



# Brain Metastases from Non-small-cell Lung Carcinoma – CyberKnife Re-irradiation after Gamma Knife Radiosurgery

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## Abstract

Lung cancer is the most common neoplasia and the most common cause of cancer mortality. The condition is usually diagnosed at a locally advanced or metastatic stage, which is a bad prognostic factor. Around 40% of all oncology patients with brain metastases have lung cancer.

Modern linear accelerators allow clinicians to perform radiosurgery and deliver a high radiation dose to low volume with a high dose gradient. Herein we present a 55-year-old male patient who received radiosurgery four times over three years – two times with Gamma Knife and two times with CyberKnife. Re-irradiation gives the opportunity to treat a local progression of a metastasis, which already has been irradiated. A series of control brain magnetic resonance imaging confirmed a good local control of treated lesions with no necrosis in surrounding healthy tissue or significant oedema. The neurological symptoms were completely controlled and the quality of life of the patient improved considerably. Radiosurgery is a prevalent, non-invasive, painless method of treatment with proven clinical results. It may be reused as long as it has clinical benefits to the patient.

## Keywords

brain metastases, CyberKnife, gamma knife, radiosurgery, re-irradiation

## INTRODUCTION

Radiation oncology occupies a leading position in the treatment of cancer-diagnosed patients. Around 60% of them will need a palliative or definitive radiotherapy (RT) in their course of healing. National Cancer Institute reported that newly diagnosed patients with brain and other neurological tumors for the year 2014 are about 23380 – 15% of them are glioblastomas.<sup>1,2</sup> Brain metastases are 4-5 times more common than primary intracranial tumours and can be found in 20%–40% of cancer diagnosed patients.<sup>3</sup> Forty percent of them are diagnosed with primary lung carcinoma, and between 20%–25% with breast carcinoma. Patients

with brain lesions have a generally poor outcome with median survival after diagnosis of approximately 4 months. Management of the metastatic disease includes symptomatic treatment and definitive therapy, with the goal of stabilizing and improving neurologic function and survival. Depending on the number of lesions, their location and size, histology, and ECOG performance status, there are different treatment options for management of brain metastases – surgery, whole-brain RT, and radiosurgery.<sup>4</sup>

After 2D RT and 3D conformal RT, the next stage in the development of radiation oncology is stereotactic radiosurgery (SRS). Some of the most common machines that are used only for SRS are Gamma Knife and CyberKnife. The

principle difference between them is that Gamma Knife requires a large metal frame to be mounted onto the patient's head with screws before and during treatment. That is why it can be used only for brain formations, and the patient requires general or local anesthesia. The machine is using 201 cobalt-60 sources directed to one point.

On the other hand, CyberKnife is a small linear accelerator located on a robotic arm that can irradiate formations in the whole body from hundreds of different angles. It is a non-invasive and painless treatment that allows patients to lie comfortably on a treatment couch while the system moves quickly around them. Each patient with head and neck formation has an individual thermoplastic mask that fixes the head during CT and allows them to take the same position during treatment. The purpose is to restrict the movements and rotation of the head. The CyberKnife system has proven to achieve all the goals of radiosurgery by delivering high, ablative radiation dose with maximal dose fall-off outside the treatment volume with a frameless sub-millimeter accuracy.<sup>5</sup>

## CASE REPORT

A 55-year-old male patient was histologically diagnosed with non-small-cell lung cancer in February 2016. He was operated with the following adjuvant chemotherapy – 16 courses of pemetrexed, ECOG performance status 1.

