Clinical Management of Head and Neck Paraganglioma

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TABLE OF CONTENTS:

CHAPTER 1

General Introduction

TUMOUR BIOLOGY

Paraganglioma in the head and neck region (HNPGL) are vascular neuroendocrine tumours, derived from chromaffin cells of the parasympathetic paraganglia in 98-99% of cases and they occur along the paraganglia pathways of embryologic migration extending from the skull base to the pelvic Floor [1-3]. Pheogromocytomas, adrenal chromaffin derived tumours, extra-adrenal abdominal- and thoracic paraganglioma are however associated with the sympathetic nervous system. Sympathetic paraganglioma are secretory tumours that mainly secrete catecholamines and dopamine [4-9].

HNPGL are rare tumours, representing approximately 0.012% of all head and neck tumours and the estimated incidence is about 1:100.000 a year [10].

About 60% of HNPGL show clinical growth during follow-up, and growth rates are indolent and generally very slow with a mean increase of 0.83 mm/year in a single dimension and a doubling time of about 4.2 years [11]. Furthermore, these tumours are benign in the vast majority of cases, yet malignancy rates have been described. This is mainly dependent on hereditary subtype.

Overall, there is a 3-5% chance of malignant disease [12, 13].

ANATOMICAL SUB SITES AND CLINICAL PRESENTATION

The most characteristic sub sites where these tumours can be found are presented in figure 1.

These tumours are usually benign and grow in close proximity with delicate neurovascular structures throughout the head and neck region. Mainly, large vessels and cranial nerves are compromised by these tumours, which also dictates clinical presentation.

Most HNPGL are found around the carotid body, resembling about 57% of HNPLG. Carotid body paraganglioma arise from the neural crest cells at the bifurcation of the common carotid artery [4]. The classification system described by Shamblin et al. is generally used and illustrates the relation of these tumours with the common carotid and internal- and external carotid artery [14] (figure 1). Tumours classified as class I have no or minimal attachment with the carotid arteries. Class II tumours surround the carotid arteries, partially encasing them. Shamblin class III tumours surround the vessels, adhering firmly over their whole circumference [10]. Hereby, they are also associated with vagal and hypoglossal nerve palsies. Intracranial extension is rare for these tumours. They usually (50-60%) present with a painless swelling in the neck without evidence of cranial nerve palsy, the latter is found in 4-22% of cases [16, 17].

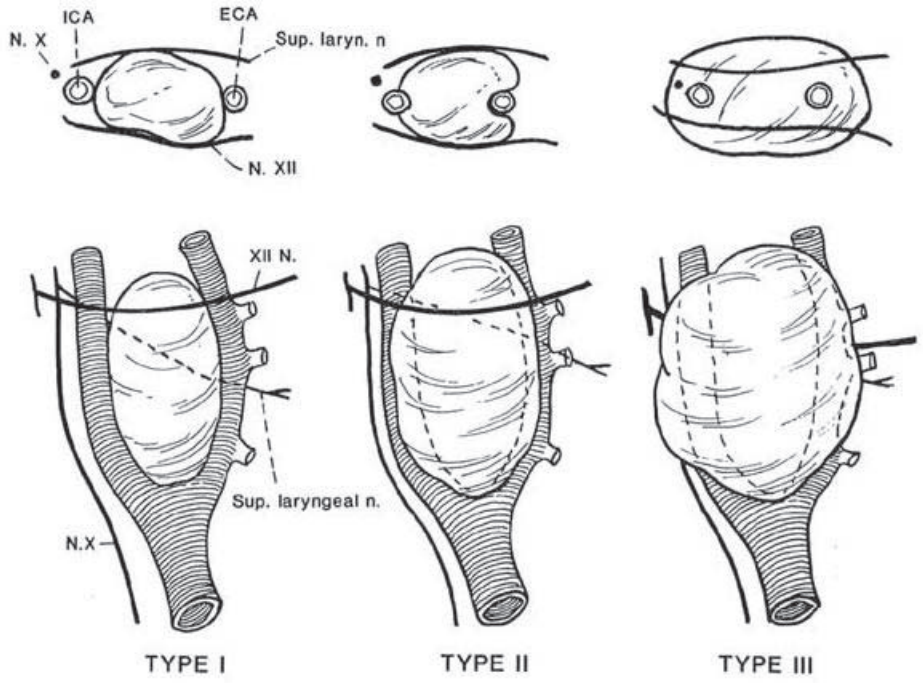

Figure 1: The classification of Shamblin et al. of the difficulty of surgical resection. Group I tumours are localized and easily resected. Group II includes tumours adherent or partially surrounding vessels. Group III paragangliomas intimately surround or encase the vessels. *ICA* = internal carotid artery; *ECA* = external carotid artery. Figure 1 taken from Hallet et al. 1988 [15].

The second most common subtype are jugulotympanic paraganglioma, which constitute about 30% of HNPGL, and they are thought to arise from the Jacobson's nerve in the tympanic cavity [4]. The classification of these tumours is according to the Fisch classification [10, 18]: class A JTPGLs are located along the tympanic plexus on the promontory, and class B tumours invade the hypotympanum, but do not erode the jugular bulb, as opposed to class C tumours (C1 destruction of the jugular bulb/foramen; C2 invasion of the vertical carotid canal; C3 invasion of the horizontal carotid canal and C4 invasion of the cavernous sinus). In class D tumours, besides the various degrees of invasion described for class C, intracranial extradural or intradural extension occurs (De1 and De2 intracranial and extradural invasion of up to 2cm or more than 2cm respectively; Di1, Di2 and Di3 intracranial and intradural extension of up to 2cm, between 2 and 4cm or more than 4cm respectively). Tympanic paraganglioma (class A and B tumours), usually present with a pulse synchronous tinnitus that might be accompanied with conductive hearing loss. In patients with jugular paraganglioma (class C and D tumours) the presence of additional lower cranial nerve deficit is found in 39-40% of cases, mainly referring to the 7th and 9-11th CN [1, 16].

The third most common site is at any point along the course of the vagal nerve (13% of HNPGL), referred to as vagal paraganglioma [4]. Therefore the clinical presentation is variable and there are no proper classification systems developed. They might present with a wide variety of symptoms ranging from a painless lateral neck mass to dysphagia, snoring, lower cranial nerve deficits and Horner syndrome . CN deficit is found in 25-36% of cases [19, 20].

Other sub sites are nasal and paranasal paraganglioma and laryngeal paraganglioma. Due to the rarity of these tumours they are not within the scope of the current thesis.

HEREDITARY HEAD AND NECK PARAGANGLIOMAS

About one third of HNPGL are part of hereditary disease [21-25]. The particular associated phenotype usually induces higher penetrance rates at younger ages, and multifocal and metachronous tumour presence is to be expected. Currently, there are ten genes associated with HNPGL syndromes, and the SDH- (succinate dehydroginase) associated genes are the most common forms [26-31]. The remaining germline mutations are of lower prevalence (MAX, TMEM127, VhL, RET, MEN2 and NF1) [32-36]. The main phenotypical characterizations of these tumours is presented in table 1. Also, information on the hereditary transmission process is provided, please note that for SDHD and –B tumours, a distinguished paternal transmission pathway has been described [26, 27]. Also, dependent on the tumour syndrome, other clinical features might be apparent such as in von Hippel Lindau disease and neurofibromatosis type 1.

DIAGNOSTIC PROCESS

Since HNPGL are potentially found to be part of a larger systemic disease, the diagnostic work-up of these tumours should consist of a multidisciplinary team that contains a dedicated endocrinologists, radiologists, clinical geneticists radiotherapist, a skull base surgeon and a head & neck surgeon with experience in vascular surgery.

The first step in the diagnostic process is imaging, in which the standard is an MRI with intravenous contrast enhancement of the head and neck region, potentially complemented with an MRA. In case a close relation to the skull base is found (e.g. in jugulotympanic paraganglioma) a subsequent CT-scan is required to determine loco regional expansion and tumour class in cases of jugulotympanic tumours. Imaging should also be focused on synchronous tumour presence [37-40].

Moreover, since 1-2% of tumours are part of the sympathetic nervous system and hereby they are potentially secretory, endocrinological analysis, focusing on cat-

Table 1: phenotype associated with genetic subtype.

	SDHD	SDHAF2	SDHC	SDHB	SDHA	VHL	TMEM127	MAX	MEN2	NF1
% HNPGL	91-98%	88-100%	12-87.5%	27%	2.2%	0.53%	0-42%	1.12%	-	0.1%
Range age presentation	25-38	33-34	38-46	19-75	32	15-42	24-51	-	15-42	-
% multif. Disease	60-79%	70-91%	69-81%	13%	ND	ND	ND	ND	ND	ND
Pheo/ extra- adr. PGL	8-21%	ND	12.5-44%	2-52%/13-85%	ND	10-15%	0.9%	1.12%	30-50%	1-14.6%
Associated disease	ND	ND	ND	Renal cell ca./ MALT lymphoma	ND	Leigh syndrome	-	ND	MEN2 associated tumours	NF1 associated disease
% malignant	8%	ND	33%	33%	ND	ND	ND	ND	ND	ND
transmission	Pat.	Pat.	Pat./ mat	Pat./ mat	ND	ND	ND	ND	Aut. dominant	ND

ND = Not described; Pat = paternal transmission; Mat. = maternal transmission; Aut. dominant = autosomal dominant.

echolamine overproduction, is required. Particularly in the case of enhanced plasma catecholamine levels, treatment with beta-blockers is required. Even more so in case surgical excision is required as this might result in enhanced catecholamine release per-operatively which is associated with potential detrimental complications such as hypertensive crisis, cardiac arrhythmia's, cardiogenic shock, pulmonary oedema and cerebral haemorrhage. Endocrinological analysis is also mandatory in case a hereditary tumour subtype is found since associated comorbidities such as SDH-related tumours such as pheochromocytoma, gastrointestinal stroma tumours, renal cell carcinoma's or pituitary adenoma's, or MEN2 associated tumours need to be managed [41-43].

Furthermore, a clinical geneticist is required to manage the hereditary diagnostics. It is suggested to test all patients presented with HNPGL. Also those with apparent sporadic disease since research has illustrated that about 25-56% of patients with apparently sporadic tumours do show a germline mutation [3].

The results of the above mentioned diagnostic work-up should be carefully discussed by a specialized working group with experience in HNPGL management. All of the above should be taken into consideration while determining the best treatment for each individual patient. Besides an experienced radiologist, clinical geneticist and endocrinologist, the working group should contain an otolaryngologist with particular experience in skull-base surgery and a head & neck surgeon with experience in vascular surgery (or close cooperation with vascular surgeons) is required. Also, an experience radiation oncologist is required as an alternative for surgery. Details on clinical management are presented underneath.

CLINICAL MANAGEMENT

The clinical management of these tumours remains a hot topic of debate and concerns the main subject of this thesis. Despite the benign nature of these tumours, morbidity can be considerable due to the close proximity of these tumours to delicate neural and vascular structures. This makes determining the moment of treatment and the treatment modality debatable. Particularly in the case of hereditary tumour syndromes, with an enhanced chance of presentation at younger age (generally with larger tumours) and a higher chance of multifocal and/or metachronous tumour growth. Managing clinicians need to keep a constant eye on the risk of tumour induced morbidity, respective to the risk of treatment induced morbidity.

Wait and scan

Recent studies have suggested that since merely 60% of HNPGL show tumour growth, and tumour since growth is generally slow, an initial wait and scan strategy should always be considered. Key studies of van der Mey et al. and Jansen et al. have illustrated that refraining from detrimental invasive strategies such as surgery or radiotherapy shows high functional CN preservation rates which enhances quality of life [11, 43]. Dependent on complaints, loco regional extension and comorbidities, tumour growth should be evaluated on a yearly basis. In case tumour growth is found, dependent on the size, location, age and comorbidities of the patient treatment should be considered again. As stated by Suarez et al. it can be argued that a wait and scan policy will increase the risk for development of additional cranial nerve deficits. Nevertheless, only 3 of 40 patients with VPG in whom a wait and scan policy was chosen, developed cranial nerve palsy during an average follow-up of 8.5 years [11, 45]. Nevertheless, the precise risk of such a wait and scan strategy remains uncertain and requires further refinement.

Surgery

In case treatment is mandatory, e.g. dependent on tumour growth or clinical symptoms, historically surgery is the treatment of choice, as this is the sole treatment modality capable of gross tumour removal. Recent work of Suarez et al. however, has illustrated that there is a considerable risk associated with surgery of HNPGL [45-46]. Particularly for larger tumours such as Shamblin class 2 and 3 in case of carotid body tumours and Fisch class C and D jugolotympanic tumours or those in close proximity to the vagal nerve. Local control rates are acceptable, yet morbidity in terms of permanent cranial nerve damage and strokes are imminent. For smaller (Fisch class A and B and Shamblin class 1 tumours) however, surgery might be a more viable option when executed by an experienced otologist/head and neck surgeon respectively. Currently however, the risk of surgery for smaller tumours when being part of multifocal disease has not been described. For larger Fisch class C and D, Shamblin class 3 and all vagal body paraganglioma morbidity is potentially considerable, and expertise in skull base surgery, neurosurgery and vascular surgery should be present [3, 45-46]. To date, the exact risk profile of surgery for different HNPGL of different tumour class remains uncertain and requires further research.

Radiotherapy

Alternatively, recent studies have illustrated the use of radiotherapy as an alternative treatment modality. Local control-rates seem to be promising, yet even more promising is the absence of collateral treatment induced morbidity when compared to surgery

[45-46]. There are however concerns with the use of radiotherapy, mainly referring to long term side effects. The precise risk of irradiation induced secondary malignancies and vascular damage remains uncertain for these tumours. As outlined by Suarez et al. other head and neck neoplasm's treated with similar radiotherapeutic techniques and dosages illustrated a risk of 0.5 and 0.1-3% for tissue necrosis and irradiation induced secondary malignancies, respectively over a course of 30 years [45-46]. Furthermore, Wilbers et al. found an increased incidence of stroke in 49 patients suffering from head and neck malignancies seven years after radiotherapy compared to the general Dutch population (8.9 versus 1.5 per 1.000 person years) [47]. It is uncertain whether or not these results apply for HHPGL treatment as well, particularly since radiotherapeutic techniques have advanced. Radiotherapeutic planning is becoming more and more accurate, and stereotactic radiation techniques have reduced the risk of collateral tissue damage. Nevertheless, although with the modern fractionated radiotherapeutic and/or stereotactic techniques these risks are reduced, the precise long-term risk remain largely uncertain. This is of particular concern for younger patients, or those in which metachronous tumour growth requiring additional treatment later in time.

Debulking

An alternative for complete tumour surgery is a dual approach. Recent studies have investigated the possibility of gross tumour mass debulking with safe margins from delicate neurological structures. The residual tumour mass might in turn be subjected to a wait and scan strategy and in case of growth it might be treated further, potentially by radiotherapy [48-49]. This new technique however requires further research.

Keeping in mind the individual risk profiles associated with each different treatment modality, we believe it is the managing clinicians task to propose an individualized treatment regimen for each patient, keeping in mind the clinical presentation, age and comorbidities of the patient. There is no "one size fits all" principle in this respect.

Furthermore, it is our current understanding that past researches have failed to properly investigate the use of a wait and scan strategy. Moreover, no research applied careful stratification per tumour type and class, and rather evaluated the effect of individual treatment modalities on mixed HNPGL cohorts. Moreover, little research is conducted on multifocal tumour presence and its impact on clinical management.

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AIM OF THESIS

The aim of the current thesis is to evaluate the risk associated with different treatment modalities for HNPGL of different sub-site and tumour class to aid the constitution of personalized guidelines for individualized patient management.

OUTLINE OF THESIS

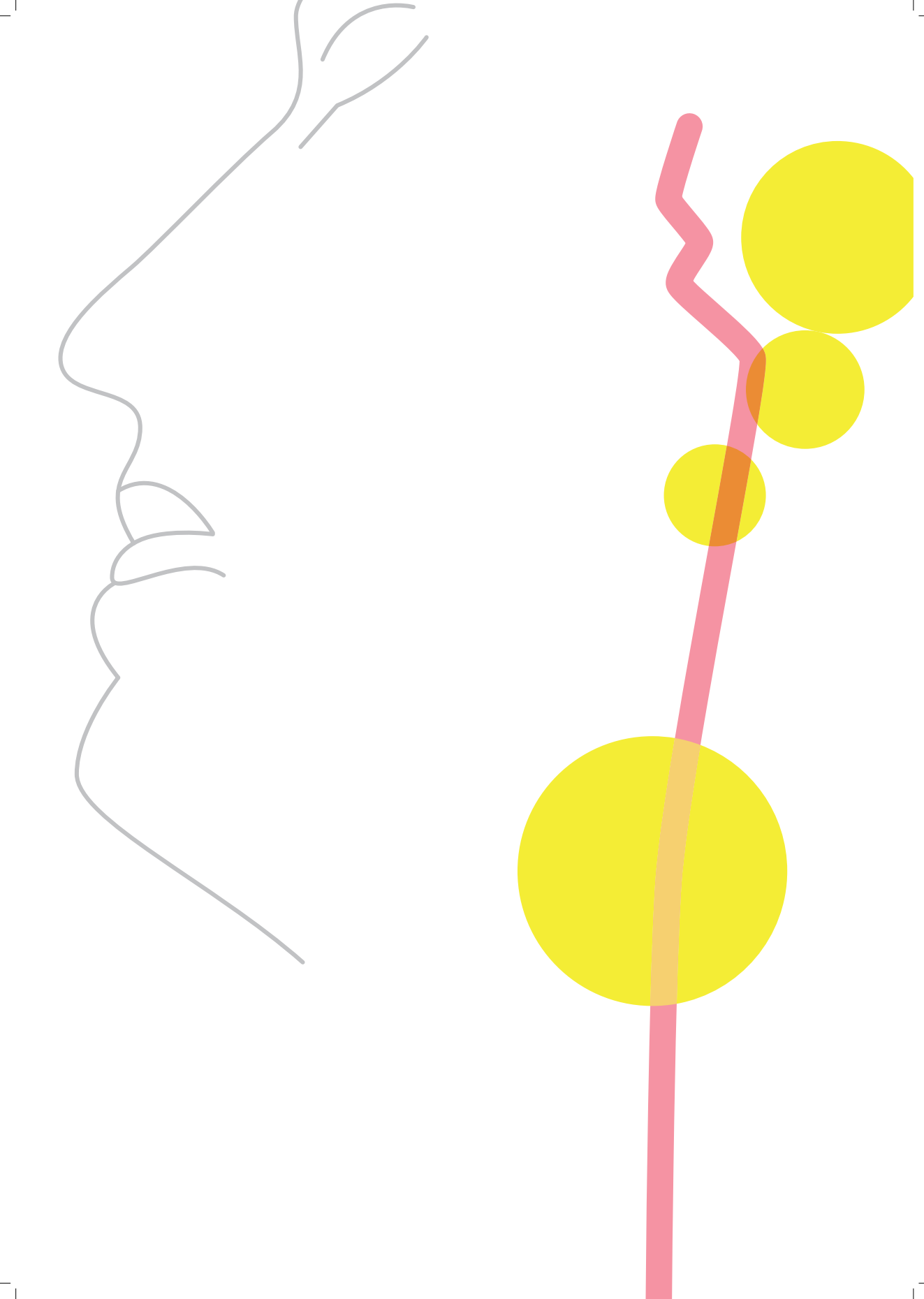
The current thesis is divided in three main parts, each covering a different subject crucial for HNPGL management. The first subject in modern HNPGL management is question whether or not treatment should be executed at all, referring to the subject of a wait-and-scan period. Due to the high risk of treatment induced morbidity in case of treatment of these tumours, such a conservative management strategy is elaborately advised in recent literature. The rationale being, that in this was potentially harmful treatment strategies can be preserved for those tumours at risk for inducing tumour induced morbidity. However, little is known about the risks associated with this management strategy and literature is sparse on this matter. Therefore, in part one, the clinical results of a wait and scan period are evaluated in a large retrospective clinical cohort study was conducted, evaluating tumour biology of HNPGL of different subclasses is described in form of tumour growth rates. Second, tumour induced morbidity is evaluated and predictors are established. Third, we evaluated the potential of a wait and scan strategy as a predictor for optimal timing of surgery or radiotherapy.

The second part of this thesis focuses on the evaluation of different treatment modalities for HNPGL of different sub-site and tumour class. For each different sub-site, a similar methodology was used to evaluate for each individual treatment modality tumour control rates, complication rates and rates of functional recovery. For each sub-site and stratified per tumour class (the Fisch classification for GJTT and Shamblin classification for CBT's) treatment outcome was first evaluated through a systematic review of literature. For each sub-site this was subsequently complemented by a (multicenter) retrospective cohort study evaluating our own treatment results. Hereby, a risk profile can be constituted per tumour class regarding the risk of morbidity for different treatment modalities. This can then be outweighed against the in part one described risk profile associated with a wait and scan cohort.

Subsequently in part three, the management of multifocal head and neck paraganglioma is considered. Currently, literature is mainly focused on treatment outcomes per tumour, little is known about the impact of patients suffering multifocal tumour presence. Therefore, we additionally compared the complication-free survival of patients suffering multifocal disease and those suffering multifocal tumour presence.

Furthermore, we evaluated the complication free survival of patients suffering low risk- (Fisch class A and B, and Shamblin class 1 tumours) and high-risk tumours (Fisch class C and D, Shamblin class 3 and Vagal body paraganglioma) as part of both unifocal and multifocal disease. Also, the effectiveness of the afore mentioned treatment modalities on the low- and high-risk tumours is evaluated in terms of complication free survival

Part four of the thesis integrates the above mentioned results in a general discussion rendering advise for the daily practice of HNPGL management. Also, a summery is provided.



PART 1

Clinical Results of a Wait-and-Scan Period

CHAPTER 2

Feasibility of a Wait-and-Scan Period as Initial Management Strategy for Head and Neck Paraganglioma

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ABSTRACT

Background: The main goal of head and neck paraganglioma (HNPGL) management is reduction of treatment- and tumour-induced complications. In the current study, tumour growth rates and tumour-induced complications, during a wait-and-scan period are evaluated.

Methods: Retrospective cohort study. Tumour growth was measured in axial plane diameter and tumour volume.

Results: Of 59 jugulotympanic-, 71 carotid body-, and 29 vagal body tumours , 44% were growing (median follow-up of 63.6 months). Median growth rates were 0.41mm/year (range 0-439), 1.6mm/year (range 0-23.68), and 1.6mm/year (range 0-23.68) respectively. Growth was significantly correlated to age at presentation (OR=0.974; $P < 0.05$). Seventeen tumours induced 20 complications. Six of these tumours were growing, and growth rates were higher than in tumours not inducing complications ($p = 0.016$; $F = 6.496$).

Conclusions: These results illustrate the feasibility of a wait-and-scan strategy for HNPGL. The management strategy could not prevent tumour-induced complications in 16% of non-growing tumours.

INTRODUCTION

Head and neck paraganglioma (HNPGL), are slow-growing, benign tumours with an indolent growth pattern, growing in close proximity to delicate neurovascular structures [1]. Although surgical techniques have advanced, surgery poses a threat to the surrounding structures and is highly associated with morbidity, particularly due to cranial nerve damage [2-4]. Radiotherapeutic options have been suggested as an alternative and results are promising, with reduced iatrogenic morbidity. The long-term results of advanced radiotherapeutic options (fractionated stereotactic techniques), however, remain unknown and complications such as xerostomia, sensorineural hearing loss, vascular stenosis with consecutive CVAs, and irradiation-induced malignancies have been described [2, 3]. Therefore, a preceding wait-and-scan period has been suggested as a viable initial management strategy for HNPGL to potentially prevent treatment-induced morbidity [5-10]. However, leaving a tumour untreated potentially results in tumour-induced complications (TICs). The main reason for implementing a wait-and-scan period is to prevent patient morbidity (particularly in the case of multiple/bilateral HNPGL), both iatrogenic and tumour-induced. A successful management strategy might be, to reserve potentially harmful treatment strategies for growing tumours, initiated before the growing tumour could itself induce morbidity.

To date, no risk factors have been isolated or related to tumour-induced complications induced by a wait-and-scan period. The assumption in applying a wait-and-scan period is that growth is a predisposing factor for future TICs. Several factors have been suggested to be of influence. It has been described that intermediate-size tumours show enhanced tumour growth [6]. Moreover, hereditary syndromes and being of young age could be related to enhanced tumour growth [1, 7]. In the current study, we describe our results in applying a wait-and-scan policy, and evaluate the influence of several predictors on growth rates. Moreover, risks associated with this conservative management strategy are further described. Thus, the current study aims to isolate predictors for tumour growth and tumour-induced complications by evaluating the outcome of standardized wait-and-scan treatment regimen in the case of 157 tumours. Hereby, we aim to contribute to the development of guidelines for HNPGL management.

METHODS

A retrospective cohort study was conducted for which records of patients presenting between 1980 and 2016 in the Radboudumc, the Netherlands, were accessed. All HNPGL cases at this location were evaluated, and a total of 358 patients were reviewed.

To gather data from patient files, a standardized extraction protocol was used to obtain the following: gender, age at presentation, symptoms at presentation, tumour type, genetic analysis, clinical signs for tumour progression, radiological signs for tumour progression, actual tumour progression in millimetres, and complications due to tumour growth.

Eligibility criteria for participants were patients suffering from a jugulotympanic tumour (JTT; classified according to the Fisch class); carotid body tumour (CBT; classified according to Shamblin classification); or vagal body tumour (VBT classified according to Obholzer et al.) [12]. Patients suffering from metastasized tumours were excluded.

All patients were enrolled in a routine follow-up period. For the current study, in the case of tumour growth, follow-up was ended when the patient was treated. In general, patients attended a routine follow-up every year. In the main, MRI scans using the HNPGL-protocol were used. In cases where the tumour remained stable for five years, two-year follow-up intervals were considered; hereafter, five-year follow-up was considered. This regimen was, however, individualized depending on factors such as: age at presentation, mutation presence, tumour size, and comorbidities.

The outcome assessment in this model was twofold. First, tumour growth was defined as the primary outcome measure, and defined in two ways by the radiologist. First, because the craniocaudal dimension was measured less accurately, growth rates were calculated from the largest increase in dimension in the axial plane. Tumour volume measurements were also performed according to measurements described by Jansen et al. [6,] in which tumours were assumed to be ellipsoid. The following equation was used to estimate tumour volume: $V = 4/3 * \pi ((1/2\ A) * (1/2\ B) * (1/2\ C))$ in which 'V' refers to volume, 'A' to the largest dimension in the anteroposterior direction, 'B' to the largest dimension in the mediolateral direction, and 'C' to the largest dimension in the craniocaudal direction. The tumour volume increase was extrapolated to mean/median volume increases, provided in mm^3 per year. Tumour growth was defined as an increase of more than 15%, ascertained by a standard group of neuro-radiologists with expertise in this field using the same methods for growth evaluation, which likely decreased intra-observer variability. The second outcome measure was tumour-induced complications (TICs), which were defined by the clinician as major complications attributed to tumour growth, such as (cranial) nerve damage (including perceptive hearing loss and vertigo), or potentially life-threatening complications such as respiratory distress, carotid artery compression, or brain stem compression. The outcome measures were assessed at every clinical contact.

Age at presentation was a predictor of tumour growth, and was defined as age at first diagnosis of HNPGL. Mutation presence was defined as the presence of SDH-associated paraganglioma syndrome (SDHA, -B, -C, -D, and AF2) gene mutations. Type of tumour was defined as described above. Larger tumours were Shamblin class

3, Fisch class C, and Obholzer class 3 tumours. For prediction of tumour-induced complications, tumour growth itself as a binary value, and mean percentage of spherical increase per year, was examined.

The number of patients lost to follow-up are reported. Missing data were handled by using multiple imputation methods. Predictors implemented in the model were isolated from previous research and analyzed using multiple logistic regression. Binary logistic regression was employed, and the best predictive model was constituted using Wald backwards step-by-step variable exclusion (probability for stepwise entry was set at 0.05 and removal at 0.1). Internal validation was optimized using bootstrapping sampling techniques.

The data was collected using FileMaker Pro, and was analysed using IBM SPSS Statistics 22 (IBM, Armonk, New York, United States).

RESULTS

Participants

Of 258 tumours, a total of 157 tumours were evaluated by wait-and-scan, spanning 109 patients (61 women, 56%) with a median follow-up of 63.6 months (range, 2-260 months). After one year, three patients were lost to follow-up (1 JTT and 2 CBTs); after two years one additional patient suffering a JTT was lost. After five years, 79% of JTTs, 82% of CBTs, and 89% of VBTs (overall 86%) were still in follow-up. After 10 years, this rate was 41%, 43%, and 72% respectively. Of the 109 patients, median age at presentation was 65, and ranged from 13 to 90. Mutations were related to 93 tumours (59%); 42% were SDHD; 9.6% were SDHA; 7% SDHAF2; and 2.5% were SDHB and 0.6% SDHC. Further baseline characteristics are presented in table 1.

Age of presentation was significantly related to hereditary tumour syndromes ($p = 0.016$ CI:-16- -6). The median age at presentation when a mutation was present was 41.01 (SD13.7), and 52 (SD 17.6) when there was no mutation present.

Tumour growth

As demonstrated in table. 1, 70 of the 157 tumours (44%) grew. For all tumours, median follow-up was 51 months, (range, 6-261 months) (20 years). Non-growing tumours had a median follow-up of 57 months (range, 6-261 months). In cases of tumour growth, follow-up was measured until the point of treatment, and median follow-up was 35 months (range, 0.9-131 months). Tumour growth was generally found after 32 months (range, 0.5-131 months). Overall, 90% of tumours showed growth within 52 months.

Table 1: Growth characteristics per tumour type

	JTT*			CBT*			VBT*			Total		
	Growing tumour **	Non-growing tumour **	*Tot.* **	Growing tumour **	Non-growing tumour **	*Tot.* **	Growing tumour **	Non-growing tumour **	*Tot.* **	Growing tumour **	Non-growing tumour **	*Tot.* **
No. Tumours (%)	**24 (48%)**	**35 (52%)**	***59 (38%)***	**34 (47%)**	**37 (53%)**	***71 (45%)***	**12 (46%)**	**17 (54%)**	***29 (18%)***	**70 (44%)**	**87 (56%)**	*157*
Max. diameter in mm/ year	2.68	0	*0.41*	6.36	0	*1.6*	10.9	0	*1.6*	4.68	0	*1.09*
% Growth (mm3/year) median (range)	31.2 (13-53)	0	*18.5 (13-53)*	37.4 (10-97)	0	*17.9 (10-97)*	25 (15-42)	0	*10.34 (15-42)*	26.6 (10-97)	0	*18.6*
No. Complications (%)	5 (21%)	4 (11%)	*9 (15%)*	0	7 (19%)	*7 (10%)*	1 (8%)	3 (18%)	*4 (14%)*	6 (9%)	14 (16%)	*20 (13%)*
Follow-up (months) median (range)	32 (19-123)	66 (6-201)	*52 (19-201)*	32 (9-131)	67 (7-170)	*(53 9-170)*	55 (26-131)	107 (27-261)	*86 (26-261)*	35 (9-131)	57 (6-261)	*51 (6-261)*
No. Consecutive treatment(%)	13 (54%)	16 (46%)	*29 (49%)*	8 (23%)	10 (27%)	*18 (25)*	2 (16%)	3 (18%)	*5 (17%)*	23 (44%)	29 (33%)	*52*

* JTT: jugulotympanic tumours; CBT: carotid body tumours; VBT: vagal body tumours

** Growing tumours; Non growing tumours, Total tumours

Median growth rates were 0.41mm/year (range 0-439) for JTT; 1.6mm/year (range 0-23.68) for CBTs; and 1.6mm/year (range 0-23.68) for VBTs. Using a one-way anova, there was no significant difference between tumour growth rates for different tumour types (df = 2, F=1.87, p = 0.157). In the case of tumour growth, average growth rates were 2.68 (range 1.23-4.9), 6.36 (range 0.29-23.68), and 10.9 (range 2.57-23.62) mm/year respectively. Again, there was no significant relation (df = 2, F=1.89, p = 0.171). Median percentage spherical volume increases in mm^3/year were 31.2 (13-53), 37.39 (10-97,) and 25 (15-42), for JTT, CBT, and VBTs respectively (df = 2, F=1.92, p = 0.671).

