

# Two Giant Glomus Jugulare Tumors with Multiple Cranial Nerve Involvement: The Results of Radiotherapy: Case Report

## Çoklu Kafa Çifti Sinir Tutulumu Olan İki Dev Glomus Jugulare Tümörü: Radyoterapi Sonuçları

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**ABSTRACT** In this case report, we present two patients with advanced and aggressive giant glomus tumour with multiple cranial nerve involvement and evaluate the treatment options of the glomus tumour in the light of the literature. The patients have been operated long time ago and followed up by magnetic resonance imaging only. Their history revealed that a valuable time was lost with observation and cranial nerve malfunction got gradually worse in that period. Both cases were irradiated using image guided intensity modulated radiotherapy techniques to a prescribed dose of 54 Gy in 30 daily fractions. Planning and therapies were applied with tomotherapy. During and after radiotherapy many cranial nerve function got better in spite of the fact that many years had been passed with cranial nerve paralysis.

**Key Words:** Glomus jugulare tumor; skull base; cranial nerve injuries; radiotherapy, intensity-modulated; radiotherapy, image-guided

**ÖZET** Bu vaka raporlamasında, hızlı seyirli ve ilerlemiş çoklu kafa çifti sinir tutulumları olan iki dev glomus tümörü sunulmuş ve literatür ışığında glomus tümörlerinin tedavi seçenekleri değerlendirilmiştir. Hastalar uzun zaman önce ameliyat edilmiş ve manyetik rezonans görüntü tarama yöntemleri ile takip edilmişti. Hikayelerinden değerli bir zaman diliminin takip ile kaybedildiği ve bu süre içinde kafa çifti sinir hasarlarının giderek kötüleştiği öğrenildi. Her iki vaka, görüntü rehberliğinde yoğunluk ayarlı radyoterapi tekniği kullanılarak 30 günlük fraksiyonda reçete edilen 54 Gy doz eşdeğerine ışınıldı. Planlama ve tedavileri tomoterapi cihazı ile yapıldı. Kafa çifti sinir tutulumlarının üzerinden yıllar geçmiş olmasına karşın radyoterapi esnasında ve sonrasında çoğu sinir hasarında düzelme görüldü.

**Anahtar Kelimeler:** Glomus jugular tümörü; kafa tabanı; kranial siniri hasarları; radyoterapi, yoğunluk ayarlı; radyoterapi, görüntü kılavuzlu

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The glomus tumours (GT) are rare, benign neoplasms which are situated in the adventitia of jugular bulb or along the course of the ramus tympanicus of the glossopharyngeal nerve.<sup>1-4</sup> Because invasive GT in this region frequently involve cranial nerves (CN) and extend into the posterior fossa, complex surgical intervention including advanced skull base surgery is necessary.<sup>1,2</sup> The most frequently seen initial symptoms of these tumours are pulsatile tinnitus and hearing loss.<sup>4,5</sup> Some patients endure ear symptoms for 3 to 5 years before seeking medical attention.

As they expand eventually, they produce cranial nerve paralysis resulting from invasion of the skull base. Invasion of cranial nerves (CN) V-XII may result with dysphonic speech, hoarseness of voice, vertigo, ptosis, facial paralysis, difficulty in swallowing.<sup>1-5</sup> Primary therapy in the carotid region is generally surgical resection after embolization. External beam radiotherapy (RT) or stereotactic radiosurgery are often favoured at the skull base lesion with CN deficits because of risky neurosurgical interventions.<sup>1-15</sup>

## CASE REPORTS

### CASE 1

A 38-year-old woman with a history of left-sided severe otorrhea, otalgia, hearing loss and CN VII palsy had an operation three years ago. But she denied any symptomatic relief and had been followed by observation in that period. A well known cancer centre evaluated the case unsuitable for fractionated stereotactic radiotherapy (FSR) because of huge dimension, brain stem invasion and close vicinity to the critical structures. Approximately 5 to 6 months before her admission, besides aforementioned CN paralysis, left-sided ptosis, diplopia, dysphonic speech, vertigo, swallowing and balance problems had also occurred.

On clinical examination, she had a semi mobile left sided neck mass with the following neurological deficits: CN IV (ptosis), CN VI (diplopia and restriction at gazing into left side), CN VII (left sided peripheral facial paralysis), CN VIII (left sided conductive hearing loss), and CN XII (left side deviation of tongue).