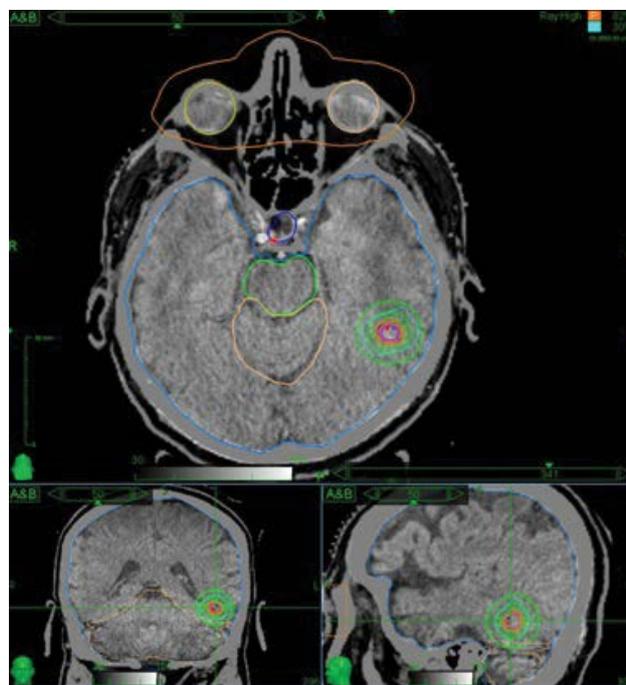
In July 2017, during a control magnetic resonance imaging (MRI), one brain metastasis 14/9 mm was detected in the right frontal lobe. The patient was treated with Gamma Knife radiosurgery (RS) in Istanbul, Turkey – 1 fraction 18 Gray (Gy). There were no complains except for temporary hair loss in some areas. The primary and metastatic disease was under control with no new metastases until 2019.

In January 2019, the patient had another MRI exam due to the complaints of a headache – the treated metastasis in the right frontal lobe reduced to 11×8 mm, but there was a new 17×12-mm one in the left temporal lobe. The patient continued the treatment in the same clinic with Gamma Knife RS, again, one fraction 18 Gy.

In April 2019, the patient came for a consultation in the Clinic of Radiotherapy at St George University Hospital in Plovdiv because of persistent headache. The MRI scan showed that the treated metastasis in the right frontal lobe had shrunk to 11×8 mm, and the other one in the left temporal lobe had shrunk to 10×10 mm, but there was a new one in the left temporal lobe under the treated one measuring 5.5×4.5 mm. Thorax, abdomen, and pelvis computed tomography (CT) scan with contrast showed no other metastases or positive lymph nodes. After discussion, the patient decided to continue his treatment in our clinic.

The new lesion was treated with robotic stereotactic radiosurgery (SRS) using CyberKnife. One fraction 21 Gy, biological effective dose (BED) ~65 Gy, equivalent total dose in 2-Gy fractions (EQD2) ~54 Gy. Gross tumor volume (GTV) to planning target volume (PTV) margin was 2 mm, and the

coverage was respectively 100% and 98.77% (Fig. 1). The estimated treatment time was 36 min, and the fraction was with 50 nodes and 122 beams. Doses in all organs at risk (OAR) – optic chiasm, eyes, optic nerves, brain stem, cerebellum, pituitary gland, etc. were in tolerance according to ICRU report 91 (Fig. 2).



**Figure 1.** CyberKnife treated metastasis in left temporal lobe – PTV and OAR.

In May 2019, the control MRI showed all treated metastases to be the same size, without any new lesions. The patient had no more headaches or any other side effects, ECOG performance status 0-1.

In July 2019 the patient had a control MRI – the CyberKnife treated metastasis in the left temporal lobe was not visible anymore; the other two lesions were of the same size. PET/CT was performed at that time with the conclusion of stable disease.

In October 2019, a control MRI showed that the Gamma Knife treated metastasis in the right frontal lobe had the same size as before, but the other one in the left temporal lobe had increased to 17×13 mm with edema (Fig. 3). The patient complained of a headache. He did not accept our advice to continue treatment of this metastasis in the clinic in Istanbul (where he started originally), so we connected with our colleagues there, and after discussion decided to perform SRS with CyberKnife – 5 fractions, 5 Gy per fraction, BED ~38 Gy, EQD2 ~32 Gy, remaining dose in the metastasis was around ~32 Gy. PTV coverage was 96.8%. The estimated treatment time per fraction was 22 min, with 44 nodes and 85 beams. Doses in the OAR were in tolerance. During the treatment, the patient received 4 mg of dexamethasone, 2×1 amp and mannitol 10%.

