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Radiation Therapy, an Important Mode of Treatment for Head and Neck Chemodectomas

Didier A. Verniers, Ronald B. Keus, Paul F. Schouwenburg and Harry Bartelink

Between 1970 and 1990, 22 patients with 44 chemodectomas in the head and neck region were seen at the Netherlands Cancer Institute in Amsterdam. All patients were treated with radiation therapy (17 patients with radiation therapy only and 5 in combination with surgery). One patient was treated two times with an interval of 12 years at each side of the neck. Standard dose was 50 Gy in 25 fractions over 5 weeks. A radiation portal arrangement with oblique fields with paired wedges was used most frequently. The follow-up period ranged from 1 year to 20 years. Two recurrences at 2 and 9 years after treatment were observed. The actuarial local control rate was 88% at 10 years follow-up. Comparison of the results of surgery and radiotherapy demonstrates that radiation therapy is an effective treatment modality without mutilation or severe late morbidity for chemodectomas in the head and neck region.
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INTRODUCTION

CHEMODECTOMAS OR glomus tumours are slowly growing tumours originating in the chemoreceptor bodies [1, 2]. The glomus bodies are responsive to changes in blood oxygen, carbon dioxide tensions and pH. They belong to the APUD system (amine precursor uptake and decarboxylating system), that embryologically originates from the neural crest cells [3–8], and are composed of neurovascular structures. It is a very rare tumour type, with an incidence of 2/100 000. There is a female predominance with a sex ratio of 3 and the peak age range is 50–60 years [9]. The incidence is higher in patients with chronic hypoxia, such as long standing hypoxemia in chronic heart diseases, or living at high altitude [7]. Because of the indolent clinical course, a long follow-up period is necessary to evaluate the treatment [5].

Chemodectomas can occur in multiple sites in the head and neck region in the same patient. Frequent localisations are the middle ear, the mastoid air cell system (glomus tympanicum), the jugular bulb (glomus jugulare), the carotic bifurcation (glomus caroticum) and the hypopharynx (glomus vagale tumour) [7, 9–13]. In the early stages of the disease, each of these localisations gives different clinical symptoms. In late stages the symptomatology is less specific. Although their clinical progression is slow and indolent, in advanced cases cranial nerve palsies and bone destruction can cause important morbidity. Therefore, treatment is to be considered at an early stage.

A controversy, however, about the treatment of choice exists. These tumours have been treated by surgery alone, radiation therapy alone, embolisation or a combination of these treatment modalities. The debate about irradiation arises because of the slow tumour regression after radiotherapy. The purpose of this paper is to study the value of radiation therapy in the treatment of head and neck chemodectomas in the Netherlands Cancer Institute.

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PATIENTS AND MATERIALS

Between March 1970 and December 1990, 22 patients with 44 chemodectomas in the head and neck region were seen at our institute, presenting 17 carotid body tumours, eight glomus tympanicum tumours, six glomus jugulare tumours, eight glomus vagale tumours and five glomus jugulotympanicum tumours. 1 patient also had a paravertebral intrathoracic paraganglioma. 13 patients had multiple tumour sites. The lesions were on the left side in 7 cases, on the right side in 5 cases and bilateral in 10 cases. 4 patients showed familial chemodectomas: all showed multiple tumour sites, whereas 3 of these 4 patients had primarily bilateral glomus caroticum tumours. There was a female preponderance, 7 patients were male and 15 were female. The mean age at presentation was 44 years, ranging from 24 to 82 years (medium 40 years). In most patients, the symptoms had been slowly progressive, the shortest history was 2 months and the longest was 10 years. 30 chemodectomas were irradiated, consisting of eight glomus caroticum, eight glomus tympanicum, six glomus jugulare, five glomus vagale and three glomus jugulotympanicum tumours. In 9 patients, who were irradiated for symptomatic chemodectomas, 14 concurrent head and neck tumours were not treated. Due to the absence of clinical symptoms there was no indication for immediate treatment.

Clinical presentation

Presenting signs and symptoms most often observed were: a neck mass (64% of all patients), hearing loss (50%), pulsatile tinnitus (41%), a mass behind the tympanic membrane (32%), an external aural polyp (27%), a pulsatile sensation in the ear (27%) or other otologic symptoms (Table 1). Cranial nerve involvement was observed in 25% of the patients. Nerve palsies of the VIIth, VIIIth, IXth, Xth and XIIth cranial nerves are frequently presented. Paralysis of the Vth, VIth and XIth cranial nerves were less often diagnosed. In our series, cranial nerve damage was secondary to surgery in 5 cases (Table 2). 1 patient showed a bilaterial Babinsky caused by intracranial invasion of the brainstem. Another patient had dyspnoea due to the presence of extensive bilateral cervical masses with compression of the trachea.

