Evolving Concepts in the Management of Jugular Paraganglioma: A Comparison of Radiotherapy and Surgery in 88 Cases

Patrice Tran Ba Huy, M.D.,[1] Romain Kania, M.D.,[1] Michèle Duet, M.D.,[2] Bernadette Dessard-Diana, M.D.,[3] Jean-Jacques Mazeron, M.D.,[3] and Rania Benhamed, M.D.[1]

ABSTRACT

Surgery for jugular paraganglioma (PGL) tumors often results in the acquisition of neurological deficits where none had been present previously. This has a significant impact on the quality of life. Radiotherapy is a recognized alternative therapy. The aim of this study was to compare the results of radiotherapy and surgery for the management of jugular PGL in terms of function and tumor control to define a treatment algorithm. We conducted a retrospective and comparative analysis of the treatment of 41 patients by conventional radiotherapy and 47 patients by surgery via tertiary referral at an academic medical center. Forty-seven patients with type C and/or D jugular PGLs (mean age, 46 years) underwent surgery after endovascular embolization between 1984 and 1998 using an infratemporal fossa type A approach. The facial nerve was transposed in 18 patients. An adjunctive neurosurgical procedure was required in 14 patients. Mean follow-up was 66 months (range, 17 months to 14 years). Forty-one patients with type C jugular PGLs (mean age, 59.5 years) were treated by external beam or conformational radiotherapy between 1988 and 2003 with a total mean dose of 45 Gy (range, 44 to 50 Gy). Mean follow-up was 50 months (range, 18 months to 13 years). The primary outcome measures were tumor control and cranial nerve status. Surgical resection, total or subtotal, yielded an overall 86% rate of either cure or tumor stabilization. Radiotherapy achieved local control in 96% of patients. For surgery, the main postoperative complications were dysphagia, aspiration, and facial paralysis. Patients treated by radiotherapy developed minor disabilities. We concluded that radiotherapy and surgery achieve similar oncologic outcomes, but the former achieves tumor control with less morbidity. Our data favor radiotherapy as treatment for jugular PGLs, but we acknowledge that the aims of these two treatment modalities are different, namely, eradication of tumor by surgery versus stabilization of tumor with radiotherapy. The search for the better quality of life has to be weighed against the uncertainty of the long-term behavior of the tumor.

KEYWORDS: Jugular paraganglioma, surgery, radiotherapy

[1]Hôpital Lariboisière, Service ORL; [2]Hôpital Lariboisière, Service de Médecine nucléaire, Université Paris 7, Paris, France; [3]Hôpital Pitié-Salpêtrière, Service de Radiothérapie, Université Paris 5, Paris, France.

Address for correspondence and reprint requests: Patrice Tran Ba Huy, M.D., Service ORL, Hôpital Lariboisière, 2, rue Ambroise Paré, 75010 Paris, France (e-mail: patrice.tran-ba-huy@lrb.aphp.fr).

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Remarkable advances have been made over the past 20 years in embolization, nerve monitoring, and surgical techniques. These have improved the ability of the surgeon to remove paragangliomas (PGLs) arising in the jugular foramen that extend into the temporal bone or into the posterior fossa.[1–6] Total resection of these tumors risks significant neurological deficits because of their vascular nature, deep-seated location, and proximity to important neurovascular structures. Some consider these risks unacceptable, bearing in mind the benign nature of these tumors and the fact that for many there is no preoperative neurological abnormality. The potential acquisition of a significant disability, along with an ever-increasing concern for quality of life, has rendered radiotherapy an attractive alternative treatment. Indeed, an increasing number of reports have emphasized the effectiveness of radiotherapy in controlling tumor growth while minimizing permanent disability.[7–9] In this article, we compare oncologic and functional results in a series of 41 patients with jugular PGLs treated with radiotherapy between 1988 and 2003 and those of a previously published series of 47 patients treated with surgery between 1984 and 1998.[10] We discuss parameters that should be considered when making the decision for surgery or radiotherapy and define indications for management protocols currently advocated, namely, wait and scan, surgery, radiotherapy, or a combination of treatments.

PATIENTS AND METHODS

Surgical Group

The surgical group consisted of 47 patients (mean age, 46 years; range, 18 to 73 years). The 28 women and 19 men had type C and/or D jugular PGLs, according to Fisch's classification,[1] and underwent surgery between January 1984 and October 1998. Ten patients had multiple vagal or carotid body PGLs. The time interval between onset of the first symptom and diagnosis ranged from 5 months to 8 years (mean, 17 months). Five had preoperative incomplete or complete facial paralysis, and four had increased catecholamine levels with symptomatic hypertension.

