

# Evaluation of Brainstem Subcortical Auditory Pathways with Diffusion Tensor Imaging After Gamma Knife Radiosurgery in Intracanalicular Vestibular Schwannoma

## *İntrakanaliküler Vestibüler Şivannomada Gamma Knife Radyocerrahisi Sonrası Beyin Sapı Subkortikal İşitme Yollarının Difüzyon Tensör Görüntüleme ile Değerlendirilmesi*

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### ABSTRACT

**Objective:** To investigate changes in DTI (Diffusion Tensor Imaging) parameters in brainstem subcortical auditory pathways after Gamma Knife Radiosurgery (GKR) in patients with intracanalicular vestibular schwannoma (ICVS) and to analyze the relationship between tumor volume and ADC (apparent diffusion coefficient) and FA (fractional anisotropy) values.

**Method:** Seventeen patients with ICVS were evaluated before and after GKR. ADC and FA values of the lateral lemniscus (LL) and inferior colliculus (IC) and tumor volume were calculated. Patients who responded to GKR were classified as Group 1 and those who did not respond adequately as Group 2. The relationship between ADC and FA values and changes in tumor volume were analyzed.

**Results:** Tumor volume significantly decreased after GKR. ADC values obtained from the tumor increased after GKR ( $p<0.002$ ). There was no significant difference in LL and IC before and after GKR in terms of FA and ADC values ( $n:17$ ). There was a positive correlation between response to treatment and contralateral LL ADC values after GKR ( $p=0.005$ ,  $r:0.652$ ). There was a negative correlation between contralateral IC FA values after GKR and response to treatment ( $p=0.017$ ,  $r:-0.568$ ). There was a significant difference between Groups 1 and 2 in regards to contralateral LL ADC ( $p=0.03$ ) and IC FA values ( $p=0.017$ ).

**Conclusion:** Since the cochlear nerve and subcortical auditory pathways have low regeneration potential after nerve damage, ADC and FA changes in LL and IC may be explained with the presence of intracanalicular tumors prior to GKR. Since GKR does not cause additional damage to the subcortical auditory pathways at the brainstem level, we think that GKR is a noninvasive treatment method that can be used safely in patients with ICVS.

**Keywords:** Diffusion Tensor Imaging, Intracanalicular Vestibular Schwannoma, Gamma Knife Radiosurgery, Radiosurgery, Auditory Pathways

### ÖZ

**Amaç:** İtrakanaliküler vestibüler schwannomlu (ICVS) olgularda Gamma Knife Radyocerrahisi (GKR) sonrası beyin sapı subkortikal işitsel yollarda DTG (Difüzyon Tensör Görüntüleme) parametrelerinde değişiklik olup olmadığını araştırmak ve tümör hacmi ile ADC (görünür difüzyon katsayısı) ve FA (görünür difüzyon katsayısı) değerleri arasındaki ilişkiyi analiz etmek

**Yöntem:** ICVS'li 17 hasta radyocerrahi öncesi ve sonrası değerlendirildi. Lateral lemniscus (LL) ve inferior kollikulus (IC) ADC ve FA değerleri ve tümör hacmi hesaplandı. Radyocerrahi tedavisine yanıt verenler Grup 1, yeterli yanıt vermeyenler ise Grup 2 olarak sınıflandırıldı. ADC ve FA değerleri ile tümör hacim değişiklikleri arasındaki ilişki analiz edildi.

**Bulgular:** Radyocerrahi sonrası tümör hacmi belirgin azalmıştı. GKR sonrası tümörden elde edilen ADC değerleri arttı ( $p<0,002$ ). GKR öncesi ve sonrası LL ve IC'de FA ve ADC değerleri ( $n:17$ ) açısından anlamlı farklılık saptanmadı. Tedaviye yanıt ile GKR sonrası kontralateral LL ADC değerleri arasında pozitif korelasyon mevcuttu ( $p=0,005$ ,  $r:0,652$ ). GKR sonrası kontralateral IC FA değerleri ile tedaviye yanıt arasında negatif korelasyon saptandı ( $p=0,017$ ,  $r:-0,568$ ). Grup 1 ile Grup 2 arasında kontralateral LL ADC ( $p=0,03$ ) ve IC FA değerleri ( $p=0,017$ ) açısından anlamlı fark vardı.

