SHORT COMMUNICATION

Usefulness of CyberKnife Therapy in Patients with Differentiated Thyroid Cancer with Distant Metastases

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Abstract

Aim and objective: We reported seven cases in which external beam radiotherapy (EBRT) with CyberKnife therapy was effective against distant metastases from differentiated thyroid carcinoma (DTC).

Materials and methods: The subjects included seven patients (6 males, 1 female; age 53–77 years, average age 65.85 years) who underwent CyberKnife therapy for metastatic lesions of DTC (pathological diagnosis: differentiated papillary carcinoma). The target lesions included 12 lymph node, 6 bone, and 2 brain metastases. All patients had previously undergone total thyroidectomy, followed by radioactive iodine therapy (RAIT). Since RAIT was not expected to have a therapeutic effect, CyberKnife treatment was selected. CyberKnife irradiation was performed 1–5 times. The radiation doses covering 95% of the planning target volume (D95) ranged from 15 to 26 gray (Gy). To determine the therapeutic effect, lesion size was evaluated by computed tomography (CT) and magnetic resonance imaging (MRI) before and 6–12 months after treatment.

Results: No increase in size was observed in the brain and bone metastases. Among the lymph node metastatic lesions, a therapeutic effect involving internal necrosis without an increase in size was noted in two lymph node metastases in the cervix. Additionally, two lymph node metastases in the neck had reduced in size. No increases in size were observed in the other lymph node lesions, reflecting the therapeutic effect of CyberKnife.

Conclusions: CyberKnife may be useful in treating distant metastatic lesions of papillary thyroid cancer.

Clinical significance: CyberKnife is useful as a multidisciplinary treatment for cases in which radioactive iodine therapy is maladjusted.

Keywords: CyberKnife, Differentiated thyroid carcinoma, Distant metastases, External beam radiotherapy, Papillary adenocarcinoma, Radioactive iodine therapy.

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Introduction

Radioactive iodine therapy (RAIT) is administered for lung and bone metastases from differentiated thyroid carcinomas (DTCs).[1,2] DTCs may become malignant in cases involving undifferentiated cell carcinomas or metastasize to the brain during follow-up.[1,2] In these cases, multidisciplinary treatment, including palliative surgery, external beam radiotherapy (EBRT),[3,4] and molecular-targeted drug treatment, is required.[5,6] Among EBRT techniques, CyberKnife provides accurate irradiation in a small number of treatment sessions,[7,8] and radiation damage to the surrounding tissues is also limited.[9,10]

We report 20 distant metastases in seven cases of DTC, against which CyberKnife treatment showed therapeutic effects.

Materials and Methods

Patients

The subjects included seven patients (6 males, 1 female; age 53–77 years, average age 65.85 years) who underwent CyberKnife therapy for metastatic lesions of thyroid cancer between October 2012 and March 2019. All patients had undergone total thyroidectomy for thyroid cancer and were pathologically diagnosed with papillary cancer (Table 1). The target lesions included 12 lymph node lesions, 6 bone metastases, and 2 brain metastases. For metastatic lesions other than brain metastases, RAIT was performed before CyberKnife treatment. Scintigraphy performed after RAIT showed no significant RI accumulation at the treated site. The brain metastases were detected during the follow-up after RAIT for cervical lymph node metastases.

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All procedures in this study were performed in accordance with the ethical standards of our institutional research committee and in accordance with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

At our facility, we obtained written informed consent from all patients undergoing RAIT to use clinical data from their visits for educational and research purposes.

Follow-up and Evaluation

The sizes of the bone metastases and lymph node lesions on computed tomography (CT) were compared before and 6–12 months after CyberKnife treatment. The sizes of the brain metastases, as measured using contrast-enhanced T1-weighted fat

Table 1: Characteristics of the seven patients

Patient	*Sex*	*Age*	*Pathological subtype*
1	M	71	Papillary carcinoma
2	M	53	Papillary carcinoma
3	F	64	Papillary carcinoma
4	M	62	Papillary carcinoma
5	M	65	Papillary carcinoma
6	M	77	Papillary carcinoma
7	M	69	Papillary carcinoma

suppression magnetic resonance imaging (MRI), were compared before and 6 months after treatment.

