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Editor
Antonio A. F. DeSalles, MD
University of California,
Los Angeles, CA, USA

Stereotactic radiosurgery for the treatment of Glomus Jugulare Tumors

Emerson Magno de Andrade, José Reginaldo Brito, Susana Dias Mario, Suely Maymone de Melo, Salomon Benabou

Stereotactic Radiosurgery Service, Hospital Bandeirantes, São Paulo-SP, Brazil

E-mail: *Emerson Magno de Andrade - emersonmagno@hotmail.com; José Reginaldo Brito - jrnbrito@gmail.com; Susana Dias Mario - sd.mario@uol.com.br; Suely Maymone de Melo - suelymmm@ig.com.br; Salomon Benabou - neurorad@terra.com.br

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Abstract

Background: The glomus jugulare tumor is a slowly growing benign neoplasm originating from neural crest. There is a high morbidity associated with surgical resection of glomus jugulare. Radiosurgery play a relevant role as a therapeutic option in these tumors and its use has grown in popularity. The authors describe a retrospective series of 15 patients and reviewed the literature about the glomus jugulare tumors.

Methods: We reviewed retrospectively the data of 15 patients treated with stereotactic linear accelerator stereotactic radiosurgery (LINAC) radiosurgery between 2006 and 2011.

Results: The average tumor volume was 18.5 cm^3. The radiation dose to the tumor margin ranged between 12 and 20 Gy. The neurological status improved in three patients and remained unchanged in 12 patients. One patient developed a transient 7^{th} nerve palsy that improved after clinical treatment. All tumors remained stable in size on follow-up with resonance magnetic images.

Conclusions: The radiosurgery is a safe and effective therapy for patients with glomus jugulare tumor. Despite the short follow-up period and the limited number of patients analyzed, we can infer that radiosurgery produce a tumor growth control with low morbidity, and may be used as a good option to surgical resection in selected cases.

Key Words: Chemodectoma, glomus jugulare tumor, radiosurgery

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INTRODUCTION

Glomus jugulare tumors (GJT) are considered benign, slow-growing and highly vascularized, and are also known as paragangliomas or chemodectomas.[5,14] They are rare tumors, with an incidence of one case per one million inhabitants, and correspond to 0.6% of head and neck tumors.[20] They originate from paraganglionic tissues that can be found in the adventitia of the dome of the jugular bulb (glomus jugulare), but also along the Jacobson's nerve (glomus tympanicum), the vagus nerve (glomus vagale), and the body of the carotid artery.[30]

In general, GJT exhibit an indolent clinical behavior, with a long interval (between 4 and 6 years on average) between the first symptoms and their diagnosis.

Several classification systems are used in the evaluation of GJT, yet the system of Glasscock–Jackson [Table 1] and that of Fisch are used most often to describe cases.[1,9,11,15] Despite the differences of classes and descriptions, these classifications are useful in the surgical planning and follow-up of patients.

The aim of this study was to retrospectively evaluate the preliminary results in a series of 15 patients submitted to stereotactic radiosurgery for the treatment of GJTs, and to conduct a review of the literature about recent advances in the radiosurgical treatment of this pathology.

MATERIALS AND METHODS

From June 1996 to November 2011, 39 patients were admitted into our institution with a diagnosis of GJT for treatment with linear accelerator stereotactic radiosurgery (LINAC) or stereotactic fractionated radiotherapy. Of this total group of patients, 8 cases were excluded from the present analysis as they had been submitted to fractionated radiotherapy, and 16 patients had insufficient data for analysis or were lost to follow-up. We selected 15 cases submitted to LINAC stereotactic radiosurgery for a preliminary evaluation.

The data were obtained by consulting the patients' medical records, analysis of neuroimaging and performing clinical evaluation of the patients at the clinic, or via telephone contact. Based on a retrospective reviewed of patient's records, we analyzed all the following variables: Sex, age, location and volume of the lesion, neurological symptoms presented before and after treatment, previous surgery, prescription dose, maximum dose, and change in characteristics image. Despite the differences of the many classification systems used in the evaluation of GJTs, we opted to use the Glasscock-Jackson classification as we consider it to be more reproducible and simple [Table 1].