Table 1. Presenting signs and symptoms in 22 patients with chemodectomas

Symptom	No. of patients	%
Neck mass	14	64
Ear symptoms		
Hearing loss	11	50
Pulsatile tinnitus	9	41
Mass behind TM*	7	32
Mass in EAC†	6	27
Pulsatile sensation	6	27
Pain	4	18
Vertigo	4	18
Otorrhea	3	14
Nystagmus	1	4
Pharyngeal mass	6	27
Others		
Miosis (Horner S.)	3	14
Headache	3	14
Dyspnoea	1	3

* TM = Tympanic membrane.
† EAC = External auditory canal.

Table 2. Cranial nerve involvement in 22 patients with chemodectomas

Nerve	No. of patients	%
V	2	9
VI	2	9
VII*	7	32
VIII*	11	50
IX*	7	32
X	6	27
XI	2	9
XII†	7	32

* One cranial nerve involvement secondary to surgical damage.
† Two cranial nerve involvements secondary to surgical damage.

In 12 patients the duration of the presenting symptoms before diagnosis was 3 years and 2 months on average. Obvious intracranial tumour extension was demonstrated by computed tomography (CT) in 6 patients.

The evaluation and examination included a complete physical examination and radiographic studies. In the early 1970s the radiological technology consisted of mastoid radiographs, conventional tomograms of the mastoid and arteriograms. From 1978, all patients were investigated by CT using contrast enhancement.

The diagnosis was mainly based on typical clinical symptoms and on radiological investigation. In 8 patients the diagnosis was based on histological examination (performed with a biopsy sample from a polypoid mass or radical mastoidectomy).

Treatment

Surgery was performed in 5 patients. 1 patient underwent a resection of a polypoid mass in the external auditory canal followed by a transtympanic excision because the first biopsy sample had shown no tumour. Another patient also underwent an excision of a polypoid mass in the external auditory canal. Partial removal of a tumour in the neck was performed in 3 cases.

These 5 patients all received postoperative radiotherapy because of incomplete resection, the adherence to important blood vessels or cranial nerves entrapment in the tumour. 17 patients were treated with radiation therapy alone, except for a diagnostic biopsy in 3 patients.

All patients were treated with megavoltage photons. 21 patients were treated with 8 MV X-rays and 1 patient with cobalt 60 gamma rays. 1 patient was treated two times with radiation therapy to each side of the neck with an interval of 12 years. 21 patients were treated with a wedged portal arrangement designed to spare the contralateral normal tissues. 2 patients were treated with a rotation technique. The dose ranged from 50 to 60 Gy in 20 to 25 fractions over 4 to 5 weeks. The most frequently used dose was 50 Gy in 25 fractions over 5 weeks specified at the 90% isodose. The follow-up period ranged from 1 year to 20 years (mean 10 years and 3 months.)

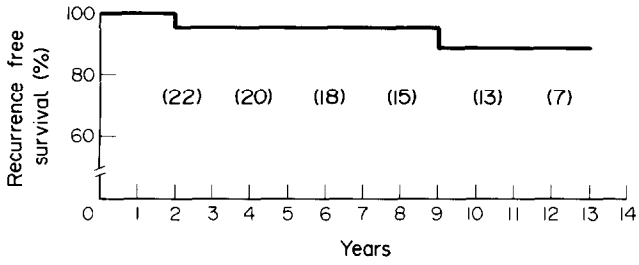

Fig. 1. The actuarial local recurrence free survival following radiotherapy of glomus tumours.

RESULTS

The actuarial local recurrence and progression free rate was 88% at 10 years (Fig. 1), tumour control being defined as no clinical or radiographical evidence of progression or recurrence of disease [14, 15, 16].

The tumour response after radiation therapy alone was evaluable in 15 patients with clinical palpable or visible tumour. This evaluation was performed with physical examination or CT scan of the head and neck. In 2/15 (13%) of the irradiated cases there was a complete remission of the tumour mass. An example of complete intracranial tumour regression is demonstrated in Fig. 2a and b. The regression usually developed slowly. A partial remission (more than 50% reduction of tumour volume) of the tumour mass was observed in 9/15 (60%) of the irradiated cases. In 2/15 (13%) there was stable disease while in 2/15 (13%) there was tumour progression (Table 3).