**Sonuç:** Kohlear sinir ve subkortikal işitme yollarının düşük rejenerasyon potansiyeli sahip olması nedeniyle LL ve IC'deki ADC ve FA değişiklikleri mevcut olan intrakanaliküler tümör varlığı ile açıklanabilir. Radyocerrahi, beyin sapı düzeyinde subkortikal işitme yollarına ek hasar vermediğinden dolayı GKR'nin ICVS'li hastalarda güvenle kullanılacak noninvaziv bir tedavi yöntemi olduğunu düşünüyoruz.

**Anahtar kelimeler:** Difüzyon Tensör Görüntüleme, İtrakanaliküler vestibuler şivannoma, Gama Knife radyocerrahi, işitme yolları

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## INTRODUCTION

Vestibular schwannomas (VSs) are benign neoplasms of Schwann cell origin<sup>1</sup>. Approximately 8% of these cases are localized intracanalicular VSs<sup>2</sup>. The most common symptom is progressive sensorineural hearing loss<sup>3,4</sup>. In addition, dizziness, tinnitus, headache, and symptoms related to the trigeminal or facial nerve may be seen<sup>1,3-5</sup>. The management of intracanalicular VS (ICVS) includes microsurgery, observation, and radiosurgery. The goals of treatment should be long-term tumor control, protection of hearing, fewer side effects, and maintaining a high quality of life<sup>6-9</sup>. Recently, Gamma Knife Radiosurgery (GKR) has been considered the first-line treatment for ICVS<sup>6</sup>.

Diffusion Tensor Imaging (DTI) can detect tissue damage in an early period at the cellular level. The most commonly used parameters are FA (fractional anisotropy) and ADC (apparent diffusion coefficient). Recently, DTI has been used commonly to evaluate auditory pathways in patients with VS<sup>10,11</sup>. As far as we know, there are a few studies in the literature investigating the effects on tumor volume and subcortical auditory pathways using DTI parameters in patients with ICVS treated with GKR<sup>1,2,9</sup>. Our study aims to investigate whether there is a change in ADC and FA values in brainstem subcortical auditory pathways after GKR in ICVS and the relationship between tumor volume and DTI parameters.

## MATERIALS and METHODS

The ethics committee of our institution approved this study (2020-6566). Written and oral consents were obtained from the patients immediately before GKR. Seventeen patients (8 men, 9 women, mean age 55±11 years, in 36-75 age range) with unilateral ICVS were included in the study. Patients with microsurgical operations and/or VS located in the cerebellopontine corner were excluded from the study. The mean duration of follow-up was 17.5±13.7 months.

## Gamma Knife Radiosurgery

All patients included in our study were treated in the GKR unit of our university. Treatment planning was carried out with the Gamma Knife 4C model and its software (Elekta, Sweden). Leksell stereotactic head frame was placed and images of volumetric MRI sequences of 3D T2 and 3D T1 MPRAGE (rapid acquisition of gradient echoes prepared by magnetization) were obtained. The maximum cochlear dose was 5.8 Gy, the cochlear treatment dose was 3.5 Gy, the maximum brainstem dose was 3.88 Gy, and the treatment dose was 12.5 Gy. No neurological additional deficit was detected in follow-up MRIs after GKR.

## MRI Protocol

The patients with unilateral ICVS who were considered for GKR treatment were evaluated with the 1.5T MRI system (Avanto, Siemens). Imaging sequences taken on MRI include axial and coronal FLAIR (fluid-attenuated inversion recovery) (TR:8000 ms, TE:90 ms, TI:2500 ms), sagittal, and axial T2 TSE (TR:4500, TE:90 ms), axial T1 (TR:550, TE:14 ms) weighted images. Contrast-enhanced T1-weighted images in the axial, sagittal, and coronal planes were obtained (iv Gd-DTPA). With and without contrast 3D T1 MPRAGE images were added to our study. All subjects were evaluated with standard DTI parameters (single-shot SE echo-planar, TR/TE:6000/89 ms, FOV; 230 mm, matrix; 128x256 and slice thickness; 5 mm, spatial resolution; 1,54). Thirty-two diffusion-encoding directions were used at b=1000 s/mm<sup>2</sup>. The DTI maps were reconstructed in the workstation (Leonardo console, Siemens). 3D T1 and T2 images were taken as the anatomical reference for the placement, measurements of regions of interest (ROIs) (ROI sizes; 4 pixels).