For dosimetry planning, all patients underwent a noncontrast and contrast-enhanced T1-weighted magnetic resonance imaging (MRI) sequences done few days prior to treatment [Figure 1]. These images are fused to a computed tomography (CT) scan performed in the current day of treatment. The patient's head is immobilized thorough a frameless system using a relocatable thermoplastic mask where the fiducial coordination is attached. All patients were treated using a

Table 1: Glasscock-Jackson classification of glomus jugulare tumors

Class	Description
I	Small tumor involving jugular bulb, middle ear, and mastoid
II	Tumor extending under internal auditory canal; may extend into the intracranial canal
III	Tumor extending into petrous apex; may extend into the intracranial canal
IV	Tumor extending beyond petrous apex into the clivus or intratemporal fossa; may extend into the intracranial canal

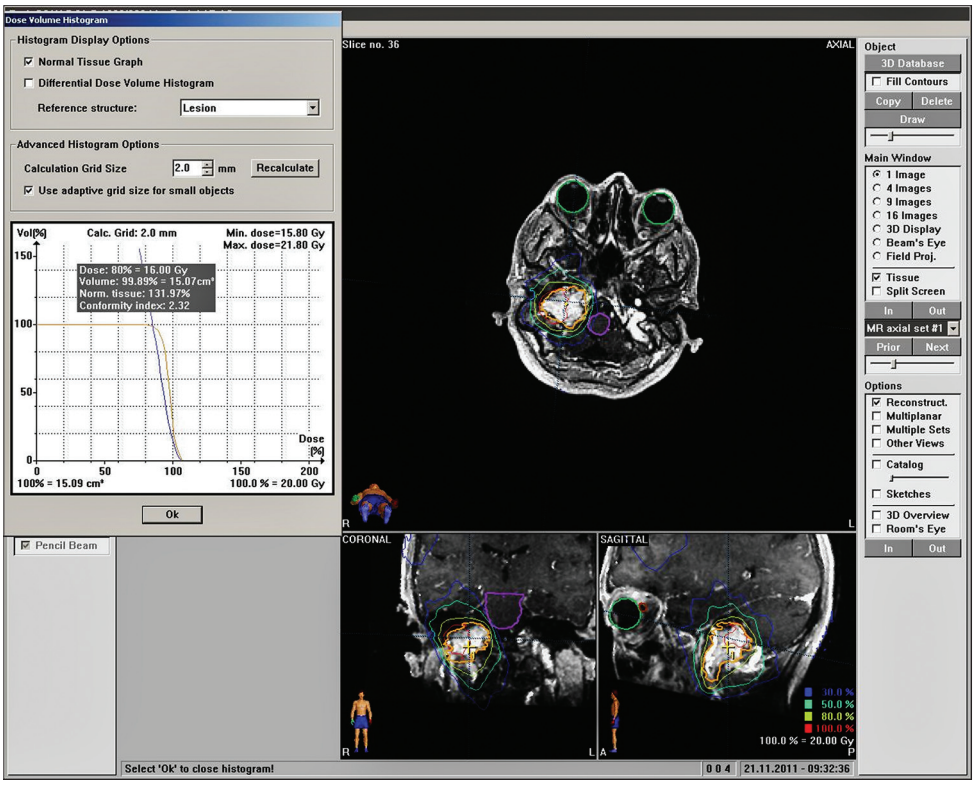

Figure 1: Treatment planning for a patient harboring a Glomus Jugulare Tumor. The 80% isodose line represents the prescribed dose of 1600 cGy and the tumor volume is 15.07 cm³

Novalis® Radiosurgery system (Brainlab AG, Feldkirchen, Germany) and discharged home on same day after some hours of clinical and neurological observation.

The authors carried out an extensive review of the literature through the Medline, Scielo, and Lilacs indexers, using the keywords "glomus jugulare," "radiosurgery," "gamma knife," "LINAC," and "CyberKnife," making sure to include only GJTs. The data on glomus tympanicum and vagale tumors and paragangliomas present in other locations were analyzed and included if necessary.