Furthermore, we found a significant relation between tumour growth incidence and age at presentation (t=-2.46, df 145, p = 0.015). In investigating a cut-off point, a Chi square test revealed that growth incidences were significantly higher when patients presented before the age of 50 (58.6%) versus patients presenting later in life (31.7%; df = 1, p = 0.001). Furthermore, using a Pearson's Correlation test, we found a significant inverse correlation between age at presentation and growth rates, measured both in median spherical volume increase per year (p=0.011; r = -0.439); and growth in mm/year (p = 0.021; r = -0.237). The younger the patient, the higher the volume increase per year (figure 1). Using logistic regression analysis, we found that age at presentation remained a significant predictor of growth after stepwise adjustment for the potential confounders of age, mutation, tumour type, and tumour size (B=-0.026; OR=0.974; P < 0.05).

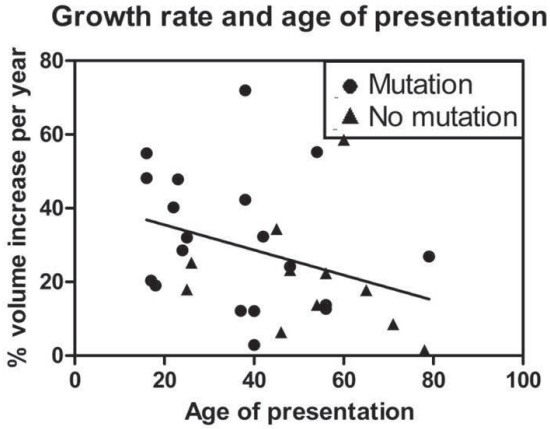

Figure 1: growth rate and age of presentation

The accuracy with which age predicts tumour growth was evaluated using an ROC curve, for which an AUC of 0.629 was found, indicating poor predictive value. When

determining a cut-off point, we found that being younger than 50 is associated with significantly higher growth rates when compared to baseline growth rates.

Moreover, we found that there is no significant relation (p= 0.31; df 1) between mutation presence and tumour growth incidence (65.7 versus 57.7%) or growth rates, when compared to the no-mutation group (median 39.7 mm^3/y versus 21.38 mm^3/y; p = 0.064).

Complications

Tumour-induced complications are presented in table 2. Of 17 tumours inducing 20 complications, six were growing, and these illustrated a significantly higher tumour growth rate when compared to those not presenting complications (75.6 mm^3/y versus 30.3 mm^3/y resp.; p = 0.016; F = 6.496). However, using a logistic regression, with step-by-step correction for the confounder's age, mutation presence, and tumour type and size, tumour growth rate was not found to be an independent predictor for tumour complications (B=11.418; OR=90937,576; P = 0.963). Moreover, we did not find higher complication rates in younger patients or patients with a mutation; nor was there a relation between type of tumour and complications. We further stratified our results for larger tumours such as Fisch class D, Shamblin class 3, and Vagal class 3 tumours, and again no relation was found (results not shown). Eleven tumours were not growing, of which six (55%) illustrated a tumour syndrome, and seven (64%) were larger-size tumours.

Table 2: Number of tumour induced complications

Complication	*No.* Total	*No.* growing tumours (% of total)
Local complications due to tumour mass	**7**	**2 (28)**
Perceptive hearing loss	5	
Carotid stenosis	1	1 (100)
Tracheotomy	1	1 (100)
Cranial nerve paresis	**13**	**4 (31)**
VII paresis	2	
IX paresis	1	
X paresis	5	2 (40)
XI paresis	1	
XII paresis	2	2 (100)
Total	20	6 (30)

Motivation for secondary intervention

A total of 52 patients underwent additional treatment. The main reasons for intervention were: reported growth (44%); tumour-induced complications (50%); and patient preference (6%). For 31 tumours in which growth was found (out of a total of 70 growing tumours), no intervention was executed and no complications due to tumour growth found after a median follow-up of 36 months (range 8-72). Fourteen (45%) of these were smaller tumours. The mean age at presentation in this group was 47, and in 65% mutations were found (these differences were not statistically significant). Moreover, in 14 patients, multifocal HNPGL disease was found. Reasons for non-intervention were: small tumour without morbidity (39%); prevention of bilateral CN damage in the case of bilateral HNPGL (32%); patient preference (20%); and patient not fit for treatment (10%).

In the case of secondary treatment due to TICs, for two patients' cranial nerve function improved post treatment: one facial nerve paresis (House-Brackmann 3) in a Fisch class C3 tumour improved after an inftratemporal fossa approach with facial nerve rerouting. After an initial decline to full facial paralysis, 11 months postoperatively a House-Brackmann grade 1 facial paralysis was found. In the second case, a jugulotympanic tumour Fisch class C1 was treated with gammaknife, rendering full regain of function of an initial IX, X, and XI pareses approximately 10 months' post treatment.

DISCUSSION

This study illustrates the feasibility of a wait-and-scan period as the primary management strategy for HNPGL. Evaluating 157 HNPGLs, we found tumour growth in 44% of cases after a median follow-up of 63.6 months (range, 2-260 months). Tumour-induced complications were found in 12% of patients, and all received consecutive treatments, rendering regain of CN function in 2 patients (and 4 cranial nerves). Overall, 51 patients (32%) were treated, and for 67% of patients, a potentially harmful treatment regimen was prevented.

In cases of TICs, growth rates were significantly higher when compared to patients remaining free from TICs. On the other hand, the presence of tumour growth itself – as opposed to growth rate – was not a risk factor for TICs. Furthermore, we found that in 14 out of 20 complications, no radiological growth was found; neither was any relation between age of presentation, mutation presence, tumour type, or tumour size found in this sub-population. On the other hand, 31 out of 70 growing tumours were not treated, and no complications were found after a median follow-up of 36 months.

We could not associate genotype, tumour type, or tumour class with either tumour growth or TICs. The age of presentation, however, was an independent predictor of tumour growth and showed a significant inverse correlation with growth rates: the younger the age of presentation, the higher the growth rate. In investigating the cut-off point determining higher growth rates and incidences, we found that being 50 years of age or younger was associated with higher growth incidence, when compared to being older than 50. These results suggest that an initial wait-and-scan strategy is a feasible management strategy for HNPGL of different subclasses, whereby potentially harmful treatment regimens are reserved for those patients suggested to be at risk of high morbidity by established tumour growth. The management strategy as presented by the current authors could not prevent TICs, as complications were found in 17% of non-growing tumours. However, the risk of treatment with radiotherapy and surgery is potentially higher. Systematic reviews have illustrated that there is no significant difference in tumour control rates between radiotherapy and surgery. The risk of complications such as cranial nerve damage has been found to be 0.9 per patient post surgery, and 0.08 post radiotherapy [2,3]. For Shamblin class 2 and 3 tumours, these reviews have illustrated that surgery induced new cases of permanent cranial nerve deficit in 22% of 2175 patients; before radiotherapeutic treatment, a total of two cranial nerves were affected, which decreased to one post-radiotherapy. The follow-up rates of the studies included in these reviews were variable, and all radiotherapeutic techniques were pooled in this analysis. A more recent large study evaluating the long-term effects of radiotherapy in 131 patients with 156 benign paragangliomas however, describes no severe complications post treatment with a minimal follow-up of 11.5 years [13]. Considering these results, the risk of TIC brought about by an initial wait-and-scan policy should be weighed against the risk of treatment, of which radiotherapy seems to be the better option. Physicians taking this approach should recognize that cranial nerve deficits that may result from tumour progression are potentially more permanent, and should be weighed against the morbidity of radiotherapy [13]. Therefore, a wait-and-scan policy can be considered a viable treatment option, particularly when radiotherapy is not a treatment option.

Tumour-induced complications

To date, it remains uncertain which factors might generate an enhanced risk of complications. Several studies have described the results of a wait-and-scan approach, and these found a wide variety of complication incidences (4-30%); tumour growth incidences also widely differed, at between 5 and 60% [5,7-10]. Methodological differences in growth estimation and small sample sizes, however, make it hard to interpret these results. Considering the results of the current study, it seems reasonable to suggest two

main mechanisms as being responsible for TICs. The first of these is enhanced tumour growth. Although this was not an independent predictor of complications, tumour growth rates in patients suffering TICs were significantly higher when compared to baseline growth rates.

The overall median growth rate found in our study (1.09), is similar to that described by Jansen et al. (0.83), who used the same methods for volume estimation [6]. Secondly, although we could not predict TICs, we did find that age of presentation was an independent predictor of tumour growth, and being 50 years or younger was associated with significantly higher growth rates. Huy et al. suggested such a relation, based on the observation that patients presenting before the age of 20 generally suffered from larger C3De-type jugular paraganglioma, rather than jugular tumours of a lower Fisch class [11]. The finding was, however, not statistically verified. We have found no other reports describing age of presentation and paraganglioma growth rates. An important consideration in interpreting these results is that we also found that patients with a mutation presented at a younger age in general, which might mean that mutation presence is a confounder. Nonetheless, we corrected for mutation presence in the analysis, and found that it could not be associated with growth or the incidence of complication. Obviously, we cannot exclude the possibility that patients presenting at a younger age (and with higher growth rates) in our series did not suffer from a hitherto unknown tumour syndrome. This is particularly likely given that previous reports have illustrated that 25-56% of apparently sporadic tumours do in fact turn out to be part of a tumour syndrome [14-16]. Nonetheless, in the current series, all patients were subjected to a careful diagnostic work-up process, in which screening for hereditary syndromes is common practice. Furthermore, we also found that, in line with Jansen et al., when comparing different tumour locations, jugulotympanic paragangliomas tended to be smaller and less progressive than paragangliomas developing at other locations.

As we also found that in 64% of TICs no growth was found, we suggest that there must in fact be a second mechanism involved in TICs, other than tumour growth. It is suggested that there is a form of tumour activity resulting in local invasiveness rather than expansion, which has been described regarding HNPGL in the past. Although this is a mechanism that has been described before, it is one which has usually been attributed to the presence of more aggressive tumour types [17, 18] and genotypes [19]. In the current study however, we could not find a relationship with tumour type or the presence of mutation. Neither was age of presentation related to complications in this group. However, it should be noted that this finding concerns just 11 cases in total, which might hinder robust statistical analysis.

Methodological considerations

There are several methodological considerations which merit discussion. The problem with research of rare conditions is the fact that RCTs are largely not feasible. The current study is a retrospective cohort study, and therefore the level of evidence provided remains at level 2. With respect to HNPGL research, tumour incidence, low tumour growth rates, and ethical considerations all combine to make comparison between different prospective management strategies especially difficult. This tends to reduce external validity. Therefore, the current data on success rates is mainly a reflection of the clinical outcomes of the current centre. Nonetheless, a protocol for the employed wait-and-scan policy administered by our centre is provided in the Methods section.

Another important aspect is tumour growth evaluation, for which we used two different methods: increase per year (assessed in millimetres); and volume determination. It has been suggested that growth should be evaluated in three dimensions, since volume estimates are more reliable than two-dimensional measurements; and that HNPGL could be assumed to be conical [6, 20, 21]. For JTTs such an ellipsoid shape might not be applicable, since these tumours are largely confined to the confirmation of the petrous bone.

Another limitation of this study is the follow-up interval. The mean follow-up interval was 51 months (range, 6-261 months). It should be noted that we found tumour growth up until the 245-months (20 years) mark. Given that 90% of tumours presented growth within 52 months, it is likely that tumour growth will be apparent in these cases in the future, and that such patients are to be subject to treatment regimens. Furthermore, in the current protocol we found that although growth rate is associated with complications, it should not be considered as the sole predictor of TICs. In this vein, we found that in none of the non-treated growing tumours were complications found; and in 65% of complication cases, no tumour growth was reported. Therefore, additional research is required into predictive parameters for what tumour traits are responsible for the induction of complications.

The current study sample is subject to loco-regional factors, potentially resulting in a relative overrepresentation of hereditary syndromes, such as SDHA, AF2, and D tumour syndromes. This might also have rendered the current study population relatively young, due to familial screening programmes.

CONCLUSION

The results of this study illustrate that a wait-and-scan policy is a feasible treatment option in cases for HNPGL, as it potentially prevents treatment-induced morbidity in the majority of patients, including those presenting larger tumours. It is suggested this

option should, therefore, be carefully weighed against the risks of alternative options such as radiotherapy. Moreover, the study suggests that the wait-and-scan policy should be altered for patients of 50 years or younger, by decreasing the follow-up interval between scans to evaluate tumour biology more closely. Our results also suggest that radiological follow-up is not an optimal management strategy, since a large group of tumours were found not to grow, though they did elicit complications, in the main, years after the initial diagnosis. Issuing long-term follow-up protocols, and careful clinical examination, should therefore remain crucial aspects of HNPGL management, in order to prevent TICs. No evidence was found for altering the wait-and-scan regime in cases where other theoretical risk factors are found to be present, such as hereditary tumour syndromes, and particular tumour types and sizes.

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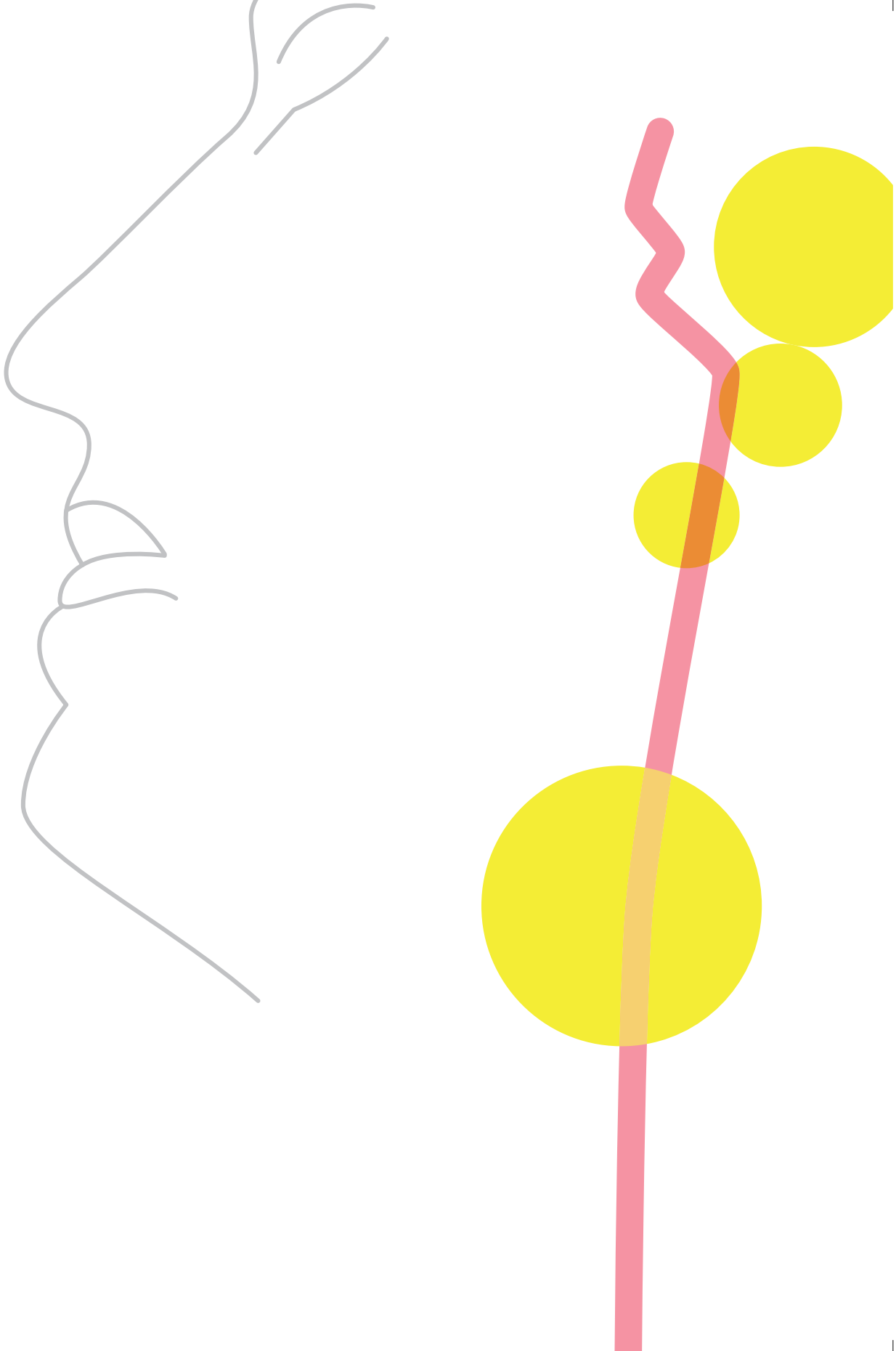

PART 2

The Evaluation of Different Treatment Modalities for Head and Neck Paraganglioma of Different Sub-Sites and Tumour Class

CHAPTER 3

Results of a Systematic Literature Review of Treatment Modalities for Jugulotympanic Paraganglioma, Stratified per Fisch Class

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ABSTRACT

Objective: Key for successful jugulotympanic paraganglioma management is a personalized approach aiming for the best practice for each individual patient. To this end, a systematic review is performed, evaluating the local control- and complication rates for the different treatment modalities stratified by the broadly accepted Fisch classification.

Design: A systematic literature review according to the PRISMA statement was performed. A detailed overview of individual treatment outcomes per Fisch class is provided.

Main outcome measures: local control, cranial nerve damage, complications, function recovery.

Results: Eighteen studies were selected, resembling 83 patients treated with radiotherapy and 299 with surgery. Excellent local control was found post surgery for class A and B tumours and risk of cranial nerve damage was <1%. For class C1-4 tumours, local control was 80-95% post surgery (84% post radiotherapy) and, cranial nerve damage was found in 71-76% (none post radiotherapy; $p < 0.05$). There was no difference in treatment outcomes between tumours of different C class. For class C1-4De/Di tumours, local control was 38-86% (98% post radiotherapy; $p < 0.05$) , cranial nerve damage/complication rates were 67-100% (3% post radiotherapy; $p < 0.05$). C1-4DeDi tumours showed lesser local control and cranial nerve damage rates when compared to C1-4De tumours.

Conclusions: An individual risk is constituted for surgery and radiotherapy, stratified per Fisch class. For class A and B tumours surgery is a suitable treatment option. For class C and D tumours radiotherapy results in lower complication rates and similar or better local control rates when compared to the surgical group.

Keywords: review, treatment, jugulotympanic, paraganglioma, Fisch class

INTRODUCTION

Paragangliomas of the head and neck (HNPs) are rare, comprising about 0.6% of head and neck tumours and 0.03% of all tumors[1]. Thirty percent of HNPGLs are jugulotympanic tumors[2]. Jugulotympanic paragangliomas (JTPGL) are slow growing neuro-endocrine tumours that are benign in almost all cases. Despite the benign nature, symptomatology can be considerable and is mainly caused by growth towards delicate surrounding structures such as cranial nerves (CN) and large vessels. However, their indolent growth pattern makes it difficult to predict if and when these tumours will become clinically apparent; some tumours cause CN damage or invade the intracranial space, while others show spontaneous regression[3].

It is due to the rarity of paragangliomas, and their variable yet potentially debilitating clinical presentation that the management of these tumours remains a matter of debate. The more since the main treatment options considered for JTPGL, surgery and radiotherapy, may also cause cranial nerve damage or other serious adverse effects. Therefore, if clinical presentation does not require immediate therapy, most authors recommend an initial "wait and scan" strategy[2,4,5,6]. However, in case active intervention is advised, it remains uncertain what the best practice would be since each treatment modality has its limitations: Traditionally, surgery is considered the number one treatment option as it actually removes tumour mass[7]. However, recent developments have advocated the role of radiotherapy as it renders comparable local control rates and less iatrogenic cranial nerve damage or other complications such as cerebrospinal fluid leakage, wound infection or a stroke[8]. The long term risks of radiotherapy in terms of sensorineural hearing loss, tissue necrosis or irradiation induced malignancies remain uncertain however.

It is clear that for JPGL there is no "one fits all" approach and the key for successful JPGL management, is a personalized approach, aiming for the best practice for each individual patient. In order to achieve this, a better understanding of the risks associated with treatment of each tumour class is required. Therefore, a systematic review is performed, evaluating the local control- and complication rates for the different treatment modalities stratified by the broadly accepted Fisch classification.

METHODS

Ethical considerations

This study was conducted in line with the ethical guidelines of the Radboud University Medical Centre, the Netherlands.

Search protocol

We performed a systematic literature review according to the PRISMA statement[9]. We searched the Pub Med Database for articles using the following search strategy (no Mesh terms were used for inclusion of the most recent articles):

(((Treatment [Title/Abstract] OR Treatment [MeSH Terms] OR Management [Title/Abstract] OR Management [MeSH Terms] OR therapy [Title/Abstract] OR therapy [MeSH Terms] OR approach [Title/Abstract] OR approach [MeSH Terms] OR procedure [Title/Abstract] OR procedure [MeSH Terms] OR Radiotherapy [Title/Abstract] OR Radiotherapy [MeSH Terms] OR radiation therapy [Title/Abstract] OR radiation therapy [MeSH Terms] OR X-ray therapy [Title/Abstract] OR X-ray therapy [MeSH Terms] OR radioisotope therapy [Title/Abstract] OR radioisotope therapy [MeSH Terms] OR Radiosurgery [Title/Abstract] OR Radiosurgery [MeSH Terms] OR Gamma Knife [Title/Abstract] OR Gamma Knife [MeSH Terms] OR CyberKnife [Title/Abstract] OR CyberKnife [MeSH Terms] OR Linear Accelerator [Title/Abstract] OR Linear Accelerator [MeSH Terms] OR Linac [Title/Abstract] OR Linac [MeSH Terms] OR LINAC [Title/Abstract] OR LINAC [MeSH Terms] OR Surgery [Title/Abstract] OR Surgery [MeSH Terms] OR operative [Title/Abstract] OR operative [MeSH Terms] OR invasive [Title/Abstract] OR invasive [MeSH Terms] OR operations [Title/Abstract] OR operations [MeSH Terms] OR peroperative [Title/Abstract] OR peroperative [MeSH Terms] OR perioperative [Title/Abstract] OR perioperative [MeSH Terms] OR intraoperative [Title/Abstract] OR intraoperative [MeSH Terms] OR excision [Title/Abstract] OR excision [MeSH Terms] OR resection [Title/Abstract] OR resection [MeSH Terms] OR Wait and scan [Title/Abstract] OR Wait and scan [MeSH Terms] OR Wait and see [Title/Abstract] OR Wait and see [MeSH Terms] OR Conservative [Title/Abstract] OR Conservative [MeSH Terms] OR Expectative [Title/Abstract] OR Expectative [MeSH Terms] OR Embolotherapy [Title/Abstract] OR Embolotherapy [MeSH Terms] OR Embolization [Title/Abstract] OR Embolization [MeSH Terms] OR Occlusion [Title/Abstract] OR Occlusion [MeSH Terms]))) AND (((((((Tumour [Title/Abstract] OR Tumour [MeSH Terms] OR Tumour [Title/Abstract] OR Tumour [MeSH Terms] OR Tumours [Title/Abstract] OR Tumours [MeSH Terms] OR Tumours [Title/Abstract] OR Tumours [MeSH Terms]))) AND ((Carotid body [Title/Abstract] OR Carotid body [MeSH Terms] OR Vagal body [Title/Abstract] OR Vagal body [MeSH Terms]))))) OR ((((Jugulare [Title/Abstract] OR Jugulare [MeSH Terms] OR Caroticum [Title/Abstract] OR Caroticum [MeSH Terms] OR Carotis [Title/Abstract] OR Carotis [MeSH Terms] OR Vagale [Title/Abstract] OR Vagale [MeSH Terms] OR temporale [Title/Abstract] OR temporale [MeSH Terms] OR jugulotympanicum [Title/Abstract] OR jugulotympanicum [MeSH Terms] OR tympanicum [Title/Abstract] OR tympanicum [MeSH Terms])))) AND ((Glomus [Title/Abstract] OR Glomus [MeSH Terms]))))) OR ((((Head and neck [Title/Abstract] OR Head and neck [MeSH Terms] OR Cervical [Title/Abstract] OR Cervical [MeSH Terms] OR Temporal [Title/Abstract] OR Temporal [MeSH Terms] OR Jugular [Title/Abstract] OR Jugular [MeSH Terms] OR Tympanic [Title/Abstract] OR Tympanic [MeSH Terms] OR jugulotympanic [Title/Abstract] OR jugulotympanic [MeSH Terms] OR Carotid [Title/Abstract] OR Carotid [MeSH Terms] OR Carotis [Title/Abstract] OR Carotis [MeSH Terms] OR Vagal [Title/Abstract] OR Vagal [MeSH Terms]))) AND ((paraganglioma [Title/Abstract] OR paraganglioma [MeSH Terms] OR paragangliomas [Title/Abstract] OR paragangliomas [MeSH Terms] OR chemodectoma [Title/Abstract] OR chemodectoma [MeSH Terms] OR chemodectomas [Title/Abstract] OR chemodectomas [MeSH Terms] OR glomus tumour [MeSH Terms] OR glomus tumour [Title/Abstract] OR glomus tumours[Title/Abstract] OR glomus tumours [MeSH Terms] OR glomus tumour [MeSH Terms] OR glomus tumour [Title/Abstract] OR glomus tumours[Title/Abstract] OR glomus tumours [MeSH Terms])))))

Eligibility Criteria

Criteria for eligibility according to the PICO methodology were used[8]: The investigated population constituted of patients affected by JPGL, stratified by Fisch class (table 1)[9]. The intervention was any form of surgery or radiotherapy, with or without a prior "wait and scan" period. The results of treatment outcome were compared to the patients' situation before treatment. Treatment outcomes were local control, cranial nerve function and complications. The definitions of control and complications were adopted from Suarez et al.[7]. Post surgery, local control was defined as a patient alive without evidence of disease throughout the entire follow-up period. Symptom relief, e.g. in form of decompression of tumour mass, was not considered as local control in the current study. Post radiotherapy local control was defined as a patient alive with regression of the tumour, or without any evidence of progression of the disease throughout the entire follow-up period. CN damage was defined as deterioration of CN function post treatment when compared to the pre-treatment setting, substantiated by a physician. Symptom recovery was defined as any improvement of CN function in post treatment setting when compared to pre-treatment conditions, substantiated by a physician. For class A and B tumours, post-treatment hearing loss and tinnitus was considered a treatment outcome as well. The complications CSF leakage, wound infection, CVA, aspiration resulting in pneumonia and/or tracheotomy and death were included.

Table 1: Fisch classification.

Tumour class	Location and extension of tumour
A	Tumours that arise along the tympanic plexus on promontory
B	Tumours with invasion of hypotympanum; cortical bone over jugular bulb intact
C1	Tumours with erosion of carotid foramen
C2	Tumours with destruction of carotid canal
C3	Tumours with invasion of carotid canal; foramen lacerum intact
C4	Tumours with invasion of foramen lacerum and cavernous sinus
De	Tumours with intracranial but extradural extension
Di	Tumours with intracranial and intradural extension

Study selection

To be selected, articles had to be written in English, German, French or Spanish. Mean follow-up had to be at least 12 months for both treatment modalities. The short term results of radiotherapy (1 year post treatment), were compared with those 5, 7 and 10 years post treatment. The tumours had to be classified according to the Fisch classification or we personally classified the tumours in case sufficient diagnostic information was provided. The treatment modality (surgery, radiotherapy technique) and outcome measures had to be reported for each Fisch class separately. To evaluate results of

radiotherapy, we pooled C1-4 tumours as "class C tumours", and C1-4De1-2/Di1-2 tumours as class D tumours. For evaluation of surgical results however, results were presented individually. Information on at least one of the afore-mentioned outcome measures had to be described. This selection procedure was executed twice by the researcher (first author). In case of discordance, the issue was discussed with supervising authors (Kunst, Marres).

Risk of bias in individual studies

A critical appraisal per study was performed, with respect to risk of bias using the PRIMSA 'Risk of bias' tool. The following terms were addressed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other forms of bias. The majority of the studies did not comply with PRIMSA and therefore we decided not to use this as an exclusion criterion.

Risk of bias across studies and synthesis of results

It was evaluated whether the study properly addressed the research question and the inclusion of subjects was assessed. Pooled results of all studies are presented, as well as the individual study results in Appendix A. Hereby, the internal and external validity of the current research was enhanced. Pooled results were provided in mean, actual numbers and range.

RESULTS

Study selection

Figure 1 illustrates the flow chart of study selection. Using the above mentioned research question 3505 articles were identified. These were screened for title and abstract, and a total of 81 articles were selected for full article review. Most articles were excluded based on different anatomical tumour localization. Out of these 81 articles, 63 articles were excluded mostly because results were not stratified per Fisch class. Three were excluded due to small sample sizes, and four were excluded due to insufficient follow-up. Ultimately, 18 studies were selected for the current review.

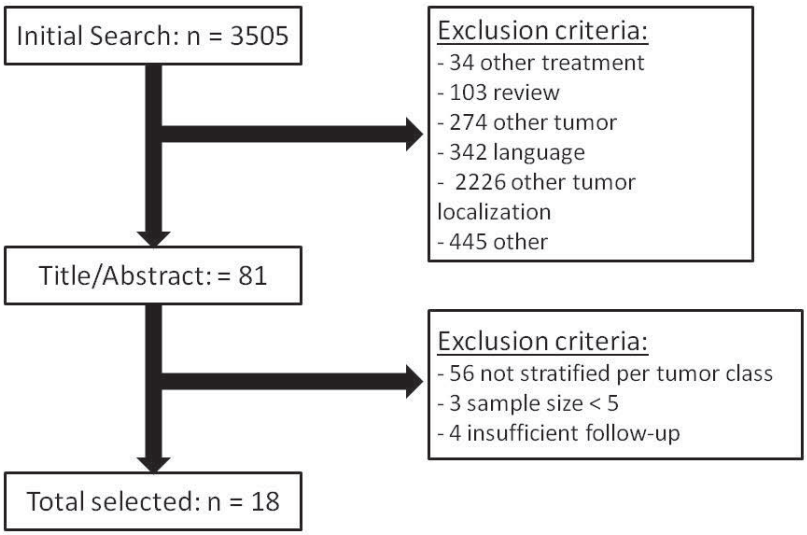

Figure 1: flow chart

Surgical results

For class A and B tumours, 100% local control and no complications were found. A single case of NVII damage was described in a class B tumour and no cranial nerve damage was found for class A tumours. Post treatment, improvement of hearing loss and pulsatile tinnitus was found in 0%-23% (mean 11%) for class A tumours, and in 0%-8% (mean 3%) for class B tumours.

Surgical results for class C and D tumours are presented in figure 2,and table 3, describing the local control and cranial nerve damage rates per tumour class. Unfortunately, complication rates, other than cranial nerve damage, were not stratified sufficiently to present per Fisch class. The main complications and cranial nerve damage rates found for class C and CD tumours combined are presented in table 2. Symptom recovery was described in 2 patients (1%)post surgery.

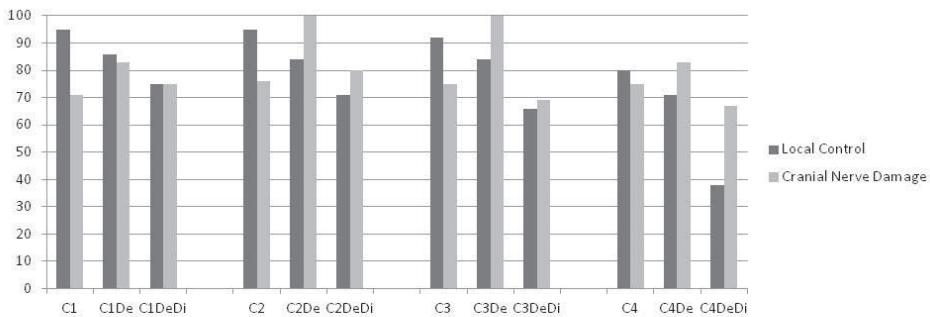

Figure 2: local control and cranial nerve damage rates per tumour class

Table 2: complications and cranial nerve damage rates

Complications found	(%) N/Ntotal
CSF leak	14 (43/299)
Stroke	5 (16/299)
Wound infection	3 (9/299)
Tracheotomy	2 (6/299)
Bleeding	1 (1/299)
N. VII palsy	18 (54/299)
N. VIII palsy	3 (9/299)
N. IX palsy	23 (69/299)
N. X palsy	21 (63/299)
N. XI palsy	13 (39/299)
N. XII palsy	3 (9/299)

A significant correlation was found between local control and cranial nerve damage rates and increasing Fisch class (df 11, p = 0.00; df 11, p = 0.001). Using a bonferroni post test, we found that having a C4DeDi tumour shows significantly worse local control rates when compared to tumours of lower Fisch class. For Fisch class C1-4 tumours (without intracranial invasion), local control rates, cranial nerve damage rates and complication rates were not significantly related to increasing C class (df 3, p = 0.307; df 3 p = 9.997; df 3 p = 0.7). Within class D tumours, intra-dural invasion was related to lesser local control rates (df1, p = 0.004) and higher cranial nerve damage rates (df1, p = 0.005) when compared to extradural growing tumours, independent of C-classification. There was no increased risk of complications in this group.