The volumetric analysis was performed by a 3D semiautomated quantitative assessment of tumor volume in the workstation (Siemens workstation, Syngo.via). The tumor volumes before and after GKR were outlined and calculated on the 3DT1-MPRAGE with contrast-enhanced images. Volumetric tumor analysis was performed in cubic centimetres (cm<sup>3</sup>).

The tumor total volume (TTV) was derived by subtracting the follow-up volume (postoperative tumor volume; TVat) from the initial tumor volume (pre-treatment tumor volume: TVbt) and dividing by the initial tumor volume<sup>4,12</sup>. The percentage change in volume was calculated by comparing it to the initial tumor volume % =  $\frac{TVat-TVbt}{TVbt}$

An objective radiographic response (shrinkage) is defined as 20% reduction in tumor volume compared to the baseline volume measured during treatment<sup>12-14</sup>. Patients who responded to treatment were classified as Group 1 and those who did not respond adequately were classified as Group 2. The relationships between FA and ADC values at subcortical auditory pathways and tumor volumes were investigated. FA and ADC values were measured in the ipsilateral and contralateral inferior colliculus (IC) and lateral lemniscus (LL). The relationship between tumor volume and DTI parameters were evaluated.

### Statistical Analysis

All evaluations were made using SPSS (IBM Corp. Released 2013. IBM SPSS for Windows, Version 22.0. Armonk, NY: IBM Corp). A Kolmogorov-Smirnov test was used to see the normality of quantitative variables. Comparisons between quantitative variable groups were evaluated with Mann-Whitney U test. Changes in different values of the variables were analyzed by the Wilcoxon test within groups. We used Spearman correlation coefficient to assess the association between quantitative variables, and  $p < 0.05$  was considered statistically significant.

### RESULTS

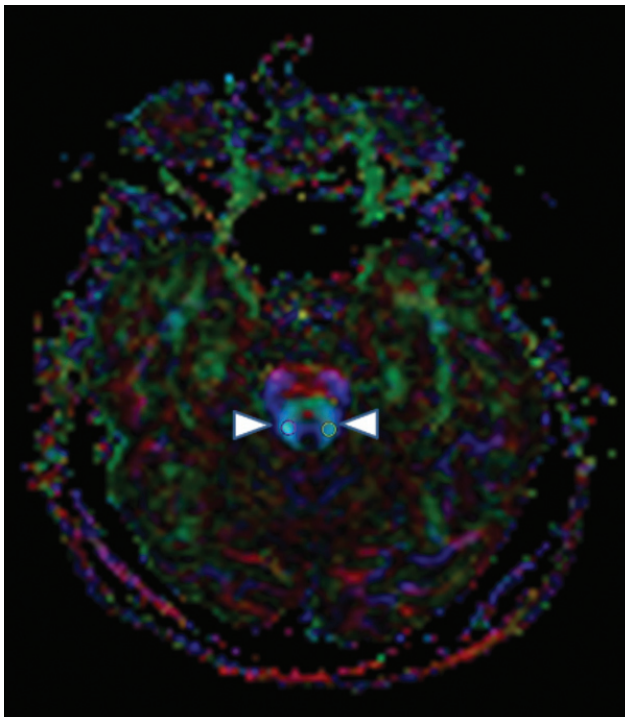
FA and ADC values of the LL and IC, tumor volume, and follow-up times in patients with ICVS are presented in Table 1.

There was a significant difference in terms of tumor volume before and after GKR ( $p:0.011$ ). TTV significantly decreased after GKR (Figures 1 a-d). ADC va-