Admission MRI study revealed a giant mass based on the left jugular foramen at the skull base level, destructing posterior part of the clivus, wall of the left carotid canal and the structures of the middle and inner ear; at the posterolateral location, spreading over the mastoid cells; intracranially, invading of the foramen luschka, filling in the left cerebellopontine angle and elongating the middle cerebellar peduncle; on the left, sitting on the prepontine and perimesencephalic cisterns

and invading and noticeably compressing to the brain stem. At the inferior side of the lesion, filling in left carotis and parapharyngeal spaces and laying down to compress the oropharyngeal structures and at this level encircling and contracting carotid artery; tumour also invades cavernous sinus and dura at the level of craniocervical junction.

The giant mass intensely and heterogenously enhanced after intravenous Gd-DTPA contrast administration. Craniocaudal (CC), anteroposterior (AP) and mediolateral (ML) dimensions of the tumour are measured as 89 mm, 58 mm and 61 mm respectively. In contrasted computed tomography there is extensive destruction of skull base bones and invasion of cerebellar and cerebral compartments of the brain. Figures 1, 2 illustrate pre RT images of the first patient.

### CASE 2

A 66 year old woman reported with chief complaints of hoarseness of voice without causal link of any known illness for 8 years; with right-sided hearing loss, difficulty in swallowing, mass lesion in the submandibular region and right cranial nerve palsies of VII, IX, and XI for 1 year. From past history we realized that the patient underwent a subtotal surgery five years ago and after that she was followed up by observation only. In the histopathological evaluation, there were neoplastic cells infiltrating bony tissue and forming nests "zellballen pattern" in the extremely vascular stroma. On admission clinical examination, she had a semi-mobile right neck mass, and evidence of right peripheral facial paralysis, shoulder weakness and ptosis. CT scan of the neck with intravenous contrast demonstrated a 48x90x55 mm (CC, AP, ML) giant mass which is beginning from the right jugular foramen, extending up to cerebellopontine angle, and mastoid bone and at this level destructing right part of the occipital condyle, clivus, mastoid bone, middle and inner ear bone structures; at posterior laying down to the sigmoid sinuses; at the caudal side invading infratemporal fossa. MRI revealed a huge tumoral mass at the right jugular foramen which is filling



FIGURE 1: Sagittal and coronal CT images with contrast of the first case.

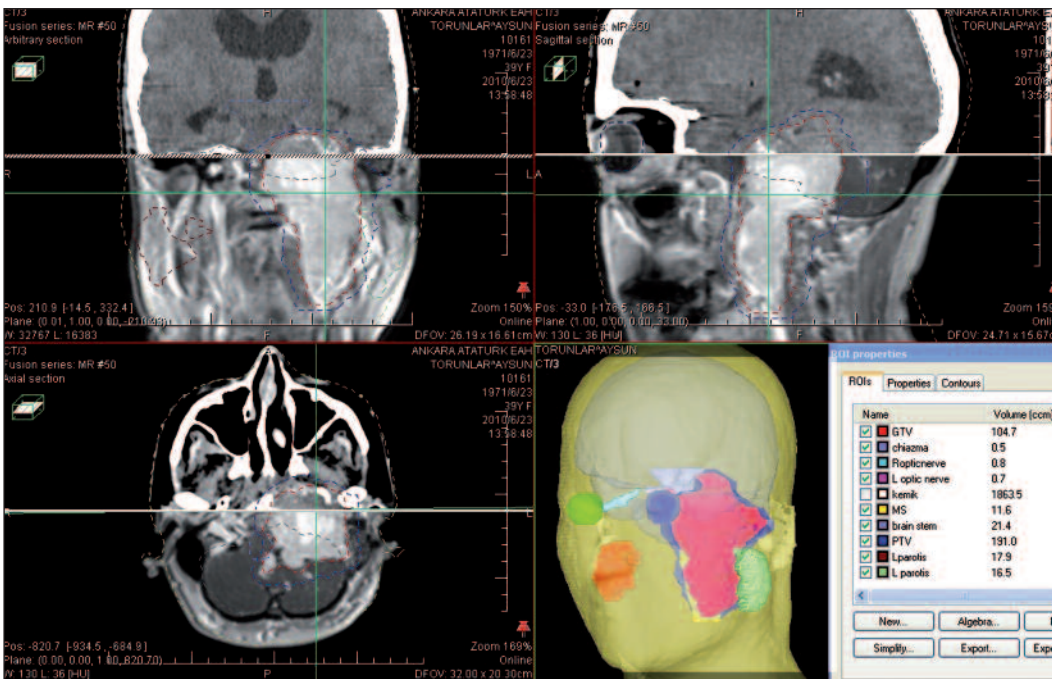


FIGURE 2: Sagittal, coronal, and axial images of CT registered to MR and 3-D image reconstruction, of the first case.

in the right parapharyngeal space, abutting on right carotid artery and extending deep in to the sternocleidomastoid muscle and parotid gland; invading infratemporal fossa and indenting prominently middle cerebellar peduncle at the posterior region. Post-Gd MRI showed homogeneously and

densely enhanced tumour mass with salt and paper sign which is highly diagnostic of GT.<sup>16</sup> Figures 3, 4 illustrate pre RT images of the second patient.