Radiotherapy results

Short and long term local control rates post radiotherapy are presented in figure 3. There was no significant difference between results of class C and D tumours (F = 0.054, p = 0.82), neither was there a difference in local control or cranial nerve damage / complication rates in 1 versus 5 (p = 0.9; p =0.7), 7 (p = 0.99; p =0.8) and 10 (p = 0.6; p =0.5) years post treatment in general, nor for class C and D tumours individually.

In 13 patients (16%) of all irradiated patients, symptom recovery was found post treatment. A n. VII palsy and complete sensorineural hearing loss was found post-irradiation of 2 class D tumours. No further complications were found post-radiotherapy in the included studies.

Comparison of treatment modalities

In table 3 the differences in treatment outcome per treatment modality are provided, stratified per tumour class. For class C 1-4 tumours, local control rates did not differ

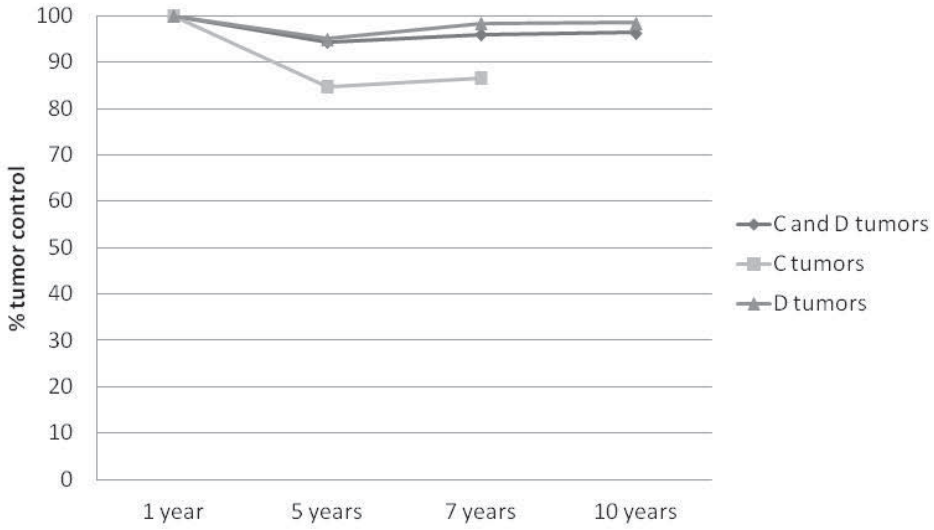

Figure 3: Short and long term results post radiotherapy

Table 3: Differences in treatment outcome per treatment modality, stratified per tumour class.

		Local control		Cranial nerve damage/ complications		
	Surgery	Radiotherapy (long term results)	Surgery vs. Radiotherapy	Surgery	Radiotherapy (long term results)	Surgery vs. Radiotherapy
	% (N/N_{total})	% (N/N_{total})	P value	% (N/N_{total})	% (N/N_{total})	P value
A	100 (84/84)	-	-	0 (0/84)	-	-
B	98 (39/40)	-	-	6 (3/47)	-	-
C1	95 (40/42)	84 (13/15)	0.6	71 (25/35)	0 (0/15)	*0.00*
C1De	86 (19/22)	98 (65/66)	*0.04*	83 (4/17)	3 (2/66)	*0.00*
C1DeDi	75 (6/8)	98 (65/66)	0.13	75 (6/8)	3 (2/66)	*0.00*
C2	95 (39/41)	84 (13/15)	0.28	76 (19/25)	0 (0/15)	*0.00*
C2De	84 (26/31)	98 (65/66)	*0.01*	100 (12/12)	3 (2/66)	*0.00*
C2DeDi	71 (17/24)	98 (65/66)	*0.00*	80 (12/15)	3 (2/66)	*0.00*
C3	92 (12/13)	84 (13/15)	0.64	75 (6/8)	0 (0/15)	*0.00*
C3De	85 (11/13)	98 (65/66)	*0.01*	100 (4/4)	3 (2/66)	*0.00*
C3DeDi	66 (35/53)	98 (65/66)	*0.00*	69 (9/13)	3 (2/66)	*0.00*
C4	80 (4/5)	84 (13/15)	0.78	75 (3/4)	0 (0/15)	*0.04*
C4De	71 (5/7)	98 (65/66)	*0.02*	83 (5/6)	3 (2/66)	*0.00*
C4DeDi	38 (8/21)	98 (65/66)	*0.00*	67 (2/3)	3 (2/66)	*0.014*

significantly from long term radiotherapy results, yet cranial nerve damage rates were significantly higher post surgery. For class De/DeDi tumours local control and cranial nerve damage rates were significantly worse post surgery when compared to results of radiotherapy.

DISCUSSION

Summary of main results

The current review evaluates the effect of radiotherapy and surgery on JTPGL of different Fisch class, in order to gain insights for individualized JTPGL management in the future. Although surgical procedures varied, class A and B tumours seem to be properly managed surgically with respect to local control, cranial nerve damage and complication rates. Presenting symptoms like conductive hearing loss and pulsatile tinnitus generally persisted post-operatively. Few articles described the effect of radiotherapy on class A and B tumours, therefore more research is required on this matter. For class C and D tumours, surgical treatment outcomes were less uniform between studies. A wide range of local control rates between studies was found as well as a higher risk of cranial nerve damage and complications when compared to radiotherapy. Overall, these results provide valuable insights for JTPGL management in daily practice: Based on the current evidence, early surgery is advised for class A and B tumours. For class C1-4 tumours local control was similar to radiotherapy results, yet radiotherapy had significantly lower morbidity rates. For class C1-4De/Di tumours both local control and morbidity rates were more favourable post radiotherapy. Therefore, in case treatment is required, radiotherapy is suggested as the favourable treatment option, albeit both treatment modalities potentially induce iatrogenic morbidity. A dual approach suggesting tumour debulking and occasional additional radiotherapy is discussed underneath.

Overall completeness and applicability- and quality of evidence;

Inevitably, the level of evidence for these recommendations is low. There are no randomized controlled trials available on this subject. Also, there are no studies that used proper control-groups evaluating two treatment modalities. All studies were retrospective of nature with inherent biases of all sorts. In order to reduce the interpreters-bias, we conducted our research according to the methodology of the PRISMA statement. Moreover, we provided the study details of each study separately, including the methodology of the study and the results of a critical appraisal. Hereby, studies could be assessed for reliability/methodological quality and the impact can be regarded in the context of other studies.

Potential biases in review

A potential bias in this study is that we did not stratify for additional treatments other than radiotherapy and surgical techniques. The influence of pre-treatment embolization was not considered. Nonetheless, whether or not these techniques were used was presented in the table.

Also, we did not stratify our results for tumours with hereditary biology for which counselling might be different due to a higher chance of multiple HHPGL's during a patient's life. Also, the growth rate of these tumours differs and might alter counselling of patients.

Comparison with other reviews

There are two main reviews conducted on this matter subject and the treatment outcomes are in line with the current review. First, Suarez et al. described for a total of 1084 patients with JPGs with different surgical procedures that control of the disease was achieved in 93.3% of patients7. A total of 715 patients with JPG were treated with radiotherapy: 461 with EBRT and 254 with SRS. Control of the disease with both methods was obtained in 89.1% and 93.7% of the patients, respectively. The treatment outcomes of a JPG treated with surgery or radiotherapy were compared. The control failure, major complication rates, and the number of cranial nerve palsies after treatment were significantly higher in surgical than in radiotherapy series. Unfortunately however, treatment outcomes are not stratified per Fisch class which hinders individual patient counselling. A second review was conducted by van Hulsteijn et al., which provided an overview of regression rates after radiotherapy in HNPGLs by means of a meta-regression analysis23. Fifteen studies were included, concerning a total of 283 jugulotympanic HNPGLs. Pooled regression proportions for initial, combined and salvage treatment were respectively 21%, 33% and 52% in radiosurgery studies and 4%, 0% and 64% in external beam radiotherapy studies. Pooled local control proportions for radiotherapy as initial, combined and salvage treatment ranged from 79% to 100%. Again, results were not stratified per tumour class, yet cranial nerve damage-, complication- and recovery rates are not reported in this review.

Implications for clinical practice and research

The biology of paragangliomas has proven to be unpredictable, and spontaneous (partial) regression has been described3,6. This, as well as the fact that cranial nerve damage and complication rates post treatment are not trivial, support an initial conservative wait and scan management for class C and D tumours. Studies that describe the experience with a wait and scan strategy (excluding patients with brainstem compression

or malignant disease) illustrated that merely 20-60% of HHPGL showed further tumour growth, and that additional treatment was required in only 0-5% of patients due to progression of existing cranial nerve damage without tumour growth4,5,6,24. Huy et al. noted that particularly in younger patients, tumour progression rates might be higher, and therefore, wait and scan might be less favorable25. Conversely, Carlson et al. found that there was a trend toward higher rates of tumour progression in patients who were followed longer—a finding that was also reported by Prasad et al.4,24. Therefore, more information on the risks of wait and scan procedures is required. However, given the complication rates post class C and D tumour treatment, we believe that an initial wait and scan strategy is justified also for younger patients, particularly since younger patients have a higher life-time risk of radiation-induced malignancy and other complications such as atherosclerosis of the carotid artery and subsequent ischemic stroke.

Our results demonstrate that if a conservative management strategy does not suffice in the case of class C and D tumours due to tumour progression, one should consider the use of radiotherapy over surgical management. The current results show that chances for achieving local control with surgery are unsatisfactory for class D tumours and for both C and D tumours at least transient cranial nerve damage seems inevitable and complications occur frequently. No difference was found between C class 1-4 tumours, and in case of intracranial invasion intradural growth was associated with lesser local control rates enhanced cranial nerve damage rates when compared to extra-dural intracranial tumours. The adverse event rates can be explained since gross tumour removal often requires manipulation of delicate neurological and/or vascular structures. Lower cranial nerve palsies of Nn IX and X (nerves at risk during frequently used infra-temporal fossa approaches) impose a potential life-threatening risk of aspiration. In the current review, six patients required a tracheotomy post-surgery due to such lesions. Moreover, manipulation in the area of greater vessels is considered a risk-factor for the development of strokes, which were identified in 16 patients post-surgery. Additionally, physical manipulation of the dura induced CSF leaks (found in 43 patients), and rendered wound infection in 9 cases. In comparison, no radiotherapy-induced Nn. IX or X lesions were found, and merely one stroke was described, although this could increase with extended follow-up.

Obviously, the risk associated with surgery of Fisch class C and D tumours is dependent on multiple factors, one of the most important ones being the expertise of the centre. Nevertheless, when considering the large series (N > 30) published by expertise-centres higher cranial nerve damage and complication rates post surgery, and lower local control rates remain when compared to radiotherapy series 26, 27, 28. It seems as if high local control rates come at the cost of high morbidity rates and vice versa .

However, there are also limitations to radiotherapy to be considered: First, radiotherapy generally does not produce tumour mass reduction. It might rather cause a transient swelling of the lesion due to oedema which induces further compression of surrounding structures5. Second, little is known about the long-term effects of radiotherapy, although we found no significant difference in treatment outcome 1 year post treatment, and those 5 to 10 years post treatment. However, irradiation induced sequelae might become apparent later in time, and the follow-up in the literature at hand is too short to allow for proper evaluation on this matter. As outlined by Suarez et al., other head and neck neoplasm's treated with similar radiotherapeutic techniques and dosages illustrated a risk of 0.5 and 0.1-3% for necrosis and irradiation induced secondary malignancies, respectively, over a course of 30 years7. It is uncertain whether or not these results apply for HHPGL treatment as well. Further, although in the current review only few radiotherapy-associated vascular complications were found, this very likely is an underestimation. Cerebrovascular accidents caused by atherosclerosis of the carotids are often not recognized as potential long-term sequelae of head and neck radiotherapy7. Wilbers et al. found an increased incidence of stroke in 49 patients suffering from head and neck malignancies seven years after radiotherapy compared to the general Dutch population (8.9 versus 1.5 per 1.000 person years)31. Additional studies described a significant correlation with a longer post-RT interval and significant carotid-wall thickness, which is considered a risk factor for cerebrovascular accidents; P=0.008)32. The exact long term risks of irradiation-induced carotid atherosclerosis remains uncertain, yet it occurs after years in follow-up.

Theoretically, to reduce the risk of HNPGL irradiation, stereotactic radiotherapy techniques are suggested. This is supported by Suarez et al. who found more deaths due to tumour growth post radiotherapy when conventional radiotherapy was used (3.2%; CI 0.4 - 5.2), when compared to deaths due to tumour growth post stereotactic irradiation (0%; CI 0 – 0 respectively; p = 0.03)7. Also, more deaths due to complications post radiotherapy, were found with conventional radiotherapy (2%; CI 0.4 – 3.7) when compared to deaths due to complications of stereotactic radiotherapy (0%; CI 0 – 0 respectively; p = 0.04).However, no figures about distribution by Fish class for the two radiotherapy techniques are provided. It is likely that stereotactic techniques were reserved for smaller tumours rendering less complications. Nonetheless, overall these results suggest that (stereotactic) radiotherapy should be considered (for class C and D tumours), for at least all patients older than 40. When a conventional fractionation schedule is used IMRT or rapid arc/VMAT is considered standard of care.

Alternatively, to minimize the treatment risks authors suggested a dual approach for HHPGL management using post-operative irradiation after debulking of gross tumour mass. This way, critical neurovascular structures might be spared during surgery.

In case additional tumour growth is found with a consecutive wait and scan policy, radiotherapy could be applied. Although literature is sparse on this matter and sample sizes are small, combinations of surgery with gammaknife were described as a proper alternative; local control was found in 80-100%, complications were found in 0-7%, and cranial nerve damage in 0-20% after 11 months -7 years follow-up5, 33, 34, 35, 36. Please note however, that these results were comparable to results of radiotherapy alone. Furthermore there is the risk that patients may suffer from both surgical and radiotherapeutic complications.

Furthermore, hereditary HHPGL syndromes also affect HHPGL management. Particularly, tumours arising from an SDHB, -AF2 and -D mutation, are thought to show more aggressive growth when compared to tumours arising from other mutation syndromes36,37. Also, due to multifocal tumour growth, there is a risk of bilateral cranial nerve deterioration; for N. VII lesion this might cause a drastic decrease in quality of life, for Nn. IX and X lesions this may even cause life-threatening aspiration risks. Therefore, in case of a multifocal HHPGL syndrome surgery for Class C and D tumours should be prevented. When treatment is inevitable, for larger tumours the use of radiotherapy is advised since cranial nerve pareses is best avoided using this modality, or conservative tumour debulking could be attempted. It is important to realize that after radiotherapy, alterations in cranial nerve function are known to occur up to one year post-treatment. Therefore, consecutive HHPGL treatment involving radiotherapy should be performed with an interval of at least one year.

Taken together it should be noted that HNPGL management is complex. To manage these patients correctly, treatment of these tumours should be confined to centralized multidisciplinary teams that include an extremely experienced surgeon, radiation oncologists, clinical geneticists, endocrinologists and speech and language therapist which should work together to reduce both tumour and treatment induced morbidity.

CONCLUSION

The current review has demonstrated that although surgical procedures varied, for class A and B tumours surgery seems to be a suitable treatment option. For class C and D tumours an initial wait and scan period should be considered. In the case of tumour growth (confirmed by imaging) or clinical progression of the tumour (indication of early CN palsy) radiotherapy might be the better option due to lower complication rates and similar or better local control rates when compared to the surgical groups. The proposed dual approach including tumour debulking followed by a wait and scan period and radiotherapy in case of recurrent progression, requires more research. More research is required as well on the long-term effects of radiotherapy. Furthermore, research on

the best treatment modality for HHPGL tumours needs to be stratified in the future for the different (genetic) subgroups.

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Table 1: main study characteristics of included studies

Study	Methods used; initial wait and scan?; pre-treatment embolization?	Follow-up	N Surg*	N RT*	Treatment outcome N > 4			Incomplete outcome data**	Selective reporting **
					Local control	CN damage	Complications		
Briner et al. 1999	Surgical techniques not mentioned	15 years after surgery	A: 1		1/1	0/1	0/1	High	Low
			B: 1		1/1	?	?		
			C: 14	-	13/14	14/14	?		
			D: 20	-	15/20	?	?		
Chen et al. 2010	Gammaknife	43.2 months		C: 6	4/6	?	?	Low	Low
				D: 9	8/9	?	?		
Dállagna et al. 2005	Radiotherapy, LINAC	3 to 35 years (mean of 11.6 years)		B: 3	3/3	0/3	?	Low	Unclear
				C: 5	5/5	0/5	0/5		
				D: 4	4/4	0/4	0/4		
Eustachio et al. 2002	Craniotomy, gammaknife	Median 37,6 months (5±68 months)	C: 1	C: 7	1/1; 7/7	2/1; 0/7	0/1; 0/7	Low	Low
				D: 8	8/8	0/8	0/8		
Gerosa et al. 2006	Gammaknife	Follow-up (mean, 50.85 mo		C: 2	2/2	0/2	0/2	Low	Low
				D: 18	17/18	1/18	0/18		
Karaman et al. 2010	infratemporal fossa type A, complemented with transsigmoid route	Not mentioned	C: 8		?	3/8	0/8	Low	High
			D: 3		?	1/3	1/3 (CSF leak)		
Kunzel et al. 2012	Gammaknife Surgery: tympanic acces route, mastoidectomy and tympanotomy, transmastoid-transcervical route, infratemporal fossa approach type A-D.	56.5 months (range, 3– 107 months),	B: 13	B: 3	?; 3/3	0/13	0/13	Low	Low
			C: 6	C: 7	3/6; ?	5/6; 2/7	0/6; 1/7 (tracheostomy)		
			D: 8	D: 1	8/8; ?	5/8; 0/1	6/8 (6 CSF leaks); 0/1		
Majdoub et al. 2015	LINAC	Median 11 years (range 5.3-22)		D: 27	27/27	0/27	0/27	Low	Low
Maglulio et al. 2008	infratemporal and retrosigmoid approache, retrosigmoid surgery combined with a subtotal petrosectomy, combined infratemporal and transcochlear approach	6 to 8 years in protocol.	D: 11		7/11	21/11	?	Unclear	Unclear

Table 1: main study characteristics of included studies (*continued*)

Study	Methods used; initial wait and scan?; pre-treatment embolization?	Follow-up	N Surg*	N RT*	Treatment outcome N > 4			Incomplete outcome data**	Selective reporting **
					Local control	CN damage	Complications		
Mazzoni et al. 2006	Petro-occipital trans-sigmoid approach	5 year follow-up in protocol	C: 3		?	0/3	?	Low	Low
			D: 2		?	1/2	?		
Moe et al. 2000	Transcanal, transmastoid, infratemporal fossa type A and B.	2.1 (range 2 to 11) years	A: 8		8/8	0/8	0/8	Low	Low
			B: 5		5/5	0/5	0/5		
			C: 17		16/17	25/17	3/17 (3 CSF leak)		
			D: 86		73/86	257/86	17/86 (1 CVA, 11 CSF leaks, 5 wound infections, 1 bleeding)		
Nonaka et al. 2013	Infratemporal fossa, transjugular approach with Fallopian bridge technique	Not mentioned	D: 39		24/39	31/39	7/39 (3 CSF leaks, 4 wound infections)	Low	Low
Oglahai et al. 2004	Transjugular lateral craniotomy	3.1 ± 4.2 years (range, 0–15 yr)	D: 6		?	?	?	Low	Low
Patel et al. 1994	Transteporal/ infratemproal fossa combined with subtemporal- retrosigmoid, and/or extreme lateral transcondylar approaches	3 year	C: 2		2/2	2/2	0/2	Low	Unclear
			D: 10		8/10	7/10	6/10 (1 CVA, 1 CSF leak, 4 tracheostomy)		
Sheehan et al. 2005	Gammaknife	28 months median		C: 2	2/2	?	0/2	Low	Unclear
				D: 6	6/6	0/6	0/6		
Tosun et al. 2016	Cyberknife	22-28 months		D2	2/2	0/2	0/2	Low	Low
Wang et al. 2013	Infratemporal fossa approaches	42.7 months	D: 89		80/89	57/89	23/89 (14 CVA, 18 CSF leak, 1 tracheotomy)	Low	Low

Surg: Surgery; RT: radiotherapy

* Represents the number of tumours that could be followed for required outcome measures.

** both are expressed in Low risk of bias = 1, High/unknown risk of bias = 0.

CHAPTER 4

Surgery, radiotherapy or a combined modality for jugulotympanic paraganglioma of Fisch class C and D

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ABSTRACT

Objectives: To identify the risks associated with surgery, radiotherapy or a combined treatment approach for Fisch class C and D jugulotympanic paraganglioma, in order to develop an individualized approach for each patient depending on Fisch class, age, mutation presence, tumour size growth rate and presenting symptoms

Design: A retrospective multicenter cohort study with all patient records of patients with a HNPGL in the Radboudumc, Nijmegen and the St. Elisabeth Hospital, Tilburg, the Netherlands.

Main outcome measures: local control, cranial nerve damage, complications, function recovery.

Results: We found highest local control rates after tumour debulking with postoperative

radiotherapy in case of residual tumour growth, referred to as the combined treatment group, (100%; n = 19), which was significantly higher than the surgical group (82%; n = 17; p = 0.00), but did not differ from the radiotherapy group (90%; n = 29). There were significantly less complications in the radiotherapy group, when compared to surgery (63 vs. 27%; p = 0.002) and the combined group (44 vs. 27%; p = 0.016). Furthermore, using a logistic regression model, we found that pre-treatment tumour growth was a negative predictor for post treatment cranial nerve function recovery (OR = 50.178, p = 0.001), reducing the chance of symptom recovery (67.3% versus 35.7%) post-treatment.

Conclusions: Radiotherapy should be the treatment of choice for the elderly. For younger patients tumour debulking should be considered, with potential radiotherapy in case of residual tumour growth.

INTRODUCTION

Jugulotympanic paragangliomas (JTPGL) are slow growing neuro-endocrine tumours that are usually benign. Due to their local invasiveness in the skull base, tumour morbidity can be considerable when there is growth towards cranial nerves (CN) and vascular structures [1]. However, their indolent growth pattern makes it difficult to predict if and when tumours become clinically apparent and debilitating; some tumours cause CN damage or invade the intracranial space, while others show spontaneous regression [2].

The main treatment options considered for JTPGL, surgery and radiotherapy (including conventional radiotherapy, stereotactic radiotherapy and radiosurgery), may induce cranial nerve damage or other complications. The management of these rare tumours should be carefully discussed with patients in order to develop a customized approach complying with patient's preferences. Patient factors such as age, comorbidities, tumour size and hereditary tumour syndrome presence should be considered. In this light, it has been suggested that younger patients show enhanced tumour growth and, consequently paraganglioma found in younger patients are likely to be of higher tumour class when compared to tumours of older patients, which makes decision making more difficult due to an enhanced risk of complications rates [3, 4, 5, 6, 7].

Therefore, in the current study we aim to evaluate the benefits and risks associated with radiotherapy, surgery and combined treatment regimens in relation to Fisch class, age, gene mutations, tumour size and growth rate, and presenting symptoms.

METHODS

Ethical considerations

The procedures followed were in accordance with the ethical standards of the Radboudumc, the Netherlands and with the Helsinki Declaration.

Study population and definitions

A retrospective multicenter cohort study was conducted with all patient records of patients presenting with a HNPGL between 1980 and 2016 in the Radboudumc, Nijmegen and the St. Elisabeth Hospital, Tilburg, the Netherlands. Eligibility criteria were patients with a benign Fish class C or D jugulotympanic tumour.

Out of 358 patients with HNPGL, 93 patients with a Fisch class C or D JTPGL were identified. To collect data from patient files a standardized extraction protocol was

used for the following information: gender, age at presentation, signs and symptoms at presentation, tumour class, gene mutation analysis, clinical and radiological signs and symptoms of tumour progression.

The pre-treatment work-up was as follows; generally, all patients are subjected to an initial wait and scan period and consecutive treatment is considered in case of tumour growth, tumour induced cranial nerve damage or other complications (such as pulsatile tinnitus, pressure sensation or hematootorrhoea) or wish of patient to be treated. In case this is not found consecutive treatment is generally not performed. A wait and scan period is not applied in case at initial presentation patients suffer from cranial nerve damage or other tumour induced morbidity. A wait and scan period was also not applied in those patients presenting between 1980 and 1987 as this was not general practice at that time.

Based on treatment three groups were distinguished. Group 1: patients treated with radiotherapy as initial treatment either with LINAC or Gammaknife. Group 2: patients that underwent surgery as primary treatment, in whom complete tumour resection was the main goal. Group 3: patients in whom planned safe tumour debulking was the main goal, with preservation of delicate surrounding structures. The residual tumour was followed using wait and scan period and in case of tumour growth additional radiotherapy was given.

The outcome of the treatment was compared to the patients' situation prior to treatment. Treatment outcomes were local control, cranial nerve damage and other complications. The definitions were according to Suarez et al. [8]. Post surgery, local control was defined as a patient alive without evidence of disease or with a non-growing residual tumour throughout the entire follow-up period. Post radiotherapy local control was defined as a patient alive without any evidence of progression of the disease throughout the entire follow-up period. CN damage was defined as deterioration of CN function post treatment when compared to the pre-treatment setting, objectified by a physician. CN recovery was defined as any improvement of CN function in post treatment setting when compared to pre-treatment conditions, objectified by a physician. The complications cerebrospinal fluid leakage, wound infection, cerebrovascular accident, aspiration resulting in pneumonia and/or tracheotomy, radiation induced necrosis, malignancies and CNS syndrome and death were included. Furthermore, an additional analysis was performed evaluating the control of pulsatile tinnitus for the different treatment modalities.

Patients were subjected to a routine follow-up. Post treatment, patients were seen within 2 weeks to evaluate immediate post-treatment complications. Thereafter patients were seen every six months for two years and then yearly. Post-treatment MRI-scans were done one year post treatment and continued on a yearly basis. In case

follow-up intervals were prolonged, MRI's were conducted every 2 or 5 years. This regimen could have been individualized.

For evaluation of tumour growth the mean percentage of volume increase per year was evaluated according to the protocol described by Jansen et al. [2].

Statistics

Predictors implemented in the model were analyzed using multiple logistic regression. Binary logistic regression was used, and best predictive model was constituted using Wald backwards step-by-step variable exclusion (probability for stepwise entry was set at 0.05 and removal at 0.1). Internal validation was optimized using bootstrapping sampling techniques. The data was collected using filemaker pro, and was analyzed using IBM SPSS Statistics 22.

RESULTS

Long-term treatment outcomes of 93 Fisch class C and D tumours were evaluated. Table 1 describes the baseline criteria of the total wait and scan cohort, and the direct treatment group. There was no significant difference in baseline criteria between these groups. However, when we corrected for patients directly treated due to timeframe, we found that patients directly treated (due to cranial nerve damage at presentation) were generally older (56 versus 49 years; $p = 0.017$, $F = 1.585$).

Table 1: Baseline criteria of total wait and scan group and direct treatment group

	Total wait and scan group	Total direct treatment group	Direct treatment due to cranial nerve damage
N	66	27	17
Fisch D N, (% total)	11 (17%)*	7 (26%)*	5 (29%)*
Mutation N, (% total)	25 (38%)*	12 (44%)*	7 (41%)*
Age (range)	49 (13-60)*	47 (20-77)*	56 (21-77)**
Tumour volume (range)	10.7 (0.8-55,3)*	13.3 (1.9-36.5)*	9.7 (2,5-26.8)*

*; no significant difference between treatment groups, p values > 0.05.
**; significant difference between treatment groups, p values < 0.05.

Table 2 provides baseline criteria of patients within each treatment group. There was no significant difference in baseline-criteria between each group.

In table 3, background information on pre-treatment counselling of the different treatment groups is provided. A total of 66 patients were subjected to a wait and scan period, of which 28 were not treated as no growth or tumour induced morbidity was

Table 2: Baseline characteristics per treatment modality

	Radiotherapy	Surgery	Combined treatment modality	Wait and scan	Total
n	**29**	**17**	**19**	**28**	**93**
Fisch class D n, (%)	8 (28%)*	2 (12%)*	5 (26%)*	5 (18%)*	20 (22%)
Mutation n, (%)	8 (28%)*	7 (41%)*	7 (37%)*	15 (54%)*	37 (40%)
Median Age(range)	50 (20-77)	41 (13-78)	43 (18-66)	55 (14-90)	48 (13-90)
Median volume (range) in cc	13 (12-47) *	15 (3-55) *	15 (6-28) *	9 (1-33)*	11 (1-33)
Growing n (%)	8 (28%) *	3 (53%) *	5 (68%) *	0 (-)*	16 (17%)
Presenting symptoms					
Tinnitus	9 (31%)	11 (65%)	9 (47%)	14 (50%)	43 (46%)
Hearing loss	17 (59%)	12 (71%)	13 (68%)	17 (61)	59 (63%)
CN damage	12 (41%)*	9 (53%)*	14 (73%)*	0 (-)	35 (38%)
VII	4 (13.8%)	5 (29%)	5 (26%)	0 (-)	14 (15%)
VIII	3 (10%)		2 (11%)	0 (-)	5 (5%)
IX		2 (12%)	2 (11%)	0 (-)	4 (4%)
X	5 (17%)	1 (6%)	2 (11%)	0 (-)	8 (9%)
XI			1 (5%)	0 (-)	1 (1%)
XII		1 (6%)	2 (11%)	0 (-)	3 (3%)
Median follow-up months (range)	82 (8-182)*	43 (10-372)*	98 (8-432)*	80 (13-281)*	81 (8-432)

*; no significant difference between treatment modalities, p values > 0.05.

found after a median follow-up of 52 months (range 13-281). The motivation of treatment of remaining tumours is provided in table 3. Within the surgery cohort 24% of patients were treated directly due to timeframe, albeit not significant, this percentage was 14% and 11% in the radiotherapy and combined treatment group respectively.

Table 3: background information on pre-treatment counselling of the different treatment modalities

Motivation for treatment	Surgery	Radiotherapy	Combined	No treatment	Total
Wait and scan N, (% total)	**11 (66%)**	**14 (48%)**	**13 (68%)**	**28 (100%)**	**66**
No growth N , (% total)	-	-	-	28 (100%)	28
Growth N , (% total)	3 (18%)	8 (28%)	5 (26%)	-	16
Cranial nerve damage N , (% total)	3 (18%)	4 (14%)	4 (21%)	-	11
Wish treatment N , (% total)	-	2 (7%)	3 (16%)	-	5
Other N , (% total)	5 (29%)	-	1 (5%)	-	6
Immediate treatment N, (% total)	**6 (33%)**	**15 (52%)**	**6 (32%)**	-	**27**
Cranial nerve damage N , (% total)	2 (12%)	11 (38%)	4 (21%)	-	17
Timeframe N , (% total)	4 (24%)	4 (14%)	2 (11%)	-	10
Total N	17	29	19	28	93

The outcomes by treatment modality are presented in figure 1. There was a significant relation between treatment modality and local control and complication rate. Local control for the surgery group was lower when compared to the combined treatment modality group (82 vs. 100%; $p < 0.01$). Complication rates differed significantly between surgery and radiotherapy in favour of the latter (63 vs. 27%; $p = 0.002$). Also, there were significantly more complications in the combined treatment group when compared to the radiotherapy group (44 vs. 27%; $p = 0.016$). There was no relation between treatment methods and recovery from pre-treatment symptoms ($p = 0.556$).

