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Review

Radiotherapy for glomus jugulare paraganglioma

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ABSTRACT

Surgery has been long considered to be the treatment of choice for glomus jugulare paragangliomas, as it is the only modality able to totally eradicate the tumour. However, despite considerable progress in interventional radiology and nerve monitoring, surgery is associated with an unacceptably high complication rate for a benign tumour, explaining the growing place of radiotherapy in the management of these tumours. This review of the literature confirms the efficacy of conformal radiotherapy with or without intensity modulation and stereotactic radiotherapy, which both achieve tumour control rates ranging from 90% to almost 100% of cases, but for different tumour volumes, almost constant stabilization or even improvement of symptoms, and a considerably lower rate of adverse effects than with surgery. However, radiotherapy remains contraindicated in the presence of intracranial invasion or extensive osteomyelitis. In the light of these results, together with the improved quality of life and a better knowledge of the natural history of this disease, many authors propose radiotherapy as first-line treatment for all glomus jugulare paragangliomas regardless of their size, particularly in patients with no preoperative deficits.

For a long time, radiotherapy was the only treatment option available to otorhinolaryngologists to try to control glomus jugulare paragangliomas [1,2]. The complex anatomy of the region and the limited surgical techniques available discouraged a more hazardous approach, especially surgical resection of this highly haemorrhagic tumour [3,4].

However, from the 1980s onwards, the development of microsurgical techniques combined with progress in morphological interventional radiology and electrophysiological monitoring allowed surgical resection preceded by embolization to become the treatment of choice [5].

Nevertheless, the surgical iatrogenic effects frequently observed, which are increasingly unacceptable for a benign tumour, the growing importance of quality of life, the better knowledge of the natural history of the tumour and improvement of techniques and introduction of new irradiation modalities explain why radiotherapy now, once again, constitutes an essential treatment option [6,7].

This article presents a review of the literature concerning the current place of radiotherapy in the management of glomus jugulare paraganglioma.

1. Various radiotherapy modalities

1.1. Conventional external beam radiotherapy

Conventional external beam radiotherapy delivering photons emitted by Cobalt 60 at doses of 45–55 Gy in 20–25 sessions constituted the reference modality for a long time. However, it is associated with a risk of certain complications, such as temporal osteoradionecrosis, cranial nerve palsy, or even second tumour. It has now been replaced by two other techniques [8,9].

1.2. Conformal radiotherapy with or without intensity modulation

Initially two-dimensional irradiation (based on standard radiography) has become three-dimensional or conformal. By basing irradiation fields on CT and MRI data, conformal radiotherapy allows the intensity of the irradiation delivered to be adapted to the shape and size of the tumour.

Intensity-modulated conformal radiotherapy (IMRT) was introduced in 1995, allowing intensity of irradiation to be adapted to the shape and size of the tumour by means of mobile multi-leaf collimators. As a result of precise tumour delineation, irradiation is modulated in terms of time and dose: high dose to the tumour (2 to 2.2 Gy/session), lower doses to tumour margins (1.6 Gy/session), and theoretically very low doses to healthy tissues.

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The conformation and homogeneity of the doses delivered by IMRT are further improved by tomotherapy: a medium-energy accelerator is connected to the CT scan gantry and revolves around the table, which is displaced longitudinally. Helical irradiation is therefore adapted to the target volume in real time.

1.2.1. Recommended doses

The dose necessary and sufficient to control this slowly growing, benign tumour appears between 40 and 50 Gy [10,11] administered in 25 fractions, 5 days a week, for an average of 35 days. This dose avoids toxic effects, especially temporal necrosis and osteoradionecrosis, while ensuring satisfactory local control (see below). This dose schedule therefore constitutes an efficacy-safety compromise: relapses are observed at doses less than 40 Gy [12], while at doses higher than 50 Gy, the relapse rate is not lower than that observed at radiation doses between 40 and 50 Gy.

1.3. Stereotactic radiotherapy

1.3.1. Principle

Stereotactic radiotherapy consists of delivering radiation by using mini-beams converging onto the tumour target. In practice, photons are delivered to the tumour precisely delineated by CT and MRI image fusion [13]. Stereotactic radiotherapy therefore only irradiates the tumour volume and stops its biological activity. The dose delivered, initially about 50 Gy, has now been decreased to 12–14 Gy to avoid damage to adjacent tissues. This dose is delivered in a single session. However, recent studies suggest the advantages of dose fractionation [14]. Precision at the target is about 0.25 mm and this modality appears to be very effective on the tumour blood supply.

