Cyberknife Radiotherapy for Pituitary Adenomas: Monitoring Response Using Magnetic Resonance Imaging

Hipofiz Adenomlarında Cyberknife Tedavisine Yanıtın Manyetik Rezonans Görüntüleme İle Değerlendirilmesi

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ÖZET

GİRİŞ ve AMAÇ: Cyberknife tedavisi almış hipofiz adenomlu olgularda tedaviye yanıtın MR ile değerlendirilmesi

YÖNTEM ve GEREÇLER: Bu çalışmada 2010 ile 2014 yılları arasında, hipofiz adenomu tanısıyla Cyberknife tedavisi almış hastalar retrospektif olarak değerlendirildi. Cyberknife tedavisinden en az 6 ay sonra takip MR'ı bulunan olgular çalışmaya dahil edildi. 38 hastanın (erkek/kadın=1) tedavi öncesi ve sonrası MR görüntüleri, tedaviye yanıtın değerlendirilmesi amacıyla retrospektif olarak incelendi. Tümör hacimlerindeki değişiklikler, lokal kontrol oranı, hacim değişikliğinin izlem süresi ile ilişkisi ve olası çevre beyin parankim değişiklikleri araştırıldı.

BULGULAR: Çalışmaya dahil 38 hastanın ortalama takip süresi 25 ay (dağılım, 6-51 ay) idi. Tedavi öncesi ve sonrası ortalama tümör hacimleri arasında istatistiksel olarak anlamlı bir azalma vardı (sırasıyla 4722 mm3 ve 3475 mm3). Otuzsekiz hastanın 2 tanesinde radyolojik progresyon, 18 tanesinde stabil hastalık, 18 tanesinde ise regresyon saptandı. Tümör lokal kontrol oranı %94.7 olarak hesaplandı. Ayrıca, stabil ve regresyon grupları arasında yapılan analizde izlem süresinin uzamasının daha anlamlı hacim düşüşüne neden olduğu görüldü. Hasta cinsiyeti, ek tıbbi tedavi, hasta yaşı, önceki ameliyatların sayısı gibi durumların tedavi sonucunu etkilemediği saptandı. Hiçbir vakada çevre dokularda patolojik sinyal ortaya çıkmadı.

TARTIŞMA ve SONUÇ: Cyberknife hipofiz adenomlu olgularda etkili bir tedavi yöntemidir. Bu sonuçlar Cyberknife radyoterapisinin çevre dokularda radyopatolojik değişiklik oluşturmaksızın oldukça tatmin edici lokal tümör kontrol oranları sağladığını desteklemektedir.

Anahtar Kelimeler: CyberKnife Radyocerrahisi, MRG, Hipofiz Adenomu, Stereotaktik Radyocerrahi

ABSTRACT

INTRODUCTION: Our aim is to determine treatment response to Cyberknife based on follow-up MRI in patients with pituitary adenoma.

METHODS: We retrospectively identified the patients with pituitary adenoma treated with Cyberknife between 2010 – 2014. Patients with postreatment eligible follow-up MRI scan after at least 6 months of Cyberknife treatment were included in this study. Pre- and posttreatment MRI scans of 38 patients (male/female=1) were retrospectively analysed to evaluate tumor response. Volumetric changes of the tumors, local control rate, volumetric changes over time and signal alterations on the surrounding brain parenchyma were assessed.

RESULTS: The mean follow-up time of 38 patients was 25 months (range, 6-51 months). Significant mean tumor volume reduction was found between pre- and posttreatment mean tumor volumes, which were 4722 mm3 and 3475 mm3, respectively. There were 2 cases with radiological progression, 18 cases with stable disease and 18 cases with regression. Thus, tumor local control rate was calculated as 94.7% in our study. There was also a significant follow-up time difference between stable and radiological regression groups which indicates that increased follow-up time may be related with better volume decrease. Patient gender, additional medical treatment, age, the number of previous surgeries did not affect treatment response. Lastly, there was no case with signal alteration on the surrounding brain parenchyma.