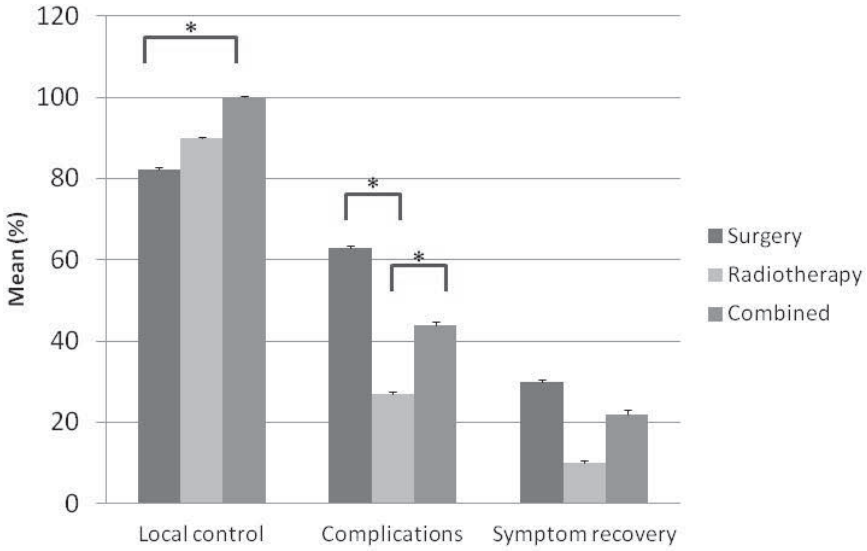

Figure 1: treatment outcome per treatment modality (* refers to a significant difference between treatment outcomes $p < 0.05$)

Out of 19 patients undergoing the combined treatment modality, eight patients underwent additional radiotherapy 12 to 108 months post treatment (median 52 months).

No difference was found with respect to local control, complications, and functional recovery when comparing the results of patients that were treated after an initial wait and scan period and those immediately treated, and no statistical difference was found.

Out of 29 patients undergoing radiotherapy, 17 (59%) were treated with the Gammaknife. Median tumour volumes for the group treated with Gammaknife, and the group treated with LINAC were 6.6 cc (range 1.3 – 16.8) and 16.9 cc (range 1.2 – 47.4) respectively. This difference was statistically significant ($P = 0.009$). There

was a small difference in local control rates between gammaknife and LINAC treated patients (100 vs. 81%;, p = 0.068), albeit not significant. No differences were found in complication (33.3 vs. 17.6%; p = 0.331) and recovery rates (16.7 vs. 37.5%; p = 0.227) between Gammaknife and LINAC.

Table 4 presents the complications found post treatment, by treatment modality.

No statistical difference in pulsatile tinnitus-control was found for the different treatment modalities. Tinnitus-control was found in 2 of 11 (18%) patients post surgery, 4 of 9 in the combined treatment group (44%) and in 2 of 9 patients treated with radiotherapy (22%). When pooling the results of surgery and the combined treatment group, there was still no statistically significant difference.

Table 4: complications by treatment modality.

	Radiotherapy	Surgery	Combined	Total
SNHL/Tinnitus/Vertigo	7	6	2	14
CN damage	**1**	**15**	**5**	**21**
III. IV, VI		2		2
VII		5	1	6
IX		3		3
X	1	3	2	6
XI			1	1
XII		2	1	3
Total n. complications/ n. patients per treatment group	8/29	21/17*	7/19	37/65

* there was more than 1 complication in some patients.

Univariate analysis of variance

The results of the univariate analysis of variance are presented in table 5. Overall, no factors were found that were associated with local control. A trend towards higher complications rates in case of pre-treatment tumour growth was found (57.9% versus 34.6%), albeit not significant (p = 0.07). However, significantly higher symptom recovery rates were found in case of mutation presence (36.4% in mutation group versus 14.6% in non-mutation group; p = 0.048) and pre-treatment tumour growth (13% in growing group versus 45% in non-growing group; p = 0.03).

With respect to the surgery group, patients suffering a complication were significantly older (mean 46 years), when compared to patients not suffering a complication (mean 30 years) (p = 0.047) and mutation presence was found to be related to lesser symptom recovery rates (0% versus 42.9%; p = 0.03). In the radiotherapy group, there were no factors significantly associated with treatment outcome.

Table 5: Results of univariate analysis

	Surgery *p* value			Radiotherapy *p* value			Combined *p* value			Overall *p* value		
	Local control	Complication	Recovery	Local control	Complication	Recovery	Local control	Complication	Recovery	Local control	Complication	Recovery
Mutation	0.69	0.38	**0.02**	0.39	0.36	0.11	0.67	0.67	0.89	0.58	0.85	**0.04**
C/D	0.24	0.38	0.46	0.34	0.33	0.79	0.86	0.86	0.76	0.62	0.82	0.81
Growth	0.33	0.11	0.93	0.17	0.15	0.1	0.41	*0.06*	0.59	0.12	*0.07*	**0.03**
CN damage	0.33	0.35	0.14	0.11	0.59	0.40	0.10	0.76	0.94	0.48	0.59	0.78
Age	0.57	**0.02**	0.79	0.13	0.82	0.29	0.37	0.48	0.95	0.38	0.72	0.70
Size	0.44	0.40	0.30	0.16	*0.07*	0.46	0.42	**0.02**	0.90	0.25	0.65	0.21

Underlined bold: results were statistically significant; *Underlined cursive*: results were barely significant

With respect to the combined treatment regimen, patient suffering a complication generally had smaller tumour volumes when compared to patients not suffering a complication (9.3 cc versus 24.1 cc; p = 0.02).

Binary logistic regression

Using a logistic regression model with step by step correction for potential confounders in the total group only pre-treatment tumour growth was identified as an independent negative predictor for symptom recovery (OR = 50.178, p = 0.001). This means that if there is tumour progression before the start of treatment, there is a significantly lower chance of symptom recovery (67.3% versus 35.7%). Furthermore, with respect to the combined treatment approach, there was an indication that presence of cranial nerve damage was associated with poorer local control rates (p = 0.06).

DISCUSSION

To our knowledge, this study presents the largest cohort of patients with Fisch class C and D JTPGL that compares different treatment modalities. In this study we compared the benefits and adverse effects of different treatment strategies for jugulotympanic paragangliomas of Fisch class C and D.

Local control rates were highest with combined treatment modality, and complication rates were lowest in the radiotherapy group. One independent predictor of treatment outcome was found: if treatment is delayed until tumour growth occurs, the chance of function recovery is lower.

Our results suggest, that attempts to achieve radical excision as a primary goal, should not be performed since for this group local control rates were lowest and highest complication rates were found when compared to the combined treatment approach and radiotherapy. Hence, we believe that radiotherapy and or a combined treatment modality with nerve sparing debulking surgery should be attempted.

These results can provide a basis for the counselling of patients suffering from HNPGL, and support the decision making process to a customized management strategy for these patients.

Comments on management

The current study presents the motivation for treatment of Fisch class C and D tumours. At first presentation, feasibility of a wait and scan protocol is evaluated. In case no treatment-requiring tumour induced morbidity is found, such a protocol is initiated.

In our cohort 66 patients were initially managed by a wait and scan protocol, and 27 patients were treated directly. When comparing these two groups at baseline, we found that patients which were treated directly were significantly older than patients in the wait and scan group (56 vs. 49 years). Potentially, this difference can be explained by more progressive disease at older age, however, no difference in pre-treatment tumour volumes could be found between those groups. Evaluating the 66 patients in which a wait and scan period was initiated, tumour growth was found in 24% of cases and treatment was necessary in 58% of cases. The choice of treatment was based on patient factors and no significant factors predicting treatment outcome were found. Hence, at baseline we are unable to predict which tumour will in the near future become clinically apparent. Therefore, the current results emphasize that an initial wait and scan therapy should always be performed in the absence of readily present morbidity, particularly since we found that overall, a preceding wait and scan protocol does not affect future treatment outcome.

The mere drawback we found with a wait and scan policy is, that in case tumour growth is found in combination with tumour induced morbidity, chances for symptom recovery post treatment reduce. Therefore, we believe that in case tumour growth is found, treatment should be considered seriously. Moreover, growth does not affect treatment outcome in general with respect to local control rates or complications independent of treatment modality in our centre. Hence, the timing of treatment initiation is crucial and the most challenging aspect of the management of JTPGL.

Furthermore, please note that a previous study of our group (Jansen et al. 2017) illustrated that age of presentation was a risk factor for enhanced risk of tumour growth incidences and rates. Patients under the age of 50 years were at particular risk of suffering from such enhanced aggressive tumour biology. We state that an initial wait and scan is feasible also for the younger population, however, a reduced time-interval between scanning of those patients should considered.

In case treatment is required, we found lowest local control rates when patients were treated with surgery which is in line with previous literature. A systematic review demonstrated that local control rates were found in 80%-95% for class C1-4 tumours and 38%-86% for class De/Di tumours [9]. Post surgery, in the current study complication rates were 63%. The same review showed that complications were found in 71%-76% of class C1-4 and 67%-100% for class De/Di tumours. The main complication found in the current study was CND (71% of all complications), with a particular risk of n. VII damage (23% of all complications). Therefore, we do not advise the use of complete surgical excision for Fisch class C and D tumours.

We believe debulking seems a promising alternative for radical surgical excision. We found excellent local control with this approach. This is also observed by van Hulsteijn et al., who found 100% local control with adjuvant radiotherapy (95%CI 66-100)

[10]. Unfortunately however, no data on complication rates are reported in the latter study. This makes it hard to put these results in context since rendering local control while preserving CN function seems to be the main challenge in HNPGL management. Moreover, similar results were found by Willen et al, treating 5 elderly patients with limited surgical resection, rendering excellent local control and no cranial nerve damage [11]. In our study we found lower complication rates when compared to radical surgery, yet higher when compared to radiotherapy alone. The main complications found was CND. Ultimately, 42% of patients in whom debulking was performed were subjected to additional RT. Although few irradiation induced complications were found after a follow-up of 82 months (range 8-182), a potential criticism on this management strategy could be that potentially patients are subjected to risks of both treatment modalities. Moreover, the role of surgery in the management of pulsatile tinnitus requires further investigation.

As outlined above, radiotherapy seems to be the treatment of choice in general as it provides excellent local control and fewest complications. These results are in line with a systematic literature study conducted by our group, as outlined above [9]. It was previously suggested that radiotherapy should be reserved for older patients due to the risk of induction of malignant tumours or cerebrovascular accidents [8, 10]. Nevertheless, the lifetime risk of irradiation-induced secondary malignancies is only 0.3% which is almost negligible compared to the 38% lifetime risk of developing cancer of any type in the general population in the Western world [11, 13]. What is less well known is that there is an increased risk of 8.9 versus 1.5 per 1000 person years of cerebrovascular accidents after radiotherapy to the neck due to carotid atherosclerosis [7, 11, 14]. These late sequelae manifesting up to 30 years post treatment should be considered as calculated risks and weighed against the advantages of radiotherapy over surgery. Overseeing this, and considering sequalae up to thirty years post treatment, we feel that radiotherapy as monotherapy is a viable option from the age of 50 years onwards [11]. Please note that this suggestion is based on theoretical grounds, nevertheless, it is in line with suggestions of previous studies [8-10]. Moreover, such severe and life threatening complications were not found in the current study after a follow-up of 82 months (range 8-182). Currently, the main complications found seemed to be due to radiotoxic effects on the cochlea (87% of all complications).

Methodological considerations

First, the current study is a retrospective cohort study and therefore the external validity is limited. However, given the rarity of these tumours and their slow growth rate, prospective (randomized controlled studies) are hardly possible. Furthermore, although

the current study provides one of the larger sample size on this particular tumour type, for sub-group analysis the population might have been too small.

Furthermore, as discussed above, the long-term treatment outcomes of radiotherapy remain uncertain. Therefore, the results of the current study might be too optimistic since tumour growth and recurrences may be expected over time for this group. This is also a limitation when considering the results of the combined treatment modality: perhaps additional treatment of residual tumour growth is required over time as tumour growth might occur later in time.

Also, in the future automated tumour volume measurement software should be used to evaluate tumour volume, rather than manual three dimensional measurements. This will provide more accurate tumour volumes and reduces the inter and intra-observer variability.

CONCLUSION

Our results confirm the feasibility of a wait and scan period as initial management strategy, and demonstrate a significant relation between treatment modality and local control and complication rates. Complete surgical excision is not a suitable treatment strategy since it induces the highest incidence of complications and local control is lowest when compared to tumour debulking methods and radiotherapy as monotherapy. Radiotherapy produces excellent local control rates and has the fewest complications and therefore it seems to be the treatment of choice for older patients. However, as radiotherapy seems undesirable for patients under the age of 50 due to an enhanced life-time risk of secondary tumours and stroke, tumour debulking should be at least considered for younger patients. The greatest challenge is the timing of therapy initiation because once tumour growth occurs there is less chance of symptom recovery. More research is required on this matter and it also implies that patients presenting with CND should be treated without delay to increase chances of functional recovery or these patients should be followed-up more carefully so that with a minimal impression of tumour growth, treatment should follow.

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CHAPTER 5

A Meta-Analysis on the Surgical Management of Paraganglioma of the Carotid Body per Shamblin Class

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ABSTRACT

Objective: The aim of the current study is to evaluate the risk associated with different types of surgery for carotid body paraganglioma of different Shamblin class. A meta-analysis was conducted to evaluate per tumour class, the local control, cranial nerve damage and complication rates of different techniques using internal carotid artery (ICA) and external carotid artery (ECA) ligation, clamping or bypassing, as well as the cranio-caudal versus caudo-cranial techniques.

Design: A meta-analysis is conducted after a systematic search in Pub Med and the Cochrane library, in accordance with the PRISMA guidelines.

Main outcome measures: local control, cranial nerve damage, complications, function recovery

Results: Out of 3565 articles, 27 were selected. The overall quality of evidence of studies was low. Cranial nerve damage (3%, 17% and 39%) and complication rates (0%, 1%, 10%) were significantly related to Shamblin class (class 1, 2, 3, respectively, $p < 0.01$). For class 3 tumours an increased risk of complications was found associated with routine ICA manipulation/reconstruction (RR 3.12 with a 95% CI of 1.29-7.59), as well as a trend towards enhanced risk of routine ECA ligation (RR 3.48 with a 95% CI of 0.88-13.81).

Conclusions: For class 1 and 2 tumours surgery seems a viable treatment option. For class 3 tumours, morbidity in terms of cranial nerve deficit and complications is considerable, particularly the use of ICA manipulation/reconstruction and potentially ECA ligation seems to be accompanied by high a stroke incidence.

Keywords: Meta analysis, head and neck, carotid body paraganglioma, meta-analysis, surgical techniques

INTRODUCTION

Carotid body paragangliomas (CBPGL) are benign neuro-endocrine tumours which constitute 57% of HNPGLs.[1] Symptomatology of these tumours can be considerable, due to their relation with the internal (ICA)/external carotid artery (ECA), the vagal, hypoglossal and accessory nerves. Only a small portion of these tumours grow, and most of these grow very slowly. Therefore, recent literature agrees that these tumours should first be followed-up to evaluate tumour growth via a wait and scan period[2]. However, when tumour growth is demonstrated, or the tumour becomes clinically apparent, the best way of treatment remains uncertain.

Surgery is considered the main treatment of choice, as this offers complete tumour removal. However, neurovascular structures are at risk when surgery is applied which might impose life threatening complications such as aspiration pneumonia's and CVA's[3]. The precise risk associated with surgery stratified per Shamblin class remains uncertain, yet recent works suggested that tumour class is related to local control and adverse event rates.[3-6] Moreover, surgical techniques have advanced to reduce complications and to facilitate a dry operation field with better preservation of neurovascular structures.[7] To achieve this, routine ICA and ECA (temporary) ligation and reconstruction methods have been used. Preservation of the internal and external carotid arteries and the smaller supplying vessels is crucial. Caudo-cranial surgery techniques have been described in the past but more recently cranio-caudal techniques are suggested to cause less cranial nerve damage as it allows for early proximal control of the nerves.[8] However, the risks associated with these different surgical techniques are not well documented.

Therefore, in the current study, we aim to evaluate the risk associated with different types of surgery for CBPGL of different Shamblin class. Hereby, we aim to optimize individualized treatment protocols for patients suffering from CBPGLs. We performed a systematic literature search to evaluate treatment outcome per tumour class, and to evaluate treatment outcome of different surgical techniques such as ICA and ECA /ligation, clamping or bypassing, as well as the cranio-caudal versus caudo-cranial techniques.

METHODS

The methods as presented underneath are similar to previous literature studies of our group.[8]

Ethical considerations

This study was conducted in line with the ethical guidelines of the Radboud University Medical Centre, the Netherlands.

Eligibility criteria

Studies evaluating the effect of surgery were included. The population consisted of patients suffering a CBPGL, stratified per Shamblin class as described Shamblin et al..[9] The intervention was any form of surgery, with or without a preceding wait and scan period. Treatment outcomes were local control, cranial nerve damage and other complications. The definitions were defined according to Suarez et al..[3] Local control was defined as a patient alive without evidence of disease throughout the entire follow-up period. CN damage was defined as deterioration of CN function post treatment when compared to the pre-treatment setting, objectified by the treating physician. CN recovery, was defined as any improvement of CN function in post treatment setting when compared to pre-treatment conditions, objectified by the treating physician. The complications CSF leakage, wound infection, CVA, baro-reflex failure syndrome, aspiration resulting in pneumonia and/or tracheotomy and death were included.

Additionally, the following surgical techniques were evaluated: whether or not standard extensive ICA/ECA manipulation techniques were used including clamping, ligation or bypassing techniques. Also, it was evaluated whether or not a cranio-caudal-or a caudo-cranial resection technique was used.

Literature review

A systematic literature review was conducted according to the PRISMA statement for meta-analyses of observational studies.[10] On Feb. 2016 the first author searched the Pub Med database for articles using the search strategy as mentioned below (no MeSH terms were used for inclusion of the most up to date articles). References of key articles were scrutinized for additional relevant articles.

(((Treatment [Title/Abstract] OR Treatment [MeSH Terms] OR Management [Title/Abstract] OR Management [MeSH Terms] OR therapy [Title/Abstract] OR therapy [MeSH Terms] OR approach [Title/Abstract] OR approach [MeSH Terms] OR procedure [Title/Abstract] OR procedure [MeSH Terms] OR Radiotherapy [Title/Abstract] OR Radiotherapy [MeSH Terms] OR radiation therapy [Title/Abstract] OR radiation therapy [MeSH Terms] OR X-ray therapy [Title/Abstract] OR X-ray therapy [MeSH Terms] OR radioisotope therapy [Title/Abstract] OR radioisotope therapy [MeSH Terms] OR Radiosurgery [Title/Abstract] OR Radiosurgery [MeSH Terms] OR Gamma Knife [Title/Abstract] OR Gamma Knife [MeSH Terms] OR CyberKnife [Title/Abstract] OR CyberKnife [MeSH Terms] OR Linear Accelerator [Title/Abstract] OR Linear Accelerator [MeSH Terms] OR Linac [Title/Abstract] OR Linac [MeSH Terms] OR LINAC [Title/Abstract] OR LINAC [MeSH Terms] OR Surgery [Title/Abstract] OR Surgery [MeSH Terms]

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Study selection and the data collection

Articles written in English and German were selected and tumours had to be classified. The treatment modality and outcome measures needed to be reported for each tumour class individually. Cohort sizes had to consist of 5 or more patients. Information on at least one of the afore-mentioned outcome measures had to be available. Also, information on the surgical technique and corresponding outcome measures had to be provided. No unpublished articles were used, and full-text had to be available. Shamblin class was retrieved from each publication, appreciating that classification was reported based on CT, MRI or per-operative findings.

Risk of bias in individual studies

A critical appraisal was performed using the PRISMA checklist for meta-analyses of observational studies (Moher et al. 2009). The following terms were addressed: random sequence generation, allocation concealment, blinding of participants and personnel,

blinding of outcome assessment, incomplete outcome data, selective reporting and other forms of bias. Risk of bias was considered high in case subjects were not mentioned. The risk was considered low in case the subject was addressed by the authors. However, please note that no articles were excluded from the study based on the critical appraisal since the majority of the studies show poor risk of bias prevention. The risk of bias is merely presented for information purposes of the readership.

Statistical analyses

The outcome of the presented meta-analysis was the pooled result of several surgical techniques on different outcome measures after CBPGL treatment. For all studies, the proportion of local control, cranial nerve damage and serious adverse events were evaluated. Results were presented with an exact 95% confidence intervals (95% CI) were calculated. Meta-analysis was performed a logistic regression with a random effect model. All analyses were performed using RevManager 5.3.

RESULTS

Study selection

A total of 3,565 articles were screened for title and abstract. Based on title and abstract, a total of 155 articles were selected for review of full text and the following studies were excluded: In 96 cases the results were not specified per tumour location or Shamblin class, 27 studies were case series-/reports of less than 5 patients and a total of 9 reviews were excluded too. Ultimately 27 articles were included in the review (figure 1).

Study characteristics and outcomes of studies

Ultimately, a total of 139 class 1 tumours are described in 10 articles, 228 class 2 in 16 articles and 201 class 3 in 17 articles. Detailed information on the studies included in this systematic literature review are presented in appendix A. All study designs were retrospective cohort studies. Random sequence generation, proper prevention of allocation concealment or blinding of the participants or personnel was not performed in any of the studies. The risk of incomplete data presentation and risk of selective reporting are provided in appendix A as well. Outcome measures per tumour class post surgery are summarized in figure 2.

For Shamblin class 1 tumours, local control was achieved in 82%-100% (mean 98%), CND was reported in only one study (25%) and no other complications were

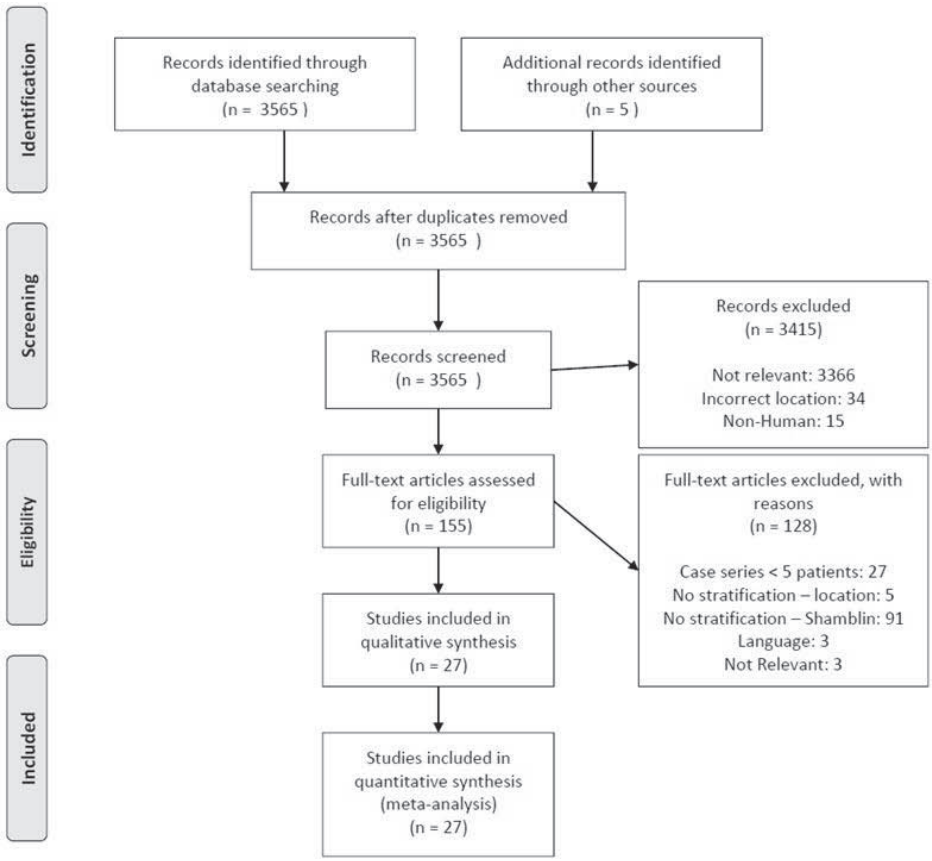

Figure 1: flow chart.

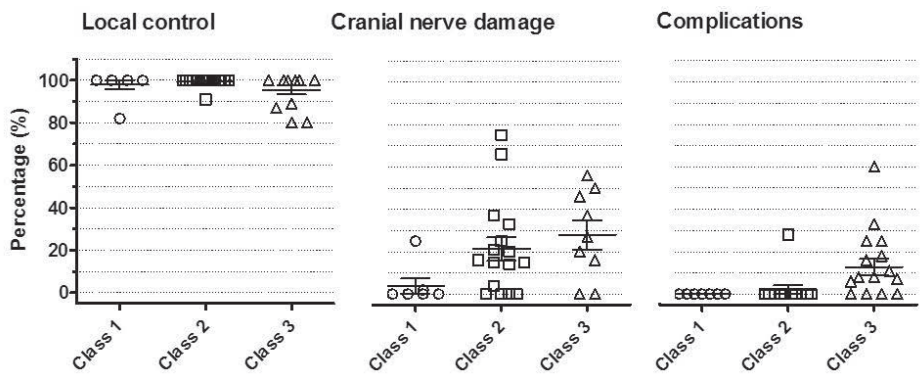

Figure 2: treatment outcome per tumour class

reported in these studies. For class 2 local control was 92%-100% (mean 98%). Cranial nerve damage was found in 0%-78% (mean 17%). Complications were reported in 0-34% (mean 2%). For class 3 tumours mean local control was 92% (range 73-100%), mean CND rate was 29% (range 0-75%), and mean complication rate was 12% (range 0- 60%).

Pooled results

Pooled results per Shamblin class are provided underneath in table 1. Not all outcome measures were reported in the included studies, therefore, the denominator might vary per treatment outcome. Local control was not significantly correlated with Shamblin class. Cranial nerve damage rates (p = 0.00, df = 2, F = 25) and complications (p = 0.00 df = 2, F 15) were, significantly related to Shamblin class. Bonferroni post-test illustrated that with respect to cranial nerve damage, there was a higher risk for class 2 when compared to class 1, and a higher risk for class 3 when compared to class 2 (p both 0.00). There was no difference in complication rate between class 1 and 2, class 3 differed significantly from class 2 (p = 0.00)

Table 1: Pooled treatment outcome per Shamblin class

Shamblin class	Local control % (n/ntotal)*	Cranial nerve damage % (n/ntotal)*	Complications % (n/ntotal)*
Class 1	93% (130/139)	3% (4/145)	0% (0/145)
Class 2	98% (214/217)	18% (36/200)	1% (3/222)
Class 3	94% (126/134)	32% (50/155)	10% (18/177)

*Denominator ntotal refers to the total number of patients for which the outcome measure was reported.

Details on cranial nerve damage and complications are presented in table 2, stratified per tumour class. Not all studies reported which cranial nerve was affected. The total number of CND reported might therefore be higher than the sum of the reported n. IX, X XI and XII damages.

Meta-analysis (surgical methods and treatment outcome)

Appendix A describes the risk of bias for each included study. Also, per study the use of potential ICA manipulation and/or reconstruction and ECA ligation techniques and the corresponding complication rates are presented. Outcome measures could not be compared per surgical technique for Shamblin class 1 and 2 tumours, because sample sizes were too small as few ICA and ECA reconstructions were performed for tumours of these classes. For Shamblin class 3 tumours, a meta-analysis was performed to

Table 2: CN damage and complication rates post surgery per Shamblin class

Shamblin class	Total CND % (n/n_{total}) *	n. IX % (n/n_{total}) *	n. X % (n/n_{total}) *	n. XI % (n/n_{total}) *	n. XII % (n/n_{total}) *	Total complications % (n/n_{total}) *	CVA % (n/n_{total}) *	Death % (n/n_{total}) *
class 1	3% (4/145)	1% (1/145)	1% (1/145)	1% (1/145)	1% (1/145)	0% (0/145)		
class 2	18% (36/200)		4.5% (9/200)	9% (18/200)	2% (4/200)	1% (3/222)	0.9% (2/222)	0.5% (1/222)
class 3	32% (50/155)	2.5% (4/155)	23% (36/155)	3.9% (6/155)	1.3% (2/155)	10% (18/177)	9% (16/177)	1% (2/177)
Total	18% (90/500)	1.7% (5/300)	9.4% (46/490)	5.1% (25/490)	1.4% (7/490)	4% (21/544)	4.5% (18/399)	0.7% (3/399)

*Denominator n_{total} refers to the total number of patients for which the outcome measure was reported.

evaluate treatment outcome of specified surgical techniques. The treatment outcomes considered were local control, CND and other complications. The surgical techniques evaluated were: pre-operative embolization, ECA manipulation and/or reconstruction and ICA manipulation/reconstruction and craniocaudal versus caudocranial resection methods. Unfortunately, outcome measures were not properly stratified for embolization techniques and cranio-caudal versus caudocranial resections. With respect to ECA ligation and ICA manipulation and/or reconstruction techniques, complications were properly stratified, CND rates were not. However, no estimable risk ratio could be found with respect to local control. Therefore, only the results on ICA and ECA manipulation for Shamblin class 3 tumours are described (figure 3 and 4 respectively).

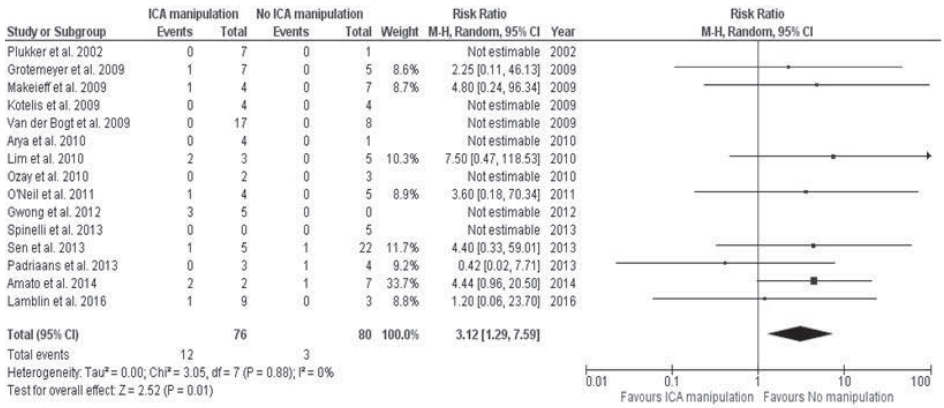

Figure 3: meta-analysis regarding risk of extensive ICA manipulation/reconstruction on serious adverse events.

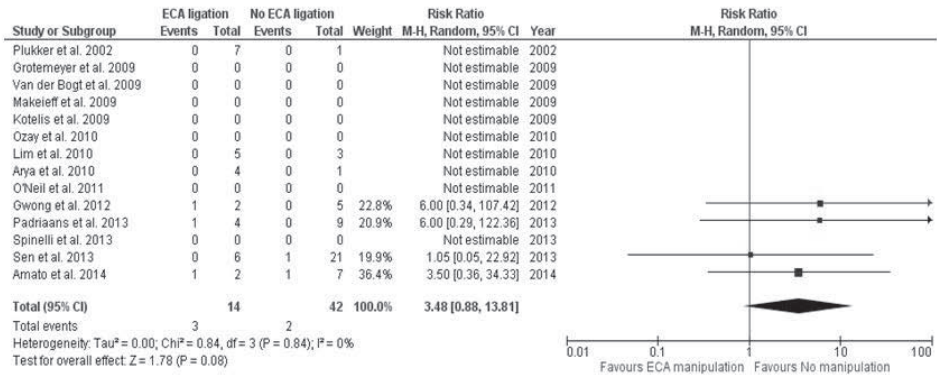

Figure 4: meta-analysis regarding risk of extensive ECA ligation on serious adverse events.

Pooled results illustrate a Risk Ratio of 3.12 with a 95% CI of 1.29-7.59, illustrating an enhanced risk of complications in case of ICA manipulation/reconstruction.

Pooled results illustrate a Risk Ratio of 3.48 with a 95% CI of 0.88-13.81, illustrating a trend towards enhanced risk of complications in case of ECA ligation.

DISCUSSION

Summary of main results

This study describes the risk profile associated with surgery of CBPGLs of different Shamblin class. After evaluating 25 studies and 559 patients we found that post surgery, adverse events increased with Shamblin class, and that local control rates decreased. With respect to Shamblin class 2 tumours, we found high adverse event rates in case standardized internal carotid artery clamping was used. Moreover, with respect to class 3 tumours, we found that ICA manipulation/ reconstruction and ECA ligation techniques were associated with complications (mainly CVA's). These results provide valuable insights for CBPGL management in daily practice. We believe that class 1 and 2 tumours could be treated relatively safely with surgery, when ICA manipulation/ reconstruction and ECA ligation is prevented. For class 3 tumours however, surgery should be applied with great caution as it goes hand in hand with high cranial nerve damage and higher complication rates.

Overall completeness and applicability of evidence

Unfortunately, there are no randomized controlled trials available on this subject due to the rarity of the disease and the slow growth rate of these tumours. Hence, the level of evidence for these recommendations is not optimal, and based on retrospective

cohort-studies albeit with a control group. The retrospective nature of these studies however, reduces the internal and external validity of the results. Please note that we reduced this bias by applying a critical appraisal according to the PRISMA-statement. Furthermore, the individual study details of included studies are provided, including methodology and the results of a critical appraisal. Hereby, studies could be assessed for reliability/methodological quality and the impact can be regarded in the context of other studies.