Both of the cases were staged Class D2 and Type IV according to Fisch and Glasscock-Jackson

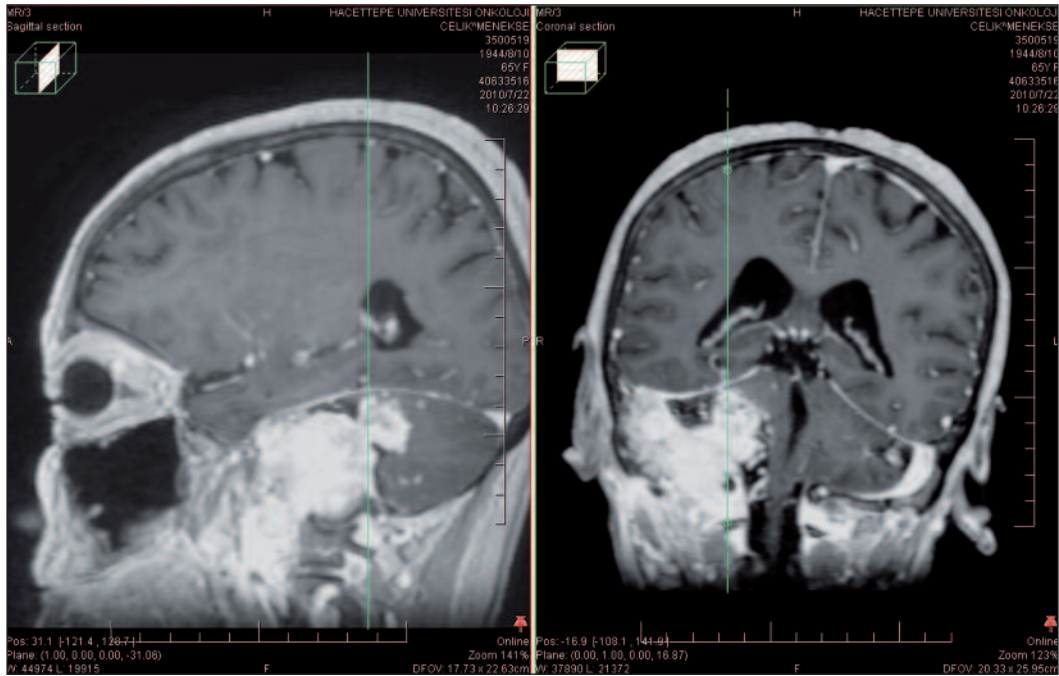


FIGURE 3: Sagittal and coronal T1-weighted MR images with contrast, of the second case.

