to 124.8 months). The median survival time was 48.2 months, and the 5-year and 10-year OS rates were 68.2% and 45.5%, respectively (Figure 1). At the last follow-up, 5 patients (41.7%) were alive without disease, 3 (25%) was alive with disease, and 4 (33.3%) had died. 3 patients were dead from the progression of thymic malignancy, the cause of death of the other patient was unknown.

### Recurrence patterns

A high response rate for the tumor lesions irradiated with CK was obtained. Only one patient (8%) experienced in-field recurrence, and the 5-year local recurrence free survival was 90.9% (Figure 1). Five patients (42%) experienced regional recurrence, among whom, 4 had pleural metastasis, and 1 had regional lymph node recurrence. The 5-year and 10-year regional recurrence free survival was 62.9% and 41.9%, respectively (Figure 1). 4 patients (42%) experienced distant metastasis, among whom, 1 had bone metastasis, 2 had lung metastasis, and 1 had both bone and lung metastasis. The 5-year and 10-year DMFS was 58.7% and 39.1%, respectively (Figure 1).

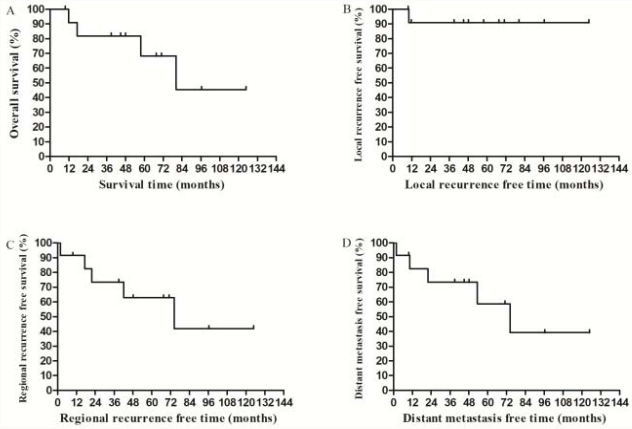


**Figure 1:** Overall survival (A), local recurrence free survival (B), regional recurrence free survival (C), and distant metastasis free survival (D) of 12 patients treated with Cyberknife.

### Adverse effects

Among 12 patients treated with CK, one patient had mild thoracic pain after radiation, and recovered in three months without treatment, and one patient had acute grade 1 pneumonitis. No other radiation related toxicities were observed, and no treatment related death occurred.

### A case report

A male patient with thymic carcinoma who had lung metastasis when diagnosed initially in March 2015. He received two cycles of chemotherapy, in the basis of VP-16 and cisplatin. Thoracic CT was repeated, which reported that the tumor diseases increased slightly. He was treated with CK for the primary site, and observed afterwards. The tumor diseases in the mediastinum decreased, and the lung metastasis diseases did not progress for 42 months.

## Discussion

Traditionally, thymic malignancies are refractory to CFRT, but may respond to higher doses per fraction, as the previous studies on other malignancies reported [19,20]. Stereotactic Body Radiation Therapy (SBRT) which provides highly accurate, precisely focused radiation that allows higher doses to be delivered in fewer treatments has been extensively applied in a variety of solid tumors, such as lung cancer, liver cancer, renal cell cancer, etc., and it has been shown to have good outcomes, with low toxicities [21,22]. Accordingly, SBRT may improve the local control and survival of patients with thymic malignancies as well. At present, only several literatures have reported the outcomes of SBRT for thymic tumors, and most of these reports are case reports [23-26]. A patient with a 38 mm × 20 mm anterior mediastinal mass who had MG symptoms underwent SBRT. The anterior mediastinal mass experienced complete resolution by PET/CT 2 months after treatment, and MG symptoms were much better.

23 CK is one of the modern radiation techniques to conduct SBRT. Our study found that CK achieved excellent local control and good survival in 12 patients with primary or recurring thymic malignancies, with minimal treatment related toxicities, which suggests that SBRT is feasible for patients who have inoperable diseases, who cannot tolerate surgery, and who have loco regionally recurring diseases or oligometastasis diseases.

The relapse of thymoma is common even after radical resection, with a post-complete resection recurrence rate ranging from 5% to 50% [11,27]. Thymic carcinoma even recurs more frequently than thymoma [28]. The pleura and tumor bed are the most common recurrence sites for thymoma [11], whereas, the distant metastasis is not uncommon for thymic carcinoma. Re-operation is routinely recommended for patients who has the potential to receive complete resection [10,29]. However, there is always some difficulty in re-operation for patients with recurrence diseases, because these tumors commonly invade adjacent structures or metastasize to distant organs. Thus, alternative modalities, such as radiation or chemotherapy, should be attempted as they might still provide survival benefit.