Table 1 Clinical Symptoms and Signs at Presentation of Patients Undergoing Surgery and Radiotherapy for Jugular Paragangliomas

	Surgical Series ($n=47$)	Radiotherapy Series ($n=41$)
Tinnitus	62%	76%
Hearing loss	78%	61%
Cervical mass		15%
Retrotympanic mass		73%
Dizziness	27%	32%
VII paralysis	11%	17%
IX and X paralysis	40%	49%
XI paralysis	26%	12%
XII paralysis	32%	17%

All patients underwent endovascular embolization 2 to 4 days before surgery. For 18 patients, an infratemporal fossa type A approach, as described by Fisch,[1] was employed. The facial nerve was sacrificed in five patients because of extensive tumor infiltration. In the remaining 24 patients, the facial nerve was not transposed. In 19 patients, the cochlea was sacrificed either because of tumor invasion ($n=13$) or to gain access to tumor medial to the internal carotid artery ($n=6$). Resection of tumor from the posterior fossa was necessary in 14 patients and undertaken by neurosurgical colleagues. Follow-up examination consisted of contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI) performed annually for the first 2 years after surgery and, when possible, at 3 years, 5 years, and even longer after surgery. The clinical features and outcomes of patients treated by surgery were previously published[10] and are listed in Table 1.

Radiotherapy Group

The radiotherapy group consisted of 41 patients with 45 jugular PGLs (mean age, 59.5 years; range, 28 to 81 years). The 34 women and 7 men were treated between May 1988 and March 2003. Four

patients had bilateral jugular tumors. All had type C tumors, and none had posterior fossa extension. Three patients had a family history of PGL. Eleven patients had multiple tumors, bilateral vagal ($n = 8$) or carotid body ($n = 3$) PGLs. The clinical symptoms of this cohort of patients are listed in Table 1. The mean time between the onset of the first symptom to diagnosis was 20 months (range, 3 months to 10 years). Our indications for radiotherapy as primary treatment included the following, sometimes multiple, reasons: advanced age (older than 65 years) in 18 patients, unresectable or bilateral PGLs in 14, contralateral lower cranial nerve paralysis in 12, and the patient's choice in 8.

Up until 1995, patients were treated with two-dimensional (2-D) conventional radiotherapy using two laterally opposed beams. Since 1995, conformal radiotherapy has been used with MRI to delineate the gross tumor volume. The mean total dose was 45 Gy (range, 44 to 50 Gy), delivered in 1.8-Gy fractions 5 days per week for 5 weeks. Mean follow-up was 50 months (range, 18 months to 13 years). As in the surgical group, follow-up consisted of contrast-enhanced CT and/or MRI performed annually during the first 2 years following treatment and, when possible, at 3, 5, and more years subsequently.

RESULTS

Tumor Control

SURGICAL GROUP

Total resection of PGL was achieved in 33 patients (70%). Eight patients were lost to follow-up within 2 years. A total of 23 patients showed no clinical or radiologic evidence of tumor at a mean follow-up of 66 months—a cure rate of 92% in patients available for follow-up ($n = 25$). Two patients are being followed clinically and radiologically without additional treatment because of asymptomatic and slow-growing recurrent tumor.

Subtotal resection, defined as coagulated remnants < 1 cm, was achieved in 14 patients (30%). Eight patients have been shown to have either stable or shrinking residual tumor load as assessed radiologically after a mean period of 66 months (range, 17 months to 14 years)—a tumor control rate of 73% in patients available for follow-up ($n = 11$). Three patients developed a recurrence. Two of the patients with recurrent tumors were treated with radiotherapy and the other by surgery. Three patients were lost to follow-up: one returned to his country; two others died, one from intraoperative displacement of a balloon in the ICA and the other from HIV acquired as a result of an infected blood transfusion.

In summary, total or subtotal surgical resection resulted in an 86% rate of either cure or tumor remnant stabilization in patients available for follow-up (31 of 36). Oncologic results of this group are listed in Table 2.