Radioiodine and CyberKnife Treatments

All patients received I-131 as RAIT before CyberKnife treatment. The cumulative dose of I-131 ranged from 80 mCi (2.96 GBq) to 780 mCi (28.86 GBq), with an average dose of 267 mCi (9.88 GBq). Scintigraphy after RAIT showed no RI accumulation of I-131 in the treated area, indicating a therapeutic effect. Therefore, we determined that RAIT could not provide a further therapeutic effect.[8] The lymph node lesions on the cervical surface had developed after multiple surgical treatments. Conventional EBRT, which uses high doses and irradiates a large area, has a risk of radiation skin damage. Therefore, we opted for CyberKnife treatment.[7,8] CyberKnife was selected to provide immediate treatment to prevent pathological fractures of the vertebral bones due to bone metastases. RAIT requires iodine restriction before treatment.[8] Moreover, RAIT is performed at our facility if brain metastases are found, as brain metastases are associated with a risk of bleeding under iodine-limited conditions. CyberKnife treatment was performed based on the potential for an increase in brain metastases.

CyberKnife treatment was performed at Osaka Medical College Mishima-Minami Hospital CyberKnife Center. Irradiation planning, including planning regarding the fraction and dosage, was performed by experienced radiologists based on lesion size and location. The gross tumor volume (GTV) was defined based on the tumors visible on CT or MRI. The GTV was considered to be the same as the clinical target volume (CTV). The planning target volume (PTV) included the CTV with a 1.2- to 2.0-mm margin.

Results

Table 2 shows the details of the treated lesions and the CyberKnife treatments. CyberKnife irradiation was performed 1–5 times (average: 3.14). The radiation dose covering 95% of the PTV (D95), considered the actual dose to the lesion, ranged from 15 to 26 Gy (average: 18.86 Gy). No lesions, including six bone metastasis lesions, showed an increase in size during follow-up. Figure 1 shows the CyberKnife dose distribution for the brain metastasis in the right cerebellar hemisphere in Patient 3. The metastatic lesion in the right cerebellar hemisphere before treatment appeared as a 7 × 6-mm^2 mass lesion showing a contrast effect on contrast-enhanced T1-weighted fat suppression MRI (arrow in the upper image of Fig. 2). MRI performed 6 months after treatment showed no clear tendency to an increase in size, surrounding edematous changes, or bleeding (arrowhead in the lower image of Fig. 2). In two lymph node metastases in the left cervical region (arrow in the left image of Fig. 3) in Patient 3, a therapeutic effect involving internal necrosis (arrowhead in the right image of Fig. 3) was seen.

Table 2: Details of the target lesions and CyberKnife treatment

		Details of CyberKnife		*Lesion size (mm)*	
Patient	*Sites*	*Fr*	*D95(Gy)*	*Pre*	*Post*
1	Pretracheal LN	3	21.8	18 × 11	18 × 11
	Lt submandibular LN	1	22	9 × 8	8 × 8
	Lt supraclavicular LN	5	23	10 × 11	10 × 11
2	Rt side of CI	3	18	15 × 11	12 × 9
	Lt side of CI	4	16	25 × 12	25 × 11
	Rt side of C3	3	20	17 × 11	15 × 12
3	Rt cerebellar hemisphere	3	26	7 × 6	7 × 6
	Lt corona radiata	3	25	2 × 2	2 × 2
	Lt nasopharyngeal LN	3	24	19 × 10	15 × 5
	Rt neck LN	1	22	9 × 6	9 × 6
	Lt neck LN	1	18	7 × 6	7 × 6*
	Lt lower neck LN	2	23	9 × 9	8 × 6*
4	Rt submandibular LN	3	21	8 × 8	7 × 6
5	Lt petroclival—CI	4	15	58 × 31	55 × 30
	Lt side of C4/5	3	15	38 × 28	34 × 24
	Lt upper neck LN	1	21	15 × 9	6 × 3
	Lt lower neck LN	1	21	13 × 7	7 × 4
6	Lt side of tracheal LN	5	17	14 × 11	12 × 11
	Rt nasopharyngeal LN	3	22	25 × 17	22 × 11
7	C7	5	21	19 × 20	19 × 20