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DISCUSSION and CONCLUSION: Cyberknife is a known and effective treatment method in patients with pituitary adenoma. Our results also support that Cyberknife provides excellent local tumor control without any radiological obvious side effects on surrounding tissues.
Keywords: CyberKnife Radiosurgery, MRI, Pituitary Adenoma, Stereotactic Radiosurgery.

INTRODUCTION

Pituitary adenomas (PAs) are common sellar tumors with a prevalence around 20% (1,2). PAs are clinically important due to their mass and/or hormonal effects and symptoms are often associated with these effects. According to hormonal activity status PAs can be divided into two groups: functional and non-functional. Another classification is based on maximum tumor dimension: microadenomas (smaller than 1 cm) and macroadenomas (equal or greater than 1 cm).

Although surgical resection is the method of choice for treatment of PAs except prolactinoma, stereotactic radiosurgery (SRS) has gained popularity in recent years. SRS can be an effective treatment for medically inoperable or recurrent - residual tumor cases. Tumor control rates with surgical treatment alone range from 50 to 90% and SRS can be a treatment option for recurrent or residual tumors(1,2).

For more than fifty years, SRS techniques have been used to treat PAs. A newly developed SRS method called CyberKnife gained popularity for PA treatment in the last decades and thriving results have been published recently (3-11).

In this study, we aimed to demonstrate magnetic resonance imaging (MRI) findings of CyberKnife treatment; such as effect of the treatment on the volume of the tumor, relationship between volume difference and follow-up time, local control rate and potential signal alterations on the surrounding brain parenchyma.

MATERIALS and METHODS

This retrospective study includes 38 PAs which were treated with CyberKnife between 2010-2014 at Izmir Katip Celebi Ataturk Training and Research Hospital. The average dose given was 25,4 Gy (range, 20 – 32 Gy) in five or seven fractions.

Patient inclusion criteria were pretreatment adequate MRI scans and the presence of eligible follow-up MRI scan after at least 6 months of CyberKnife. We would like to state that there was no particular follow up schedule in our hospital due to lack of patient cooperation after CyberKnife.

Pre-treatment MRI scans, obtained for CyberKnife treatment planning, were retrospectively analysed and compared with latest routine follow-up MRI scans available in our PACS archive. MRI scans were obtained with 1,5 Tesla Signa Excite (GE, Milwaukee, WI) MRI scanner. High resolution, volumetric, postcontrast T1-weighted (BRAVO) images were obtained in addition to routine brain MRI sequences. Pre-treatment and latest follow-up MRI scans were evaluated to measure tumor volume and to note any emerging signal anomaly on brain parenchyma. We used post-contrast axial volumetric T1-weighted (BRAVO) images to measure tumor volume. These images were recruited from our PACS archive and loaded into our radiology workstation (A.W. 4.1, General Electric). On axial sections, PAs were carefully separated from surrounding tissues by manually drawn ROIs. After this manual segmentation process, tumor volumes were measured by the software. In order to standardise statistical tests and to avoid measurement mistakes, tumors smaller than 1000 mm^3 were excluded from the study.

We assessed radiologic treatment responses as follows: radiologic progression (20% or more volume increase), radiologic regression (20% or more volume decrease) and stable disease (less than 20% volume difference).

Lastly, brain parenchyma, in particular parasellar structures and cerebral white-matter, was evaluated in terms of signal abnormalities. When necessary, pre- and posttreatment images were compared side by side to determine if there were any differences.

All statistical analyzes were performed using SPSS 17.0 software. All statistical tests were performed at 95% confidence interval and a P value <0.05 was considered to indicate statistical significance. Mann Whitney-U Test was used to compare the mean of two different groups. We compared categorical variables

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using Chi-square test. Finally, Spearman correlation analysis was performed to analyse the relationship between different numeric variables.