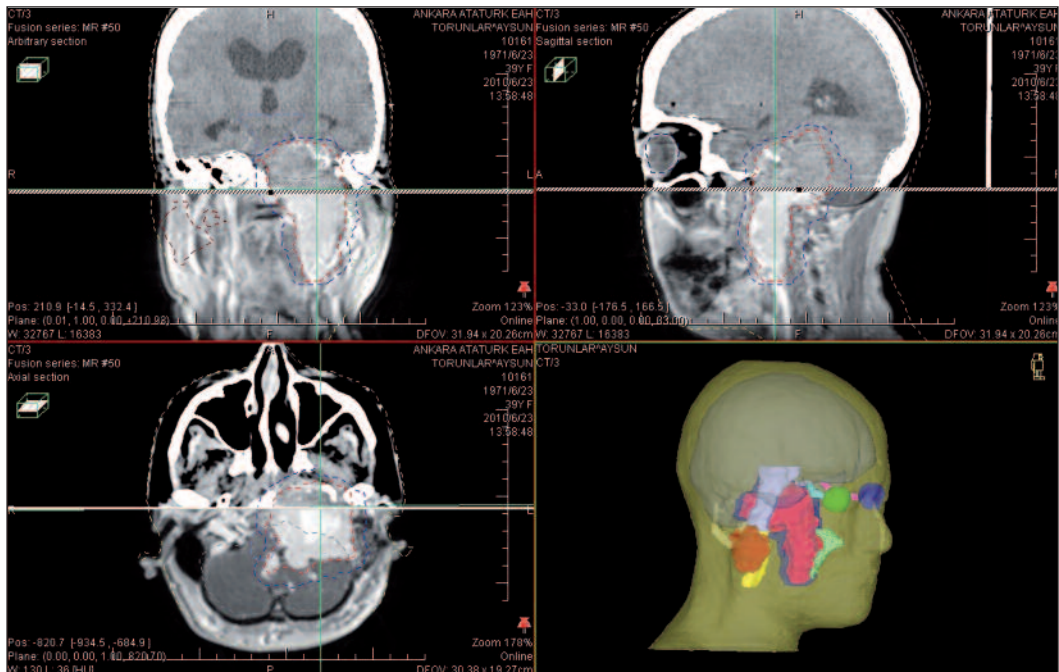


FIGURE 4: Sagittal, coronal, and axial images of CT registered to MR and 3-D image reconstruction, of the second case.

classification of GT respectively. Before RT, the patients were given detailed information about treatment side effects, and informed consent forms were signed.

### RADIATION THERAPY

Helical tomotherapy (HT) (TomoTherapy, Inc., Madison, WI) is a new device and concept for Intensity Modulated Radiotherapy (IMRT) and Image

Guided Radiotherapy (IGRT) of sophisticated RT. The ring gantry-based HT platform combines integrated CT imaging with conformal radiation therapy to deliver complicated radiation treatments with speed and precision while reducing radiation exposure to surrounding healthy tissue. It utilizes hydraulically driven 64-leaf fan beam collimator synchronously with gantry rotation and table movement. Following definition of prescription and constraints, the 32-CPU Optimization Cluster optimizes the weight of the tens of thousands of beamlets used in a typical HT radiation treatment fraction.

Before obtaining computed tomography with and without contrast, patients were immobilized in the supine position by use of standard head-and-neck thermoplastic masks. CT and MRI images both with 3 mm slice thickness were registered. Gross tumour volume and organs at risk (OAR) were outlined on CT slices by using guidance of fused images of contrasted CT and T1 gadolinium-enhanced MRI. A total of 5 mm margin was given to gross tumour volume for obtaining planning target volume (PTV) in the absence of close relation to critical organs such as brain stem and optic chiasm. Margin was re-

duced to 1 mm in case of close proximity to critical organs. PTVs of first and second cases are 190 and 286 cm<sup>3</sup> respectively. Patients underwent planning on a HT treatment-planning system (Tomotherapy Planning Station V3; Tomotherapy Inc.) using of the 2.5 cm collimator setting, with 0.3 pitches and a modulation factor of 2. The prescription dose (100%) was specified such that at least 95% of PTV receives the prescription dose of 54 Gy (D95%>100%). Irradiations were given by guidance of megavoltage tomography imaging in every fractions of treatments for both patients. Axial, sagittal and coronal planes of planning images were illustrated in Figure 5, 6 for both patients. Tumour and sensitive structure constraints were illustrated in Table 1.

## RESULTS

Prescribed doses to the PTV (54 Gy in 1.8 Gy daily fractions) were well tolerated and besides grade II mucositis no other early side effects were observed. In the first case, severe bloody otorrhea and purulent discharge from external ear were seen 1.5 months after completion of RT. It lasted three days and resolved with medical therapies (antibiotics and irrigation) without major surgical intervention.