D95, radiation dose covering 95% of planning target volume; Fr, number of divided irradiations for CyberKnife treatment; Rt, Right; Lt, Left; LN, lymph node; C, cervical vertebral body; *Necrotic change

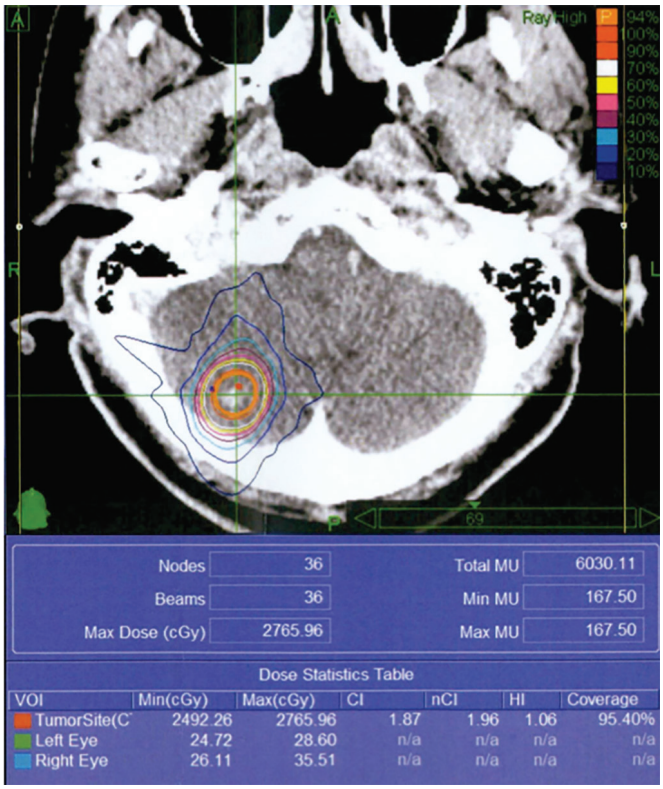

Fig. 1: CyberKnife dose distribution in the cerebellar hemisphere of Patient 3. The planning target volume is indicated by the thin orange line

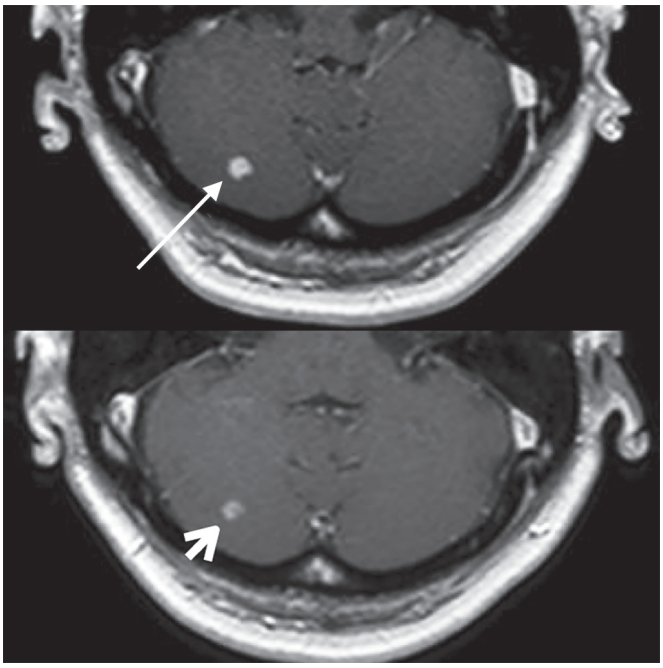

Fig. 2: Metastatic brain lesion in the left cerebellar hemisphere before treatment in Patient 3. The white arrow in the contrast-enhanced, T1-weighted, fat suppression magnetic resonance on the upper image indicates metastatic lesions. Contrast-enhanced, T1-weighted, fat suppression magnetic resonance image taken 6 months after treatment. The metastatic lesions (white arrowhead) show no increase in size

In Patient 5, two lymph nodes in the left cervical region showed size reduction (Table 2).