RESULTS

The mean age of 38 patients (male/female=1) included in this study was 47.1 ± 13.7 years. The mean and median follow-up times were 25 and 27 months, respectively (range, 6-51 months). Among 38 patients, 3 (7.9%) patients had prolactin-secreting, 12 (31.6%) patients had non-functional and 23 (60.5%) patients had growth hormone-secreting adenomas. Median number of previous surgical resection was 1 (range 0-4). Twenty-one of 38 patients were receiving medical treatment. Among these, 4 patients were under cabergolin, 11 patients were under ocreotid, 1 patient was under lantreotid, 4 patients were under cabergolin and ocreotid and 1 patient was under ocreotid - lantreotid treatments. Demographic profiles, additional medical treatment regimes and PA types of the patients can be seen in Table 1.

Pre- and post treatment mean tumor volumes were 4722±3679 mm^3 and 3475±2579 mm^3 respectively, which indicated statistically significant ($p<0.001$) mean tumor volume reduction after CyberKnife treatment (Table 2).

Among 38 patients, there were 2 cases with radiologic progression (20% or more volume increase) , 18 cases with stable disease and 18 cases with radiologic regression (20% or more volume decrease). Tumor volumes were successfully controlled in 36 of 38 patients after CyberKnife. The sum of stable and regressed tumors was assessed as local control. Therefore, the local control rate in our study was 94,7% (36/38). A comprehensive summary of the patients can be seen in Table 3. A representative case (case number 30) with obvious radiologic regression is available in Figure 1.

There were 18 cases with radiologic regression. Four of them were followed up shorter than 24 months and 14 of them were followed up longer than 24 months. There were 18 cases with stable disease. Twelve of them were followed up shorter than 24 months and 6 of them were followed up longer than 24 months. The relationship between volume difference and follow-up time was statistically significant ($p = 0.007$) (Table 4).

The correlations between the volumetric differences and the other variables were examined. There was no significant correlation between volumetric difference and age ($r=-0.195$, $p=0.241$). Similarly, there was no significant correlation between the number of previous surgical operations and volumetric difference (0.149, $p=0.371$). When the correlation between volumetric difference and follow-up time was examined, we noticed a moderate positive correlation ($r=0.477$, $p=0.002$) (Table 5).

There was no significant difference in the volumetric difference between the sexes ($p=0.619$). Similarly, there was no significant difference in the volume difference between those who received additional medical treatment and those who did not ($p=0.369$) (Table 6).

Lastly, brain parenchyma, in particular parasellar structures and cerebral white-matter, was evaluated in terms of potential signal abnormalities. When necessary, pre- and posttreatment MRI scans were compared side by side. However, none of the cases showed posttreatment newly developed signal abnormalities.

Tablo 1: Demographic Profiles, Additional Treatments and Adenoma Types of the Patients

AGE (Mean, SD)	47.1	13.7
SEX (n, %)		
MALE	19	50
FEMALE	19	50
FOLLOW-UP DURATION (MONTHS) (Median, Min.-Max.)	27	6-51
Previous Surgical Resections (Median, Min-Max)	1	0-4
Additional Medical Therapy (n, %)		
None	17	44.7
Cabergolin	4	10.5
Ocreotid	11	28.9
Lantreotid	1	2.6
Cabergolin and Ocreotid	4	10.5
Ocreotid - lantreotid	1	2.6
ADENOMA TYPE (n, %)		
Prolactin Secreting	3	7.9
Non - Functional	12	31.6
Growth hormone secreting	23	60.5

SD: Standart Deviation, min: Minimum, max: Maximum

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Table 2: Comparison of pre- and posttreatment mean tumor volumes