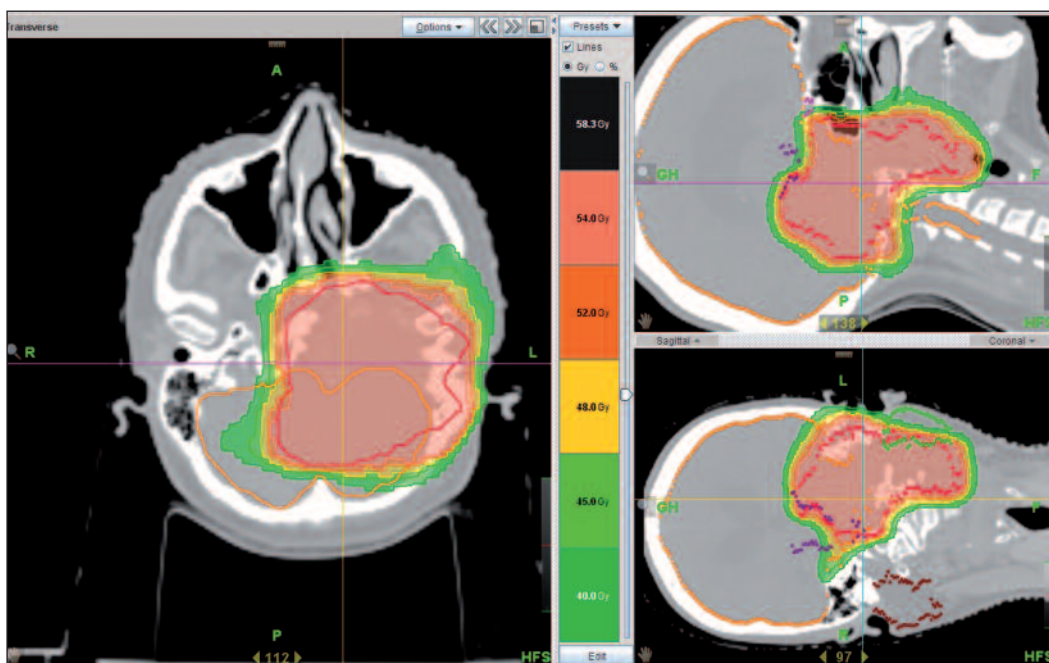


FIGURE 5: Sagittal, coronal, and axial planning images showing dose distribution of the first case.

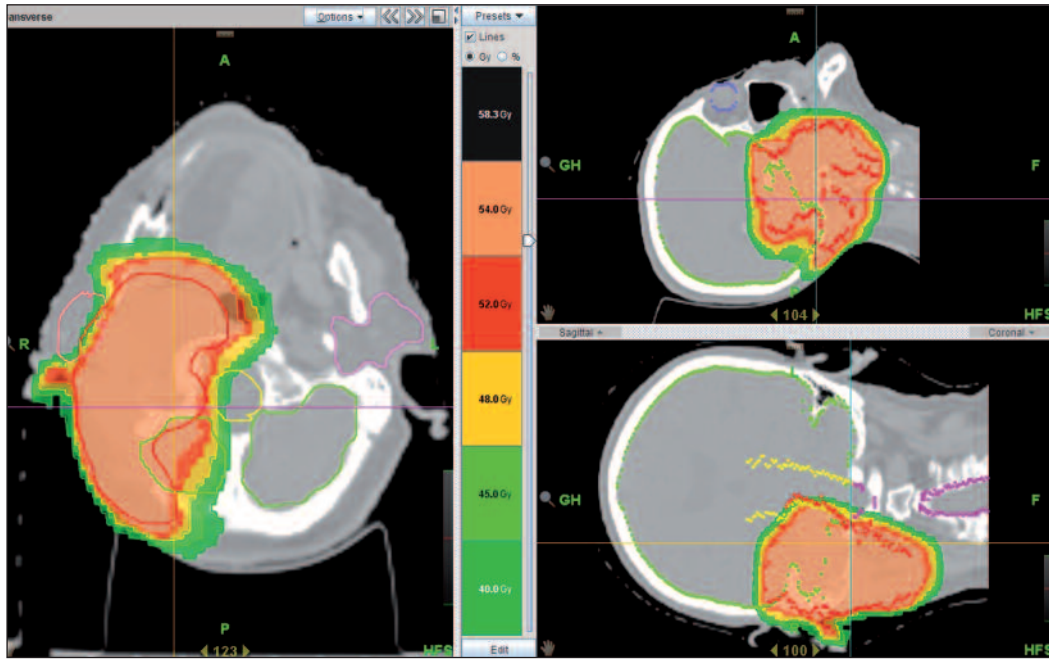


FIGURE 6: Sagittal, coronal, and axial planning images showing dose distribution of the second case.

TABLE 1: Planning target volume (PTV) and critical organ doses.