Discussion

We reported on the cases of seven patients who underwent CyberKnife treatment for distant metastatic lesions of papillary thyroid cancer. We observed no bone metastases and no increase in brain metastases within the follow-up period. Two lymph node metastases were reduced in size, and a therapeutic effect involving internal necrosis was seen in two other lymph node metastases.

Distant metastatic lesions of DTC are less sensitive to EBRT.[1] In particular, RAIT and EBRT are reported to have low therapeutic effects on bone metastases.[4] In contrast, high doses of EBRT for distant metastatic lesions are reportedly useful in controlling locoregional thyroid cancer.[11,12]

Among the modalities used for high-dose radiation therapy, CyberKnife treatment is reportedly useful for spinal metastases and recurrent lesions of DTC.[13,14] With CyberKnife treatment, the reduced irradiation frequency, compared to that for normal EBRT, decreases the burden of going to the hospital.[8] In addition, CyberKnife treatment minimizes the irradiation of surrounding tissues by enabling stereotactic, accurate, and high-dose irradiation of the target lesion.[9,10] This is useful in avoiding side effects such as skin damage due to long-term irradiation with conventional EBRT.[9,10] Our patients showed no symptoms of radiation damage, such as acute skin damage, after CyberKnife treatment. It was possible to treat multiple lesions such as brain and cervical lymph node metastases in the same patient, suggesting that CyberKnife treatment may be useful for local control.

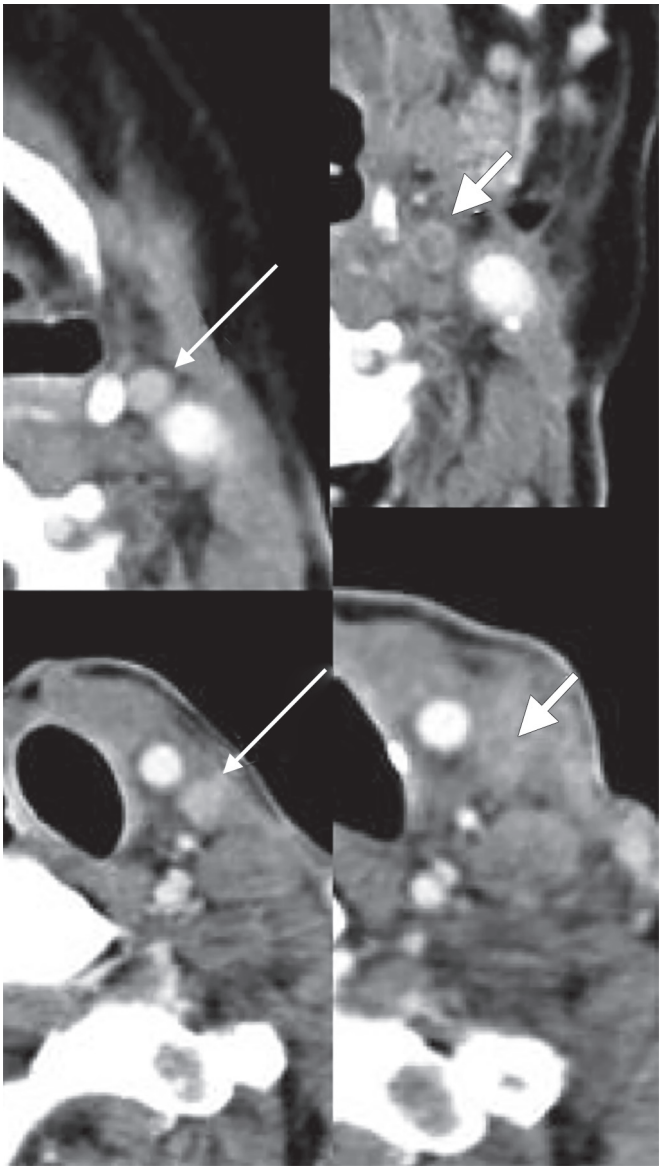

Fig. 3: Cervical-enhanced computed tomography scans of Patient 3. On the left image, white arrows indicate two lymph node metastatic lesions in the left neck before CyberKnife treatment. Contrast-enhanced computed tomography scans after treatment showing a therapeutic effect involving internal necrosis in the cervical lymph node metastases (white arrowheads on the right image)