Radiation is an important modality in the treatment of thymic tumors. For patients with inoperable or recurrent diseases, radiation is routinely utilized in the definitive and salvage setting, often in combination with systemic chemotherapy [30,31]. However, CFRT for patients with thymic tumors has historically been associated with acute and long-term toxicities, including radiation pneumonitis, pericarditis, myocardial infarction, and congestive heart failure, etc [32,33]. The treatment toxicities may reduce the overall benefit of radiotherapy. Thus, reducing toxicity may shift the risk-benefit ratio favorably. CK enables to deliver high dose per fraction accurately and precisely [17,18]. On one hand, by improving the single dose, CK not only shortens the total radiation treatment, but also increases the total dose of equivalent biological effects; On the other hand, CK, with more precise conformal radiation therapy, significantly reduces the damage to the surrounding normal tissues. Therefore, CK may potentially to obtain better local control and survival for patients with thymic diseases; with minimal toxicities. A prospective study by Hao et al. including 32 patients with thymoma and thymic carcinoma reported that SBRT with CK had a preferably local control rate, with the tumor response rate of 96.9%. Average tumor size was 1.9 cm after SBRT and it was markedly smaller than the baseline tumor size (average 5.3 cm; P=0.000) [26]. Consistent to this finding, our study found that CK achieved excellent local control rate. The possible reason is that CK increases the biological equivalent dose (BED, $\alpha/\beta=10$) as compared with CFRT, and the median BED in our study regarding the GTV was 85.5 Gy (range, 65.25 Gy to 100 Gy), which represented an obvious increase dose. In the study by Hao etc. including 32 patients with thymic tumors who received SBRT with CK, a total dose of 35 Gy to 50 Gy was delivered to the 50% isodose line covering 100% of the PTV, with 49 Gy to 70 Gy to the 70% isodose line covering 95% of the GTV. The BED of GTV was 73 Gy to 119 Gy, which was also much higher than CFRT.

SBRT plays an important role in variety of solid tumors with oligometastasis diseases, and it may improve the local control of the metastasis diseases and OS [20]. In the study by Wang et al. including 175 metastatic lesions from 85 patients treated with SBRT, SBRT demonstrated excellent local control of metastatic renal cell carcinoma with a favorable safety profile when an adequate dose and coverage were applied [20]. The distant metastasis of thymoma is very rare, whereas, it is more common in thymic carcinoma. Most of time, it has oligometastasis diseases. Harada Y. et al. reported 10 patients with thymic carcinoma (5 patients with distant metastasis) treated by CK. The dose ranged from 31 Gy to 50 Gy, and the fraction ranged from 7 to 12 times. Two patients had complete response, and the Objective Response Rate (ORR) was 90% [25]. This study suggested that SBRT with CK was successful in patients with primary tumor, relapse, and metastatic lesions of thymic carcinoma [25]. This is consistent to our findings. In our study, one patient who had sternum metastasis achieved complete response 10 months after CK. For patients with oligometastasis diseases, CK may improve the OS and progression free survival than CFRT.

The abscopal effect is a phenomenon in which local radiotherapy is associated with the regression of metastatic cancer at a distance from the irradiated site [34]. The abscopal effect may be mediated by activation of the immune system after radiation. We found that one patient with lung metastasis who received CK for the primary site when primary tumor site and distant metastasis diseases increased slightly after two cycle's chemotherapy. The primary tumor site achieved complete response, and the lung metastasis diseases remained stable for 42 months. Thus, we assume that CK might improve the outcomes by activating the immune system to anti-tumor., which provides the potential to combine CK and immunotherapy. Several kinds of anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies, such as nivolumab and pembrolizumab, have been approved by the U.S. FDA for a variety of malignancies [35], such as non-small cell lung cancer, melanoma, and the squamous cell cancer of head neck, etc. The role of immunotherapy is still unclear, given the rarity of thymic malignancies. With high expression of PD-L1 and PD-1 in thymic tumors [36]. The patients may gain benefit from anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies. Some phase II trials evaluating the clinical availability of pembrolizumab for thymic carcinoma are currently in progress [37,38]. Cho et al. investigated 33 patients with thymic tumors (26 with thymiccarcinomas and 7 with thymomas). The eligibility criteria included progression after chemotherapy. The overall response rate was 24.2%; 8 patients had partial response, 17 had stable disease, and 8 had progressive disease. In this study, various ≥ grade 3 immunological side effects were observed, including hepatitis, myocarditis, myasthenia gravis, thyroiditis, glomerulonephritis, colitis, and subcutaneous myoclonus [37]. The combination of CK and immunotherapy for thymic tumors may improve the outcomes further, since the role of CK in activation of immune system to anti-tumor. Perspective studies on the safety and effectiveness of the combination of CK and immunotherapy are needed in the future.

Surgery achieves good outcomes for patients with inoperable or recurring diseases, however, postoperative mortalities and morbidities may reduce its overall benefit. CK may decrease the radiation-induced toxicities, such as radiation pneumonitis and arrhythmia, since CK has the advantages to decrease the dose to the OARs over CFRT [25]. In the study by Harada Y et al. including 10 patients with thymoma receiving CK, only four patients had mild radiation pneumonia that did not require treatment [25]. Hao et al. found that SBRT did not result in any grade 3-4 toxicities, and the grade 2 toxicities were also few [26]. This is consistent to our findings. Thus, CK is well tolerate for patients with thymic tumors.

This study is limited by small patient numbers and heterogeneous indications for treatment, including patients receiving definitive radiation therapy, salvage radiation therapy, and others with a variety

of radiation doses. Furthermore, this study analyzed both thymoma and thymic carcinoma together, which limits the recommendation for individualized treatment of patients, given the different features and prognosis thymoma and thymic carcinoma. Given the rarity of thymoma and thymic carcinoma, homogeneous patient populations with long term follow-up are limited as well. More studies with larger sample are needed in the future to explore the safety and effectiveness of CK for thymic tumors, particularly the combination of CK and immunotherapy.

## Conclusion

In conclusion, good local control and long-term survival can be achieved using CK, with limited treatment related toxicities, in highly selected patients with primary and recurring thymic tumors. More studies are needed in the future.

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