RESULTS

Tables 2 and 3 summarize the clinical, neurological, and follow-up characteristics of the 15 patients analyzed. At the time of the treatment, the patients' mean age was 58.4 years, ranging between 19 and 78 years. Thirteen of the patients were female and two were male. In relation to the class of tumors, according to the Glasscock-Jackson classification, six cases were classified as Class I, six as Class II, two as Class III, and one case as Class IV. The average tumor volume at the time of treatment was 18.5 cm^3, oscillating between 4.58 and 42.93 cm^3. The prescription dose ranged between 1200 and 2000 cGy, and the professionals performed hypofractionation with five fractions of 400 cGy in one of the cases (case 12). The average peripheral dose was 1400 cGy. Two of the fifteen patients were submitted to previous surgical treatment a few months before the radiosurgery. The follow-up durations were in range of 3-61 months (mean 35.4 months).

The most frequent neurological symptom in the initial evaluation was hypoacusis (n = 11), followed by tinnitus (n = 9) and vertigo (n = 3). One patient presented paralysis of 9th, 10th, 11th, and 12th cranial (case 6) while paralysis of 7th and 12th cranial nerves was observed in another patient (case 10). Improvement of the symptoms was verified in three cases, and one patient presented transient facial paresis after radiosurgery, but evolved with improvement after clinical treatment. No alteration of the lesions was observed in the imaging examinations during follow-up.

DISCUSSION

The GJT mostly affect people in the sixth and seventh decades of life, with mean presentation age of 55 years, and are more frequent in the female sex. Bilateral GJTs are found in 1-2% of cases, however, they most frequently present solitary, and in up to 10% of patients can be observed at the same time as carotid body tumors.[23,28,30] GJT are frequently locally aggressive, causing invasion and bone destruction, and may invade the jugular foramen and the tympanic cavity, expanding inside the skull with involvement and destruction of neurovascular structures.[1,14,16,20,27] Uncommon locations of pararanglioma have been reported in the literature. Ectopic paragangliomas have been found in the Meckec's cave, tongue, and frontal skull base.[33]

GJT present growth of just 0.8 mm per year, doubling in size in 4.2 years.[16,28] The most frequent symptoms found include: Tinnitus, migraine, hypoacusis, vertigo, and multiple cranial nerve palsy, with possible involvement of 5th to 12th cranial nerves. The neurological symptoms are related to the region affected by the tumor. This can infiltrate neurovascular structures, the temporal bone, the jugular foramen, the hypoglossal canal, the clivus, the

Table 2: Characteristics in 15 patients who underwent LINAC radiosurgery for glomus jugulare tumors

Case no.	Age (years)/ Sex	G-J grade	Dose (Gy)	Tumor volume (cm^3), Side	Previous surgery
1	73/F	I	13	1.57, rt	No
2	66/F	I	14	7.12, lt	No
3	52/F	IV	13	20.66, rt	No
4	54/F	III	13	37.90, rt	No
5	70/F	II	13	17.79, lt	No
6	75/F	I	13	4.58, rt	No
7	57/M	II	13	25.30, rt	Yes
8	50/F	III	12	42.93, lt	No
9	78/F	II	15	23.30, lt	No
10	64/F	II	16	22.77, lt	No
11	19/F	II	12	28.60, rt	Yes
12	62/F	I	5×400	10.73, lt	No
13	51/F	I	16	11.02, lt	No
14	64/M	II	16	15.07, rt	No
15	41/F	I	16	9.45, rt	No

LINAC: Linear accelerator stereotactic radiosurgery, M: Male, F: Female, Gy: Gray

Table 3: Neurological and clinical data in 15 patients

Case no.	Signs and symptoms	Clinical response	Follow-up (months)
1	Decreased hearing, tinnitus	I	61
2	Decreased hearing, tinnitus, vertigo	I	0
3	Decreased hearing, tinnitus	U	51
4	Hearing loss, tinnitus, ear pain	U	51
5	Decreased hearing	U	51
6	Decreased hearing, palsy of 9th, 10th, 11th, and 12th cranial nerves	U	49
7	Decreased hearing, tinnitus	U	46
8	Decreased hearing, tinnitus	U	35
9	Decreased hearing, tinnitus, vertigo	U	31
10	Hearing loss, palsy of 7th and 12th cranial nerves	U	24
11	Decreased hearing, dysphagia, facial pain	U	20
12	Tinnitus, vertigo	U	18
13	Decreased hearing, headache	I	18
14	Tinnitus	U	14
15	Decreased hearing, headache	U	3