Treatment of DTC with molecular-targeted drugs is premised on total thyroidectomy and RAIT.[15,16] In addition, starting the administration of molecular-targeted drugs is recommended when the tumor becomes refractory to RAIT or when the thyroid cancer is undifferentiated and the disease progresses rapidly.[17] Our institution selects the best treatment method for patients as a part of multimodal treatment comprising surgical treatment, RAIT, and EBRT for thyroid cancer, in anticipation of the initiation of treatment with molecular-targeted drugs as the final treatment method.

Although many studies have demonstrated the usefulness of molecular-targeted drugs for the treatment of DTC lesions, various side effects can cause the deterioration of patients'

quality of life.[18] Additionally, once targeted therapy is started, it is difficult to discontinue medication or change to another treatment method.[19] Therefore, for the control of locally recurrent lesions and the treatment of multiple metastatic lesions, we believe that it is important to use treatments other than molecular-targeted drugs as much as possible and to delay the introduction of molecular-targeted drugs. The results of this study demonstrated the usefulness of CyberKnife treatment for local control of multiple metastatic lesions including brain metastases.

In patients with thyroid cancer, lymph node metastatic lesions in the deep cervical region and mediastinum may invade the blood vessels and bronchi if they increase in size. The safest treatment is surgical removal; however, additional surgical treatment is often difficult due to reasons such as total thyroid cancer removal.[20] A risk of bleeding has been reported with the use of molecular-targeted drugs for the treatment of lymph node lesions adjacent to major blood vessels.[21] The accurate irradiation provided by CyberKnife treatment may be useful in such instances.

Conclusions

CyberKnife may be useful in treating distant metastatic lesions of papillary thyroid cancer.

Clinical Significance

CyberKnife is useful as a multidisciplinary treatment for cases in which radioactive iodine therapy is maladjusted.