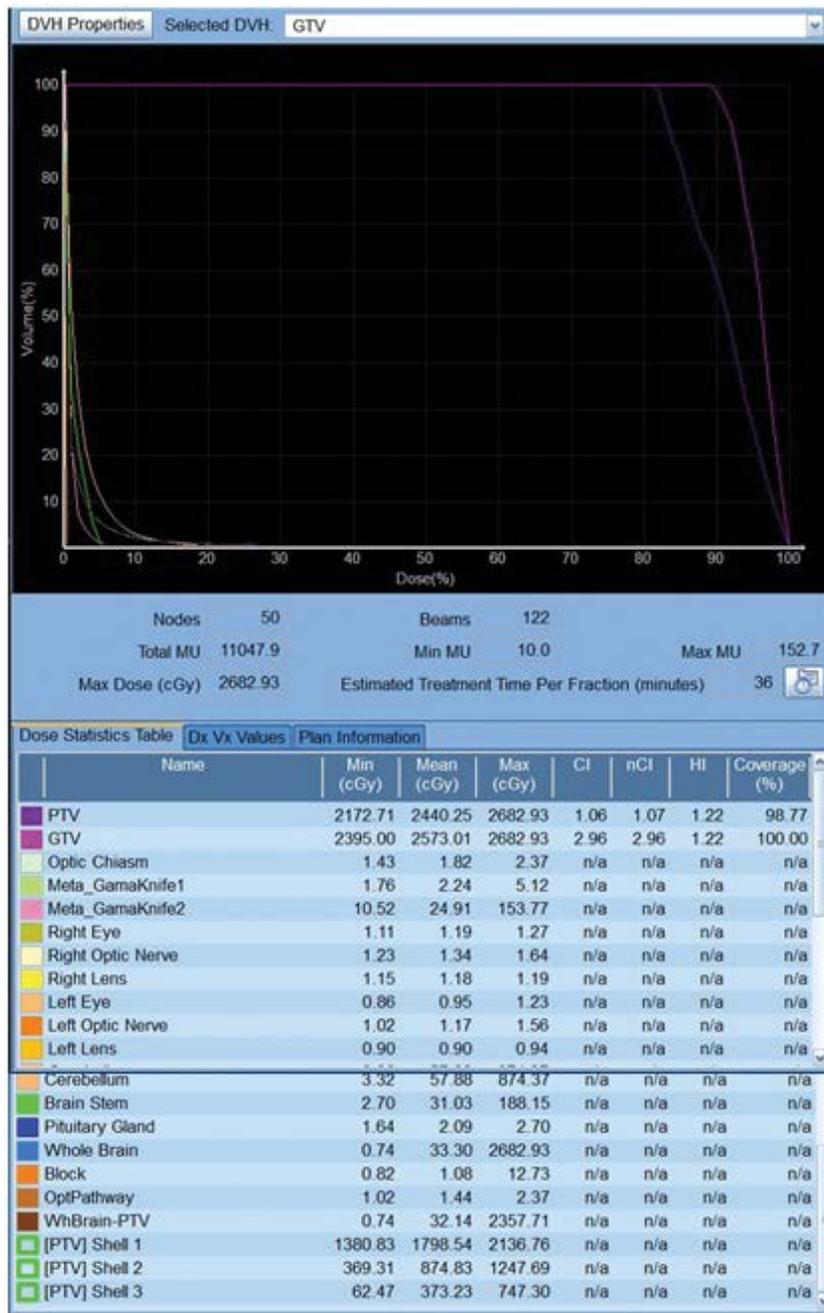


Figure 2. Dose-volume histogram (DVH) for GTV, PTV and OAR.