I: Improved, U: Unchanged

cavernous sinus, and cervical region.[1,11,12] Both familial and sporadic variants have been described. The familial form represents about 20-40% of the cases described, yet its genetic basis is still poorly understood, and may involve mutations in chromosome 11 (11q23.1 and 11q13.1) and 1q.[16,18]

In spite of the long surgical experience in the approach to GJT, their treatment is still a subject of debate and controversy. The therapeutic options for GJT treatment include surgery, radiotherapy and embolization, which can be used combined or individually.[1-10,23-29] Their management should also take into account two important aspects. The first is that most patients have benign, very slow-growing tumors, although malignancy can occur infrequently. The second aspect is that the consequences of injury to the low cranial nerves, which are typically involved in GJT, are very severe.[22]

Surgical treatment remains a treatment option for patients who desire an immediate cure, which can be achieved with the complete resection of the lesion.[1,34] The presence of multiple cranial nerve palsy, important intracranial extension, and vascular insufficiency due to tumor involvement are among the indications for surgical approach. In cases with initial surgical indication in which complete resection is not feasible due to the high risk of neurological deficit or of postoperative morbidity, professionals opt for subtotal resection and therapeutic supplementation with radiosurgery or stereotactic radiotherapy.[1,11,13,17] The total removal of the tumor can be achieved in about 40-80% of the cases and local control of the lesion can range from 0% to 90% according to some published series.[1,11,13,28,34]

According to Al-Melfty and Teixeira, even the most complex tumors can be resected safely and with low morbidity.[1] In a review with 374 patients submitted to surgical treatment, the appearance of deficit in one or more cranial nerves occurred in 22-59% of the cases after surgery.[11] The same review showed the following incidence of other postoperative complications: Liquoric fistula (8.3%), aspiration (5.5%), infection of surgical wound (5.5%), and meningitis (2.3%).[11]

The recurrence of the tumor can range between 0% and 5.5% after surgical treatment and the mean recurrence time was 82.8 months according to some series.[1,19,22,33,40] In tumors with intracranial extension the rate of postoperative cranial nerve palsy ranges between 22% and 100%.[19,20,26,39] Mortality is significant, and can oscillate between 4.2% and 6.4% according to some studies. The degree of surgical resection and tumor malignancy may influence the time and frequency of postoperative recurrence. In general, data relating to the rate of resection and recurrence are difficult to interpret due to the heterogeneity of the series and the limited number of cases.[1,19,22,26,33,40]

Preoperative embolization can reduce intraoperative blood loss and help to reduce the surgical time, but has no influence on the decrease of the incidence of postoperative neurological deficit and hospitalization time. Embolization is a merely palliative treatment option due to the noncomplete coverage of the tumor volume and to the high rates of recanalization.[10,11]

Some tumors are classified as complex as they are considered inoperable or present high surgical risk. To be included in this category, tumors must present one or more of the following criteria: Giant tumor, multiplicity, malignancy, secretion of catecholamines, and association with other lesions such as arteriovenous malformations (AVMs) or adrenal tumor.[1]

Approximately 4% of GJTs are catecholamine secretors, yet in most cases the level of catecholamines produced is of no clinical importance. Due to the risk of hypertension crisis and other complications that may occur in the intraoperative period, patients with hypersecretory tumors need preoperative preparation with the use of alpha or beta blockers.[33,37,41] The catecholamines producing capacity can be decreased by radiosurgery but caution is required to avoid provoking a hypertensive crisis at some point in treatment of functional GJT with radiosurgery.[4]

The literature contains few described series of radiosurgery for GJTs to date, reflecting the limited use and knowledge of this technique.[22,24,27,28,34,38,42] However, the use of the LINAC and Gamma Knife as a primary or secondary indication in the treatment of GJT has increased considerably, in spite of the resistance of some centers to this therapeutic approach.[1,34]