References

1. Kenji M, Yasushi H, Shintaro T, et al. Treatment intensity and control rates in combining external-beam radiotherapy and radioactive iodine therapy for metastatic or recurrent differentiated thyroid cancer. Int J Clin Oncol 2020;25(4):691–697. DOI: 10.1007/s10147-019-01591-y.
2. Bacourt F, Asselain B, Savoie JC, et al. Multifactorial study of prognostic factors in differentiated thyroid carcinoma and a re-evaluation of the importance of age. Br J Surg 1986;73(4):274–277. DOI: 10.1002/bjs.1800730410.
3. Kim TH, Yang DS, Jung KY, et al. Value of external irradiation for locally advanced papillary thyroid cancer. Int J Radiat Oncol Biol Phys 2003;55(4):1006–1012. DOI: 10.1016/s0360-3016(02)04203-7.
4. Brierley JD, Tsang RW. External-beam radiation therapy in the treatment of differentiated thyroid cancer. Semin Surg Oncol 1999;16(1):42–49. DOI: 10.1002/(sici)1098-2388(199901/02)16:1<42::aid-ssu8>3.0.co;2-4.
5. Kiess AP, Agrawal N, Brierley JD, et al. External-beam radiotherapy for differentiated thyroid cancer locoregional control: a statement of the American Head and Neck Society. Head Neck 2016;38(4):493–498. DOI: 10.1002/hed.24357.
6. Ford D, Giridharan S, McConkey C, et al. External beam radiotherapy in the management of differentiated thyroid cancer. Clin Oncol 2003;15(6):337–341. DOI: 10.1016/s0936-6555(03)00162-6.
7. Naohiro K, Hideya Y, Takuji T, et al. Stereotactic body radiation therapy for head and neck tumor: disease control and morbidity outcomes. J Radiat Res 2011;52(1):24–31. DOI: 10.1269/jrr.10086.
8. Joji K, Shigeaki H, Mitsuharu S, et al. Usefulness of stereotactic radiotherapy using cyberknife for recurrent lymph node metastasis of differentiated thyroid cancer. Case Rep Endocrinol 2017;2017:7956726. DOI: 10.1155/2017/7956726.
9. Hideya Y, Mikio O, Naohiro K, et al. Frequency, outcome and prognostic factors of carotid blowout syndrome after hypofractionated re-irradiation of head and neck cancer using CyberKnife: a multi-institutional study. Radiother Oncol 2013;107(3)305–309. DOI: 10.1016/j.radonc.2013.05.005.
10. Hideya Y, Mikio O, Kengo H, et al. Carotid blowout syndrome in pharyngeal cancer patients treated by hypofractionated stereotactic re-irradiation using CyberKnife: a multi-institutional matched-cohort analysis. Radiother Oncol 2015;115(1):67–71. DOI: 10.1016/j.radonc.2015.02.021.
11. Terezakis SA, Lee KS, Ghossein RA, et al. Role of external beam radiotherapy in patients with advanced or recurrent nonanaplastic thyroid cancer: memorial Sloan-kettering cancer center experience. Int J Radiat Oncol Biol Phys 2009;73(3):795–801. DOI: 10.1016/j.ijrobp.2008.05.012.
12. Meadows KM, Amdur RJ, Morris CG, et al. External beam radiotherapy for differentiated thyroid cancer. Am J Otolaryngol 2006;27(1):24–28. DOI: 10.1016/j.amjoto.2005.05.017.
13. Takayuki I, Takashi U, Kiminori S, et al. Stereotactic radiotherapy using the CyberKnife is effective for local control of bone metastases from differentiated thyroid cancer. J Radiat Res 2019;22;60(6):831–836. DOI: 10.1093/jrr/rrz056.
14. Takayuki I, Takashi U, Tomoaki T, et al. Usefulness of stereotactic radiotherapy using the CyberKnife for patients with inoperable locoregional recurrences of differentiated thyroid cancer. World J Surg 2019;43(2):513–518. DOI: 10.1007/s00268-018-4813-5.
15. Martin SG, Makoto T, Lori JW, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med 2015;372:621–630. DOI: 10.1056/NEJMoa1406470.
16. Hiroshi T, Koichi I, Kiminori S. Development of molecular targeted drugs for advanced thyroid cancer in Japan. Endocrine J 2014;61(9):833–839. DOI: 10.1507/endocrj.ej14-0107.
17. Ye X, Zhu Y, Cai J. Relationship between toxicities and clinical benefits of newly approved tyrosine kinase inhibitors in thyroid cancer: a meta-analysis of literature. J Cancer Res Ther 2015;11(2):C185–C190. DOI: 10.4103/0973-1482.168182.
18. Nigel F, Rachel H, Marty C, et al. A systematic review of lenvatinib and sorafenib for treating progressive, locally advanced or metastatic, differentiated thyroid cancer after treatment with radioactive iodine. BMC Cancer 2019 Dec 12:19(1):1209. DOI: 10.1186/s12885-019-6369-7.
19. Anderson RT, Linnehan JE, Tongbram V, et al. Clinical, safety, and economic evidence in radioactive iodine-refractory differentiated thyroid cancer: a systematic literature review. Thyroid. 2013;23(4):392–407. DOI: 10.1089/thy.2012.0520.
20. Chen L, Shen Y, Luo Q, et al. Response to sorafenib at a low dose in patients with radioiodine-refractory pulmonary metastases from papillary thyroid carcinoma. Thyroid 2011;21(2):119–124. DOI: 10.1089/thy.2010.0199.
21. Lee EM, Lee JW, Lee JY, et al. Lower starting dose of sorafenib for thyroid cancer: a case report and literature review. J Thyroid Disord Ther 2015;4:4. DOI: 10.4172/2167-7948.1000196.