1.3.2. Types of equipment

Three types of equipment can be used:

- Gamma Unit or Gamma Knife uses gamma radiation of photons emitted from the nucleus of the Cobalt 60 atom and projected by a comb-line arrangement of 201 sources distributed in 5 crowns around a steel hemisphere inside a primary collimator that directs the radiation to the centre. A rigid metallic frame is fixed to the patient's head under local anaesthesia to prevent any head movements. Treatment lasts 30 to 90 minutes;
- the LINAC is a linear particle accelerator producing X photons used according to kinetic radiotherapy. This conformal radiotherapy adapts the irradiated volume to the tumour volume by modulating the direction of the beams and by means of a multileaf collimator that modulates the dose rate delivered by each beam;
- the CyberKnife® is a miniaturized version of the LINAC attached to an industrial robot with 6 axes of mobility. Combining highly flexible targeting and beam orientation, it can be used to detect, track and correct real time displacements of the tumour and the patient's movements during treatment with an accuracy of less than one millimetre. In contrast with the Gamma Knife, the CyberKnife system does not use a stereotactic frame but two X-ray cameras.

The radiation source can therefore be either single (LINAC or Cyberknife) or multiple (Gamma knife), with either single (Gamma knife or LINAC) or fractionated dose delivery (LINAC and Cyberknife).

1.3.3. Advantages and limitations

The advantages of stereotactic radiotherapy are:

- sparing of healthy tissues by means of perfect conformation of the radiation onto a well defined target, stabilized by a specific contention system;
- it can be used after failure of normofractionated radiotherapy;
- the patient is immobilized for only one session and therefore only 1- to 2-day hospitalisation is required.

The patient can therefore rapidly return home and can return to work the following week. In terms of economic impact (duration of immobilization, hospital expenses, sick leave, etc.), this technique is also 25 to 30% less expensive than a neurosurgical procedure [15].

Its limitations are:

- it can only be used to irradiate a small tumour volume and is therefore reserved for small paragangliomas;
- it can only be applied to intracranial paragangliomas, i.e. arising in a region that can be easily repositioned from one session to the next and which can be immobilized, although the Cyberknife overcomes this limitation.

2. Tumour control

The efficacy of radiotherapy is defined not by disappearance of the tumour, but by tumour control, i.e. stabilization and absence of recurrence of symptoms and absence of tumour growth and radiological signs of progression [16]. This definition is now widely accepted and the published results all appear to be concordant, regardless of the technique used.

2.1. Conventional radiotherapy

All studies published since the 1970s have reported tumour control rates close to 90% [12,16–25]. In his doctorate thesis, Dupin reported a 5-year local control rate of 97% and a 10-year local control rate of 94%, i.e. better results than those obtained with surgery [24]. He also suggested that advanced age and large tumour volume appeared to constitute risk factors for failure of radiotherapy, in which case the tumour could be treated by salvage surgery.

2.2. Stereotactic radiotherapy

Most recent data of the literature show that Gamma Knife, LINAC and/or Cyberknife achieve very good tumour and symptom control rates, ranging from 71% to 100% and 88% to 100%, respectively, with much lower morbidity than with surgery [26–33]. Several transient adverse effects have been reported, such as facial paralysis and headache. In contrast, pulsatile tinnitus and deafness generally remain unchanged. However, this stereotactic irradiation modality only concerns residual paragangliomas less than 3 cm in diameter or that have relapsed after surgery. Fractionated irradiation delivering low doses in 30 sessions equivalent to a single dose of 15–16 Gy also appears to be an interesting option for inoperable giant paraganglioma [14].

3. Functional results

Functional results are difficult to assess in view of the wide range of symptoms and the heterogeneous methodologies of the studies evaluating these results. However, regression of signs of nerve paralysis (dysphonia, swallowing disorders or even facial paralysis) are observed in about 20% of cases.

4. Adverse effects

The introduction of intensity-modulated conformal radiotherapy (IMRT) that adapts the intensity delivered to the shape and size of the tumour has markedly decreased iatrogenic effects [22,26] without affecting tumour control rates in practically all series published to date.

Acute toxicity symptoms are frequently observed, such as nausea, weight loss or mucositis, which may require interruption of treatment or even hospitalisation [24].

Long-term adverse effects are dominated by xerostomia with dysphagia, ear problems such as serous otitis media or external otitis and stenosis of the external auditory canal, and more rarely neurological disorders such as headache, ageusia or transient glossopharyngeal, vagus, and accessory nerve paralysis with swallowing disorders, aspiration or dysphonia. Other complications are very rare: temporal osteoradionecrosis, cerebral radiation necrosis or vascular disorders such as labile blood pressure or, more serious, carotid artery stenosis with resolving or permanent hemiplegia.

Paradoxically, stereotactic radiotherapy is responsible for more severe neurological toxicity than conventional normofractionated radiotherapy, as delivery of stereotactic radiotherapy as a single dose results in a dose equivalent to 15 Gy, or even 35 Gy on the 50% isodose [16] versus about 2 Gy per session for conventional normofractionated radiotherapy.