1 patient treated with irradiation for a glomus tympanicum tumour developed a local in field recurrence after 9 years. This recurrence was treated successfully with embolisation, followed by radical mastoidectomy. The other patient was previously

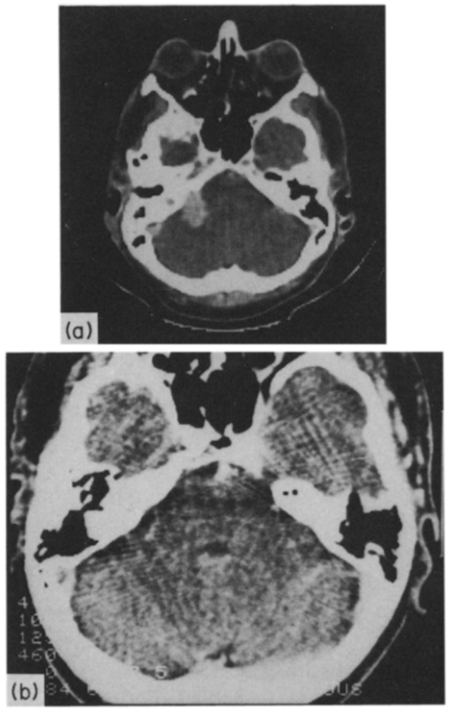

Fig. 2.(a) CT demonstrating a left glomus jugulotympanicum tumour with intracranial extension. (b) Control CT 9 years after irradiation showing a complete regression of the intracranial tumour localisation.

Table 3. Tumor status after radiation therapy alone in patients with clinical palpable or visible tumour

Localisation	CR	PR	SD	Progression
Neck	1/7	4/7	2/7	0/7
Behind TM*	0/5	4/5	0/5	1/5
EAC†	1/3	1/3	0/3	1/3
All patients	2/5(13%)	9/15(60%)	2/15(13%)	2/15(13%)

* TM tympanic membrane.
† EAC External auditory canal.
CR Complete remission.
PR Partial remission.
SD Stable disease.

treated with several excisions of polypoid masses in the external auditory canal. She presented with an extensive recurrence in the os petrosum, the base of the skull and the cerebello-pontine angle and underwent radiation therapy. After 2 years she developed a recurrence within the radiation fields with destruction of the clivus and the foramen magnum and with intracranial tumour extension. This process was treated by surgical debulking. She is still alive 10 years later.

Also, after a combined treatment modality, the results were scored. All 5 patients, who were treated with radiation therapy after incomplete resection, had tumour control. 3 patients remained completely tumour-free, 1 showed a partial remission and 1 a tumour stabilisation, but in 2 of the 22 irradiated cases the evaluation was more difficult to perform because they showed no clinical palpable tumour. 1 patient had normalisation of the otologic symptoms, except for the hearing loss; another patient showed stabilisation of the cranial nerve defects. Both patients were considered as locally controlled.

There was no significant acute or chronic side effects noted except in 1 patient who developed a temporary perforation of the tympanic membrane caused by otitis media.

Case report

A 30-year-old female patient had a history of progressive loss of hearing acuity of the left ear for 5 years, and a pulsatile tinnitus for 3 years. Physical examination showed a blue polypoid mass in the left external auditory canal and a blue glimmer behind the right tympanic membrane. A mandarin-like pulsatile mass was palpable under the left mastoid. A vaulting of the left pharyngeal wall was visible.

Computed tomography of the base of skull showed extensive bone detruction in the left os petrosum and bone erosion around the foramen magnum. The structures of the left middle and inner ear could not be distinguished. After intravenous bolus injection of contrast, a strongly enhancing tumour was visualised in the left os petrosum with intracranial tumour extension in the fossa posterior. A smaller tumour behind the right tympanic membrane and at the right foramen jugulare was observed. At the base of the skull there were bilateral glomus jugulotympanicum tumours and tumour was also present in the parapharyngeal space. This could have been an extension of the glomus jugulotympanicum tumour or a bilateral glomus vagale tumour.