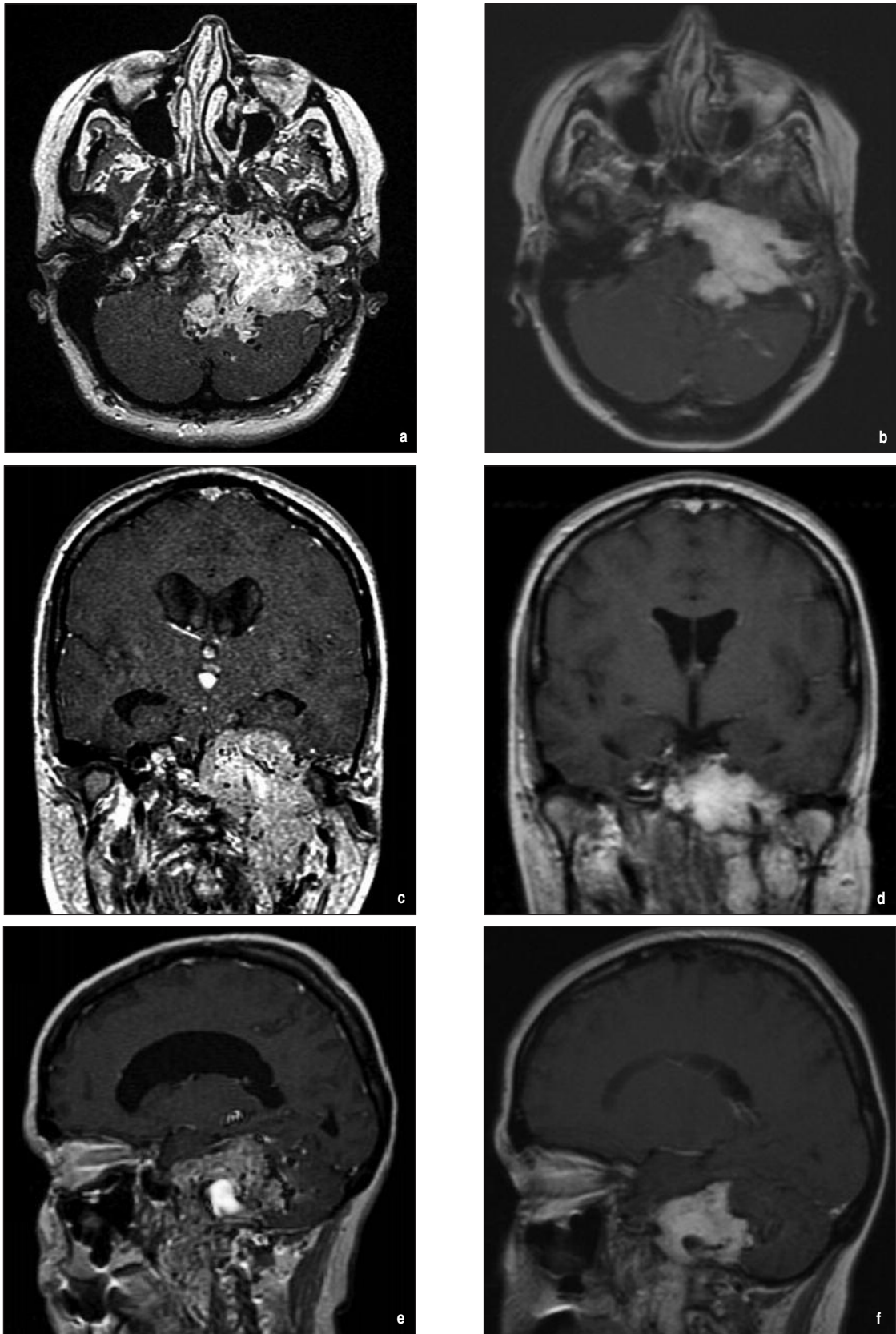
| Name          | First case        |                   |                  | Second case       |                   |                  |
|---------------|-------------------|-------------------|------------------|-------------------|-------------------|------------------|
|               | Maximum Dose (Gy) | Average Dose (Gy) | Median Dose (Gy) | Maximum Dose (Gy) | Average Dose (Gy) | Median Dose (Gy) |
| PTV           | 56                | 54.5              | 54.5             | 61                | 55                | 55               |
| Brain stem    | 56                | 45                | 42               | 56                | 12                | 17               |
| Spinal cord   | 53                | 15                | 19               | 50                | 6                 | 10               |
| Chiasma       | 52                | 42                | 32               | 42                | 20                | 21               |
| Right parotid | 9                 | 2                 | 3                | 56                | 26                | 28               |
| Left parotid  | 55                | 40                | 41               | 22                | 8                 | 8                |

The maximal tumour diameter (98 mm) of the first case decreased to a maximal diameter of 56 mm within 14 months follow up period. Pre and post RT MR images of the first case were illustrated in Figure 7a, b, c. Together with tumour shrinkage, hypoglossal motor function and left facial paralysis improved gradually, diplopia, swallowing problems, unbalance, dizziness, and hoarseness of voice recovered near completely during 28 months follow up period. Symptoms of second case (right shoulder weakness, facial paralysis, ptosis, and hoarseness of voice partially, severe headache, nausea and vomiting completely) recovered at the end of treatment. Un-

fortunately, we lost the second case during follow up. She was dead after 8 months from RT according to the data from the national civil registration bank. Death report explains the cause of death as multi-system organ failure and pulmonary insufficiency.

## DISCUSSION

The treatment of choice for GT remains controversial. In the past, observation (wait and scan), therapeutic embolization, surgery, and RT were all used as primary and secondary options for this lesions.<sup>1-15</sup>



**FIGURE 7:** a,c,e: Axial, coronal and sagittal T1MRI with contrast images obtained just before; and b,d,f: Axial, coronal and sagittal T1 MRI with contrast images obtained just 14 months after the completion of the RT.