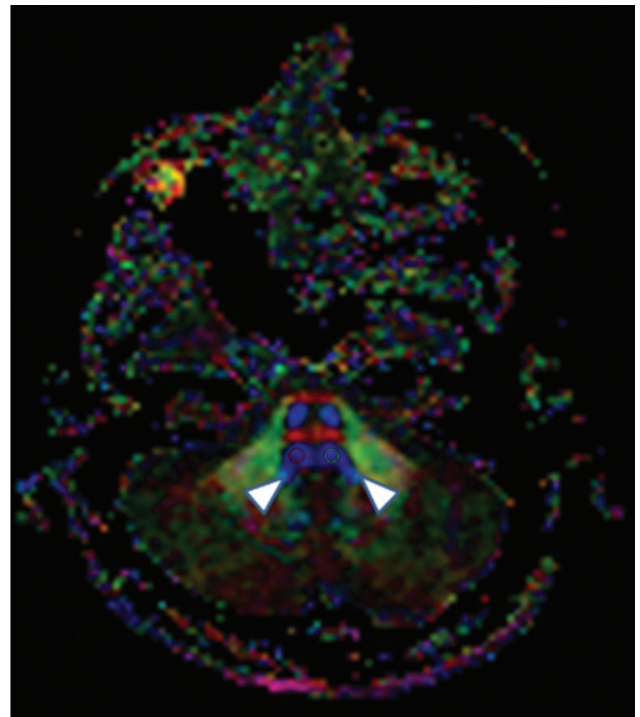
**Table 1. The FA and ADC values of the LL and IC, tumor volume and follow-up times in patients with ICVS are presented.**

		Group 1 (n:10)		Group 2 (n:7)		Total patients (n:17)	
		Pre-GKR	Post-GKR	Pre-GKR	Post-GKR	Pre-GKR	Post-GKR
Follow-up time (months)		24.30±11.33		7.85±11.15		17.52±13.73	
Tumor volume (mL)		0.57±0.55	0.27±0.26	0.46±0.317	0.47±0.26	0.53±0.46	0.37±0.26
Tumor	FA	0.23±0.90	0.24±0.90	0.26±0.85	0.19±0.60	0.24±0.84	0.22±0.92
	ADC	1237.40±0.34	1520.40±0.34	1281±0.24	1567.28±0.34	1255.35±0.29	1539.71±0.33
Ipsilateral LL	FA	0.595±0.56	0.600±0.82	0.575±0.96	0.634±0.12	0.587±0.73	0.614±0.99
	ADC	797.90±95	795.00±40	770.57±91	726.28±96	786.64±91	766.70±74
Ipsilateral IC	FA	0.699±0.75	0.730±0.86	0.694±0.60	0.694±0.91	0.697±0.67	0.715±0.87
	ADC	784.56±67	748.48±86	774.40±74	750.34±67	780.37±68	749.24±76
Contralateral LL	FA	0.506±0.87	0.589±0.79	0.595±0.34	0.577±0.47	0.543±0.38	0.584±0.57
	ADC	784.79±46	727.42±86	781.61±68,56	814.67±60	783.48±54	763.34±86
Contralateral IC	FA	0.670±0.99	0.742±0.90	0.708±0.59	0.665±0.84	0.686±0.85	0.710±0.94
	ADC	768.67±54	764.43±44	757.41±38	779.62±41	764.03±47	770.68±42

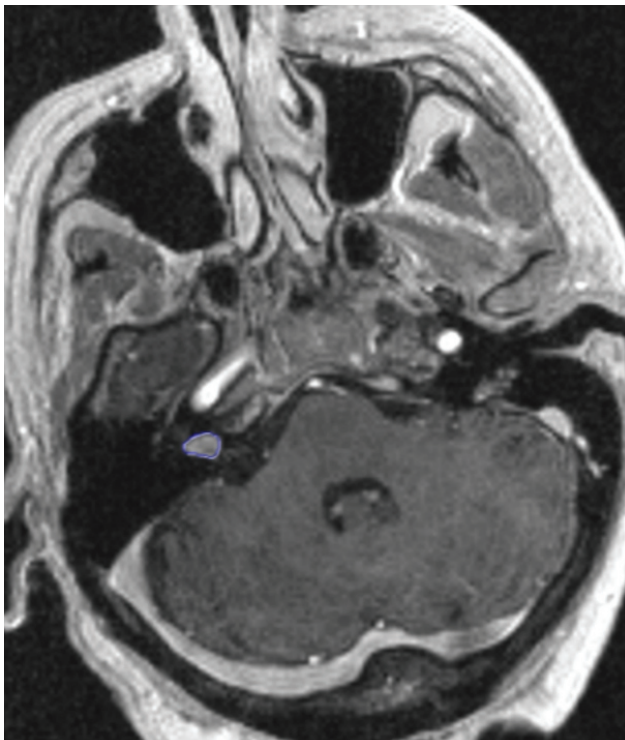
Group 1; The group that responded to treatment  
 Group 2; The group that did not respond to treatment  
 ADC; Apparent diffusion coefficient ( $\times 10^6 \text{ mm}^2/\text{s}$ )  
 GKR; Gamma- Knife Radiosurgery  
 FA; Fractional anisotropy  
 LL; Lateral lemniscus  
 IC; Inferior colliculus