Potential biases in review

There are several potential biases in the current review. The first is that we did not stratify for hereditary tumour syndromes and age of presentation. It has been suggested that both aspects are related to enhanced tumour growth or local invasiveness, potentially inducing lower local control and higher complication rates. However, stratification by these factors was not possible with the provided information in the current studies.

Another aspect is the follow-up. The minimal follow-up in the current series was 5 months which is short for CBPLG's, particularly in the light of recurrences, CN function deterioration and recovery post treatment; as stated, one might expect alteration in cranial nerve function up to 12 months post treatment. Please note however that merely the study of Dardik et al. used such short follow-up periods.[11] There are however, also studies that did not mention the follow-up interval.

Also, the majority of the studies do not correct for patients that have died or have been lost to follow-up, i.e. they report absolute control and complication rates. The proper method for reporting outcome rates is the actuarial method where patients are censored when they die or are lost to follow-up. Depending on the proportion of patients censored tumour control rates may turn out to be significantly lower and complication rates significantly higher. Although a critical appraisal is performed, loss to follow-up was poorly handled by the majority of the included papers. Therefore, we decided not to consider this an exclusion criterion. Furthermore, with respect to the evaluation of treatment outcome for ICA/ECA manipulation it should be noted that none of the studies were designed to evaluate the risk of different surgical techniques. It is likely that such techniques were used, dependent on the local situation per-operatively. Therefore a considerable inclusion bias should be kept in mind when interpreting these results. Nonetheless, we believe the results provide insights in the potential consequences of surgery for these tumours emphasizing that CBPGL management is complex and should be confined to specialized centres and multidisciplinary teams with experience in CBPGL management.

Comparison with other reviews

Suarez et al. reviewed the results of surgical management of carotid body paraganglioma, and describe that after reviewing 67 articles including 2,175 surgically treated patients, that local control was achieved in 93.8 %. Surgery resulted in 483 (483/2,175 = 22.2 %) post-operative permanent cranial nerve deficits. Three percent (n = 60) of patients developed a permanent stroke and 1.3 % (n = 26) died due to postoperative complications.[3] These are absolute rates not corrected for patients who have died or lost to follow-up and, therefore, the true incidence is very likely higher. Furthermore, these results are not stratified by growth pattern or size (tumour class), which is of relevance since tumour class is considered to be related to local control and adverse event. [3-6] Moreover, the evaluation of surgical techniques were beyond the scope of this review.

Implications for clinical practice and research

The aim of this study is to evaluate surgical techniques for these tumours once intervention is required, e.g. because of tumour growth, or symptoms. The risk of (surgical) treatment can be summarized as follows: Our results illustrate that for Shamblin class 1 tumours local control is generally 100% and there is a very low risk of CND or complications. Therefore, in case a patient requires treatment or in case growth is found after a wait-and-scan period surgery is advised as the main treatment option of choice. Mostly, a cervical approach is used, allowing for periadventitial tumour dissection.

For class 2 tumours, local control was achieved mostly in 100% as well, but CND rates were described in 0-78% (mean 17%) between studies. Other complications are rare but not entirely absent. Lees et al. described one aspiration pneumonia (out of a series of 18 patients) resulting in death.[12] Furthermore, Sanli et al. described 2 CVA's with permanent neurological impairment resulting in one death out of 7 class 2 patients.[13] Please note that Sanli et al. reported the only series using standard transient internal and carotid artery blockage for Shamblin class 2 tumours. The vast majority of patient cohorts were operated via a cervical incision, subadventitial plane dissection and occasional ECA resection/ligation and/or ICA reconstruction. No statistical analysis could be performed on the risk of surgical techniques on complications because of too few events. Due to the higher CND and complication rates, an initial wait and scan strategy should be applied before operating these tumours since potentially, these tumours do not require surgical intervention. In case of tumour resection standardized transient ICA/ECA clamping should not be applied. Alternatively, a craniocaudal resection with selective CBPGL feeder vessel ligation method is advised, as described underneath.

For class 3 tumours, although local control rates are relatively good (80-100%), CND and complications are higher when compared to class 1 and 2 groups; CND rates were

found in 0-75% (mean of 32%), and complications were found in 10% (0-60%). A total of 16/218 patients suffered a CVA, and 2 patients died because of it. A meta-analysis demonstrated a risk ratio of 3.14 with a 95% CI of 1.29-7.60, illustrating an enhanced risk of complications in case of ICA manipulation or reconstruction. This is explained by the risk of thrombosis of the graft or vascular spasms due to manipulation. Unfortunately, the lack of stratification in the selected studies did not allow for detailed analysis of the impact of such surgical techniques on CND rates. In line, there were no differences in LC rates between the ICA manipulation/reconstruction group and the remaining tumours. Nonetheless, three studies used standardized ICA manipulation methods, of which only Arya et al. describe potential adverse events.[13-15] No difference in local control or CND rates were found in these studies. This might suggest that ICA manipulation does not result in higher LC or CND rates. With respect to ECA ligation techniques, which are suggested to be beneficial since CBPGL feeding vessels derive in nearly all cases from the ECA, our results suggest a trend towards higher risks of complications in case of ECA ligation (OR 4.46; 95% CI 0.92-21.57). Therefore, in line with class 2 tumours, generally an initial wait and scan regimen is advised for these tumours and we advise prudence with surgical intervention.

In case surgery is mandatory for Shamblin class 2 and 3 tumours, selective CBPGL feeder artery ligation seems a promising alternative in reducing CND and complication rates. Such strategies were implemented by van der Bogt et al., Padriaans et al. and Spinelli et al..[7, 16, 17]

Van der Bogt et al. suggest that for class 2 and 3 tumours, the craniocaudal surgical approach with consecutive feeder vessel ligation reduced the risk of postoperative morbidity since blood loss is reduced and carotid artery clamping is prevented. Although no CVA's were found out of a total of 111 resections, their results do not support the superiority of a craniocaudal method when considering class 3 tumours alone. Please note that for class 3 tumours alone, van der Bogt et al. found that cranial nerve damage rates were actually higher in the craniocaudal resection group (23.5%), when compared to the caudocranial group (12.5%). The local control rates, however, were higher in the craniocaudal group (70.6% versus 87.5%). The authors did not perform statistical analysis of these data. For eight class 2 tumours treated with a craniocaudal resection method however, no cranial nerve damage was found, whereas in 59.1% of 22 class 2 patients treated with caudocranial resection permanent cranial nerve damage was found Local control rates were similar (90.9 versus 92.3% respectively. Again no statistical analysis was performed on these cohorts.[7] Later results by the same institute, (Padriaans et al.) found no CND damage after 45 craniocaudally resected CBPGLs (seven Shamblin I, 22 II, and 16 III) and a single case of transient hemiplegia. Local control rate was 83% after a mean follow-up of 2.5 years. No explanation is found for the relatively low local control rates in the second series.[16]

It seems that CN function preservation comes at the cost of lesser control rates and visa versa. Moreover, these results are given in absolute rates and not corrected for death or loss to follow-up. The actuarial complication rates may therefore be much higher. Critically analyzing the results of van der Bogt and Padriaans et al., we believe that for class 2 tumours indeed the craniocaudal resection techniques seems to be the preferred technique. For class 3 tumours however, more research is required to determine the potential beneficial effect of the craniocaudal technique.

Results regarding local control were not stratified per tumour class. In a smaller population Spinelli et al. found in 6 class 2 and 5 class 3 tumours, 100% local control and no CND or complications by using careful isolation of the origin of the external carotid artery and its distal branches outside the tumour and temporarily clamping all of these vessels after heparin administration.[17] This allowed a safe and bloodless resection as the tumour was dissected from the internal carotid artery in the usual subadventitial plane. In this study, the internal carotid artery was never clamped, and respect of peripheral nerves was warranted in the clean and bloodless field. Therefore, although theoretically the selective feeder artery ligation techniques, with or without a craniocaudal approach, seem promising, the risk of recurrence and CND in Shamblin class 3 tumours remains problematic and the risks of surgery should be carefully discussed with patients.

We could not identify a relation between pre-surgical embolization and outcome measures, the more since reports did not indicate which tumours were embolized and which were not. Therefore, the risks associated with embolization and its effects on treatment outcome remain unclear. Notwithstanding Power et al. described for 71 Shamblin II and 33 Shamblin III tumours, that less extensive procedures were required in case of pre-operative embolization, when compared to no pre-operative embolization (simple excision in 97% vs. 82%, P .03; internal carotid artery clamping in 15% vs. 37%, P .04) and had less blood loss (mean estimated blood loss, 263 vs. 599 mL; P .002) than the non-embolized group.[18] However, there were no significant differences in operation time, temporary cranial nerve injury, clinically apparent cranial nerve deficits after 1 year, deaths, stroke rates, or postoperative length of stay. Therefore, it was concluded that is up to the preference of the surgeon whether or not embolization is required. Please note however, that an inherent risk of 1-3% of CVA's is found post-embolization.[18] Another aspect that could not be evaluated in the current review is the risk of embolization as a tool for preoperative ECA closure , as opposed to intraoperative (surgical) closure. Particularly since intra-operative ECA ligation seems to be accompanied by higher stroke incidences. Therefore, the comparison between preoperative- and intraoperative ECA closure techniques with respect to stroke risk requires future research.

An alternative for CBPGL treatment is the use of radiotherapy. Since Shamblin is a surgical classification, the results of radiotherapy are generally not stratified per tumour class. Nonetheless, Suarez et al. described excellent local control post radiotherapy, and no cranial nerve deficits were found in this group. Albeit Suarez et al. found merely a single complication in form of CNS syndrome, the potential long-term complications of radiotherapy such as vascular damage and irradiation induced malignancies remain underreported. One of the concerns post-irradiation is the risk of carotid artery atherosclerosis.[3] The effects of radiotherapy are cumulative, with an increase of 12 % in the stroke risk within 15 years following radiotherapy.[19] In line, Wilbers et al. found an increased risk of strokes in head and neck cancer patients 7 years post-irradiation when compared to the general population (8.9 versus 1.5 per 1.000 person years).[20] The irradiation dose for HNPGL is lower compared to malignancies but it is likely that the vascular damage is nonetheless significant. Conversely, the risk of ischemic brain damage due to surgery is most evident in the immediate post-operative period; for class 3 tumours, this risk is 11%. Another long-term adverse effect of radiotherapy is induction of malignancies in the irradiated area with an estimated risk of about 1% and a latency time of at least 10-15 years. Radiation tissue necrosis has been described as well but this is a very rare event with the relatively low doses used for HNPGL, especially with contemporary techniques such as IMRT and VMAT/rapid arc. Given the above-mentioned limitations of both treatment modalities, our recommendation is, that, in case treatment is required for class 1 and 2 tumour, surgery is the better option. For class 3 tumours, surgery should be applied with caution and radiotherapy can be considered as a good alternative.

An alternative that has not been reviewed in literature is tumour debulking and a wait-and-scan strategy for the residual tumour. Perhaps, for larger class tumours, debulking should be considered, in which resection remains within save margins, reducing the risk of carotid artery lesions and cranial nerve damage. In case the residual tumour is growing, additional radiotherapy could be applied. Unfortunately, little is known about this strategy and more experience with proper documentation is required on this approach.

Another aspect is the fact that approximately 33% of CBPGL's are part of an hereditary paraganglioma tumour syndrome and multifocal tumour management might be more problematic.[1] Particularly if a larger class 2 or 3 tumour is involved. Bilateral n. X damage for example is a life threatening condition for which a permanent tracheotomy might be required. Therefore, in the case of bilateral tumour management, a conservative approach is advised and for larger tumours the use of radiotherapy seems the best choice to avoid CND. Bilateral CBPGL surgery should be avoided at all times in order to prevent a baro-reflex syndrome.[21] Generally, it should be noted that CBPGL management is complex and should be performed by a skilled surgeon with

extensive experience in head and neck PGL management. Decision making should be done in a multidisciplinary team of surgeons, neurologists and radiation oncologists.

CONCLUSION

The current review and meta-analysis illustrates that a wide variety of surgical methods are used. For Shamblin class 1 and 2 tumours, surgery renders proper local control and relatively low risk of cranial nerve damage or adverse events, particularly when carotid artery manipulation is minimized. For class 3 tumours, however, morbidity in terms of CN deficit and complications is considerable. Particularly the use of ICA manipulation/ reconstruction and potentially ECA ligation seem to induce high risks of morbidity. Therefore, it is advised that surgery for these tumours should be reserved for those patients in which tumour induced morbidity is inevitable, and should be performed by an experienced surgeon. Potentially, tumour volume reduction with consecutive post-operative radiotherapy in case of residual tumour growth could be applied for these higher class tumours. Primary radiotherapy is an alternative for these tumours as well. Future research is required to evaluate such alternative treatment strategies for Shamblin class 3, CBPGL.

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APPENDIX A:

Reference	Follow-up	N per Shamblin class	Methods used	Local control: n/n total	CN damage: n/n total	Complicationn/n total	Risk of incompl. data/ Risk of selective report
Amato et al. 2014	44 months	Class 1: 11	Transcervical approach, pharyngeal artery cleavage, bipolar/radiofrequent periadventitial dissection, covering of carotis with temporalis fascia; 3x ECA resection, 2x ICA resection/ reconstruction	11/11	0/11	0/11	Low /Low
		Class 2: 14		14/14	3/14	0/14	
		Class 3: 9		9/9	5/9	3x CVA; one with permanent damage	
Arya et al. 2010	?	Class 3: 5	4x ICA and ECA ligation /graft	4/5		0/5	High/ Low
Dardik et al. 2002	24.0 ±5.5 months	Class 1: 12	Eleven (41%) patients required either external carotid artery (ECA) ligation or internal carotid artery (ICA) resection and reconstruction with a vein graft for tumour removal	12/12	3/12	?	Low/ High
		Class 2: 9		9/9	3/9	?	
		Class 3: 6		6/6	3/6	?	
Davidovic et al. 2005	6.2 years	Class 2: 7	a subadventitial tumour excision	7/7		0/7	Low/ High
		Class 3: 5	both external and internal carotid arteries were resected. One of these was repaired by end-to-end anastomosis, one with interposition of Dacron® graft, and other3 were repaired with reversed saphenous vein graft	5/5	?	?	
Dixon et al. 2016	1-126 months (mean 56 +/-} 34)	Class 1: 7	one class 3 arterial resection with a primary end-to-end anastomosis; one class 3 reconstruction with a polytetrafl uoroethylene hybrid vascular graft	7/7	0/7	0/7	Low/Low
		Class 2: 8		8/8	0/8	1/8 (stroke)	
		Class 3: 2		2/2	1/2	0/2	
Ghilardi et al. 1991	?	Class 2: 10	?	?	2/10	0/10	High/ Low
		Class 3: 15	?	?	3/15	0/15	

Reference	Follow-up	N per Shamblin class	Methods used	Local control: n/n total	CN damage: n/n total	Complicationn/n total	Risk of incompl. data/ Risk of selective report
Grotemeyer et al. 2009	?	Class 2: 13	1x Met vagus resectie; 1x ECA resection	?	?	?	High/ High
		Class 3: 12	1x Met vagus resectie; 9x ECA/7x ICA resection/reconstruction	?	?	1/13 (CVA with permanent hemiplegia)	
Gwong et al. 2012	?	Class 1: 8	anterior neck incision, accompanied by mandibular subluxation;	8/8	?	0/8	High/ High
		Class 3: 5	anterior neck incision, accompanied by mandibular subluxation; ICA manipulation, and saphenous vein harvest for ICA (5x) reconstruction.	5/5	?	3/5 (CVA without recovery)	
Kotelis et al. 2009	6.4 years, range 1.5-20	Class 2: 7	From periadventitial plane, ICA repair	7/7	?	?	Low/ High
		Class 3: 8	From periadventitial plane, ICA repair/ replacement; 4x ICA and ECA ligation	7/8	6/8	1/6 (death due to malignant disease)	
Lamblin et al. 2016	17 months (IQR, 10–67 months).	Class 1: 17	Occasional ICA reconstruction methods used (4 class 2 patients, 9 class 3 patients).	17/17	1/17	0/17	
		Class 2: 25		25/25	4/25	0/25	
		Class 3: 12		10/12	9/12	1/12 (CVA resulting in death)	
Lees et al. 1981	Up to 52 years	Class 2: 18	4 ECA ligation	18/18	3/18	1/18 (death by pneumonia)	Low/ Low
Liapis et al. 2000	30 months to 23 years, mean 5 years	Class 1: 6		6/6	?	0/6	Low/ High
		Class 2: 6	?	6/6	?	?	

Reference	Follow-up	N per Shamblin class	Methods used	Local control: n/n total	CN damage: n/n total	Complicationn/n total	Risk of incompl. data/ Risk of selective report
Lim et al. 2010	29 (15 to 64 months)	Class 3: 8	transverse cervical incision; All neurovascular structures were identified and periadventitial dissections; 3x ICA ligation/reconstruction with saphenous/synthetic graft	8/8	2/8	2/8 (2x CVA, 1x permanent	Low/ Low
Luna-Ortiz et al. 2005	Range 22 years	Class 3: 24	Three (6.3%) patients required vascular reconstruction; one with a synthetic shunt and two with autologous saphenous vein graft.	?	11/24	?	Low/ High
Luna-Ortiz et al. 2010	?	Class 2: 6	?	6/6	4/6	?	High/ High
Makeieff et al. 2009	Up to 6 year	Class 1: 15	cervical approach	15/15	0/15	0/15	Low/ Low
		Class 2: 28	cervical approach; periadventitial plane; no standart ECA ligation	28/28	1/28	0/28	
		Class 3: 11	cervical approach; periadventitial plane; 4x ECA/ICA ligation	11/11	3/11	2x CVA	
O'Neil et al. 2011	1801 days (range 159-9208 days).	Class 3: 9	6x saphenous reconstruction; 4x ICA ligation/ reconstruction	8/9	?	1x death due to metastasis	Low/ High
Ozay et al.	Mean follow-up was 2.1 years	Class 1: 5	periadventitial tumour dissection	5/5	0/5	0/5	Low/ Low
		Class 3: 5	periadventitial tumour dissection; 2x ICA resection with saphenous vein graft or goretex graft	5/5	0/5	0/5	
Padriaans et al. 2013	mean follow up was 2.5 years	Class 1: 7		7/7	0/7	0/7	Low/ High
		Class 2: 22		22/22	?	0/22	
		Class 3: 13	Craniocaudal resection; 3x ICA and ECA removal + saphenous reconstruction; 4x ECA removal without reconstruction; 3x ICA ligation/reconstruction	13/13	?	1/13 (transient CVA)	

Reference	Follow-up	N per Shamblin class	Methods used	Local control: n/n total	CN damage: n/n total	Complicationn/n total	Risk of incompl. data/ Risk of selective report
Plukker et al. 2002	Median follow-up 10 years	Class 1: 5	Curved horizontal incision; subadventitial plane dissection	5/5	0/5	0/5	Low/ Low
		Class 2: 21	Curved horizontal incision; subadventitial plane dissection; occasional ECA excision	21/21	0/21	0/21	
		Class 3: 8	Curved horizontal incision; subadventitial plane dissection; occasional ECA excision; 7x ICA manipulation, no reconstruction	8/8	?	2/8 (2x CVA)	
Sanli et al. 2012	?	Class 1: 9	?	9/9	0/9	0/9	High/ Low
		Class 2: 7	internal and external carotid veins were temp. blocked	7/7	1/7	2/7 (2x CVA, from which 1 died)	
Schneider et al. 2013	mean of 64 months (range 23–78 months	Class 2: 6	?	6/6	1/6	0/6	Low/ Low
Sen et al. 2013	ranging from 1 month to 5 years	Class 2: 6	sub-/periadventitial dissection; retrograde (craniocaudal) dissection	?	1/6	0/6	Low/ High
		Class 3: 27	sub-/periadventitial dissection; retrograde (craniocaudal) dissection; 6x ECA ligation; 5x ICA manipulation/reconstruction.	?	10/27	2x CVA; once permanent	
Singh et al. 2006	Median 10 years	Class 2: 9	No ICA ligation; occasional ECA ligation	?	0/9	0/9	Low/ Low
Soto et al. 2008	?	Class 2: 8	?	?	?	0/8	High/ High

Reference	Follow-up	N per Shamblin class	Methods used	Local control: n/n total	CN damage: n/n total	Complicationn/n total	Risk of incompl. data/ Risk of selective report
Spinelli et al. 2013	mean follow-up of 42 months	Class 2: 6	subadventitial plane; Clamping of superior thyroid, lingual, facial, distal ECA, and ascending pharyngeal arteries; bipolar resection, NO ICA compromitation	6/6	0/6	0/6	Low/ Low
		Class 3: 5	subadventitial plane; Clamping of superior thyroid, lingual, facial, distal ECA, and ascending pharyngeal arteries; bipolar resection, NO ICA compromitation	5/5	0/6	0/6	
Van der Bogt et al. 2009	?	Class 1: 51	Craniocaudal approach; cervical incision; subadventitial plane	42/51	1/51	0/51	High/ Low
		Class 2: 35	Craniocaudal approach; cervical incision; subadventitial plane; occasional ECA/ICA resection/reconstruction	32/35	13/35	0/35	
		Class 3: 25	Craniocaudal approach; cervical incision; subadventitial plane; occasional ECA/17x ICA resection/reconstruction	20/25	4/25	0/25	

CHAPTER 6

Management of Carotid Body Paraganglioma: Surgery or Radiotherapy?

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ABSTRACT

Importance: The management of carotid body paraganglioma remains a topic of debate since surgery is associated with strokes and cranial nerve damage. An alternative option is radiotherapy, yet associated complication rates remain unknown.

Objective: To determine the local control and complication rates post-surgery and -radiotherapy stratified per tumour class.

Design: First a retrospective cohort study was conducted with patient records from 1986 to 2016 of all patients suffering carotid body paraganglioma. Minimal follow-up was 6 months post surgery, and 5 years post radiotherapy. Second, a systematic review was conducted to evaluate literature on effects of radiotherapy. A 2016 Pub Med search was performed according to the PRISMA statement.

Setting: A population based study was performed on primary referrals to the Radboudumc, Netherlands.

Participants: A total of 112 patients suffering carotid body paraganglioma referred to our centre. Eligibility criteria were proper diagnostic work-up and (long term) follow-up post-surgery/radiotherapy and 54 patients of different Shamblin class were included.

Interventions: Interventions were surgical excision using a cervical approach and LINAC based radiotherapy.

Main outcome measures: The main outcome measures were local control and complications, stratified as cranial nerve damage, and other.

Results: Thirteen class 1, 25 class 2 and 16 class 3 tumours were included (median age 38; range 13-70). Seven class 2 and 3 patients were treated with radiotherapy (median age 74; range 29-83). Post surgery, local control rates were 100%, 90% and 93% for class 1-3 respectively, cranial nerve damage rates were 0%, 8% and 18% and complication rates were 0% 4% and 6%. No complications were found post radiotherapy after median follow-up of 11 years (range 4-30), local control was 100%. In the systematic review, constituted of 10 cohort-studies (selected out of 136 studies) resembling 118 patients with median follow-up of 9.5 years (range: 1-34), local control as found in 96-100%, no irradiation induced cranial nerve damage and 1 potentially irradiation induced meningeoma was found.

Conclusions and Relevance: Post surgery, the risk of complications in class 2 and 3 tumours is low, yet, complications are potentially severe. In case patients are not fit for surgery, radiotherapy should be applied.

INTRODUCTION

Carotid body paraganglioma (CBPGL) are the most common form of HNPGL and grow in close proximity with the carotid artery bifurcation and can also damage the surrounding the vagal and hypoglossal nerves.[1] The management of these tumours remains a matter of debate. Surgery is still the mainstay of treatment, however, it poses a threat since it is related to neurovascular incidents and cranial nerve (CN) damage. Although surgical techniques have advanced, there is a still considerable risk of iatrogenic morbidity, particularly in the case of CBPGL of higher Shamblin class.[2]

It has been advocated that a conservative treatment method should be pursued to prevent morbidity. Particularly in the case of multifocal HNPGL (HNPGL) disease which is associated with hereditary tumour syndromes, surgery should be applied with caution. Bilateral surgery should be avoided as this might be associated with severe complications such as bilateral vagal or hypoglossal nerve palsy or baroreflex syndrome.[3] Therefore, mainly in the above mentioned scenario, alternative treatment methods such as radiotherapy should be regarded as a viable option. However, radiotherapy is accompanied with minor and more serious acute and long-term complications as well. The main acute complications found in radiation of this area are mucositis and loss of hair in a small area. Later, chronic fatigue has been found post-radiation as well as xerostomia. More life threatening long term complications are arteriosclerosis of the carotid artery which might result in strokes. Also, there is a risk of radiation-induced malignancies such as sarcomas. [4, 5]

In the current study we aim to evaluate the local control, cranial nerve and overall complication rates post surgery and radiotherapy of CBPGL of different Shamblin class. Also, we provide a systematic review of the currently available literature on CBPGL radiotherapy outcomes. Ultimately, we aim to provide insights that aid the constitution of guidelines for the management of HNPGL.

METHODS

Clinical analysis

Methods were similar to a previous manuscript of our group. [6] A retrospective cohort study was conducted with all patient records of patients presenting with a HNPGL between 1980 and 2016 in the Radboud University Medical Centre a dedicated tertiary Head and Neck Surgery and Cancer Centre, Nijmegen. Eligibility criteria were patients with a CBPGL. Patients with a malignant tumour were excluded. Out of a total of 358 patients, 112 patients had a CBPGL and 54 were treated with surgery , seven were treated with radiotherapy and the remaining patients were subjected to a wait and

scan strategy. The following information was extracted from the records: gender, age at presentation, signs and symptoms at presentation, tumour class, gene mutation analysis, clinical and radiological signs and symptoms of tumour progression Tumour volume was estimated by expert radiologists as by the researchers themselves, measuring the largest size in the antero-posterior, medio-lateral and cranio-caudal direction.

Patients were stratified by Shamblin class, class 1 tumours entailed no encasement of carotid arteries. Class 2 referred to partial encasement of either internal or external carotid arteries and class 3 implied full encasement of both internal and external carotid arteries with or without inclusion of hypoglossal nerve.

The intervention was any form of surgery or radiotherapy, with or without a prior wait and scan period. The outcome of the treatment was compared to patients' situation at first presentation, before any form of treatment and evaluated by a routine follow-up schedule. Follow-up had to be at least 6 months post treatment. Treatment outcomes were local control, CN damage and other complications. Definitions of treatment outcome were according to Suarez et al.[2] Post-surgery, local control was defined as a patient alive without evidence of disease or with a non-growing residual tumour throughout the entire follow-up period. Post-radiotherapy local control was defined as a patient alive without any evidence of progression of the disease throughout the entire follow-up period. CN damage and CN recovery were defined as deterioration and improvement, respectively, of CN function post-treatment when compared to the pre-treatment setting, objectified by a physician. The complications wound infection, cerebrovascular accident, aspiration resulting in pneumonia and/or tracheotomy, , malignancies and death were included.

Patients were subjected to a routine follow-up which was organized as follows: Post-treatment, patients were seen within 2 weeks to evaluate immediate post-treatment complications. Generally. routine follow-up was then every six months for patients in all treatment groups for two years. After two years usually a yearly follow-up protocol was organized. In case tumours remained stable for 5 years, 2 year-follow-up intervals were adopted for ten years. Hereafter a five year interval follow-up was used. Post-treatment MRI-scans were done one year post treatment. In case local control was achieved, MRI-scans were subsequently done on a yearly basis. In case follow-up intervals were prolonged, MRI's were done every 2 or 5 years. MRI scans were performed according to a local HNPGL screening protocol, optimized for paraganglioma growth and new tumour localization detection. In case patients suffered from severe comorbidities, post-treatment symptoms or in case complications were to be expected due to larger tumour sizes, follow-up intervals could have been reduced. Intervals were also reduced in case of multifocal tumour presence or in case of SDHD or –B mutations. Visa versa, in case patients were completely complication free and no mutation was found, follow-up intervals could have been prolonged. Also,

in case there was any sign of clinical tumour progression or potential new tumour localization, MRI scans were performed.

For prediction of tumour growth the following variables were considered:, age at presentation defined as age at first diagnosis of HNPGL. Mutation presence was defined as presence of succinate dehydrogenase gene complex (SDH) associated paraganglioma syndromes (SDHA, -B, -C, -D, -AF2). Fisch classification was defined as described above.

As presented by Jansen et al. tumours were considered to have an ellipsoid shape and the following equation was used to estimate the tumour volume:

$$V = \frac{4}{3}\pi\left(\frac{1}{2}A * \frac{1}{2}B * \frac{1}{2}C\right)$$

in which V = volume, A = the largest dimension in the antero-posterior direction, B = the largest dimension in the medio-lateral direction, and C = the largest dimension in the cranio-caudal direction.[7] The measurement error was expected to be at least 15%-20%, therefore, tumour growth was defined as a volume increase of at least 20%.

Literature study

Studies evaluating the effect of radiotherapy on CBPGL were included. Treatment outcomes collected were local control, cranial nerve damage and other complications. The definitions were no different from the analysis of the retrospective cohort.

A systematic literature review was conducted according to the PRISMA statement.[8] On February 2017 we searched the Pub Med database for articles using the search strategy as mentioned underneath (no MeSH terms were used for inclusion of the most up to date articles). References of key articles were assessed for additional relevant articles.

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[Title] OR Gamma Knife [MeSH Terms] OR CyberKnife [Title] OR CyberKnife [MeSH Terms] OR Linear Accelerator [Title] OR Linear Accelerator [MeSH Terms]) AND (Tumour [Title/Abstract] OR Tumour [MeSH Terms] OR Tumour [Title/Abstract] OR Tumour [MeSH Terms] OR Tumours [Title/Abstract] OR Tumours [MeSH Terms] OR Tumours [Title/Abstract] OR Tumours [MeSH Terms])))

Articles written in English, German or Dutch were selected and tumours had to be classified. The treatment modality and outcome measures needed to be reported for each tumour class individually. Cohort sizes had to be 5 or more patients. Information on at least one of the afore-mentioned outcome measures had to be available. Also, information on the radiotherapy technique and corresponding outcome measures had to be provided.

A critical appraisal was performed using the PRIMSA 'Risk of bias' tool.[8] The following terms were addressed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other forms of bias. Risk of bias was considered high in case these factors were not mentioned. The risk was considered low in case the factors were addressed by the authors. However, please note that no articles were excluded from the study based on the critical appraisal since the majority of the studies show poor risk of bias prevention. The risk of bias is presented for information of the readers.

Statistical analysis

The number of patients lost to follow-up is reported per treatment outcome. Missing data were handled by using multiple imputation methods. The data was collected using filemaker pro, and was analyzed using IBM SPSS Statistics 22. For tumour-class correlations a one way ANOVA test was used, with post-testing for individual characteristics using a Bonferroni test. For correlations between treatment outcomes and patient characteristics a Chi-square test was used.

RESULTS

Clinical results

Out of 112 CBPGL , 54 tumours were treated with surgery, and 7 with radiotherapy, the remaining tumours were subjected to a wait and scan management strategy. The baseline results are provided in table 1.

Mutation presence was evaluated in 14 Shamblin class 1, 16 class 2 and 7 class 3 patients, mutations were found in 69%, 87.5% and 71.4% respectively There was no significant correlation between Shamblin class and treatment outcome overall, nor when stratified per treatment modality. A Bonferroni post-test found no differences

Table 1: Baseline results and treatment outcome post surgery per Shamblin class.

	Shamblin class 1	Shamblin class 2	Shamblin class 3	Total
N (%)	13	25	16	54
Median age, (range)	39 (13-63)	41 (13-73)	32 (14-70)	38 (13-70)
Tumour growth n (%)	6 (45%)	13 (53%)	8 (50%)	27 (50)
Symptomatic presentation n (%)	6 (45%)	19 (76%)	12 (75%)	37 (68%)
Median volume (Range) in cc	64 (6-238)	115 (14-348)	391 (132-800)	197 (6-800)
Median follow-up, (range) surgery/ Radiotherapy in months	73 (12-199)/ -	67 (10-251)/ 88 (48-120)	65 (13-166)/ 192 (132-360)	68 (10-251)/ 147 (48-360)

in treatment outcome per tumour class. Neither was there a relation between treatment outcome and presenting symptoms, age at presentation, pre-treatment tumour growth, mutation presence or tumour size

Two cranial nerve deficits were found in Shamblin class 2 tumours: one transient accessory nerve palsy and one permanent case of a Horner syndrome. Also, a complication in form of baroreflex syndrome was described in a patient suffering a contralateral vagal body tumour. In a class 3 tumour a complication was observed resembling a stroke without long term effects as well as two permanent cranial nerve deficits: one case of hypoglossal nerve palsy and one case of a Horner syndrome.