The risk of radiation-induced cancer, either malignant transformation of the residual tumour occurring years later or malignant transformation of irradiated healthy tissues, appears to be very low, ranging from 0.28% [34] to 1/2000 [35]. Several cases of fibrosarcoma [35], malignant astrocytoma or glioma [36], and meningioma [24] have been reported in the literature. This risk must be weighed up against the much higher risk of neurological lesions and complications secondary to tumour progression.

5. Implications for the indications of radiotherapy

This review of the literature therefore appears to demonstrate that first-line radiotherapy provides better results than those of surgery, regardless of the tumour volume:

- all published series report tumour control rates of up to 95 to 100% for follow-ups that are now up to ten years;
- in terms of functional results, radiotherapy appears to stabilize or even improve neurological lesions and induces few iatrogenic effects, and certainly far fewer iatrogenic effects than surgery [6,37–39].

Hearing and facial nerve functions are usually preserved after treatment, especially since reduction of the doses are delivered.

These findings suggest the need to redefine the place of radiotherapy, which is classically indicated in three main situations:

- exclusive radiotherapy for inoperable tumours due to tumour size, internal carotid artery invasion with poorly tolerated clamping test or exclusively ipsilateral venous return or deficient contralateral venous return – various types of surgical contraindications – or bilateral tumours;
- as an adjunct to incomplete surgery;
- salvage therapy after failure of surgery or relapse.

The published results together with the improved quality of life and a better knowledge of the natural history of the disease suggest that radiotherapy can be proposed as first-line treatment for all glomus jugulare paragangliomas regardless of their size, particularly in patients with no preoperative deficit.

Surgery remains indicated in certain situations: young patients; preoperative facial nerve or glossopharyngeal, vagus, and accessory nerve paralysis; low probability of surgical complications; intracranial extension; recurrence after irradiation; major petroclival extension with internal carotid artery invasion and well tolerated clamping test. An emerging concept, which used to be sacrilegious but which is now recommended by many authors, is that of subtotal or almost-total resection leaving residual tumour in contact with critical nerves or blood vessels and systematic adjuvant radiotherapy or when radiological follow-up suggests growth of the residual tumour. Another argument justifying first-line surgery can be that resection of surrounding bone reduces the risk of late osteoradionecrosis in the event of subsequent radiotherapy.

6. Special indications: malignant and/or secreting forms

The place of radiotherapy is not clearly defined in this particular setting.

Surgical resection is theoretically the only curative treatment for primary and secondary malignant paragangliomas. However, the treatment options for these tumours depend on their site and their operability. Surgery is obviously indicated in the case of isolated or multiple cervical, thoracic or abdominal lymph node metastases, especially as it allows histological confirmation of malignancy. Similarly, a solitary liver metastasis may be amenable to surgical resection. Complete surgical resection allows long-term survival [40–43].

However, two-thirds of metastases are situated in bone, usually the vertebrae, and are therefore unresectable. Decompression laminectomy followed by vertebroplasty can be proposed in the presence of signs of spinal cord compression. Combined medical and surgical treatment can also be proposed: analgesics and anti-inflammatory drugs to control pain and nerve compression phenomena, as well as biphosphonates and localized radiotherapy or sometimes embolization and radiofrequency ablation.

Surgery of secreting tumours is always very delicate and must be preceded and accompanied by very careful medical preparation [44–46]. Surgical dissection must comprise control of feeding arteries and every effort must be taken to avoid capsular effraction. Many authors consider radiotherapy to be a particularly valuable alternative.

7. Conclusions and perspectives

This review of the literature appears to demonstrate that radiotherapy now constitutes an effective treatment for glomus jugulare paragangliomas with an equivalent if not better tumour control rate and considerably fewer iatrogenic effects than surgery. The management of glomus jugulare paraganglioma therefore closely follows the changing approach to the management of acoustic neuroma.

However, the potential late toxicity of radiotherapy suggests that treatment will inevitably evolve towards chemotherapy.

Tenenbaum et al. [47], using cold (non-radioactive) octreotide, demonstrated a 50% reduction of the size of a parotid metastasis of paraganglioma, and Kau and Arnold [48] reported 22% and 47% reductions of tumour size, respectively, after 6 months of treatment in 2 patients. Metabolic scintigraphy or chemotherapy can raise objections related to their cost, the low tumour growth rate and their adverse effects [49]. The future will therefore probably consist of targeted molecular treatments designed to inhibit genes targeted by hypoxia-induced factors. Ongoing trials in the treatment of malignant paraganglioma may provide a positive response to the hopes for purely medical management of this disease [50].

Disclosure of interest

The author declares that he has no conflicts of interest concerning this article.

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