RADIOTHERAPY GROUP

Repeated MRI or CT scans at 18 months to 13 years showed a complete response in just one patient. Partial response (tumor reduction of $> 20\%$) was achieved in 11 patients, and no further growth was documented in 31 patients. In two cases, the tumor continued to grow and required resection. Thus, local control was achieved in 96%

Table 2 Oncologic Results

	Surgery Group		Radiotherapy Group (45 tumors in 41 patients)
	Total Resection ($n = 33$)	**Subtotal Resection ($n = 14$)**	
Oncologic Results	Tumor free ($n = 23$)	Stable or regressive tumor ($n = 8$)	Complete response ($n = 1$)
	Slow growing recurrence ($n = 2$)	Recurrence ($n = 3$)	Partial regression ($n = 11$)
	Lost for follow-up ($n = 8$)	Lost for follow-up ($n = 3$)	Stability ($n = 31$)
			Tumor growth ($n = 2$)

of tumors. Oncologic results of this group are listed in Table 2.

Cranial Nerve Function

SURGICAL GROUP

After transposition of the facial nerve in 18 patients, 10 (56%) developed facial paralysis (House-Brackmann [HB] grade V or VI) as assessed 1 month after surgery. At 1 year after surgery, six patients recovered to a grade of III or IV weakness (60%). The facial nerve was not transposed in 24 patients. One month after surgery, 20 of these patients had grade I or II facial nerve function, and 4 (16%) had grade V or VI weakness. A year later, two patients (8%) still had a grade III or IV weakness. Thus, the overall incidence of long-term facial sequelae for both groups was 33% (6 of 18).

Four patients had significant aspiration, developed pneumonia, and required a tracheostomy. All of these patients had intracranial tumor extension and had required a combined otologic and neurosurgical approach. They all recovered within 2 to 4 months. Thyroplasty to medialize the paralyzed vocal cord was performed in two of these patients and in seven others to improve quality of voice. Functional vocal results were satisfactory in four cases, moderate in three, and poor in the other two patients. Some patients experienced swallowing problems, which subsided over a few weeks without any need for a complementary surgical procedure.

Seven patients with type D jugular PGL experienced cerebrospinal (CSF) fluid leakage through the skin incision. In two instances, CSF leaked through the tracheostomy. Meningitis developed in five patients and all recovered.

RADIOTHERAPY GROUP

Clinical symptoms such as tinnitus and dizziness were improved in 52% of patients. Paralysis of the VII and X nerves regressed in 16% of patients. Acute side effects were mucositis in 20% and nausea in 20%. Late side effects were xerostomia in 34%, serous otitis media in 4%, and vertigo in 4%. One patient became hemiplegic 6 years after radiotherapy as a result of stenosis of the cervical carotid artery, but this subsided within a few weeks.

DISCUSSION

Treatment of jugular PGL remains controversial. Surgery has been considered the treatment of choice for a long time because it was the only way to destroy and remove the tumor completely, a potential cure. Radiotherapy had usually been offered to elderly patients who presented with comorbidities. In recent years, this strategy has been questioned and now the results of both modalities are under critical review.[11–13] Clearly, the functional consequences of postoperative complications had to be more carefully considered, bearing in mind the benign nature of the tumor. The present study confirms this view and has been instrumental in guiding our management decisions.

A properly conducted, robust clinical trial of therapies would seem to be impossible for several reasons. The main reasons for this are the difficulty of acquiring sufficient numbers of similar patients within a reasonable period of time at any one center for treatment and prolonged follow-up that may last 10 to 15 years. Therefore, retrospective studies must be considered a valid means of conducting a risk-benefit assessment of the two therapeutic strategies. We recognize that a strict comparison between our two groups is also difficult for two main reasons. First, the patients in the two groups were not similar: the surgical series included 29% of cases with extension to the posterior fossa, and it included younger patients than those in the radiotherapy group. Second, the criteria of success differed: surgery aimed to eradicate the tumor completely, whereas radiotherapy aimed to prevent further growth or reduce the tumor load.

From an oncologic standpoint, surgery achieved an overall tumor cure of 86%, whereas primary irradiation yielded a 96% tumor control.

Although these figures appear to be similar, they cannot be interpreted the same way. Patients were tumor free in the surgical group, whereas in the radiotherapy group they still had tumor—tumor that, to maintain their health, had to remain stable for the rest of their lives. However, the functional results differed between the two groups. Even if we ignore our patient who became hemiplegic after embolization and those with CSF leaks after resection of intracranial tumor, surgical resection still caused significant morbidity—morbidity previously experienced by others as well.[14–16] Eleven patients (23%) experienced severe aspiration, pneumonia, and/or marked dysphonia or swallowing problems. These complications were not only observed in patients who did not have preoperative neurological deficits, they also affected those who had preexisting lower cranial nerve palsies (i.e., patients who should have compensated for their handicaps).[16] Despite various procedures such as vocal fold injection, thyroplasty, and speech and language rehabilitative measures, which should diminish the debilitating consequences of these paralyses, swallowing disorders persist for extended periods of time. There is no doubt that dysphagia is a significant postoperative problem, especially in elderly patients.[17]