## THERAPEUTIC EMBOLIZATION

Therapeutic intra-arterial embolization of vascular lesions was suggested in 1930 by Brooks.<sup>13</sup> It can be used as an adjunct to surgery or as definitive therapy. The aim of intravascular embolization is to occlude the blood vessels of a tumour by using various embolic materials including coils, ethanol, sodium tetradecyl sulphate, cyanoacrylate, polyvinyl alcohol, microspheres, and gelatine sponge. The contraindications to embolization comprise allergy to angiographic contrast medium, and atheroma of the carotid bifurcation, which precludes selective catheterization. After embolization, some transient pain and swelling of the area usually accompanies a slight fever. These symptoms are due to the thrombosis within the embolized vessels, which usually continues seven to fourteen days after the procedure. If surgery is to follow embolization, it should, therefore be carried out within seven to ten days of procedure.<sup>13</sup>

## SURGERY

Because it is the only treatment alternatives that can offer immediate and complete tumour removal, surgery is the preferred treatment modality for operable patients.<sup>1,2,5,6,8,14,15,17,18</sup> Approximately 40% of GT can extend into the cranial cavity and cause lower CN palsies (glomus jugulare syndrome). In such cases, surgery is not an easy task to manage and presents diagnostic and technical problems. Throughout the 1950s, all surgical attempts to remove the jugular bulb tumours via sub occipital route were unsuccessful.<sup>1</sup> The early 1960s brought advances in diagnostic imaging that enabled surgeons to describe and understand tumour extension and anatomy of this region in much more detail which in turn led to better surgical excision techniques.<sup>5,10</sup> In 1965, it was reported that complete tumour resection of four cases, with removal of jugular bulb and translocation of the facial nerve which was the similar procedure performed in 1964 by Shapiro and Neues.<sup>1</sup> There were no major side effects and neurological deficit but minimal haemorrhage. Further interest in and refinement of surgical techniques continued in the next

decade. In 1977, Gardner et al. detailed surgical techniques in which a combined lateral skull base approach was used by a multidisciplinary team. Also in 1977, Fisch introduced the infra-temporal approach to gain complete access to the internal carotid artery within the temporal bone which allowed larger glomus tumours to be treated with increased safety. Fish also added a classification scheme for glomus tumours. Over the next two decades, the importance of team approach was established. In 2002, AL Mefty and Teixeira reported a series of 28 patients whose of 24 (86%) were operated by gross total resection.<sup>1</sup> They have no surgical mortality and only 2 (7%) local recurrences. Complication reported in their study included one patient with hemiplegia which was successively treated with urokinase, four patients with cerebrospinal fluid leaks, and five with infection. Nevertheless, 11 patients with new cranial nerve deficits required tracheostomy and gastrostomy at follow up period.<sup>4,5</sup> The most important contribution to the surgical treatment of GT occurred with the development of preoperative superselective embolization. Superselective angiography with embolization aids in identifying and blocking the feeding arteries, thereby reducing bleeding during surgery.

## STEREOTACTIC RADIOTHERAPY

While new surgical methods made progress, the improvements on new radiosurgical modalities came into daily practice. Frame-based Linac systems were succeeded by sophisticated frameless Cyber Knife radiosurgery. After the mid-1990s, the use of stereotactic radiosurgery (SRS) for GT has grown in popularity.<sup>1,6,7,12,19-26</sup> GT are generally ideal for SRS, because they have well-defined margin and small volumes. The steep dose gradient of SRS minimizes critical organ dose and provides delivery of larger dose to the tumour without exceeding the radiation tolerance of normal tissues. Since SRS takes one or two days, it is more cost-effective than both surgery and conventionally fractionated external-beam radiation. The drawbacks associated with SRS include large tumour size, complete encircling of ICA by tumour, brain stem and cerebel-