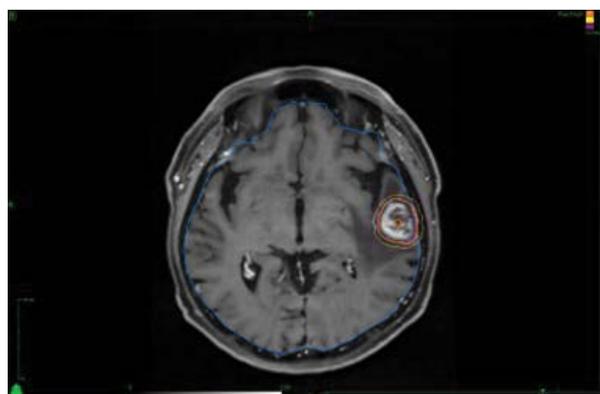


Figure 3. GTV and PTV for metastasis in the left temporal lobe.

*In February 2020 at a control MRI, the Gamma Knife treated metastasis in the right frontal lobe had the same size, Gamma Knife and CyberKnife treated lesion in left temporal lobe was reduced to 12×11 mm. The patient had no complains or any side effects, ECOG performance status 0-1. PET/CT confirmation for stable primary disease.*

## DISCUSSION

Although brain metastases are the most common brain tumors, neurologically asymptomatic patients with cancer do not routinely have brain CT or MRI, hence we get an incomplete cancer database. On the other hand, cancer patients live longer due to earlier detection and better therapy, which means that the frequency of brain lesions may increase.<sup>6</sup> Brain metastases are suitable for SRS because they are well enhanced on magnetic resonance images and show clear margins setting them off from the surrounding healthy tissue.

Chemotherapy does not achieve the desired effect in patients with brain metastases, despite the great successes in systemic treatment. For decades, whole-brain radiotherapy has been conducted as the only option for RT, but it provides limited local control with side effects. Modern linear accelerators like CyberKnife, Gamma Knife, or Linac are improving the treatment of these patients.<sup>7</sup> Despite the use of the same gamma rays, there is a lot of difference between conventional external beam linear accelerators and specialized SRS machines. In an SRS procedure, highly concentrated radiation is given to a predefined target so that every cell inside it is affected.<sup>8</sup> Even if a patient has more than four lesions, SRS provides survival benefits because total treatment volume is the most significant predictor of survival. The total volume of brain metastases, rather than the number of metastases should be considered in identifying appropriate radiosurgery candidates.<sup>9</sup> A 79% local control rate in the first year is achieved with SRS treatment to resection the cavity of brain lesions. The recommended margin

is 2 mm around the resection cavity, which will guarantee a better local control.<sup>10</sup>

In the last years, a lot of new drugs and modern linear accelerators have allowed us to extend the life expectancy of cancer-diagnosed patients. That is why it is so important to have the opportunity for re-irradiation if it is necessary. SRS achieves excellent overall survival and local control rates with low toxicity in patients with brain metastases.

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# Метастазы немелкоклеточного рака лёгких в мозг – повторное облучение при помощи системы „Кибер – Нож“ после радиохирургии на установке „Гамма-нож“

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## Резюме

Рак лёгкого – наиболее частое новообразование и самая частая причина смерти от рака. Состояние обычно диагностируется в фазе местного распространения и метастазов, что является плохим прогностическим фактором. Около 40% всех онкологических больных с метастазами в мозг страдают раком лёгких.

Современные линейные ускорители позволяют клиницистам выполнять радиохирургические операции и подавать высокие дозы радиации в участки небольших размеров с градиентом высоких доз. Речь идёт о 55-летнем мужчине, который за три года четыре раза подвергался радиохирургии – дважды с помощью гамма-ножа и дважды с помощью кибер-ножа. Повторное облучение позволяет лечить локальное развитие уже облученного метастаза. Серия контрольных МРТ подтвердила хороший местный контроль обработанных поражений и отсутствие некроза в соседних здоровых тканях или значительного отека. Неврологические симптомы полностью контролировались, и качество жизни пациента значительно улучшилось. Радиохирургия – это основной неинвазивный безболезненный метод лечения с доказанными клиническими результатами. Его можно использовать повторно, если он имеет клинические преимущества для пациента.

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## Ключевые слова

метастазы в головной мозг, кибер-нож, гамма-нож, радиохирургия, повторное облучение

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