A total of 7 patients were treated with radiotherapy. Characteristics of these patients can be found in table 2. Local control was 100% in this group, no CN damage or adverse events were found after a median of 147 months follow-up (range 48 -360). There was no significant difference between results of radiotherapy and surgery for all CBPGL s combined with respect to local control ($p = 0.44$), CN damage rate ($p = 0.32$), or complications ($p = 0.19$),nor when stratified per Shamblin class (results not shown).

Results of the systematic literature-study

Our Pub Med search generated 136 studies that were screened for title and abstract. A total of 34 studies were selected for full review, and 10 articles were selected based on adequate follow-up, detailed information on treatment outcomes of malignant and non-malignant tumours. These are presented in table 3. Exclusion criteria are presented in figure 2.

In these 10 studies, a total of 118 patients with CBPGLs were described who were treated with radiotherapy, of which 8 were malignant. Local control was achieved in 80-100% of cases (median of 97%); 1 patient died after re-irradiation after residual tumour growth, it is possible that tumour growth was due to malignant progression. When malignant tumours are excluded, local control was achieved in 96-100% of cases (median 100%). No irradiation induced cranial-nerve damage was found and a single (potentially radiation-induced) meningioma was found after multifocal tumour

Table 2: characteristics of patients treated with radiotherapy

Patient	Age	Shamb. class	Tumour syndr.	Volume in cc (max diameter in mm)	Treatment motivation	Motivation for RT	RT tech.	Follow-up (years)
1	74	3	-	720 (45)	Complaints and growth	Comorbidities and size of tumour	50Gy in 25 fractions	11 year
2	83	2	-	122 (23)	Tumour growth	Comorbidities	46 gy. in 23 fractions	10 year
3	76	3	-	290 (29)	Tumour growth	Size of tumour	47Gy in 25 fractions	30 year
4	78	3	-	1200 (60)	Complaints	Size of tumour and comorbidities	50Gy in 25 fractions	11 years
5	46	3	SDHD	140 (35)	Tumour growth	Bilateral/ multifocal disease/ Comorbidities and size of tumour	40 Gy, 20 fractions	12 year
6	48	2	SDHD	55 (23)	Tumour growth/ CN damage	Bilateral/ multifocal tumour localisation	25 Gy in 12 fractions	4 year
7	29	2	SDHD	39 (20)	Tumour growth	Bilateral/ multifocal tumour localisation	25 Gy in 12 fractions	8 year

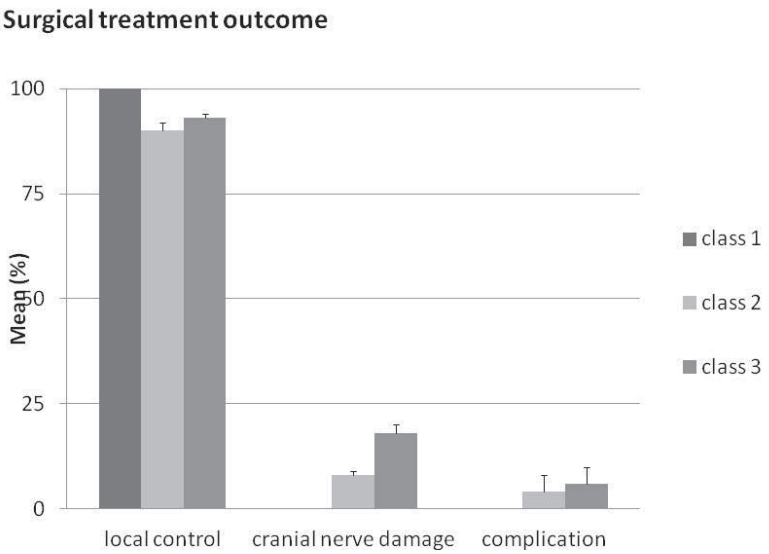

Figure 1: treatment outcome per Shamblin class

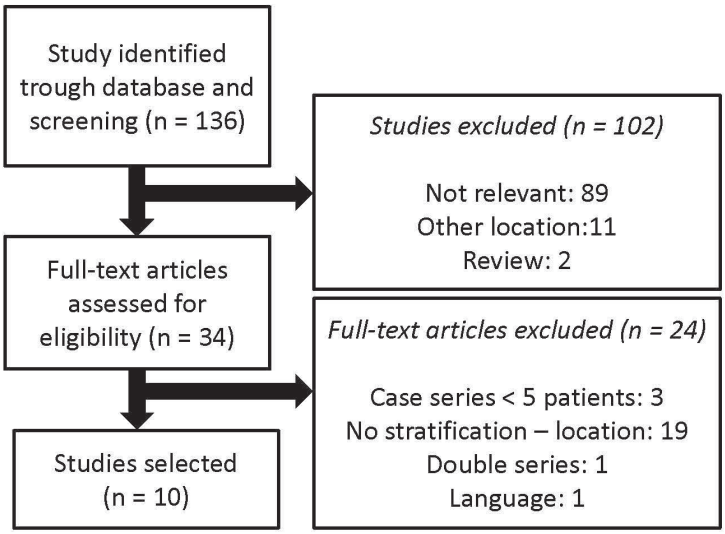

Figure 2: flow chart.

irradiation. This patient was treated at age 30 for 3 paragangliomas (1 carotid and 2 Fisch type D2 skull base) and presented a parietal meningioma 15 years after irradiation. It was treated by surgery and has been in complete remission for 5 years at time of writing.

DISCUSSION

The current results illustrate that surgery is a proper treatment option for CBPGL . However, particularly for class 2 and 3 tumours, there is a risk of serious complications including cerebrovascular accidents and CN damage. In the current study, no predictor of complications could be found. Radiotherapy is an alternative option. For 7 of our patients suffering class 2 and 3 tumours, radiotherapy gave 100% local control without complications. The main motivations for radiotherapy were comorbidities (not fit for surgery) and bilateral tumour presence. Our literature review, evaluating the results of 123 patients shows that, when excluding malignant paraganglioma (6%, 8/123), local control is indeed achieved in 96-100% without any cranial nerve damage. A single case of a (potentially) radiation-induced meningioma was found.

These results underline that in case treatment is mandatory, for class 1 tumours surgery is a good option. For class 2 and 3 tumours, radiotherapy is a serious alternative, particularly in the case of mulitiple tumours or in case a patient is not fit for surgery.

Table 3: study characteristics and treatment outcome of included studies.

Reference	N carotid body PGL	Malignant	Treatment modality/ Gy (range)	Follow-up	Local control	Complication/ CN damage
Mitchell and Clyne 1986[9]	5	2	EBRT Gy 4565;(3750; 5500)	65 months (18-96)	80%; 100% for non malignant	One death of malignant disease
Valdagni and Amicheti 1990[10]	13	0	EBRT 46-60 Gy (mean 52.25 Gy	12-228 months	100%	None
Verniers et al. 1992[11]	8	0	EBRT 50 to 60 Gy in 20 to 25 fractions over 4 to 5 weeks.	120 (12-240)	100%	None
Evenson et al. 1998[12]	13	2	EBRT 47.8 (35-70) in 25-39 fractions	456 (12-120).	5; years, 96% and 100%; 10 years, 96% and 100%	One death after re-irradiation; thought due to CNS syndrome, in case of a potentially malignant tumour.
Luna Ortiz et al. 2005[13]	7	0	EBRT; Not reported	38 (Range not reported)	100%	Not reported
Krych et al. 2006[14]	4	0	EBRT: 45 Gy (range, 16.2–54 Gy). 25 fr.(range, 9–30). SRS: 15 Gy (range, 12–18 Gy)	161 (4–429)	100%	None
Hinerman et al. 2008[15]	24	0	EBRT 4500 cGy 25 fr. SRS in 6 patients 1250-1500 cGy	10 years (range not reported)	96%	Not reported
Chino et al. 2009[16]	3	1	EBRT 54 Gy (38–65 Gy), median fraction size 180 cGy (range: 180–356 cGy).	108 (24-420)	100%	None
Ma et al. 2009[17]	5	3	n.r.	132 (24-312)	100%	3 patients died.
Dupin et al. 2014[18]	9	0	EBRT 45 Gy (range, 45-46 Gy)	102 (12-276)	100%	(irradiation induced?) meningioma in multifocal tumour presence

Clinical considerations

Although not statistically significant, complications were mainly found for class 2 and 3 tumours. This relation has been described by several authors before and we believe the Shamblin classification is still a suitable predictor for risk of surgery.[13] In order to reduce risk of surgery several techniques have been proposed. Generating a bloodless operating field has been proposed, allowing for better

visualization of residual tumour, cranial nerves and the carotid arteries.[19] To this end, transient clamping of the carotids has been suggested.[20] However, a recent meta-analysis from our group demonstrated that such techniques were associated with an enhanced risk of cerebrovascular accidents.[21] Other approaches used external carotid artery ligaton techniques, since 90% of the CBPGL feeding arteries arise from the external carotid artery. [22-24]. However, our meta-analysis illustrated a trend towards an enhanced risk of cerebrovascular accidents with this technique as well. To prevent routine standard clamping of carotid arteries, van der Bogt et al. proposed in 2009 a craniocaudal resection technique in which the external carotid artery and its feeder branches were targeted first, rendering minimal blood loss when dissecting the tumour from the internal carotid and the common-carotid artery and more accurate visualization of cranial nerves.[19] Using this technique, no cerebrovascular accidents were found (n = 111), however, higher cranial nerve damage rates were found for class 3 tumours using this technique (23.5%), when compared to the conventional caudocranial surgical method (12.5%). Also, the local control rates were higher in the craniocaudal group (70.6% versus 87.5%). The surgical method was reviewed by Padriaans et al., who found no CN damage after 45 craniocaudally resected CBPGL's (seven Shamblin 1, 22 class 2, and 16 class 3). The local control rate of this group was 83% after a mean follow-up of 11 years.[23] The exact benefit of this technique, therefore remains uncertain and requires further systematic research.

Several other methods have been suggested to reduce morbidity, such as routine heparine administration, but there is no good evidence that this is associated with better treatment outcome.[22] Also, pre-operative embolization techniques have been suggested as these reduce intra-operative blood loss and operation time.[25, 26] Pre-operative embolization is not routinely used either, as it is not clear if it really reduces morbidity and there is an inherent risk of a stroke associated with this method.

In the current series surgery was not considered for patients with bilateral multifocal HNPGL, because of the significant morbidity if surgery-induced bilateral cranial nerve damage occurs. For these patients, radiotherapy was applied and excellent local control rates and no irradiation induced CN damage was found, albeit that we had only 7 patients in our series. The systematic literature review agrees with the excellent local control rates (96-100%) for non-malignant HNPGL's. However, radiotherapy is not free of complication risk either.

The most severe irradiation induced complications are found after re-irradiation. The first is described by Evenson et al. 1998 who found a delayed type CNS syndrome post treatment after using a high dose regimen twice (60Co single fraction and 47.8Gy in 25 fractions, respectively).[12] The tumour was re-irradiated because of progression after the first treatment. Potentially this tumour progression was due to malignant paraganglioma disease.

The second severe complication was also found after re-irradiation. This patient was treated with radiotherapy for 1 carotid and 2 Fisch type 2D skull base tumours. A parietal meningioma was found 15 years post treatment. In this series, another (supposedly) radiation-induced meningioma was found 18 years post treatment after a single RT doses of a not further specified HNPGL. Several authors have estimated the risk of irradiation induced neoplasms, Lalwani et al. suggest that the incidence of tumour induction is approximately 1 in 1.000 to 2.000.[5] Springate et al. estimated a risk of post-HNPGL irradiation of about 0.28%.[4] For example, we found no complications after use of the LINAC-based treatments. However, the long term risks of radiotherapy remain uncertain. This is underlined by results of Gilbo et al. who found no severe complications post radiotherapy and a local control rate of 96.8% after 10 years for 156 HNPGL (not stratified per tumour type).[27] Although these results are promising, one of the concerns post irradiation is the chance of carotid artery stenosis, particularly in the case of CBPGL . Gujral et al. described in 2014 that a systematic review of 34 articles illustrated that the relative risk of stroke in patients irradiated for head and neck cancer relative to the general population was 5.6 and the carotid intima-medial thickness was significantly increased by 22-36% (when compared to matched control-groups) after 1 to 2 years.[28] Obviously, head and neck-cancer patients cannot be compared to HNPGL patients, however, the late vascular effects of radiotherapy are undeniable and well-documented. The mean age of our surgery group was 38 years of age which is significant lower than the mean age of Head and Neck cancer patients. Not only do other patient factors differ between patients suffering HNPGL and head and neck cancer, also treatment regimens differ. Radiotherapy doses prescribed for HNPGL are lower (range 30-50 Gy in our series), when compared to the head-and-neck cancer population (50-80 Gy, described by Gujral et al..[28] The details of the dose-effect relation of RT-induced arteriosclerosis are not fully known yet. Nonetheless, there is a serious risk of enhanced atherosclerosis development. Another factor that theoretically enhances the risk of carotid atherosclerosis in CBPGL-patients when compared to other HNPGL, is the suggestion of Dorresteijn et al. that the larger the part of the carotid that is irradiated, the higher the risk of atherosclerosis.[29] More research is required on the risks of radiotherapy for CBPGL, especially on the long term. The option should be carefully discussed against the background of the surgi-

cal risks. Other long-term risks of head and neck irradiation is the development of radiotherapy-induced malignancies, for which the risk is about 1% after 10 years.[30]

Methodological considerations

In line with our other research on HNPGL, the current study is a retrospective cohort study and therefore the external validity is limited. However, given the rarity of these tumours and their slow growth rate, prospective (randomized controlled) studies are not possible. Furthermore, although the current study provides one of the larger sample size on this particular tumour type, for sub-group analysis the cohort is too small (Jansen et al. 2017).

Moreover, the literature search using the terms "radiotherapy" and "CBPGL" yielded few results and mostly small patient numbers because generally radiotherapy remains the second choice of treatment after surgery. Due to this selection most studies include patient cohorts that span two to three decades or even more to reach sufficient patient numbers, implicating that many patients were treated with older radiotherapy techniques. Modern techniques such as IMRT, VMAT/rapid arc and stereotactic radiotherapy are expected to reduce complication rates. However, the more clinically relevant complications are the long-term sequelae. This complicates the evaluation of treatment results because it requires meticulous life-time follow-up because the vascular effects of radiotherapy continue to progress. In the mean time radiotherapy techniques as well as methods for outcome assessment will further develop making comparisons with historical controls difficult.

CONCLUSION

The current study describes the treatment outcome of CBPGL treated in the Radboud University Medical Centre in Nijmegen, Netherlands. The risk of complications in class 2 and 3 CBPGL is low, however, complications are potentially severe. In case patients are not fit for surgery or in case there is a risk of potential bilateral cranial nerve damage, radiotherapy should be seriously considered. In our series no complications were found with irradiation in 7 patients and local control was 100% after a median of 12 years (range 4-30 years) The low complication risk was confirmed by an additional literature research. Until recently the awareness for carotid atherosclerosis as a complication of radiotherapy for CBPGL was low but studies in head and neck cancer patients indicate a significant risk of ischemic stroke years after radiotherapy. Also with the radiation doses used for CBPGL there is an increased risk of late vascular complications and stroke. Additional research is required to evaluate the overall stroke risk after irradiation of CBPGL.

With current knowledge we recommend that class 1 tumours should be treated with surgery. For class 2 and 3 tumours, radiotherapy should be discussed as alternative treatment option, particularly in the elderly or in case of multiple tumours.

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CHAPTER 7

A Systematic Literature Review of Treatment Modalities for Vagal Paraganglioma.

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ABSTRACT

Background: The treatment of vagal body paraganglioma is a hot topic of debate since surgery is associated with high morbidity rates and radiotherapy results are not systematically documented.

Methods: Systematic literature review according to the PRISMA statement in August 2017, searching the Pub Med database.

Results: A total of 17 retrospective cohort studies were selected representing 177 patients treated with surgery and 78 patients treated with radiotherapy. Compared to surgical results, post radiotherapy, there were significantly higher local control (95% vs. 100% resp.), and significantly less cranial nerve damage (97% vs. 0% resp.) and complication rates (29% vs. 0%).

Conclusions: Surgery is not the preferred treatment option for vagal body paraganglioma. Local control after radiotherapy is high but long-term side effects are not well documented. The risk of cranial nerve damage caused by radiotherapy seems small when compared to the risk of iatrogenic nerve damage post surgery.

INTRODUCTION

Vagal paraganglioma are tumours arising from the paraganglia of the vagal nerve, and form about 7-15% of all HNPGL [1]. Contrary to the carotid body and jugulotympanic paragangliomas, there is no broadly accepted classification for these tumours.

The main treatment options for these tumours are surgery and radiotherapy, which are generally applied after an initial wait-and-scan policy. Although surgery is historically the main treatment of choice, it contains a high risk of iatrogenic morbidity in terms of vagal nerve palsy [2]. Therefore, alternatively, radiotherapy has been proposed as a suitable alternative. The risks of radiotherapy of these tumours however, are not systematically documented. Suarez et al. attempted a systematic review on this topic but could find only one study containing 10 patients (100% local control, no adverse events) [2]. Obviously, more information is required on the advantages and disadvantages of surgery and radiotherapy for these tumours.

In the current study, we aim to evaluate the benefits and risks of surgery and radiotherapy for patients suffering vagal paraganglioma, in terms of local control, cranial nerve damage, complications and function recovery rates.

METHODS

The methods used were as described earlier by Jansen et al.[3].

Eligibility criteria

Studies evaluating the effect of surgery and radiotherapy in patients with vagal paraganglioma were included. The intervention was any form of surgery or radiotherapy, with or without a previous wait-and-scan period. The treatment outcomes were compared to the patients' situation before treatment. Treatment outcomes were local control, cranial nerve damage and other complications. The definitions used were according to Suarez et al.[2]. Local control after surgery was defined as a patient alive without evidence of disease throughout the entire follow-up period. Local control after radiotherapy was defined as a patient alive with stable or decreased size of the tumour. Cranial nerve damage was defined as deterioration of cranial nerve function post-treatment when compared to the pre-treatment setting, objectified by medical professionals. Cranial nerve recovery, was defined as any improvement of cranial nerve function in post-treatment setting when compared to pre-treatment conditions, objectified by medical professionals. The complications CSF leakage, wound infection, CVA, baro-reflex failure syndrome, aspiration resulting in pneumonia and/or tracheotomy and death

were included. Furthermore, immediate complications such as dysphagia, skin burns, mucositis, Eustachian tube dysfunction and xerostomia were evaluated.

Literature review

A systematic literature review was conducted according to the PRISMA statement [4]. In August 2017 we searched the Pub Med database for articles using the search strategy as mentioned below (no Mesh terms were used for inclusion of the most up to date articles). References of key articles were assessed for additional relevant articles. The search strategy is included in Appendix A.

Study selection and the data collection:

Articles written in English and German were selected and cohort sizes had to consist of 5 or more patients. Information on at least one of the aforementioned outcome measures had to be available. Also, information on the surgical and radiotherapeutic technique and corresponding outcome measures had to be provided. Furthermore, long term treatment outcomes post radiotherapy with a follow-up of more than 10 years are individually subtracted from individual studies as well evaluated.

Risk of bias in individual studies

A critical appraisal was performed using the PRIMSA 'Risk of bias' tool [4]. The following terms were addressed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other forms of bias. Risk of bias was considered high in case these aspects were not mentioned. The risk was considered low in case the subject was addressed by the authors. However, please note that no articles were excluded from the study based on the critical appraisal since the majority of the studies show poor risk of bias prevention and excluding them would result in insufficient data for subsequent review and analysis.

Statistical analyses

The outcome of the presented meta-analysis was the pooled result of several surgical techniques on different outcome measures after vagal paraganglioma treatment. For all studies, the proportion of local control, cranial nerve damage and serious adverse events were evaluated. Results are presented with 95% confidence intervals (95% CI).

RESULTS

Out of 2460 articles, after screening for title and abstract, 56 articles were selected for full text review (exclusion criteria are provided in figure 1). Ultimately, a total of 17 articles were selected representing 177 patients treated with surgery and 78 patients treated with radiotherapy. A summary of the selected articles is provided in table 1. Please note that no detailed information was provided on immediate radiotherapeutic complications. Moreover, long term treatment outcomes with a follow-up of more than 10 years were not stratified for vagal paraganglioma.

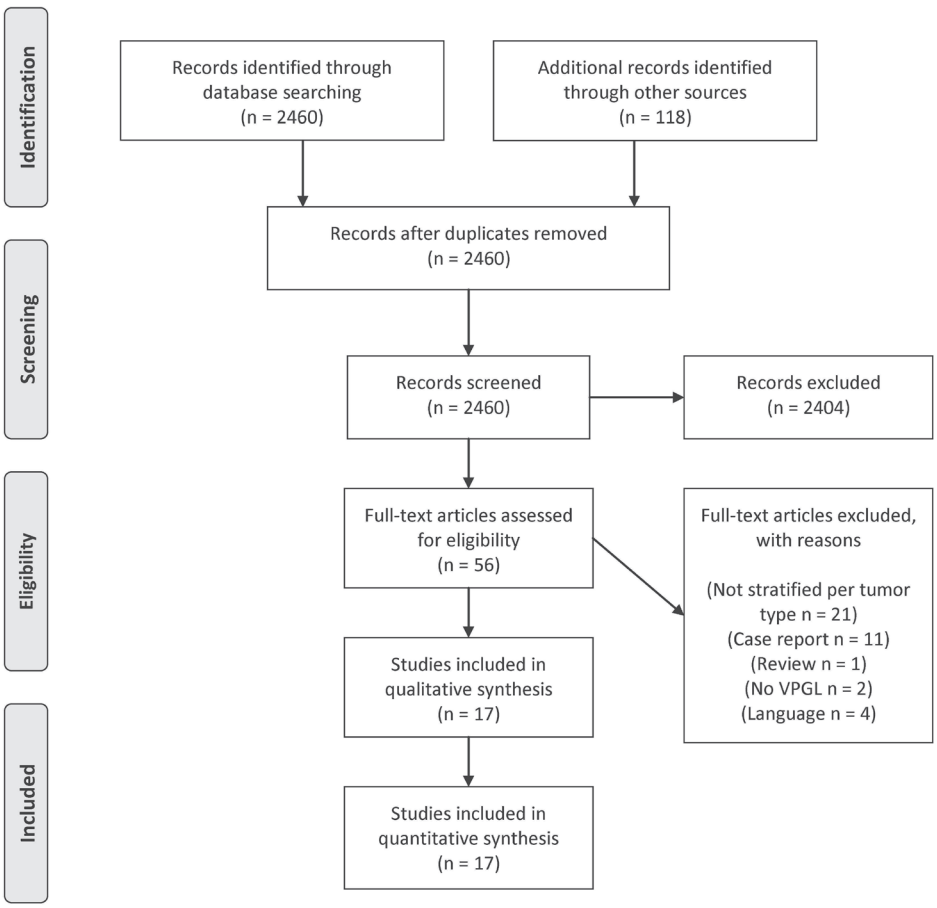

Figure 1: Flow chart

General results

The results of the individual studies are presented, without pooling of results . After surgery, local control rates were found in 67% to 100% of cases. Overall, cranial

Table 1: Summary of included studies

Study	Methods used; initial wait and scan?; pre-treatment embolization?	Follow-up	No. Surg*	No. RT*	Treatment outcome N > 4			Incomplete outcome data**	Selective reporting **
					Local control	CN damage	Complications other than cranial nerve damage		
González et al. 2015[11]	6 patients; routine pretreatment embolization	42.6 ± 33.01 months (12–132 months)	11		11/11	24/11	0/11	High quality	High quality
Dupin et al. 2013[12]	No embolization; no wait and scan	4.1 years (range, 0.1-21.2 years)		18	18/18	?	0/18	Low quality	High quality
Biller et al. 1989[13]	No embolization	7 years	18		16/18	18/18	6/18; tracheotomy, one died.	High quality	Low quality
Bradshaw and Jansen 2005[5]	40 of 48 patients, wait and scan. 10 operated in total.	?	10		10/10	14/10	2/10 (wound infection and asp. pneumonia)	High quality	High quality
Browne et al. 1993[14]	14/15 primary surgery; 1 preceding RT.	2-10 years	15		15/15	20/15	6/15 (1 wound infection; 1 CSF leakage; 4 CVA's)	High quality	High quality
Eriksen et al. 1991[16]	Surgical resection via a lateral cervical approach; 1x median mandibulotomy with carotid reanastamosis	7jr	9		9/9	11/9	4/9 (1x CVA; 3x tracheotomy)	High quality	High quality
Hinerman et al. 2008[17]	4500cGy in 25 fractions	10.6 year		17	17/17	?	?	Low quality	Low quality
Kollert et al. 2006[18]	?, Cervical resection	82 months (range, 3 to 184 months;	8		?	8/8	?	?	Low quality
Lack et al. 1977[18]	?	7 years (5-16 years)	12		8/12	6/12	0/12	Low quality	Low quality

Table 1: Summary of included studies (*continued*)

Study	Methods used; initial wait and scan?; pre-treatment embolization?	Follow-up	No. Surg*	No. RT*	Treatment outcome N > 4			Incomplete outcome data**	Selective reporting **
					Local control	CN damage	Complications other than cranial nerve damage		
Lozano et al. 2008[20]	4/6 preceding embolization; staged surgery in 2 patients	120 months (44-182)	6		6/6	15/6	0/6	High quality	High quality
Miller et al. 2000[21]	A lateral cervical approach was used in 15 patients. A midline mandibulotomy was used in 1 case; 5x preop embolizations		16		13/16	23/16	9/16 (tracheotomy)	High quality	High quality
Mitchell et al. 1985[22]	3750-5500 rad	1.5-15 years		2	2/2	0/2	0/2	Low quality	Low quality
Netterville et al. 1998[23]	Transcervical in 12; combined with transtemporal in 28; canal obliteration in 28; cala preservation in 10; EBRT in 4, SRT in 1	Overall: 68 months (range 8-146 years) RT: 4.5 years	40	5	39/40; 5/5	83/40; 0/5	22/40 1 death; 2 CVA; 3 CSF leak; 1 wound infection; 2 necrosis; 13x aspiration	Low quality	High quality
Powell et al. 1992[24]	5–50 Gy in 25 daily fractions over 5 weeks	Up to 11 years		4	4/4	0/4	0/4	High quality	High quality
Urquhart et al. 1994[25]	14x lateral cervical approach; 2x mandibulotomy	Surgery: 2 months to 12 years; RT 2-3 years	16	3	16/16; 3/3	21/16; 0/3	1/16 tracheotomy; 0/3	High quality	High quality
Verniers et al. 1992[26]	50 Gy in 25 fractions over 5 weeks	1-20 years		25	25/25	?	?	High quality	High quality

Table 1: Summary of included studies (*continued*)

Study	Methods used; initial wait and scan?; pre-treatment embolization?	Follow-up	No. Surg*	No. RT*	Treatment outcome N > 4			Incomplete outcome data**	Selective reporting **
					Local control	CN damage	Complications other than cranial nerve damage		
Zanoletti and Mazzoni 2006[27]	Cervicoparotid approach and pericapsular dissection	mean period of 75 months (median, 69 months; range, 9 to 156 months	16		16/16	24/16	0/16	High quality	High quality

nerve damage rates were found in 50%-100% of cases and reported percentage of complications varied from 0% to 56%. Post-radiotherapy local control was reported for all cases included in the studies. No cranial nerve damage was observed, albeit any information about cranial nerve damage was only reported in 4 manuscripts representing 14 patients. Serious adverse events were not found either in 27 patients.

Pooled results

Second, the pooled results of different studies are presented. Table 2 presents the treatment outcomes per tumour (some patients had multiple tumours), stratified per treatment modality. There was a significantly higher local control rate for vagal body tumours treated with radiotherapy. Moreover, there were significantly less cranial nerve deficits and complications found post radiotherapy.

Table 2: Pooled treatment outcome per tumour, post surgery and radiotherapy

	Surgery	Radiotherapy	P value(df = 1)
Local control % (n/n_{total})	95% (161/170)	100% (78/78)	0.039
Cranial nerve damage % (n/n_{total})	97%% (171/177)	0% (0/14)	0.00
Complications % (n/n_{total})	29% (50/170)	0% (0/27)	0.00

Cranial nerve damage and complications

Post surgery, the vagal nerve was affected after resection in all but 6 tumours; a total of 267 treatment induced cranial nerve damages were found post surgery in 177 tumours in 152 patients, rendering 1.51 nerves affected per tumour excision. Details on the remaining cranial nerve deficits are presented in table 3. Please note that for 12 tumours, it was not specified which nerve was affected. Moreover, post surgery complications were found 50 times (30% of cases). The main complications found are presented in table 4.

Table 3: cranial nerve deficits post-surgery

Cranial nerve	No % (n/n_{total})
N VII	5% (12/255)
N. IX	6% (16/255)
N. X	66% (168/255)
N. XI	5% (13/255)
N. XII	8% (21/255)
Horner syndrome	4% (10/255)
Other	6% (15/255)

Table 4. Complications found post-surgery

Complication	No. Complications % (n/n_{total})
Wound infection	10% (5/50)
CSF leakage	8% (4/50)
CVA	14% (7/50)
Pneumonia	28% (14/50)
Tracheotomy	36% (18/50)
Death	4% (2/50)

DISCUSSION

These results illustrate that little is known about the long term treatment effects after radiotherapy for vagal paraganglioma. Significantly higher local control rates were found post-radiotherapy when compared to surgery. Also, no complications were found post-radiotherapy, compared to 30% complication rate post surgery, including events such as aspiration pneumonia, tracheotomy, and CVA. Moreover, high cranial nerve damage rates were found postoperatively, with an average of 1.51 nerves being damaged per tumour resection in which the vagal nerve was functionally spared in merely 3% of tumour excisions, constituting 66% of a total of 255 cranial nerve deficits. The precise effect of radiotherapy on cranial nerve damage rates remains uncertain, yet, in the 14 patients for whom it was reported, no cranial nerve damage was found.

The high iatrogenic morbidity rates induced by surgery in terms of cranial nerve damage and complications are in line with previous literature. Suarez et al. found a local control rate of 93%, and a risk of 1.41 nerves being damaged per tumour resection [2]. Moreover, a complication rate of 18.9% was found in this series: 10% chance of aspiration/pneumonia, CSF leakage in 2.6% of cases, wound infections in 2.2%, stroke in 2.2% and a meningitis in 0.4%, leading to death in 1.3% of cases. No other reviews were found describing the effect of treatment of vagal paraganglioma in general. With respect to radiotherapy for vagal paraganglioma, no comparative systematic review is available at the time of writing.

Recommendations for daily practice

Considering the treatment induced morbidity found post-surgery and the potential long-term effects of radiotherapy, an initial wait-and-scan policy seems the preferred option for vagal paraganglioma management. Bradshaw and Jansen et al. presented 40 vagal paraganglioma that after an average follow-up of 8.5 years (range 1-26 years), merely three patients developed a nerve palsy (8%) following radiation [5]. Our group found a risk of tumour-induced complications in 12% of cases in a series of 157

paraganglioma (including 29 vagal paraganglioma) in which a wait-and-scan policy was adopted. This risk was independent of tumour localization [6]. These results need to be weighed against the risks of radiotherapy for these tumours.

In case treatment is necessary, our results demonstrate that surgery should be considered vigilantly because of the risk of severe iatrogenic complications. Other authors proposed exceptions where surgery can be considered. For example, Suarez et al. suggested that vagal paraganglioma can be surgically removed in case of an already present n. X palsy as this will be the main cranial nerve at risk [2]. However, our review describes a current risk of 1.58 nerves being affected per tumour excision as the N. X is damaged in almost all cases, there remains a 0.58 chance of inducing other cranial nerve damage. According to our results, the hypoglossal, accessorial, glossopharyngeal and facial nerve are mostly at risk. Given these limitations of surgery, radiotherapy should be seriously considered for patients with vagal paraganglioma, also in case of readily present N. X palsy.