	Mean (mm^3)	Standart Deviation	p[a]
Pretreatment	4722.5	3679.9	**<0.001**
Posttreatment	3475.7	2579.0	

a: Mann Whitney U Test

Table 3: A comprehensive summary of the patients

Case	PA Type	Age and Gender	Fractions - Dose (Gy)	Follow-up (Months)	Pre-Treatment Volume (mm^3)	Post-treatment Volume (mm^3)
1	GH	30 F	7 - 28	42	7398	2888
2	GH	47 F	5 - 25	48	1570	1379
3	GH	32 M	5 - 25	45	3269	1360
4	GH	61 F	7 - 28	27	9440	4188
5	GH	47 F	5 - 25	46	3040	1489
6	GH	30 F	5 - 25	39	3329	1993
7	GH	59 M	5 - 25	24	5695	5919
8	GH	55 F	5 - 25	42	2093	1359
9	GH	46 F	5 - 25	39	3028	2521
10	GH	63 M	5 - 25	29	3766	3364
11	GH	46 F	5 - 25	9	2748	3041
12	GH	47 M	7 - 28	35	9141	7937
13	GH	47 E	5 - 25	27	3274	3979
14	GH	56 M	5 - 25	14	2339	2573
15	GH	27 M	5 - 25	35	4765	2253
16	GH	31 M	5 - 25	32	2523	1511
17	GH	33 F	5 - 25	26	2641	1507
18	GH	64 M	7 - 28	31	4608	3137
19	GH	53 F	5 - 25	19	1529	672
20	GH	54 F	5 - 25	6	2800	3100
21	GH	32 M	5 - 25	13	1589	1491
22	GH	39 M	5 - 25	13	2834	2296
23	GH	36 F	5 - 25	9	3802	3001
24	PRL	37 F	5 - 25	26	5505	5324
25	PRL	63 M	5 - 23	10	9702	8026
26	PRL	76 M	5 - 20	8	8636	9352
27	NON	45 M	5 - 25	50	2525	2254
28	NON	38 F	7 - 28	40	17069	12154
29	NON	52 M	7 - 28	33	9121	5412
30	NON	55 M	7 - 32	22	15962	7250
31	NON	30 M	5 - 25	8	3122	2638
32	NON	58 F	5 - 25	36	2196	952
33	NON	31 F	5 - 25	17	4969	4485
34	NON	71 F	5 - 25	8	3583	4357
35	NON	23 F	5 - 25	11	2159	1478
36	NON	44 M	5 - 25	12	2326	1876
37	NON	40 F	5 - 25	28	2806	1493
38	NON	73 M	5 - 25	10	2554	2066

NON: Non-Functional, GH: Growth Hormone Secreting, PRL: Prolactin Secreting, M: Male, F: Female

Table 4: The relationship between volume difference and follow-up time

	Radiologic Regression		Stable Disease		p[b]
	n	**%**	**n**	**%**	
≤24Months	**4**	**22.2**	**12**	**66.7**	**0.007**
>24Months	14	77.8	6	33.3	

b: Chi-Square Test

Table 5: Correlations between the volumetric differences and other variables

	Volume Difference r	p[c]
Age	-0.195	0.241
Previous Surgeries	0.149	0.371
Follow-up (Months)	**0.477**	0.002

c: Spearman Correlation Analysis

Table 6: Volume differences between genders and additional medical treatments

	Volume Difference Mean	Standart Deviation	p[a]
Male	1312.4	2048.6	0.619
Female	1352.2	1650.4	
With Medical Treatment	1814.0	2415.2	0.369
Without Medical Treatment	942.3	1098.1	

a: Mann Whitney U Test

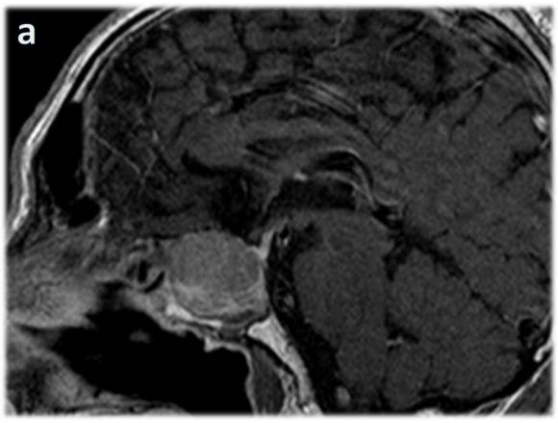

Figure 1a: A representative case (case number 30) with radiologic regression. Sagittal contrast-enhanced T1 Weighted image before Cyberknife treatment.