lar compression, multiple cranial nerve deficits. Gottfried et al. presents an article including eight SRS series with 142 patients and seven surgical series with 347 patients, which compares SRS with conventional surgery for treatment of GT.<sup>6</sup> The patients were evaluated for neurological outcome, change in tumour size (SRS), or percent of total resection (surgery), recurrences, tumour control, need for further treatment, and complications. The surgical control rate was 92.1% with 88.2% of tumours totally resected in initial surgery. Complication rate was found in 8.3% (cerebrospinal fluid leak) and mortality rate, and recurrence rate were reported 1.3%, 3.1% respectively. Among patients who underwent SRS, tumours diminished in 36.5%, whereas 61.3% had no change in tumour size. Recurrence rate was found in 2.1%, the morbidity rate was 8.5%, and there were no deaths. The authors concluded that although the SRS results are very promising, longer time (10-20 years) incidence of late recurrence is not known. Krych and colleagues reported an article concerning long term results of irradiation for GT.<sup>20</sup> They obtained 92% ten years tumour control rate in 33 patients (25 treated with External Beam Radiotherapy (EBRT), 8 with SRS). With a median follow up of 13 years (range 4 months to 32 years); no patients developed a radiation induced malignancy. Concerning radiation induced malignancy, especially in young people; the risk is to be weighted against the immediate and permanent risk of morbidity from CN deficits due to tumour progression or surgical resection. Lalwani et al noted that the incidence of radiation induced fibrosarcoma is approximately 1 in 1.000 to 2.000.<sup>27</sup>

### IMRT-IGRT BASED RT

The effect of radiation on benign tumours is to make growth retardation in consequence of fibrosis and vascular sclerosis. In a study comparing pre RT and post RT histopathological evaluation of five patients with GT, it was demonstrated that general microscopic pattern of these tumours remained recognizable after RT.<sup>11</sup> "In that study, chief or epitheloid tumour cells persisted after treatment in significant proportions of the patients. But smaller

vessels (less than 100 nm) were fewer in number and replaced by a marked increase in stromal fibrous connective tissue." This uniformly distributed fibrosis was assumed to be the direct result of diminished vascularity secondary to irradiation. IMRT is a form of three-dimensional (3D) conformal radiation therapy (CRT) in which a computer-aided optimization process is used to determine customized non-uniform fluence distributions to attain certain specified dosimetric and clinical objectives. Contrary to old RT techniques which are not able to spare critical organs from high dose regions, IMRT-IGRT provides conformal dose distribution with precision and reduces radiation exposure to sensitive areas of surrounding tissue. In this regard, imaging is obviously the most important helpful tool for delineation of target volume and precise contouring. While CT better demonstrate subtle osseous changes of the skull base and the relation of the tumour to the middle ear structures, MRI better delineate the relation of the tumour to the adjacent internal jugular vein and carotid artery.<sup>4,10,16</sup> In addition, paragangliomas which are greater than two cm in maximal diameter have a characteristic "salt and paper" MR appearance.<sup>4,16</sup> It is based on serpiginous areas of signal void representing high vascular flow among tumour cells. Giant GT which have multiple lower cranial nerve involvement and brain stem compression present many challenging problems. In one hand, several surgical attempts can bring about many complications including lower cranial nerve paralysis, aspiration pneumonia, and cerebrospinal fluid leakage. On the other hand, large surgical defects necessitate complex reconstruction with vascularized muscle flaps. The size of the lesion is directly related to the complication rate. Total resection of benign GT with large extra cranial extension may be impossible or associated with sacrificing of still functioning involved cranial nerves.<sup>28-31</sup>

Tumour volumes and doses treated by Gamma Knife Surgery (GKS) generally ranges from 1 to 25 cm<sup>3</sup> and 14 to 20 Gy in one fraction respectively.<sup>12</sup> Giant GT with brain stem com-

pression and multiple CN involvement pose risks and danger with single fraction radiosurgery. The rationale for fractionation of radio surgery is the same as that for conventional radiation. In this respect, fundamental radio biological principles are valid for large tumours of fractionated RT. FSR which is possible in linac based systems and Cyber Knife SRS have also volume restrictions. In literature, GT treated with FRS have a mean size of 3 cm and a largest measurable diameter of 6 cm.<sup>21-23</sup> Furthermore, SRS require clean-cut line of demarcation between tumour and cranial nerves that is not always manageable with the current imaging modalities.

After partial resection, patients should be monitored by MRI imaging in frequent intervals because it is vital to become aware of early recurrences. In this respect dynamic MRI may be useful to differentiate residual tumour from radiation fibrosis. In case of recurrence, IG-IMRT

should be applied before aggressiveness of the disease. Our two cases were partially operated and followed up by imaging. In this observing period the tumour reached enormous sizes and disrupted severely the functional capacity of the patients. They were accepted incurable by many physicians and RT was not offered as a therapeutic option. In this article we want to emphasize the value of post-operative RT in partially resected GT. Pemberton et al. reported a 92% recurrence-free and 96% cancer-specific survival rates of GT after EBRT.<sup>25</sup>

## CONCLUSION

While surgery and stereotactic radiosurgery are good treatment alternatives to each other in the early stage GT, IMRT-IGRT with conventional fractionation seems the only friendly solution for giant GT which have intracranial extensions, multiple CN involvement and brain stem compression.

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