As suggested by Suarez et al., it seems possible to remove small vagal paraganglioma without inducing cranial nerve damage [2]. The rationale that smaller tumours are more successfully removed has been proven for jugulotympanic and carotid body paraganglioma, in which enhanced morbidity is found with increasing Fisch and Shamblin class' respectively. In this light, it was suggested by Browne et al. in 1993 to classify the tumours with respect to the involvement of the jugular foramen [7]. Class I tumours would resemble those not involving the jugular foramen, class II would show invasion of the foramen but no bony destruction, whereas class III tumours are those with bony destruction. Unfortunately however, to date no outcome measure is associated with the classification. No other studies were found describing the relation between tumour size and surgical outcome measures. Nevertheless, it seems likely, that nerve function preservation is troublesome for vagal paraganglioma as even the smaller tumours grow in close relation with the vagal nerve, whereas small jugulotympanic and carotid paraganglioma grow in less proximity with cranial nerves and are therefore more successfully removed surgically. Nonetheless, this issue might be further explored.

Taken together, the authors suggest there is little place for surgery in the management of benign vagal paraganglioma. On the other hand, knowledge about the long-term effects of radiotherapy with respect to functional outcome and sequalae such as induced malignancies and vascular stenosis is incomplete. In our series, there were three studies that evaluated the long term effects of radiotherapy. Unfortunately, these series did not stratify results for vagal paraganglioma, rather, results are presented for all HNPGL types combined. With respect to recurrence free survival, Verniers describe in 1992, for 44 HNPGL an actuarial local control rate of 88% after 10 years using conventional external beam radiotherapy [8]. More modern techniques were used by Hinerman et al. and better results were found: after more than 10 year follow up post

radiotherapy for 42 HNPGL using radiosurgery the actuarial local control and cause-specific survival rates at 10 years were 94% and 95% [9]. In line, Dupin et al. present for 66 patients with 81 head and neck PGL, consisting of 18 vagal PGL with median follow-up of 4.1 years (range, 0.1-21.2 years) an actuarial local control rate of 98.7% at 10 years using fractionated external beam techniques [10]. These results suggest that local control rates post radiotherapy seem acceptable over a course of 10 years with use of modern techniques. These results are in line with results of a systematic review regarding radiotherapy results of Fisch class C and D tumours conducted by our group, evaluating local control rates 10 years post radiotherapy for 66 patients. In this study, local control was found in 96% 10 years post treatment.

Less is known about the long term functional nerve preservation rates. In the current study results seem promising, however, conclusions are weakened by the small patient numbers. Regarding functional outcomes of head and paraganglioma in general, Gilbo et al. in 2014 report for a particularly large series of 156 benign HNPGL no cranial nerve damage at a median follow-up of 11.5 years [11]. A recent review of our group however, found less favourable results: After systematically reviewing literature on jugulotympanic paraganglioma, we found Cranial nerve damage-rates in 3-9% of Fisch class C and D tumours, post-irradiation in 119 cases respectively [3]. However, these results are much lower than cranial nerve damage rate found post surgery.

Furthermore, besides cranial nerve damage, irradiation induced malignancies and vascular stenosis are potential detrimental late complications. Dupin et al. describe a case of carotid artery and cerebral artery stenosis 5 years post treatment, also two secondary neoplasms are found within 10 years follow-up [10]. However, large series further elucidating the risk of vascular complications following radiotherapy for paraganglioma are lacking. To further evaluate the risk of vascular stenosis and secondary malignancies following radiation, potentially conclusions can be drawn from other tumour types. In patients irradiated for head and neck cancer and with a median follow-up of 7 years, the risk of stroke has been reported to be six-fold higher compared to the general Dutch age-matched population [9]. Furthermore, Gujral et al reported a 5.6 higher risk compared to a matched control group [10]. It should be noted that the radiation dose is generally higher and treatment volumes are larger for head and neck cancer and also these patients have a higher risk profile (smoking, diet, physical activity) for vascular diseases than vagal paraganglioma patients. Nevertheless, one should be aware that also after radiotherapy for HNPGLs there is likely a significant risk of cerebrovascular complications. In conclusion, although irradiation induced sequelae might be expected lifelong after treatment, in our view, the inevitable risk associated with surgery, justifies the use of radiotherapy for treatment of these tumours. We strongly recommend counselling of these patients about risk factors for cerebrovascular disease including smoking cessation and other life style factors.

Furthermore, there are more immediate complications associated with radiotherapy of the head and neck region, mainly referring to mucositis, skin burns, dysphagia and Eustachian tube dysfunction. Again, these outcomes were not stratified for vagal paraganglioma, but rather presented for HNPGL in general. Dupin et al. present such immediate complications in 37% of 81 HNPGL, resembling 20 cases of xerostomia and 10 cases of mucositis, ulceration or herpes zoster complications [10]. Hinerman describe less complications, as it was found in 5% of 104 HNPGLs, referring to 2 cases of otitis media or external otitis, 2 cases of xerostomia and a single case of mucositis [8]. Verniers et al. 1992 mention a single case of middle ear infection in a cohort of 44 patients, resembling a complication risk of 2% [9]. Also, these more immediate complications should be taken into consideration when counselling patients as they might induce serious morbidity for patients.

Another factor that should be considered is that in case of hereditary paraganglioma syndromes, and particularly for tumours arising from SDHB, -AF2 and -D mutations, enhanced tumour growth and multifocal tumour presence can be expected [1]. Bilateral tumour growth can cause bilateral cranial nerve palsy, which in the case of n. X, is a life threatening complication that almost always requires a tracheotomy. Therefore, in the case of bilateral tumour presence, or in case of a hereditary tumour syndrome, surgery of the vagal paraganglioma should be avoided at all times.

Another treatment method considered for jugulotympanic paraganglioma is the use of tumour debulking with irradiation of the residual tumour in the case of post-operative growth. For jugulotympanic paraganglioma this may be an alternative to consider, since with leaving tumour mass on the cranial nerves, nerve function might be preserved. It remains uncertain whether or not this method can be applied for vagal paraganglioma due to an inherent close proximity of the tumour to the vagal nerve. More research is required to evaluate this treatment option.

Methodological considerations

Due to the low incidence and growth rate of these tumours no randomized controlled trials are at hand and therefore the level of evidence of the included studies is low. In order to minimize the confounding effects of reviewing retrospective cohort studies, the PRISMA tool was used to assess the quality of the studies. See appendix a, for the results of this critical appraisal.

Furthermore, it should be noted that there is an inherent bias in comparing the results of local control for surgical and radiotherapy series. Post surgery, no evidence of disease is required to achieve this, whereas post radiotherapy a stable tumour would suffice, where radiation would never achieve eradication of the tumour. However, stabilization of the tumour is the main goal in our opinion.

Also, particularly in the studies presenting results post radiotherapy follow-up might have been too short to account for late effects of radiation. Therefore, the complication rate as presented in the current series is likely an underrepresentation of total complications to be expected post radiotherapy. We attempted to overcome this issue by analyzing sub-cohorts with long term results. Unfortunately these were not stratified per tumour type.

Unfortunately, the number of studies and patients were too low to reliably estimate the risk of cranial nerve damage and other late sequelae after radiotherapy. This prevents a firm recommendation on the management of vagal paraganglioma in daily practice, and even more so with regard to multifocal HNPGL. To this end, we advise that prospective studies are initiated with protocols that carefully document presenting tumour symptoms and tumour extensions. We did not stratify our results by surgical technique. Several groups used per-treatment embolization techniques which might influence the results. The impact of different irradiation techniques, fractionated conventional *vs.* stereotactic techniques could not be analyzed because of unavailability of data and small numbers. This is worthy of mention since older studies have been included as well, resembling series of patients treated with less advanced treatment strategies, which might have resulted in poorer outcomes.

Finally, we also did not evaluate the effect of different tumour syndromes with respect to tumour outcome. Potentially, mutation presence alters the growth rate/ invasiveness of the tumour which might affect (long term) treatment outcomes.

CONCLUSION

This review demonstrates that surgery is not the preferred treatment option for vagal paraganglioma. Local control after radiotherapy is high but long-term side effects are not well documented. As with other PGLs that grow in close proximity with cranial nerves, the risk of cranial nerve damage caused by radiotherapy seems small when compared to the risk of iatrogenic nerve damage and other complications post surgery. Properly designed (long term) prospective registration studies are needed to assess the risk of ischemic brain injury due to radiation-induced atherosclerosis of the carotids. Given that both surgery and radiotherapy are not free of side effects and complication risks, a wait and scan policy seems wise to adopt as a primary step in the management of vagal paraganglioma, particularly in the case of multifocal tumours, since bilateral N. X damage is a serious, potentially life threatening condition. In our opinion, radiotherapy should be considered in case radiological follow-up indicates persistent tumour growth and tumour-induced morbidity can expected, or when N. X palsy is imminent.

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APPENDIX 1

SEARCH STRATEGY

(((Treatment [Title/Abstract] OR Treatment [Mesh Terms] OR Management [Title/Abstract] OR Management [MeSH Terms] OR therapy [Title/Abstract] OR therapy [MeSH Terms] OR approach [Title/Abstract] OR approach [MeSH Terms] OR procedure [Title/Abstract] OR procedure [MeSH Terms] OR Radiotherapy [Title/Abstract] OR Radiotherapy [MeSH Terms] OR radiation therapy [Title/Abstract] OR radiation therapy [MeSH Terms] OR X-ray therapy [Title/Abstract] OR X-ray therapy [MeSH Terms] OR radioisotope therapy [Title/Abstract] OR radioisotope therapy [MeSH Terms] OR Radiosurgery [Title/Abstract] OR Radiosurgery [MeSH Terms] OR Gamma Knife [Title/Abstract] OR Gamma Knife [MeSH Terms] OR CyberKnife [Title/Abstract] OR CyberKnife [MeSH Terms] OR Linear Accelerator [Title/Abstract] OR Linear Accelerator [MeSH Terms] OR Linac [Title/Abstract] OR Linac [MeSH Terms] OR LINAC [Title/Abstract] OR LINAC [MeSH Terms] OR Surgery [Title/Abstract] OR Surgery [MeSH Terms] OR operative [Title/Abstract] OR operative [MeSH Terms] OR invasive [Title/Abstract] OR invasive [MeSH Terms] OR operations [Title/Abstract] OR operations [MeSH Terms] OR peroperative [Title/Abstract] OR peroperative [MeSH Terms] OR perioperative [Title/Abstract] OR perioperative [MeSH Terms] OR intraoperative [Title/Abstract] OR intraoperative [MeSH Terms] OR excision [Title/Abstract] OR excision [MeSH Terms] OR resection [Title/Abstract] OR resection [MeSH Terms] OR Wait and scan [Title/Abstract] OR Wait and scan [MeSH Terms] OR Wait and see [Title/Abstract] OR Wait and see [MeSH Terms] OR Conservative [Title/Abstract] OR Conservative [MeSH Terms] OR Expectative [Title/Abstract] OR Expectative [MeSH Terms] OR Embolotherapy [Title/Abstract] OR Embolotherapy [MeSH Terms] OR Embolization [Title/Abstract] OR Embolization [MeSH Terms] OR Occlusion [Title/Abstract] OR Occlusion [MeSH Terms]))) AND (((((((Tumour [Title/Abstract] OR Tumour [MeSH Terms] OR Tumour [Title/Abstract] OR Tumour [MeSH Terms] OR Tumours [Title/Abstract] OR Tumours [MeSH Terms] OR Tumours [Title/Abstract] OR Tumours [MeSH Terms])))) AND ((Carotid body [Title/Abstract] OR Carotid body [MeSH Terms] OR Vagal body [Title/Abstract] OR Vagal body [MeSH Terms]))))) OR ((((Jugulare [Title/Abstract] OR Jugulare [MeSH Terms] OR Caroticum [Title/Abstract] OR Caroticum [MeSH Terms] OR Carotis [Title/Abstract] OR Carotis [MeSH Terms] OR Vagale [Title/Abstract] OR Vagale [MeSH Terms] OR temporale [Title/Abstract] OR temporale [MeSH Terms] OR jugulotympanicum [Title/Abstract] OR jugulotympanicum [MeSH Terms] OR tympanicum [Title/Abstract] OR tympanicum [MeSH Terms])))) AND ((Glomus [Title/Abstract] OR Glomus [MeSH Terms]))))) OR ((((Head and neck [Title/Abstract] OR Head and neck [MeSH Terms] OR Cervical [Title/Abstract] OR Cervical [MeSH Terms] OR Temporal [Title/Abstract] OR Temporal [MeSH Terms] OR Jugular [Title/Abstract] OR Jugular [MeSH Terms] OR Tympanic [Title/Abstract] OR Tympanic [MeSH Terms] OR jugulotympanic [Title/Abstract] OR jugulotympanic [MeSH Terms] OR Carotid [Title/Abstract] OR Carotid [MeSH Terms] OR Carotis [Title/Abstract] OR Carotis [MeSH Terms] OR Vagal [Title/Abstract] OR Vagal [MeSH Terms])))) AND ((paraganglioma [Title/Abstract] OR paraganglioma [MeSH Terms] OR paragangliomas [Title/Abstract] OR paragangliomas [MeSH Terms] OR chemodectoma [Title/Abstract] OR chemodectoma [MeSH Terms] OR chemodectomas [Title/Abstract] OR chemodectomas [MeSH Terms] OR glomus tumour [MeSH Terms] OR glomus tumour [Title/Abstract] OR glomus tumours[Title/Abstract] OR glomus tumours [MeSH Terms] OR glomus tumour [MeSH Terms] OR glomus tumour [Title/Abstract] OR glomus tumours[Title/Abstract] OR glomus tumours [MeSH Terms])))))

CHAPTER 8

Clinical results of Surgery and Radiotherapy for Vagal paraganglioma

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ABSTRACT

Purpose: The management of vagal body paraganglioma remains a hot topic of debate. The main treatment options are surgery and radiotherapy. However, little is known about the risk factors of associated with treatment outcomes such as local control, cranial nerve damage and complications.

Methods: First a retrospective cohort study was conducted with patient records from 1986 to 2016 of all patients suffering vagal paraganglioma

Results: Out of 16 patients 11 were treated with radiotherapy. Post surgery and radiotherapy local control rates were 100% at 20 months (range 15-38) and 11 years (Range 3-29) follow-up respectively. Significantly less cranial nerve damage was found post radiotherapy when compared to surgery 27% versus 80% (one pre-treatment n. X paralysis was already present) respectively($p = 0.02$). post surgery a total of 1. All post-treatment cranial nerve damages were N. X lesions. Post radiotherapy, two aspiration pneumonias were found for which one permanent tracheotomy was required.

Conclusions: Surgery inevitably renders n. X lesion and poses an additional risk for surrounding cranial nerves. Radiotherapy has rendered new cranial nerve damage or worsening of cranial nerve damage function in 27% of cases. Considering these risks associated with treatment, it seems wise to adopt an initial wait and scan protocol and to treat these tumours as little as possible.

INTRODUCTION

Vagal paraganglioma (VPGL) are rare neuroendocrine tumours, which are usually benign, yet, approximately one third of these tumours is associated with cranial-nerve damage [1].

Since these tumours grow in such close proximity with the vagal nerve, timing the right moment of treatment is problematic. It has been suggested that an initial wait and scan period should be applied to evaluate tumour growth [1, 2]. However, the optimal timing of treatment remains a topic of debate. In case treatment is deemed required, the main treatment modalities available are surgery or radiotherapy. Suarez et al. have illustrated that although local control rates are relatively high post surgery , cranial nerve damage seems inevitable. Life-threatening complications such as aspiration pneumonias are found in up to 10% of patients. Alternatively, radiotherapy was suggested rendering similar local control rates, however little is known about the complication rates of VPGL radiation.

To date, no risk factors have been isolated that predict reduced treatment outcomes for vagal paraganglioma. It has been suggested that tumour classification is associated with treatment outcome Obholzer et al. [3]. Moreover, mutation presence or age of presentation has been found to be associated with more aggressive tumour growth, and might predispose for lesser treatment outcomes [4].

Therefore, the current research evaluates the motivation of treatment of VPGL, and aims to isolate risk factors associated with treatment outcomes local control, cranial nerve damage and complications post-treatment. To this end, a retrospective cohort-study is conducted, evaluating the indications and results and of surgery and radiotherapy of VPGL.

METHODS

A retrospective cohort study was conducted using similar methods as presented by Jansen et al.[5]. All patient records of patients presenting with a HNPGL between 1980 and 2016 in the Radboudumc Nijmegen, the Netherlands were evaluated. Eligibility criteria were patients with a VPGL Patients with malignant tumours were excluded.

Out of a total of 358 patients with HNPGL, 45 patients were suffering from VPGL and 16 patients were treated. To collect data from patient files a standardized extraction protocol was used. The following information was extracted: gender, age at presentation, signs and symptoms at presentation, tumour class, gene mutation analysis, clinical and radiological signs and symptoms of tumour progression. Tumour

volume was estimated by expert radiologists, measuring the largest size in the antero-posterior, medio-lateral and cranio-caudal direction.

The intervention was any form of surgery or radiotherapy, with or without a prior wait and scan period. The outcome of the treatment was compared to the patients' situation at first presentation, before any form of treatment and evaluated within 6 months post treatment, at 6 months and after 1 year. Treatment outcomes were local control, cranial nerve damage and other complications. The definitions were according to Suarez et al. [1]. Post surgery, local control was defined as a patient alive without evidence of disease or with a non-growing residual tumour throughout the entire follow-up period. Post radiotherapy local control was defined as a patient alive without any evidence of progression of the disease throughout the entire follow-up period. Cranial nerve damage was defined as deterioration of cranial nerve function post treatment when compared to the pre-treatment setting, objectified by a physician. Cranial nerve recovery, was defined as any improvement of cranial nerve function in post treatment setting when compared to pre-treatment conditions, objectified by a physician. The complications wound infection, stroke, aspiration resulting in pneumonia and/or tracheotomy, radiation induced necrosis, malignancies and CNS syndrome and death were included.

Tumours were classified according to the classification system suggested by Obholzer et al. 2012.

Patients were subjected to a routine follow-up which was organized as follows: Post treatment, patients were seen within 2 weeks to evaluate immediate post-treatment complications. Generally. routine follow-up was then organised every six months for patients in all treatment groups for two years. Later, a yearly follow-up protocol was organized. In case tumours remained stable for 5 years, 2 year-follow-up intervals were adopted for ten years. Hereafter a five year interval follow-up was used. Post-treatment MRI-scans were conducted one year post treatment. In case local control was achieved, the MRI-scan was conducted on a yearly basis. In case follow-up intervals were prolonged, MRI's were conducted every 2 or 5 years. MRI scans were conduced according to a local HNPGL screening protocol, optimized for paraganglioma growth and new tumour localization detection. This regimen could have been individualized depending on factors such as: age, presence of mutations, tumour size and co morbidities of the patient. Also, in case there was any sign of clinical tumour progression or potential new tumour localisation, MRI scans were performed.

For prediction of tumour growth the following variables were considered:, age at presentation defined as age at first diagnosis of HNPGL. Mutation presence was defined as presence of succinate dehydrogenase gene complex (SDH) associated paraganglioma syndromes (SDHA, -B, -C, -D, -AF2). Fisch classification was defined as described above. For prediction of tumour-induced complications we considered

tumour growth as three-dimensional value and mean percentage of volume increase per year was used. As presented by Jansen et al. tumours were considered to have an ellipsoid shape and the following equation was used to estimate the tumour volume [6]:

$$V = \frac{4}{3}\pi\left(\frac{1}{2}A * \frac{1}{2}B * \frac{1}{2}C\right)$$

in which V = volume, A = the largest dimension in the anteroposterior direction, B = the largest dimension in the mediolateral direction, and C = the largest dimension in the craniocaudal direction.

In line with a publication of Jansen et al., the measurement error was expected to be at least 15%-20%, therefore, to distinguish growing paragangliomas from stationary tumours, we considered a volume increase of 20% a minimum [6].

Statistics

Missing data were handled by using multiple imputation methods. The data was analyzed using IBM SPSS Statistics 22. Chi square analysis was performed to compare different cohorts.

RESULTS

Demographics are provided in table 1. Fifty percent was female, 43% were part of a hereditary syndrome and 2 patients were excluded due to presence of malignant disease.

Table 1: demographics per treatment modality.

	Surgery	Radiotherapy	Total
Total n	5	11	16
Symptomatic presentation % (n)	80% (4)	45% (5)	56% (9)
Preceding wait and scan period %(n)	20% (1)	72% (8)	56% (9)
Growth % (n)	80% (4)	63% (7)	69% (11)
Volume in median cc (range)	11707 (375-23040)	58353 (338-180960)	49872 (338-180960)
Tumour class % (n)			
Tumour class 1	20% (1)	27% (3)	25% (4)
Tumour class 2	-	10% (1)	0.06(1)
Tumour class 3	60% (3)	54% (6)	56% (9)
Tumour class 4	20% (1)	10% (1)	0.1 (2)
Follow-up in median months (range)	20 (15-38)	11 (3-29)	15 (3-38)

Figure 1 illustrates treatment outcomes per treatment modality. Significantly less cranial nerve damage was found post radiotherapy (p = 0.02), for the remaining treatment outcomes, no significant difference could be found. The motivation of treatment was in all these cases indeed symptomatic presentation.

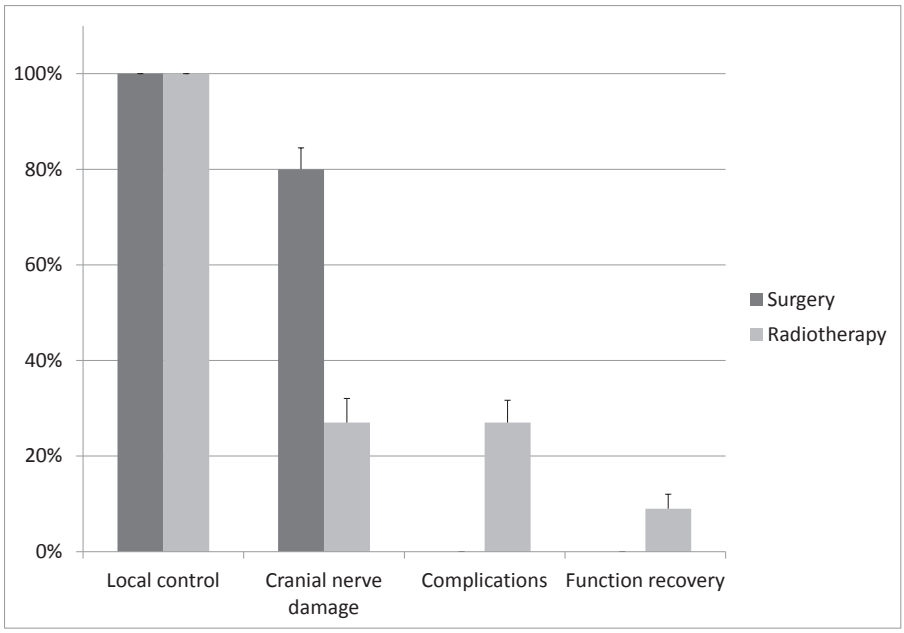

Figure 1: treatment outcomes per treatment modality

Results surgery

For all surgically treated patients, the motivation for surgery (rather than radiotherapy) were age (n = 5), presence of tumour growth (n = 4) and pre-existent N. X palsy (n = 4).

Patients treated with surgery were significantly younger than the general population (median, range 20-35). Out of 11 patients treated with radiotherapy, 2 were intentionally debulked. Overall local control was 100%. All cranial nerve damages were N. X lesions, additionally a N. IX and XI lesion were found. No predictor of adverse events could be found in our series.

Results radiotherapy

The main motivation for radiotherapy were, tumour growth (n = 5) and pre-existing N. X palsy (n = 7). Searching for predictors of treatment outcomes, we found that the age of presentation was significantly related to the risk of post-operative cranial nerve damage (p = 0.010 95% CI 6.2-34.7). Patients suffering cranial nerve damage were

generally older, than patients not suffering cranial nerve damage (61.7 SD 3.2; versus 41.23 SD 10.4). All post-treatment cranial nerve damages were N. X lesions, also a single case of sensorineural hearing loss was found. The main complications were aspiration pneumonia (n = 2), for which one permanent tracheotomy was required. Moreover, a single case of baro-reflex syndrome was found. One pre-treatment N. X palsy recovered to normal function post-irradiation.

DISCUSSION

Our results illustrate that radiotherapy seems to be the preferable treatment modality as it renders most optimal local control and cranial nerve damage rates. In our centre, the main motivation for surgery was pre-existent cranial nerve damage and tumour growth for younger patients. The main motivation for radiotherapy was tumour growth and N. X palsy. Furthermore, age of presentation was suggested to be a risk factor for cranial nerve damage post-radiotherapy.

Advise for the clinical practice

The current series describes good local control rates post surgery, including stable tumour presence in case of tumour debulking for two patients. However, a high risk for n. X lesion was found, 80% suffered cranial nerve damage post treatment. This is also described in literature, e.g. Suarez et al found local control in 93.4% of cases and cranial nerve damage was found pre-operatively in 147 of 226 cases, which increased to 445 cranial nerve palsies after surgery [2]. In fact, the vagal nerve was functionally preserved in only 11 of 226 patients. Moreover, albeit no complications were found in the current series, Suarez et al describes a considerable risk of aspiration/pneumonias (10.2%), CSF leakage (2.6%), wound infections (2.2%) and stroke (2.2%)post surgery, and 3 patents died (1.3%) because of these complications [2]. A recent review of our group describes a risk of 1.58 nerves being affected per tumour excision as the N. X is damaged in almost 100% of cases, there remains a theoretical 0.58 chance of inducing other cranial nerve damage [7]. According to our results, the hypoglossal, glossopharyngeal and facial nerve seem to be mainly at risk. In our series a n. IX and a n. XI lesion were found.

Alternatively, excellent local control was also found post radiotherapy yet cranial nerve damage/worsening of function was found in 27% of cases (3/11 patients), for two patients a consequent aspiration pneumonia was found and one of those patients required a permanent tracheotomy. Hinerman et al. describes in 2001 excellent local control rates, and no cranial nerve damage after a mean follow-up of 156 months for

10 patients [8]. In the current series, we found that patients suffering cranial nerve damage were generally older (61.7 SD 3.2), when compared to patients not suffering cranial nerve damage (41.23 SD 10.4). Potentially the mean age of irradiated patients was higher in our group. The mean age of VPGL patients treated by Hinerman et al. is not mentioned.

The finding that elderly are more prone to develop n.X lesions post VPGL radiotherapy has not been described before. A potential explanation could be the fact that elderly are less resilient towards irradiation sequelae. Nonetheless, we could not find a relation between age and irradiation induced complications in general. This topic requires further future research.

Taking these results together we believe that treatment of VPGL should be prevented as much as possible since both surgery (debulking and tot-resection) as well as radiotherapy are potentially related to considerable morbidity mainly related to n. X lesions. Therefore, a wait and scan option should always be considered. A recent study of our group illustrated that out of a total of 29 patients subjected to a wait and scan period with a median of 86 months (range 26-261months) tumour induced complications, e.g. n.X palsy, was found in 4 patients (14%). Better results were found by Bradshaw and Jansen et al. whom presented in 2005 that for 40 VPGL after an average follow-up of 8.5 years (range 1-26 years), merely three patients developed a nerve palsy (8%). Two patients being part of a hereditary tumour syndrome developed metastatic disease (both patients are alive with stable disease).

Methodological considerations

An important methodological consideration is the fact that the current is a retrospective cohort study and sample sizes are small. Therefore, the internal and external validity is limited. Given the rarity of these tumours, prospective study designs are not applicable.

Furthermore, the long term follow-up of irradiated tumours might be too short since long term sequelae might be expected after 30 to 40 years post treatment. Potentially, over time less local control rates might be found due to late tumour growth.

CONCLUSION

Treatment outcomes of VPGL treatment in the Radboudumc , the Netherlands has been presented. The risk of both surgery and radiotherapy seems considerable. Surgery inevitably renders n. X lesion in all cases, and poses an additional risk for surrounding cranial nerves. Radiotherapy has rendered new cranial nerve damage or worsening of cranial nerve damage function in 27% of cases, particularly in the elderly. Post

radiotherapy, this rendered 2 aspiration pneumonia's for which one patient received a permanent tracheotomy. Considering these risks associated with treatment, it seems wise to adopt an initial wait and scan protocol and to treat these tumours as little as possible.

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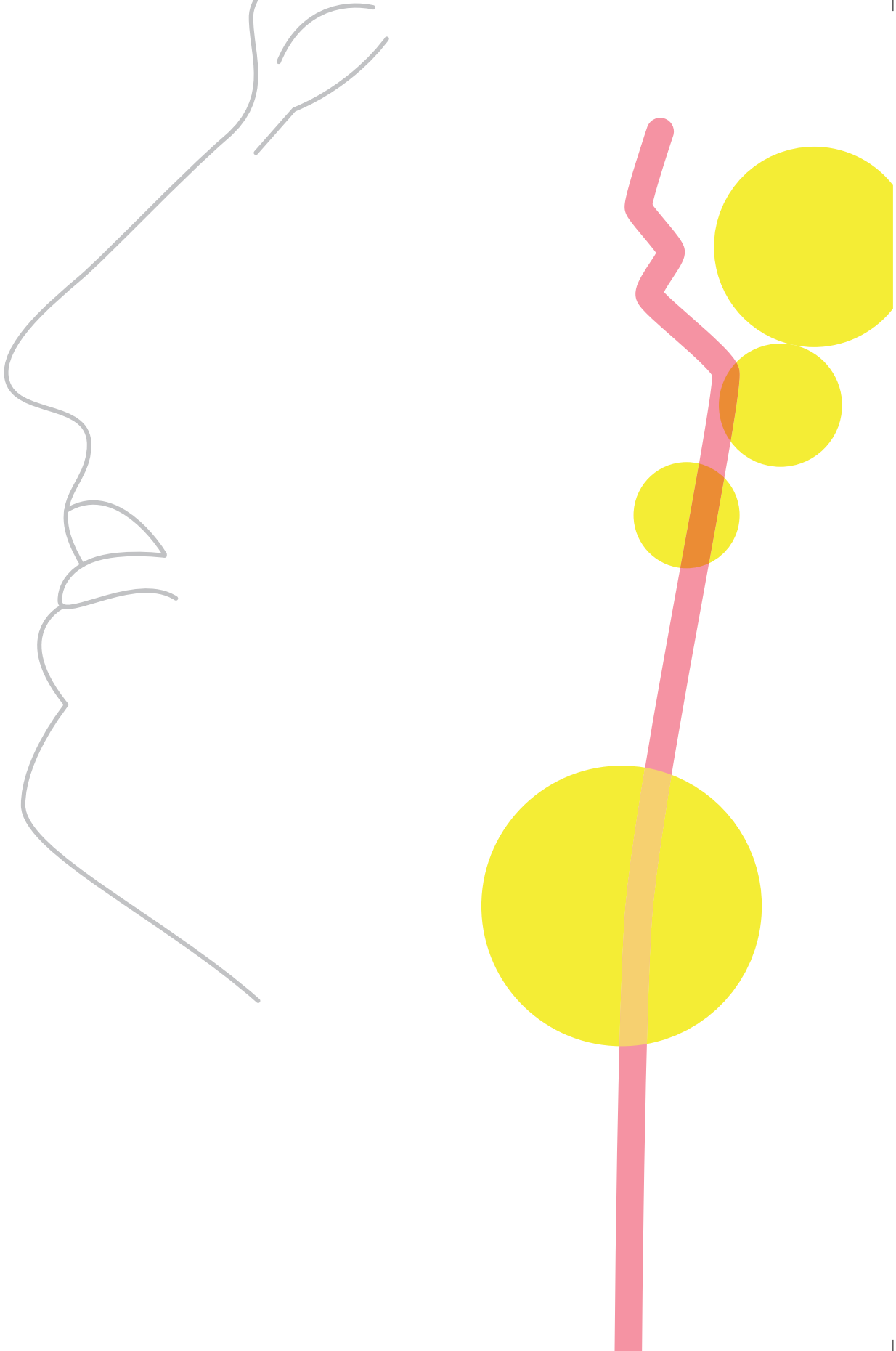

PART 3

Management of Multifocal Head and Neck Paraganglioma

CHAPTER 9

Management of Multifocal Head and Neck Paraganglioma.

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ABSTRACT

Purpose: HNPGL potentially induce significant morbidity, either tumour-, or treatment induced. About 37% of HNPGL are part of multifocal disease, yet little is known about complication free survival (CFS) in these patients, or risk factors associated with it.

Experimental design: Retrospective cohort study. Information was extracted from medical records of all our patients suffering HNPGL (n = 178). Main outcome measure was complication free survival (CFS), analyzed using Kaplan-Meier survival analysis.