GJT are ideal candidates for radiosurgical treatment since they seldom invade the brain and are clearly visualized in magnetic resonance examinations [Figure 1]. This characteristic facilitates the marking of the target and the reduction of radiation isodoses. Radiation acts by causing an obstruction and fibrosis of the tumor vessels and thus inhibiting their growth, an effect similar to that observed in AVMs.[3,8] Radiosurgery involves precise stereotactic tracking of the target region and a smaller volume of irradiated normal tissue, which decreases the rate of complications. As it is a noninvasive technique, it avoids the complications associated with surgery, yet without the potential risk of the conservative treatment.[7,9] The typical dose for these lesions ranges between 12 and 25 Gy, depending on the tumor volume, and even tumors with a volume above 30 cm^3 can be submitted to radiosurgery safely due to the limited contact of the lesion with the cerebral tissue, whereas the radiation is distributed to the bones from the base of the skull and cervical and infratemporal regions.[40,42] According to the series evaluated, radiosurgery appears to exhibit a clinical response and prolonged tumor control equivalent or superior to fractionated radiotherapy, yet with a lower rate of chronic complications.[8,9,11,13]

To the best of our knowledge, LINAC radiosurgery was used only in five of the radiosurgery series analyzed [Table 4], including studies in which patients were treated either with frame-based LINAC or Cyberknife.[23,24] Although there are few studies describing LINAC radiosurgery for GJTs, compared with a number of Gamma Knife, the results presented seem analogous.[9,12,23-28,32] The Gamma Knife is a radiosurgical device that use 201 small sources of Cobalt-60 arranged in a hemispherical structure, which converge and focus the photon beams of radiation on the treatment target. The LINAC unit is somewhat different because it utilizes a single radiation source that turn around the patient while the radiation is always focused on the target. Both dose concentration methods are accurately analogous and allow achieving dose distributions that are very close to the form of the located target, with minimal radiation to the normal brain.[22,33]

In reporting on a series of five patients treated with LINAC-based stereotactic radiosurgery, Feigenberg *et al*. described tumor control in three of five patients analyzed. The dose applied to the peripheral of the tumors varied from 12.5 to 15 Gy (median dose of 15 Gy) and the treatment volumes had a mean of 10.84 cm^3. One patient experienced 5th cranial nerve palsy 6 months after treatment, which resolved after a few months. The follow-up time ranged from 14 to 50 months (median of 27 months). The authors concluded that their previous results with stereotactic radiosurgery are unenthusiastic compared with that observed with conventional fractionated radiotherapy in the treatment of patients harboring temporal bone GJT.[8]

Maarouf *et al*. published their results in a series of 14 patients harboring a GJT treated with LINAC radiosurgery. The prescribed dose to the surface of the tumors ranged from 11 to 20 Gy (median dose of 15 Gy) and the mean follow-up was 48 months. The authors reported that improvement of neurological symptoms was achieved in 25% of the cases and remained unchanged in 67% of the patients. No acute complication related to radiosurgery was described.[27]

Lim *et al*. reported 18 patients with 21 tumors treated with radiosurgery, of which 5 were treated with frame-based LINAC radiosurgery and the others initially treated with Cyberknife. The tumors presented an average size of 3.0 cm measured over the largest diameter. The prescribed dose to the periphery of the lesions ranged between 1400 and 2700 cGy in the isodose of 80%. After an average clinical follow-up time of 60 months, 11 patients did not experience any change in tumor size, while 2 revealed volume reduction after stereotactic radiosurgery. Three patients presented neurological complication. Two patients experienced transient ipsilateral hemilingual paralysis and loss of hearing. Another patient that was treated previously with external beam radiotherapy experienced transient ipsilateral vocal cord paresis that resolved after 8 months.[24]

Poznanovic *et al*. treated eight patients with GJT using LINAC radiosurgery. All patients except one had complete resolution of presenting symptoms. The prescribed dose ranged from 1500 to 1600 cGy. The authors reported a 100% control rate of the lesions. One patient experienced a transient vertigo, and a second suffered acute gastrointestinal upset and developed a transient lower cranial nerves neuropathy.[32]

In a recently published meta-analysis study, 19 case series of radiosurgery were identified for GJT, using Gamma Knife, linear accelerator and CyberKnife, out of a total of 335 patients. The authors selected recent studies from groups or institutions that have tradition of publish articles. Of the series studied, 96% exhibited tumor regression or stabilization and 95% of the patients presented improvement or control of the neurological symptoms. On a basis of the results obtained, the authors recommend radiosurgery as a valid alternative for the primary management of patients with GJT.[12]