In December 1983, an resection of the left glomus jugulotympanicum tumour was performed. A preoperative embolisation and a balloon-occlusion test were used. By way of a infratemporal craniotomy, a radical excision of the left glomus tumour with a

Table 4. Local control of chemodectomas with radiation therapy

Institution	Local control	Dose (Gy)	Years of follow-up
M.D. Anderson Hospital [26]	17/17	42.5–50	4–18
Queen Elizabeth Hospital, Birmingham [27]	19/20	45–50	13
Univ. of California, L.A. [8]	11/14	28–65	1.3–17
Univ. Hospital Wales [28]	12/14	42–50	20
Geisinger Medical Center [10]	11/11	40–50	1–12
Universitäts-HNO-Klinik [29]	14/14		7–9
University of Virginia [30]	26/30	40–50	1–30
Princess Margaret Hosp. [1]	42/45	35	3–23
Rotterdamsch RT. Inst. [31]	28/28	40–60	1.5–18
Washington Univ. School, St Louis [32]	20/32	24–52	4–24
Univ. Hosp. Rigshospitalet, Copenhagen [33]	36/39	50–54	7.3
Univ. of Florida, Gainesville [34]	25/26	40/50	2–18
University of Iowa [16]	16/19	29–67	5–35
Baylor Medical Center, Houston [14]	18/19	23–50	3–23
St Radboud Univ. Hosp., Nijmegen [35]	30/31	40–50	11.3
Univ. of Arizona, Health Sciences Tucson [36]	10/10	45–54	2–9
U.Z. St. Rafaël, Leuven [37]	8/8	46–50	1–12
Netherlands Cancer Inst.	20/22	50–60	1–20
Total	363/399 (91%)		

subtotal petrosectomy was carried out. The left VIIth, IXth, Xth and XIth cranial nerve and the n. mandibularis were entrapped by the tumour, and consequently damaged during the operation. A repair of the left VIIth cranial nerve was performed with a direct nerve graft. Histological examination confirmed the diagnosis of a glomus tumour. Postoperatively only the VIIth cranial nerve function recovered. 3 years later she complained of a progressive deafness of the right ear and was referred to our institute for radiotherapy. Physical examination demonstrated a bulging tympanic membrane at the right side and the known cranial nerve involvements. Angiography and CT scan confirmed the existence of a large glomus jugulotympanicum tumour, and also a tumour rest in the left mastoid. From 19 February to 25 March 1986, the right glomus tumour was irradiated with a wedged two-field technique to a dose of 50 Gy in 25 fractions over 5 weeks specified on the 90% isodose. A slow tumour regression was observed, but the deafness did not change.

In 1987, a rotation of the arythenoid and a thyreoplasty were performed because of a left vocal cord paralysis as a result of the surgery performed in 1983. The quality of the voice ameliorated and the tumour is still under control in 1990.

DISCUSSION

Our results indicate that excellent tumour control of head and neck chemodectomas can be reached with moderate doses of radiation therapy without late morbidity. Although these tumours are rarely malignant and seldom give rise to metastases (occurring in 2–5% of the cases [7, 14]), treatment is often necessary to prevent symptoms caused by the local tumour progression. An untreated tumour can lead to extensive local bone destruction with brain-invasion and eventually to death [7]. A review of the literature shows that the overall local control with radiation therapy is in line with our results: about 90% long term local control (Table 4). The dose range was 23–67 Gy with follow-up of 1 to 35 years.

Surgery is an effective treatment for early tumors [13, 17, 18]. From a review of the literature, published between 1965 and 1990, local control with surgery alone can be achieved in 65% (Table 5).

However, in the case of large chemodectomas, surgical procedures are not always complete due to the tumour extension into critical normal tissues. Advanced disease at presentation and proximity to critical normal structures like important blood vessels complicate excision. The morbidity of complex base of skull surgery is high. Because of frequent cranial nerve involvement surgery can lead to irreversible neural damage. Due to hypervascularity of these tumours there is a risk of severe peroperative bleeding [4, 7, 12, 19, 20]. Side effects like infection, cerebrospinal fluid leaks and meningitis are sequelae after these complicated surgical procedures. Glasscock reported a 3% operative mortality, a 33% incidence of cranial nerve palsies and a 33% incidence of conductive hearing loss [2].

Our present series confirms that chemodectomas can successfully be treated by radiation therapy. Persisting local control rates can be obtained in 88% with moderate doses of carefully planned radiation therapy, strongly suggesting that head and neck chemodectomas should be treated with radiotherapy, reserving surgery for small tumours and recurrences. CT scanning with contrast enhancement confirms the diagnosis in most cases and gives a correct judgment of tumour extension, tumour size, intracranial tumour spread and bone destruction of the base of skull [3, 19–22].