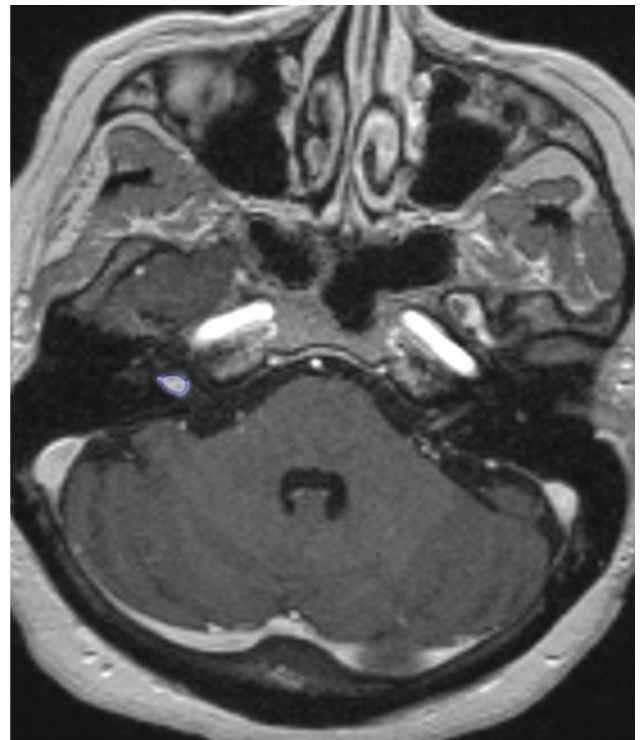
(a)



(b)



(c)



(d)

**Figure 1. Right-sided intracanalicular vestibular schwannoma (ICVS). The axial color-coded FA maps from a subject with ICVS showing the placement of region of interest (ROI) on the inferior colliculus (a) (arrowheads), lateral lemniscus (b) (arrowheads). Analysis of tumor volume using the placement of ROI on postcontrast 3D T1-weighted axial image (c). A decrease in the tumor volume known as shrinkage is shown after 34 months of follow-up (d).**

values obtained from the tumor increased after GKR ( $p:0.002$ ). ADC values obtained from the tumor increased from  $1255\pm 299$  to  $1539\pm 334$  ( $\times 10^{-6}\text{mm}^2/\text{s}$ ). There was no difference in terms of FA values.

There was no significant difference in LL and IC before and after GKR treatment in terms of FA and ADC values. There was a positive correlation between response to treatment and contralateral LL ADC values after GKR ( $r:0.652$ ,  $p=0.005$ ). There was a negative correlation between contralateral IC FA values after GKR and response to treatment ( $r:-0.568$ ,  $p=0.017$ ).

There was a significant difference between Groups 1 and 2 in regards to contralateral LL ADC ( $p=0.03$ ) and IC FA values ( $p=0.017$ ).

## DISCUSSION

Evaluating the volumetric changes in tumor after radiosurgery is an important indicator of response to treatment<sup>2,15</sup>. Some authors reported that tumor control was achieved in 91.1% of the patients followed up approximately 4.5 years after radiosurgery in patients with ICVS<sup>2</sup>. In our study, there was a significant decrease in the tumor volume and a shrinkage in tumor size in 58.82% of the patients treated with ICVS. While pre-treatment tumor volume was  $0.57\pm 0.55$  mL, it decreased to  $0.27\pm 0.26$  mL after GKR. No volume in tumor change was observed in 41.17% of the patients. In this group, pretreatment tumor volume was  $0.46\pm 0.317$  mL, while it was  $0.47\pm 0.26$  mL after GKR. To evaluate the true response after radiosurgery, it should be clearly demonstrated whether there is growth in tumor volume by successive follow-up MRIs. It is recommended to be followed up by MRI every 6 months for up to 5 years after radiosurgical treatment<sup>2,8,12,16</sup>.