One of the limiting factors of radiosurgery for GJT is the tumor size. Fractionated stereotactic radiotherapy can be an option for tumors of considerable volume, since fractionated radiotherapy combines stereotactic precision with the advantages of radiation fractionation.[13,42,43] In a series with 22 patients submitted to fractionated radiotherapy the average tumor volume was 71.8 cm^3, a value higher than that found in the radiosurgery series whose average volume ranges between 4.9 and 18 cm^3. A standard prescription uses a total dose from 45 to 55 Gy with daily fractions from 1.5 to 2.0 Gy.[42] The mechanism of action does not appear to be related to the direct destruction of the tumor cells, but instead

Table 4: Summary of LINAC radiosurgery for Glomus Jugulare Tumors

Authors and year	No. of patients	Mean margin dose (Gy)	Mean follow-up (mo)	Neurological outcome
Feigenberg *et al*., 2002	5	25	27	2U/2I/1W
Maarouf *et al*., 2003	12	15	48	4U/8I
Poznanovic *et al*., 2006	8	15	15.6	1U/7I
Lim *et al*., 2007*	18	23	60	21U
Current study, 2013	15	14	35.4	12U/3I

*5 patients were treated with LINAC and 13 patients with Cyberknife radiosurgery. mo: Months, U: Unchanged, I: Improved, W: Worse, LINAC: Linear accelerator stereotactic radiosurgery, Gy: Gray

to the obstruction of the tumor-nourishing vessels, leading to their ischemia and necrosis. The rate of complications is relatively low (0-10%) and these include osteonecrosis of the temporal bone, mastoiditis, and alopecia.[3,10,13,21,29,36,42,43]

The mean follow-up time in the present study is relatively short, particularly as it is a benign, slow-growing pathology. A prolonged follow-up of the cases is necessary to determine the postradiosurgery control rate with greater accuracy. The decision to include cases with relatively short follow-up (3 and 14 months) is important in the observation of early complications. Acute neuropathies may occur after radiosurgery, yet few cases were reported in the literature.[8,12,27]

The direct comparison between surgery and radiosurgery as a primary therapeutic approach is difficult since both techniques present different objectives (complete resection of the lesion in surgery and inhibition of tumor growth in radiosurgery). No cases of mortality associated with radiosurgery have been described, and mortality associated with surgery is just over 1% in recent series. An important difference between these two techniques is the morbidity, which can be observed in 8.5% of the patients submitted to radiosurgery and oscillates between 22% and 59% after surgical treatment.[1,11,12,41]

A review comparing radiosurgery and surgery for the treatment of GJTs, analyzed eight series describing the use of radiosurgery in these tumors. Of these series, five used Gamma Knife and three used linear accelerator as a therapeutic approach, describing a total of 143 patients. Of the 143 patients reported, 48% received radiosurgery as primary treatment and 52% were submitted to other therapies before radiosurgery. The neurological symptoms remained stable in 58.2% of the patients, 39% presented improvement, and 2.8% exhibited permanent neurological deterioration. The rate of permanent neurological deficit associated with the radiosurgery was 2.1%, a result lower than that observed in the surgical series. Neurological complications occurred in 12 of 141 patients (8.5%), yet were transient in nine of these cases. The authors recommend that radiosurgery be used as a primary therapy for patients who are either elderly or have important comorbidities, and as a secondary therapy in cases of subtotal resection and residual tumor.[11]

CONCLUSIONS

GJTs are considered histologically benign and slow growing. Due to their critical location in relation to delicate nerve and vascular structures, their surgical approach still remains a challenge to the neurosurgeon, in spite of all the progress made in neuroimaging examinations, which facilitates the surgical planning, and in microsurgical techniques. Stereotactic radiosurgery is a safe and effective treatment of this neoplasm, both for elderly patients presenting important comorbidities, and for young patients. The stereotactic fractionated radiotherapy could be a further treatment option, mainly in large tumors.

The indication of radiosurgical treatment has increased significantly in recent years due to the safety of this method and the low level of morbidity compared with the surgical treatment, as demonstrated by various published case series. Nevertheless, series with a larger number of cases and prolonged follow-up are still necessary to verify the true efficacy of the method and to identify possible late malignant transformations.

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