Tumour regression after radiotherapy is often extended over a period of many months or even years [14, 23]. A long follow-up period is therefore necessary to evaluate the tumour response after therapy. The tumour often does not disappear completely, but also the evolution of the other clinical effects like neurologic and otologic symptoms was difficult to evaluate in this retrospective study. Radiographic bone destruction is frequently seen. In most cases cranial nerve involvement and otologic symptoms do not improve. Many patients develop a second localisation of the

Table 5. Local control of chemodectomas with surgery

Institution	Local control (%)	Years of follow-up
University of Michigan [20]	4/9	
Mount Sinai Hospital, New York [38]	5/8	
Massachusetts General Hospital [39]	8/16	4
University of California, San Francisco [40]	3/14	17
Washington University [41]		
gl. tympanicum	10/11	2–27
gl. jugulare	35/45	2–27
University of Kansas, Medical Center [5]	5/15	2–22
Univ. Hosp. Rigshospitalet, Copenhagen [33]		
gl. tympanicum	9/12	9,7
gl. caroticum + vagale	1/1	6
University of Iowa [16]	6/13	5–35
St. Radboud University Hospital, Nijmegen [35]	18/24	11,3
Cleveland Clinic Foundation, Ohio [24]		
gl. caroticum	14/14	1–7
Total	118/182 (65%)	

chemodectoma. In our series 13 patients had multiple tumour sites. 3 patients had familial glomus caroticum tumours. This is in accordance with the results of other groups, where 10% of the glomus caroticum tumours appeared to have familial incidence [13, 21, 24].

The optimum dose of radiotherapy for chemodectomas is the dose that will control the tumour with the smallest complication rate [25]. Temporal bone necrosis and/or brain necrosis caused by radiation therapy should be avoided at all costs and is not seen in our patient material. Therefore, the dose is primarily determined by the tolerance of the adjacent normal tissue. A standard dose of 50 Gy in 5 weeks given in daily fractions of 2 Gy can be used with success without significant risk of complications. Because the spinal cord is one of the most important dose-limiting normal tissues in the body, treatment techniques which use precise beam angulation, spinal cord blocks must be meticulously executed throughout the treatment course to minimize the risk of cervical spinal cord injury.

Although embolisation has a place in surgery (preoperative reduction of the tumour mass), there are no convincing arguments that it is useful in combination with radiotherapy. On the contrary, it seems to be unfavourable due to the hypoxemic effect, which decreases the radiosensitivity of the tumour cells. In our view, embolisation should be reserved for the treatment of recurrences after radiation therapy.

In conclusion, while the use of surgery is restricted to small tumours only, radiotherapy is an effective treatment for all chemodectomas, giving a high tumour control rate and minimal morbidity.

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Immunocytochemistry and *in situ* Hybridisation of Epidermal Growth Factor Receptor and Relation to Prognostic Factors in Breast Cancer

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The breast tumour distribution of epidermal growth factor receptor (EGFR) was studied in 193 patients with primary breast cancer by immunocytochemistry on frozen sections. EGFR was correlated ($P = 0.0009$) with growth fraction assessed by Ki-67, and negatively correlated with oestrogen receptor (ER, $P = 0.0001$) and progesterone receptor (PR, $P = 0.0001$) status. In 47 patients, in-situ hybridisation for EGFR mRNA showed good agreement with the immunocytochemically assessed EGFR protein. There were, however, several tumours in which EGFR mRNA could be detected in the absence of EGFR protein and there were differences between the ER and PR status of those tumours in which translation of EGFR mRNA was not seen. The cause of these differences is unclear, but these findings may represent a clue as to the differential control of breast cancer cell receptors.
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INTRODUCTION

THERE IS a need to distinguish between patients with breast cancer whose disease is localised to the breast and who will be cured by tumour removal and axillary lymph node clearance, and those whose tumour has spread further and who need additional systemic therapy. At present, axillary lymph node status, tumour grade and oestrogen receptor (ER) status are three of the selection criteria used. Relapse, however, is seen in 20–30% of axillary lymph node negative patients, and response to endocrine therapy is not strictly linked to ER status [1]. This has led to the search for alternative new prognostic indicators such as growth factors and their receptors, and to the measurement of tumour proliferation rates using techniques such as monoclonal antibodies and flow cytometry.

Epidermal growth factor (EGF) is a 6045 molecular weight polypeptide which is known to mediate cell proliferation in a range of tissues including human breast epithelium *in vivo* and *in vitro* [2]. The action of EGF is mediated via the EGF receptor

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