The ventral and dorsal cochlear nuclei located in the brainstem are very important functional structures for hearing. Fibers from these nuclei project into the ipsilateral superior olivary nucleus or cross into the contralateral superior olivary nucleus, continuing

into the IC through the LL<sup>17</sup>. Efferent fibers extend from the IC to the medial corpus geniculatum in the thalamus and from here to the auditory cortex in the gyrus of Heschl<sup>9,18,19</sup>. Stimuli from the opposite side contribute much more to the processing of auditory stimuli. 20-30% of the fibers reaching auditory cortex come from the ipsilateral side and 70-80% from the contralateral side. The higher the radiation dose to which the brainstem is exposed, the greater the risk of hearing loss. Hearing loss develops due to the toxic effects of radiation in the brainstem nuclei and cochlea<sup>17</sup>.

DTI is a promising technique that allows the identification of auditory neural tracts. It may show radiation-induced diffusion changes in auditory tracts at the brainstem level in patients with ICVS<sup>15</sup>. Increased ADC values may be associated with myelin sheath disorder due to decreased cellularity or less axon number. The decrease in FA is probably caused by the loss of regular anisotropic structures due to the disruption of cytoarchitecture. In our study, ADC values obtained from the tumor after GKR increased significantly compared to pretreatment values. Increased ADC values may indicate that the presence of decreased number of tumor cells, necrosis, or cystic degeneration developing in the tumor. There was no significant difference in FA values after GKR treatment.

FA values in contralateral IC and LL were reported to decrease in patients with neurosensory hearing loss. These findings were explained by the transsynaptic degeneration of the auditory pathway<sup>11,20,21</sup>. Rueckriegel et al.<sup>10</sup> reported that volume reduction in the contralateral parts of the auditory tract was associated with transsynaptic degeneration of the auditory tract secondary to damage to the ipsilateral cochlear nerve. It can be explained by degeneration of the subcortical auditory pathways and the cochlear nerve, due to its low regeneration potential after neuronal damage<sup>10</sup>. In our study, ADC values obtained from contralateral LL after GKR were higher in Group 2 (non-responding group) than in Group 1 (responders). Also, the contralateral side IC FA values were

lower in Group 2. As response to treatment increases after GKR, contralateral side LL ADC values also increase. In addition, contralateral IC FA values decrease as response to GKR treatment increases. Increased ADC values may be associated with dysmyelination and loss of myelin and dysmyelination. It is thought that decreased FA values in contralateral IC may be due to demyelination in subcortical auditory pathways and a decrease in number of axons and fiber density.

Transient tumor growth in the first 18 months after radiosurgery has been described in patients with ICVS. The most important indicator of transient tumor enlargement after radiosurgery is development of hearing impairment<sup>21,22</sup>. It strongly supports the view that changes in ADC and FA values in the contralateral subcortical auditory pathways are associated with the normal anatomical course of the auditory fibers. We think that changes in ADC and FA values related to subcortical auditory pathways may be associated with transient expansion in tumor volumes in Group 2 patients who do not respond adequately to GKR treatment. In this group, the follow-up period was very short after GKR treatment. Especially in short-term follow-up MRI, the development of necrosis secondary to treatment may cause a false increase in tumor size. Therefore, the size criterion alone is not sufficient to evaluate response to treatment in short-term follow-up.

Low number of patients with ICVS is seen as the most important limitation of our study. The second limitation is the placement of ROI. These are problems caused by the partial volume effect that occurs when placing ROIs in different locations in the subcortical auditory pathways. Our third limitation is the short MRI follow-up time after GKR.

## CONCLUSION

ADC and FA changes in LL and IC can be explained by the presence of intracanalicular tumors due to the low regeneration potential of the subcortical auditory pathways and cochlear nerve. Since GKR does

not cause additional damage to the subcortical auditory pathways at the brainstem level, we think that GKR is a noninvasive treatment method that can be used safely in patients with ICVS. Further studies are needed to better understand the relationship between DTI parameters of subcortical auditory pathways and treatment response before and after GKR in determining the effectiveness of GKR in patients with ICVS.

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