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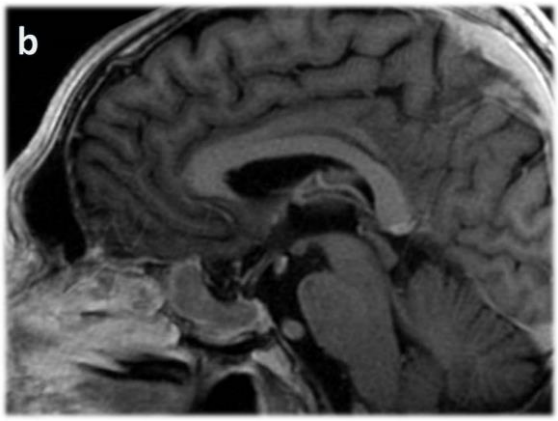

Figure 1b: Sagittal contrast-enhanced T1 Weighted image after 22 months of Cyberknife treatment.

DISCUSSION

PAs are frequent brain tumors in adults and represent approximately 10-15% of all brain neoplasms (1,2). Surgical resection is the first line treatment for PAs, except prolactinoma. However, total surgical resection is usually not possible if there is extrasellar extension, dural or cavernous sinus invasion or close proximity to the surrounding critical structures. Postsurgical residual PA tissue is a potential threat for recurrence. Tumor control rates range from 50 to 90% in surgical treatment alone (1). Consequently, stereotactic radiotherapy methods have been increasingly used in cases of residual or recurrent PAs (1,2). While there are numerous studies related to efficacy of other stereotactic radiosurgery methods for PAs, such as Gammaknife or LINAC, only a few studies have investigated the efficacy of CyberKnife (1,3-11).

Shortly after the introduction of CyberKnife, PA treatment with CyberKnife began. After a while treatment results and side effects published in some articles (1,3-11). In these articles, various criterias were used to determine local control. For instance, Cho et al. used the guideline proposed by the Committee of the Brain Tumor Registry of Japan, according to this guideline 25% or more growth of Gadolinium enhanced area is defined as progression (3). In the study of Iwata and colleagues, the Response Evaluation Criteria in Solid Tumors (RECIST) criteria was used to define treatment response (4). In our study we determined local control as the sum of stable (less than 20% volume difference) and regressed (more than 20% volume decrease) tumors according to their volumetric changes.

In the very first study about CyberKnife treatment results of PAs published by Kajiwara et al. in 2005; CyberKnife radiotherapy was applied to 21 patients with PA (5). The study group included 14 cases with non-functioning, 3 cases with prolactin-secreting, 2 cases with adrenocorticotropic hormone-secreting and 2 cases with growth hormone-secreting PAs. The follow-up time ranged from 18 to 59 months (mean 35.3 ± 10.7 months). Tumor size decreased in 4 patients and remained stable in 16 patients according to the guidelines of the Committee of the Brain Tumor Registry of Japan. In 1 case, cystic enlargement of PA and associated visual field loss was reported. The tumor control rate was 95.2%. No other radiologically apparent side effect was reported in the study.

In a study about CyberKnife treatment for acromegaly which was published in 2007, Roberts et al. released retrospective review of 9 patients with growth hormone-secreting PA. After a mean follow-up time of 25.4 months (range, 6-53 months) no case with tumor enlargement was reported according to MRI results. In addition, there was no side effect such as stroke, secondary malignancy or brain necrosis (6).