The other major complication of surgery was facial paralysis caused by facial transposition. Unquestionably, rerouting the facial nerve aids direct surgical exposure to the jugular foramen. It facilitates the removal of the PGL but carries an inescapable risk of facial paralysis. At 1 year postoperatively, we found 33% incidence of HB grades III and IV, which is close to the 27% of patients with HB grades III and IV reported by Selesnick et al in their survey of anterior transposition.[18] Briner and colleagues were able to preserve normal facial function in 80% of patients, leaving 20% with long-term impairment.[17] These results have been achieved only by highly experienced surgeons and suggest that severe facial paralysis is probably more frequent in less experienced hands. Accordingly, facial mobilization should be avoided as much as possible.

Unquestionably, radiotherapy yields a lower rate of complications. The hemiplegia secondary to radiostenosis of the cervical carotid artery was most probably due to outdated techniques. Other secondary effects could be considered minor. Xerostomia was observed only with 2-D conventional radiotherapy. We did not encounter side effects such as radionecrosis of the temporal bone, brainstem injury, or secondary malignancy.[19–21] Of significance is that paralyses of the VII and X nerves regressed or recovered in 16%.

In our series, we used a radiotherapy dosage of 45 Gy, which is similar to the dosage currently reported in the literature.[7,9,22] Advances in radiotherapeutic techniques are continually being made. Conformational radiotherapy spares the contralateral ear and the parotid glands. More recently, gamma knife or linear accelerator (LINAC) systems, which deliver a single, high dose (~13 Gy) of stereotactically guided beams on a specific well-defined target, have provided significant advantages in reducing the time of treatment and limiting the exposure of adjacent cerebral and cranial nerves. Other indirect benefits include reductions in medical costs, loss of work, travel, and housing expenses.[23–29]

Finally, our results compare well with those reported in the literature. The best surgical series report tumor control rates of ~90% with permanent disability of up to 10%,[6,30] whereas radiotherapy may achieve a 90 to 100% tumor control rate with a very low incidence of minor complications.[22,26] Our results were 86% tumor control for surgically treated patients and 96% for those treated radiologically.

The selection of the most appropriate form of therapy should rely on factors related to the patient and the tumor.

1. Age of the Patient

In "young" patients, surgery should be proposed, whereas radiotherapy or watchful waiting should be

considered for "older" patients. This current opinion relies on the following arguments:

- Young patients usually have no medical factors contraindicating aggressive surgery and cope more easily with postoperative neurological deficits, especially the loss of lower cranial nerves.
- In cases of tumor recurrence, secondary irradiation seems efficient,[31] whereas salvage surgery is technically difficult in irradiated tissue.
- Radiotherapy may stabilize the tumor growth for 10 to 15 years. Thus, the older the patient, the lower the risk of recurrence.
- Similarly, the risk of radiotherapy-induced malignancy,[7,20,21] if any, does not occur until years after the completion of irradiation. During such a period, older patients may be affected by other conditions.

The question remaining, however, is how to determine the criterion age, in other words, what defines young and old patients.

2. Natural History and Growth Rate

Most PGLs have a very slow growth rate. During a mean follow-up period of 4.2 years, Jansen et al observed an increase of $>20\%$, on average, in only 60% of head and neck PGLs with, in 60%, a median growth rate of 1.0 mm/y and a median tumor doubling time of 4.2 years.[32] Jugular PGLs in this series had an even longer doubling time. Such statistics resemble those found in vestibular schwannoma and give support to a "wait and scan" policy as the primary option in asymptomatic patients, thus allowing for a distinction between growing and nongrowing tumors. However, with increasing life span expectancy, even a slowly growing tumor left untreated in a young patient may progress in the long term and cause cranial nerve and brainstem injury. Furthermore, some jugular PGLs seem to be more aggressive. In our experience, patients younger than 20 years of age present with C3-De tumors, which suggests a much higher growth rate and possible malignancy.

3. Presence of Symptoms

There is little doubt that symptomatic patients should be treated. Preoperative neurological deficits make the surgical decision easier, as treatment is unlikely to add to the patient's handicap. However, adopting a conservative attitude in asymptomatic patients seems reasonable. A typical example is a PGL detected through genetic counseling and screening for carriers in families with PGL.[33–35] In those circumstances, resection of small asymptomatic tumors before they induce nerve paralysis seems advisable.