In the study of Cho et al., 26 patients with PA, who received CyberKnife, were followed up for a mean of 30 months (range, 7 to 47 months). 17 patients had non-functioning, 3 patients with prolactin-secreting and 6 patients with growth hormone-secreting adenomas. The authors used the guidelines of the Committee of the Brain Tumor Registry of Japan and the tumor control rate in this study was 92,3%. Except two patients with cystic tumor enlargement, no other radiologically detectable side effects reported (3).

In the study of Iwata and colleagues which was published in 2011; 100 non-functioning PAs were followed up between 12 and 118,5 months (mean: 33 months) after CyberKnife treatment. RECIST criteria were used to assess local control response in this study. 3- year local control rate was reported as 98%. No brain necrosis or any other radiologically detectable side effects on surrounding tissues were reported. The authors concluded that CyberKnife radiotherapy with 21 Gy in 3 fractions or 25 Gy in 5 fractions is a safe and

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effective treatment option for non-functioning PA (4).

In the article of Chen et al. which was published in 2013; CyberKnife treatment results of 22 PAs were released. PAs treated with 25 Gy total dose in 5 sessions were followed up for a median of 30.8 months. Since there was no case with progressive disease, local control rate was found as 100% in this study (7).

Killory et al. released their CyberKnife results of 20 patients with perichiasmatic recurrent or residual PA (8). The radiologic mean follow-up time was 29.3 months (range 10.2-40.5 months). Only 1 patient was treated with 3x5 Gy and the rest of the patients were treated with 5x5 Gy in this study. They reported that none of the tumors enlarged, which indicated 100% local control.

Puataweepong et al. reported 40 perioptic PAs treated with CyberKnife (9). The median dose was 25 Gy in 5 fractions and the median follow-up period was 38.5 months (range, 14-71 months). Among 40 patients, the authors reported only 1 case with radiologic tumor progression. According to this, tumor control rate could be calculated as 39/40 (97.5%).

Avci et al. reported the outcomes of 7 patients with PA treated with CyberKnife (10). In this study median follow-up period was 18 months (range 14-55 months) and the median dose was 22 Gy, given in 3 or 5 fractions. In this study, there was only 1 case with radiologic progression, hence local control rate in this study was 6/7 (86%).

Long-term results of 52 patients with growth hormone-secreting PAs who were treated with CyberKnife were published by Iwata et al. After a median 60 months (range 27-137 months) follow-up, Iwata et al. reported 100% 5- year local control rate. However, they reported 3 cases with local recurrence after 5 years follow-up (11).

In our study, after 27 months median follow-up; there were only 2 cases with more than 20% volume increase (case number 13 and 34). Thus, the local control rate in our study was 94.7% which is consistent with the studies mentioned above. Moreover, this local control rate is also compatible with other SRS methods, such as GammaKnife and LINAC based radiosurgery (1).

In addition, statistically significant tumor shrinkage findings were detected when the mean tumor volumes before and after CyberKnife treatments were compared in 38 patients. There were no statistically significant differences between the number of previous operations, patient age or gender and volumetric change of the tumor. However, when the relation between the volume difference and the follow-up time was examined, it was noticed that volume difference becomes statistically significant as follow-up time increases.

Like the other SRS methods, CyberKnife is very capable to concentrate radiation beams on specific target. Thus, potential side effects to surrounding tissues are minimized. In this study, no case with a side effect on surrounding tissues was detected.

As a limitation of our study, only most recent MRI scans of the patients were evaluated. Therefore, we could not assess whether there were any temporary volume increase or cystic dilatation in the PAs.

In conclusion, CyberKnife is a highly effective treatment modality for local control of PA. In addition, tumor control appears to be a time-dependent process. Brain parenchymal signal alteration should not be expected after CyberKnife treatment. Further studies with more patients and longer follow-up periods are necessary to support our results.

Conflict of interest: The authors declare that they have no conflict of interest

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