Symptoms related to secretion of catecholamines are rare and require careful screening for possible sites of active PGL.[2] Resection of these tumors is indicated but care has to be taken during embolization, anesthesia, and surgical manipulations because hypertensive crises may happen. Despite careful medical preparation, this can be a frightening situation. We had to abandon surgery once because of it in a young patient with a C3 tumor who was later treated by radiotherapy.

4. Tumor Size and Extent of Disease

For small tumor types B or C1, surgery should be advocated if it carries an acceptable risk of complications. Similarly, surgery should be proposed for "complex" PGLs: (1) those with massive intracranial or petroclival extension with mass effect on the brainstem, (2) that have previously been treated with radiotherapy, (3) that are possibly malignant, or (4) that are too large for safe irradiation.[2] In these instances, treatment with subtotal resection can often be followed by radiotherapy. Multicentricity is known to occur in $\sim$30% of cases, especially in familial forms. In those instances, the presence or the possible further occurrence of cervical and/or extracervical localizations should always be considered. Ipsilateral vagal or carotid body PGLs increase the risk of postoperative cranial nerve deficits. Bilateral tumors may represent a contraindication

to surgery because bilateral paralysis of the lower cranial nerves result in permanent and severe disabilities, including disorders resulting from tracheotomy as well as aspiration, speech, and swallowing problems. However, it may be sensible to remove the smaller tumor first to establish one functional vagus and hypoglossal nerve. A careful evaluation of the disease is mandatory before any therapeutic decision.

5. Patient Consent

Sometimes, patients are unwilling or are not able to undergo surgery, whereas others are not able to cope with the idea of radiotherapy, which leaves them with a tumor, even if it is stable. In general, patients are demanding less invasive methods of treatment more and more. In providing information about the above-mentioned benefits and risks, the physician should be aware that most patients are now self-informed—if not overinformed—through the Internet. The goals of surgery and radiotherapy differ and must be explained carefully.

TENTATIVE TREATMENT ALGORITHM

The treatment of jugular PGL should always be tailored to each individual patient. However, the following four strategies can be proposed.

1. Wait and Scan Policy

An indisputable indication for this strategy would be an asymptomatic PGL developing within the jugular foramen or, in an elderly patient, extending slightly beyond.[36] The slow annual growth rate and the exceptional accuracy of MRI in detecting volume increase favor such a choice. The same indication seems legitimate for young relatives of affected patients who present with a small tumor. In both instances, regular imaging and examination are absolutely mandatory so that either surgery or radiotherapy can be suggested if the tumor size increases.

2. Surgery

It is reasonable to propose surgery for one or more of the following indications: (1) young age (perhaps younger than 45 years of age), (2) preoperative neurological deficits including paralysis of the facial or lower cranial nerves, (3) a respectable tumor that has a low risk of complications, (4) intracranial extension of PGL, (5) unilateral PGL occasionally associated with an ipsilateral vagal or carotid body tumor, (6) evolving and aggressive PGL as demonstrated by successive imaging or bone erosion with risk of cranial nerve deficits, (7) major petroclival extension with encasement of the internal carotid artery and a well-tolerated balloon occlusion test, and (8) tumor recurrence after irradiation.

3. Radiotherapy

The indications for radiotherapy as a primary treatment are: (1) age older than 60 years, (2) surgical contraindications including medical or personal reasons, (3) unresectable and bilateral large tumors, (4) major vascular risk as seen by a failed balloon occlusion test or unique venous outflow, and (5) absence of neurological deficits.

4. Combined Radiosurgical Approach

An approach that combines surgery and radiotherapy deserves to be discussed in some instances. For example, when a patient who is suitable for surgery presents with a large tumor, with no neurological deficits, and is not prepared to accept any postoperative disability. Here, a planned combination of subtotal surgical resection followed by radiotherapy seems attractive.[37] This may be difficult for the surgeon, who has to achieve a reduction in tumor

mass without inflicting a handicap. Radiotherapy may then be undertaken systematically after surgery or if the tumor remnant regrows.

CONCLUSIONS

Over time, the management of jugular PGLs has evolved. Increasing concern about the quality of life has emphasized the need for a thorough evaluation and discussion of the respective risk-benefits of the two main therapeutic options. Although our data favor irradiation, the goals of surgery and radiotherapy are not the same (i.e., definitive surgical eradication and cure of the tumor versus stabilization of the irradiated tumor). Long-term follow-up is needed to clarify this issue.

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