Results: A significantly worse CFS was found in 58 patients suffering 159 tumours when compared to 120 patients suffering unifocal disease (LogRank 16.3, df 1, p 0.00). No significant difference was found in CFS between unilateral versus bilateral tumour presence or (0.75) the number of tumours found (p = 0.9). Using univariate regression analysis, we found that when managed only with a wait and scan strategy, this was a negative predictor of complications. Using binary logistic regression, we found that the number of surgical procedures required for disease control is an independent predictor of complications in patients suffering multifocal disease (B = 0.797, df. = 1, p = 0.047).

Conclusions: The current results demonstrate the significantly reduced complication free-survival for patients suffering multifocal tumours. Mainly the treatment modality chosen to manage these tumours are associated with complication-free survival, and radical tumour removal with sacrifice of cranial nerves should be avoided.

INTRODUCTION

Head and neck paraganglioma (HNPGL) are neuroendocrine tumors that are usually benign. In the head and neck region, paraganglioma are mainly found around the carotid body, the middle ear or jugular bulb, or the vagal paraganglia. As a consequence, they grow in close proximity with delicate neurovascular structures (1). It is generally considered that for lower class jugulotympanic (Fisch class A and B) and carotid body tumors (Shamblin class 1 and 2) surgery is the mainstay of treatment (1). For Fisch class C and D jugulotympanic, Shamblin class 3 carotid body and vagal body tumors however, treatment remains a matter of debate. Although with surgery and radiotherapy local control rates are comparable, for surgery, cranial nerve damage is a frequent complication, and other severe complications such as strokes form a considerable risk (2-4). After radiotherapy, there is the risk of atherosclerosis and strokes and a very low risk of radiation-induced malignancies (5). It is due to these complication risks and the benign nature of these tumors, that a wait and scan option is adopted for many of these tumors to delay potentially harmful treatments as long as possible.

A particular challenge for HNPGL management are multifocal HNPGL, which are found in about 37% of patients (6). Although multifocal tumor presence is not associated with decreased survival, the increased risk of cranial nerve palsy can significantly reduce quality of life. Particularly bilateral cranial nerve palsy should be avoided at all cost. Little evidence is provided for the best management strategy of multiple tumors. Most studies use theoretical argumentations considering surgery the main-stay of treatment. The rationale is that careful planning of surgery of highest risk tumors (based on size and tumor location) might prevent bilateral cranial nerve palsy (7-10). For example, in case unilateral cranial nerve sacrifice is inevitable, the contralateral tumor should be treated with radiotherapy. However, the primary use of radiotherapy to preserve bilateral cranial nerve function, or the use of an initial wait and scan strategy remains largely uninvestigated for multifocal HNPGL.

Therefore, in the current study we aim to evaluate the risk of complications for multifocal HNPGL when compared to unifocal tumors. Moreover, the treatment outcomes of surgery, radiotherapy and a wait-and-scan policy for patients suffering multifocal HNPGL disease are evaluated. The main outcome measure is complication-free survival, meaning survival without (treatment or tumor induced) cranial nerve damage, CVA's and other complications. Furthermore, a risk profile for prediction of future complications is proposed.

METHODS

Methods were similar to a previous study of our group (4). A retrospective cohort study was conducted including all patients presenting with a head and neck paraganglioma between 1980 and 2016 in the Radboud University Medical Center, a dedicated tertiary Head and Neck Surgery and Cancer Center. Eligibility criteria were patients with a head and neck paraganglioma. Patients with a malignant tumor were excluded as well as patients with a hormone secreting tumor.

Subjects

A total of 257 patients with 358 tumors were identified, treated with surgery, radiotherapy or a wait and scan strategy. The following information was extracted from the records: gender, age at presentation, signs and symptoms at presentation, tumor class, gene mutation analysis, clinical and radiological signs and symptoms of tumor progression. Tumor volume was estimated by expert radiologists. Carotid body paraganglioma were stratified according to the Shamblin classification system (11). Jugulotympanic paraganglioma were stratified according to the Fisch classification system (12). Patients were classified in low risk tumors, referring to Fisch class A, B and Shamblin 1, 2 tumors, and high risk tumors being Fisch class C and D, Shamblin 3 and vagal body paraganglioma. The interventions were a wait-and-scan policy, surgery or radiotherapy. Cranial nerve damage, strokes, post-operative cranio-spinal liquor leaks, wound infections and bleedings and radiation induced necrosis and malignancies were considered complications.

Outcome measures

The primary outcome was complication-free survival per patient. This was defined as a patient being alive without having suffered any of the above-mentioned complications (i.e. events were assessed per patient and denominator was total number of patients at risk). The secondary outcome measure was complication-free survival per tumor, which was defined as a patient not suffering a complication due to treatment of a particular tumor, or tumor-induced complications (i.e. events were assessed per tumor and denominator was total number of tumors). The time to complication was calculated by subtracting the date of diagnosis from the date the complication was first observed.

Follow-up

Patients were subjected to a routine follow-up which was organized as follows: post-treatment, patients were seen within 2 weeks to evaluate immediate post-treatment complications. Generally, routine follow-up with MRI was then performed yearly. In case tumors remained stable for 5 years, 2 year-follow-up intervals were adopted for ten years. Hereafter a five-year interval follow-up was used. Post-treatment MRI-scans were done immediately post-treatment in case of residual disease post-surgery. MRI scans were performed according to a local HNPGL screening protocol, optimized for paraganglioma growth and new tumor localization detection.

Statistical analysis

Routine cohort description analysis was performed using X2 for subgroup analysis. To determine complication free survival Kaplan-Meier survival analysis were performed for different subgroups with different risk-profiles. Differences between survival outcomes were assessed by Log-rank test. Univariate and multivariate binary logistic regression analyses were performed to determine predictor variables for treatment outcome. The data was analyzed using IBM SPSS Statistics 22.

RESULTS

Cohort description

A total of 178 patients with 279 tumors were included. The baseline characteristics for unifocal and multifocal tumors are presented in table 1.

Figure 1 presents the localization and classification of the unifocal and multifocal tumours by group. Jugulotympanic tumours were mainly unifocal, whereas carotid body tumours were mainly part of multifocal disease. A total of 106 of multifocal presentations (67%) had bilateral disease.

Table 2 describes all the complications (treatment-related and tumour-related) found after unifocal and multifocal tumour management for all treatments combined. Using X^2 analysis, we found significantly more complications within the multifocal tumour group ($p < 0.05$). Overall, there were significantly less complications in the wait and scan group (12.9%) when compared to radiotherapy (31%) and surgery (32%) ($p = 0.001$). There was no difference between the surgery and radiotherapy groups. There were significantly more complications associated with high risk tumours, when compared to low-risk tumours (71.2% vs. 52%; $p = 0.02$).

Table 1: Baseline characteristics for unifocal and multifocal tumours

	Unifocal tumours	Multifocal tumours
$N_{patients}$ /N_{tumors} (range)	120/120	58/159
Median age (range)	52 (18-90)	40 (13-73)
Mean N tumours (range)	1	2.7 (2-5)
Hereditary syndrome N (%)	6 (5%)	42 (68%)
Primary treatment strategy:		
Surgery N (%)	55 (46%)	58 (36%)
Radiotherapy N (%)	22 (18%)	17 (11%)
Wait and scan N (%)	43 (36%)	84 (53%)
Mean months follow-up (range)	59 (10-424)	99 (6-451)

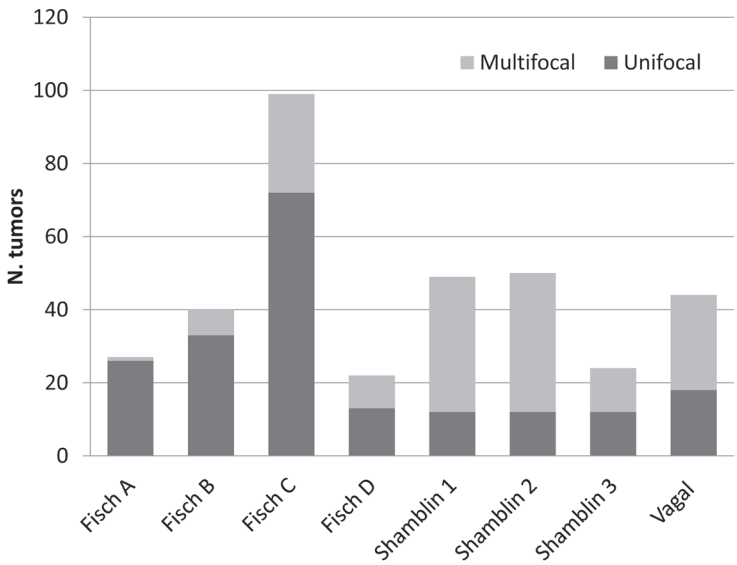

Figure 1: number of tumour types in unifocal and multifocal group

Survival analysis

Figure 2 shows complication-free survival of patients with unifocal and multifocal HNPGL and this difference was statistically significant (LogRank 16.3, df 1, p 0.00).

Figure 3 illustrates the difference in low and high risk tumours stratified for unifocal and multifocal disease. There was no significant difference in complication-free survival between low risk tumours and high risk tumours LogRank 0.831, df 1, p 0.36). The difference in complication free survival between low and high risk tumours when stratified for unifocal and multifocal presentation reached borderline significance (p = 0.06)

Table 2: Details of complications found per patient in unifocal and multifocal group

Complication	Unifocal group (N = 120)	Multifocal group per patient (N = 159)	Total (N = 279)
Cranial Nerve Damage n (%)	**34 (28%)**	**75 (100%)**	**109 (61%)**
VII	7 (6%)	12 (21%)	17 (10%)
VIII	6 (5%)	5 (9%)	11 (6%)
IX	7 (6%)	7 (12%)	14 (8%)
X	9 (8%)	26 (45%)	35 (20%)
XI	2 (2%)	11 (19%)	13 (7%)
XII	3 (3%)	11 (19%)	14 (8%)
Other Complications n (%)	**0**	**10 (17%)**	**10 (6%)**
Wound infection/ Bleeding	0	2 (3%)	1 (1%)
Stroke	0	2 (3%)	2 (1%)
Radionecrosis	0	0	0
Baroreflex Syndrome	0	6 (10%)	6 (3%)
Irradiation induced Neoplasm	0	0	0

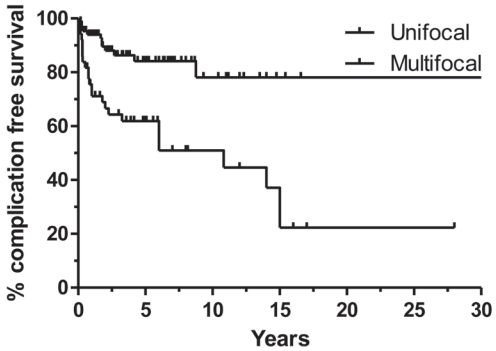

Figure 2: complication-free survival of patients suffering unifocal and multifocal tumours.

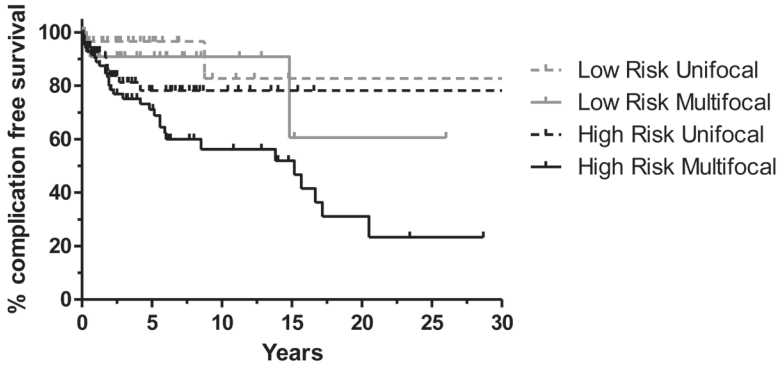

Figure 3: Complication free survival of patients suffering high- and low-risk unifocal and multifocal tumours

In case of multifocal tumour presence, there was no significant difference in complication-free survival between unilateral or bilateral tumour presence (p = 0.75). Also, there was no difference in complication free survival associated with number of multifocal tumours present (p = 0.9).

Regression analysis

Table 3 shows the results of univariate regression analysis, searching for clinical predictors of complications. Suffering multifocal disease or a high risk tumour were significant risk-factors for complications. Treatment-modality itself was not a risk-factor for complications in general, the number of surgical procedures was, however. Moreover, when managed only with a wait and scan strategy, this was a negative predictor of complications.

Using a binary logistic regression model, the number of surgical procedures was the only independent predictor of complications (B = 0.797, df. = 1, p = 0.047). The remaining variables were no longer significant when corrected for confounders.

Table 3: Results of univariate analysis of variance.

Variables predicting complications	P-value
Age of presentation	0.11
Multifocal disease	*0.00*
High risk tumour	*0.02*
High risk tumour in unifocal disease	0.2
High risk tumour in multifocal disease	*0.06*
Bilateral tumour presence	0.25
More than 2 tumours	0.16
Wait&Scan	0.01
Surgery	0.73
Radiotherapy	0.81
Surgery for high risk tumours	0.16
No surgical treatments	*0.04*
No radiotherapy treatments	0.79
Combination surgery/ radiotherapy	0.24

DISCUSSION

The current study is the first to describe a difference in complication-free survival between unifocal and multifocal head and neck paraganglioma patients. There was a significantly poorer complication-free survival in case of multifocal disease when

compared to unifocal disease. The number of tumors was not of influence for complication-free survival. However, suffering a Fisch class C/D tumor, Shamblin class 3 or vagale tumor was associated with more complications (independent of treatment modality applied). Fewest complications were found with a wait and scan strategy. The lowest complication-free survival was found post-surgery in the case of high risk tumor presence, albeit, borderline statistically significant. Furthermore, the number of surgical procedures required for tumor control per person was an independent predictor of future complications. We believe the current results aid the understanding of multifocal HNPGL management and provide insights that aid the consultation of patients suffering from such tumor syndromes.

Cohort description

Comparing the cohort of patients of multifocal versus unifocal disease, we found that patients suffering multifocal disease are significantly younger which is considered to be due to the hereditary background of these tumors. In fact, 68% of multifocal tumors were proven to be part of hereditary disease and this is expected to be an underrapportation since genetic work-up with latest understanding of associated genes has not been done for all patients included in the series, especially those diagnosed in the earlier years. Generally, we believe it is mandatory to have full understanding of the genetic subtype association, as this predisposes for synchronous and metachronous disease and it should alter clinical management. A subject further discussed underneath.

The main complications found in the current series were those associated with cranial nerve deficit, and were found more in case of multifocal disease (28% versus 100%). The most frequent cranial nerve deficit was N. X damage, and was found in 45% of patients suffering multifocal disease. This concerns a complication associated with decreased quality of life, and a potential life threatening complication in case of swallowing disorders, particularlywhen bilaterally damaged. Seventy percent of cranial nerve damage was found post-surgery, whereas 30% of complications were found to be due to radiotherapy or due to tumor growth. Furthermore, the complications other than cranial nerve damage were merely found in the multifocal group. The main complication was Baroreflex syndrome (4% of cases and all post surgery) followed by a 1% risk of stroke post-surgery (requiring surgical internal carotid artery management). Radionecrosis and radiation-induced malignancies were not observed in the current cohort.

Comments on clinical management

Several reports have suggested the difference in risk associated with low-risk tumors and high risk tumors as presented in our study. Generally, literature agrees that surgery is a sensible option for low risk tumors since excellent local control rates are found and complication rates are generally low (13-23). However, it needs to be emphasized that these papers generally did not discriminate between unifocal and multifocal disease and therefore, the risk of surgery for multifocal disease is not well investigated. Our results demonstrate that complication-free survival of low risk tumors when being part of multifocal disease is reduced when compared to unifocal low-risk tumors (albeit not statistically significant). Moreover, we found no significant difference in treatment modalities of these tumors. Generally, we believe that surgery is a viable option, yet alternatives in form of a wait and scan strategy should always be considered, particularly when tumor- or treatment-induced morbidity is already present.

With respect to high-risk tumors a larger difference is found in complication-free survival when considering tumors being part of multifocal disease versus unifocal high risk tumors. Recent literature generally leans towards non-surgical treatment methods for these tumors and our results agree (2- 4; 24, 25). Although barely significant, particularly in the background of multifocal disease surgery presented with worse complication free-survival when compared to results of wait-and-scan and radiotherapy.

While for unifocal tumors management is not always straightforward, the management of patients suffering multifocal tumors is even more complex and requires careful timing and planning of treatment. Several studies in the past have evaluated the aspect of multifocal tumor management. All management strategies acknowledge the inherent enhanced risk of surgery for "high risk tumors". Nonetheless, most studies implement a calculated surgery-associated risk in their strategies.

For example Sobol et al. (10) suggest a one staged surgical procedure for multiple ipsilateral tumors. The philosophy of the authors being that sacrifice of the cranial nerves on one site facilitates surgery of remaining ipsilateral tumors as well. In this light, Sobol et al. present a 27-year old patient with a carotid body- and a vagal tumor on one side. During vagal tumor resection N. X was sacrificed which facilitated swift resection of the ipsilateral carotid body tumor. Hereby, the authors rationalize that resection of a cranial nerve is considered a means for reduction of further complications. Alternative treatment options such as radiotherapy or tumor debulking were not discussed in this study.

Velegrakis et al. and Boedeker et al. describe a similar management strategy for bilateral paraganglioma (9, 26). Both studies suggest that after extirpation of the first HNPGL the internal carotid artery patency and cranial nerve functions be monitored postoperatively. Only in case of normal clinical and radiological findings the second stage operation of the contralateral tumor was considered. Otherwise a conservative

wait and scan policy was adopted. The main goal being to prevent bilateral cranial nerve damage and diminish the risk of stroke. Boedeker et al. follow the method of Velegrakis et al., however they particularly suggest that the largest tumor should be removed first. Depending on the post-operative cranial nerve status, therapy of the remaining tumor(s) may be individually planned. This suggests that the largest tumor carries the highest risk of tumor and treatment induced cranial nerve damage. Depending on the post-operative sequelae, contralateral surgery can be planned; in case sequalae are found, radiotherapy might be preferred for the other side. Both the strategies of Szymanska and Boedeker consider surgery as the treatment of choice also for high risk tumors and present a means to cope with the expected iatrogenic damage, rather than preventing it by initial less detrimental management strategies such as tumor debulking or primary (stereotactic) radiotherapy.

Another management strategy is presented by Makeieff et al. and Velegrakis et al., who estimate the risk of iatrogenic damage not merely based on tumor size, but also as a function of tumor location and relationship to the neural structures (9, 18). Particularly the enhanced risk of N. X palsy post-surgery of a vagal paraganglioma is taken into consideration. Therefore, they suggest that in case of combination of vagal body paraganglioma, the contralateral tumor should be operated first and in the absence of sequelae postoperatively the vagal body tumor can be "safely" removed (generally sacrificing the vagal nerve). Also for this management strategy the alternative for surgery, radiotherapy, is not considered and apparently damage of the vagal nerve is considered an acceptable clinical outcome.

Fourth, and in line with the philosophy of Makeieff et al., but opposite to Boedeker et al., Myssiorek et al. suggest that first the smaller tumor should be resected (posing the lowest risk of cranial nerve damage), and depending on the sequelae the larger tumor can be exposed either to surgery, radiotherapy or a wait and scan policy. Again, the main goal is to prevent bilateral cranial nerve damage and not cranial nerve damage in general since radiotherapy or a wait and scan policy would mainly be considered in case the first resection would have rendered cranial nerve damage.

The fifth strategy acknowledges that intervention is not always required. Van der Mey et al. suggest that for bilateral paraganglioma a more conservative monitored "wait and see" policy can be sensible and should be considered (27). The motivation being that during the follow-up period (maximal observation time 32 years, mean 13.5 years) of 108 patients (58 with hereditary disease), none of the patients died of residual or recurrent tumor or developed distant metastases, irrespective of the mode and outcome of treatment.

We believe there are several issues with the above mentioned treatment strategies. First, our philosophy is that preservation of cranial nerve function should be pursued at all cost as this is associated with highest quality of life. Therefore, we agree with van

der Mey et al. that management should start with a wait and scan period, unless partial tumor-induced cranial nerve damage is already present. In case of the latter, treatment should readily be considered. Tumor growth and cranial nerve function should be closely monitored, and in case of further deterioration, treatment should be considered. Please note however that a previous publication of our group demonstrated that apparently stable tumors have a 17% risk of inducing cranial nerve damage (4). As the progressive tumors were all treated, the precise risk of complications induced by tumor growth remains uncertain. Nonetheless, we assume that tumor growth should be considered as a predictor of potential future complications. Although this has never been proven in literature this seems a logic consequence and we therefore believe that in case tumor growth is found action should be taken. The problem with management strategies that suggest planned sacrifices of unilateral cranial nerves is not only that quality of life is reduced inevitably, but also the possibility of metachronous tumor presentation is overlooked. Szymanska et al. observed this in 16.6 % of cases 4 to 21 years post-treatment. Future contralateral tumor appearance that needs treatment might result in contralateral cranial nerve damage with further reduction of quality of life and, in the case of vagal nerve lesions even life threatening complications. We believe such a situation should be prevented by considering alternative initial management strategies with higher chance of cranial nerve preservation, such as gross tumor debulking or primary radiotherapy. Hence, planned cranial nerve damaging methods should be considered obsolete since alternative treatment strategies are at hand: numerous studies have illustrated the excellent long-term local control rates that can be achieved with radiotherapy and complications found with the current techniques remain rare. A literature review of Suarez et al. illustrated that complication rates are low after irradiation of even the carotid body paraganglioma, a group of tumors for which radiotherapy is thought to be less applicable due to the risk of radiation-induced stenosis (3). However, radiation-induced atherosclerosis is a very late event and most studies do not have sufficient follow-up for a proper risk assessment of this complication. Furthermore, especially in the earlier days, many physicians were not aware of this radiation-associated complication and may not have documented it. Based on data from head and neck cancer patients (5) the expected incidence of radiation-induced carotid stenosis in the paraganglioma population must me much higher than reported. Nonetheless, the current results illustrate the beneficial effects of radiotherapy in the presence of multifocal tumor growth, particularly in the "high risk population" when compared to the surgical group. Very late vascular damage by radiotherapy should be weighed against the immediate consequences of surgical iatrogenic cranial nerve damage.

In elderly patients the balance will be mostly in favor of radiotherapy. However, in younger patients this is different because of their longer life expectancy they are much

more likely to be confronted with the late sequelae of radiotherapy but also because of the increased risk of metachronous tumor presentation. Multiple radiotherapy courses should preferably be avoided in the head and neck region and previous radiotherapy might hinder future surgery due to fibrosis. Another issue might be that presentation at a younger age is associated with faster tumor growth rates (4). Therefore, the initial wait and scan strategy might enhance the risk of tumor-induced complications in younger patients. We believe that for these patients tumor debulking should be considered, particularly in the case of Fisch class C and D tumors. Hereby, gross tumor removal can be performed with safe margins from critical neurovascular structures, reducing the risk of iatrogenic morbidity. A previous study of our group, evaluated the treatment outcomes of debulking and a subsequent wait and scan strategy, radical surgery, and primary radiotherapy (4). We found similar local control rates with debulking when compared to radiotherapy (100 and 90% respectively), and better control rates when compared to radical surgery (82%) due to little residual tumor growth. Although there were significantly more complications post-debulking when compared to radiotherapy (44% vs 27%), complication rates were significantly lower when compared to radical surgery (63%). Potentially, for high risk tumors in other situations, debulking may also be a viable treatment option.

Recommendations for daily practice

Given the results from this analysis and discussion of the literature, we propose the following management philosophy. A wait and scan policy should be the initial step in most cases. In case multifocal tumors are present, and there is no tumor induced cranial nerve damage, an evaluation of the risk of tumor induced complications should be made first. We believe that tumor growth is still the foremost predictor of tumor-induced complications, and therefore we suggest that the growing tumor is treated first. In case this is a low risk tumor, surgery by an experienced surgeon could be applied. In case of a high risk tumor, we believe that radiotherapy should be applied for older patients. For younger patients surgical debulking should be considered with a post-operative wait and scan period, evaluating residual tumor growth. In case of growth of residual tumor radiotherapy can be applied if complications are to be expected due to further growth. An exception to this rule would be the presence of complete tumor induced cranial nerve paralysis. In such cases, surgery could be applied without leaving tumor on the vagal nerve. This should be performed however without enhancing the risk of other cranial nerve damage or strokes e.g. via manipulation of the internal carotid artery.

Methodological considerations

The main methodological weakness of this study is the fact that the conclusions are drawn from a retrospective cohort which results in a large selection bias which reduces the external validity. The choice for a treatment modality was not randomized and therefore comparison between treatment modalities is of little statistical relevance. Nonetheless we believe that the current study contributes to a functional approach in HNPGL management.

Furthermore, the long-term effects of our management strategy remain uncertain. Although the mean follow-up was 99 months (range 6 to 451), potential metachronous tumor growth can occur later and may be underestimated. Also, this follow-up might not be sufficient to evaluate the very long-term effects of radiotherapy i.e. artheriosclerosis and radiation-induced malignancies.

The impact of the genetic background particularly in multifocal tumor presence remains partly uncertain in the current series. Albeit most patients are subjected to genetic testing, not all patients received testing for various reasons. Moreover, patients presenting further back might not have been tested for the more recently discovered mutations. Furthermore, genetic sub-types SDHD and –B are thought to be associated with more aggressive tumor growth and we did not stratify our results for this. All patients with multifocal disease were grouped in the current analysis. Potentially, this is a flaw since Amar et al. showed that the presence of SDHB mutation is a potential risk factor for reduced survival and malignant disaese. In our series however, the number of patients suffering an SDHB mutations (n = 11) was too small to allow for sub-group analysis.

Finally, an overrepresentation of jugulotympanic tumors was found in our centre, which might have influenced the overall results. These tumors are overrepresented because the Radboudumc is a prominent skull-base center which might cause more referrals of jugulotympanic paraganglioma patients.

CONCLUSIONS

The current study demonstrates the complexity of multifocal HNPGL management, and the increased risk of severe complications in patients suffering multifocal HNPGL. We found that there is a significantly reduced complication free-survival for patients suffering multifocal tumours. The location, stage and growth rate of the tumour and the treatment modality chosen to manage the tumour are associated with complication-free survival. A risk assessment system was constructed, based on tumour location and stage and treatment method, which predicts the risk of future complications. In our view, multifocal HNPGL tumour presentation should be managed with optimal attention

for preservation of cranial nerve function. We believe radical tumour removal with sacrifice of cranial nerves should be avoided at all cost. Instead, radiotherapy should be considered, or, depending on age at presentation tumour debulking might be an option to consider.

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CHAPTER 10

Discussion

The aim of the current thesis is to evaluate the risk associated with different treatment modalities for HNPGL of different sub-site and tumour class to aid the constitution of personalized guidelines for individualized patient management. To this end, in part 1, we evaluated the applicability of an initial wait and scan strategy for HNPGL. In part 2 we evaluated the risk of surgery, radiotherapy and debulking for HNPGL of different subtypes. In part 3, we evaluated the impact of multifocal head and neck disease in patients and evaluated different management strategies. In the current discussion the results of these chapters are combined and a guideline for treatment of HNPGL is constituted. Aims for future research are presented as well.

The head and neck paraganglioma treatment paradigm

Historically, surgery is the main treatment modality considered for HNPGL since this is the only treatment modality rendering total tumour removal. However, attempts for radical surgery are associated with high morbidity rates. In contrast, as illustrated by van der Mey et al., tumour induced morbidity seems to be particularly low [1]. Moreover, there is a low malignancy-rate associated with these tumours [2]. Therefore, alternative treatment modalities such as tumour debulking or (stereotactic irradiation) are potential treatment options as well. Considering the benign tumour biology, it is our treatment philosophy that the main concern in HNPGL management should be functional preservation, generally referring to cranial nerve vitality. To ensure this, we believe there is no "one size fits all" approach, and we believe that in every patient the risk of treatment should always be outweighed against the risk of a wait and scan policy.

In order to allow for such a risk calibration, there are several patient factors that should be taken into consideration as they might be of influence on tumour management. Several studies have illustrated the phenotypical association of different SDHx related tumour syndromes [2]. We believe that awareness of such a syndrome is critical for tailored HNPGL management for several reasons:

Besides the risk of associated tumour growth in the case of SHD associated HNPGL presence or the enhanced risk of malignant tumour growth associated with these syndromes which are not within the scope of this thesis, these tumour syndromes are of importance since they might induce enhanced tumour growth. Although we could not confirm this in part 1, it is likely that tumour syndromes are associated with lower ages of onset. We did find in part 1 that tumour growth incidences and rates are inversely correlated to age of presentation. The younger the patient, the higher its tumour growth rate, which shows an enhanced risk of tumour induced morbidity. Furthermore, we found that the cut-off point for enhanced tumour growth is 50 years of age. This hypothesis is further supported by the finding that in case of tumour induced morbidity we found above average tumour growth rates. This factor should

be taken into consideration in managing these younger patients and should hint the managing physician to decreased follow-up intervals for patients younger than 50 years of age.

Another important risk factor associated with SDHx syndromes is the risk of multifocal/metachronous tumour presence. We described in part 4 that patient with multifocal tumour presence show a significantly lower complication free survival independent of treatment modality. The main reason for this is previous tumour or treatment induced morbidity. The particular impact of multifocal tumour presence of HNPGL management is discussed underneath.

Management of head and neck paraganglioma of different tumour class

Underneath we outline the best treatment strategies for HNPGl of different tumour class as concluded from the review and clinical data obtained in part 2.

Jugulotympanic paraganglioma.

The best treatment modality is described per Fisch class.

Fisch class A

Surgical excision of these tumours is considered the best practice since local control rates are 100% for the included studies and no adverse events were described. Although no studies on the effect of RT of these studies are available, we believe it is not a viable treatment option due to the potential radiotoxic effects on the skin and cochlea. Therefore, we advise primary surgical resection (if comorbidities of the patient allow this) in order to prevent conversion to level B tumour or further, which was little higher risks when compared to class A tumours.

Fisch class B

Surgical excision should be advised in case of presented growth by means of a wait and scan period. Nonetheless, in case tumour-induced-morbidity such as tinnitus, vertigo or facial nerve pareses outweighs the potential risk of surgery primary resection is also advised. Albeit local control was found in 100% for all included studies, serious complications have been described, such as N. VII pareses and CSF leakage. Please note that these complications were incidental, and potentially correlated to use of facial nerve rerouting. Moreover, there are suggestions that presenting symptoms such as pulsatile tinnitus and conductive hearing loss are potentially best treated with surgery. Although

there are no studies describing the effect of radiotherapy on Fisch class B tumours en no recommendations can be embodied with evidence; one could argue that in case a patient is not suitable for surgery, (stereotactic) irradiation could be used. Particularly in the case of CN paresis, since irradiation seems to potentially enhance CN function post treatment when compared to surgery as suggested in chapter 3.

Fisch class C and D

The CND and complication rates found post treatment of class C and D tumours suggest that conservative wait and scan management should always be considered. In chapter 4 we elaborately evaluated the pre-treatment work-up and effects of a wait and scan period for Fisch class C and D tumours. Out of 66 patients subjected to a wait and scan period 28 required further treatment due to tumour growth or tumour induced morbidity. There was also a cohort of patients directly treated without a preceding wait and scan period. We could not identify differences in treatment outcome between patients treated with a preceding wait and scan strategy and those immediately treated, suggesting that a wait and scan option is a safe first management strategy. Moreover, we could not identify predictors for subsequent treatment following the wait and scan period, which confirms in our opinion that all Fisch class C and D tumours should be managed conservatively. An exception to this rule would be the presence of treatment requiring tumour induced morbidity at time of presentation. This mainly refers to readily present cranial nerve damage at initial presentation.

In case treatment is required, in general we found that radiotherapy seems to provide overall best treatment outcome, with local control rates of 90%, a complication risk of 27% and 10% function recovery. Local control rates were best when gross tumour debulking was attempted (100%), with postoperative radiation of potential growing residual disease. This rendered complications in 44% of cases. We believe attempts for radical surgery should not be undertaken, given the chance of local control of 82% and a complications risk of 63%. Functional recovery was found in 30% of cases. Please note however, that we believe there are several factors that should be taken into consideration when deciding which treatment modality suits best. The main concern would be the age of presentation. In case patients present at younger age (most often found due to hereditary syndrome presence) late sequelae of radiotherapy are potentially severe (e.g. referring mainly to the risk of stroke and secondary malignancies). We believe that for patients younger than 50 years of age radiotherapy should be handled with caution. Obviously this should be outweighed against the risks of other treatment options. For patients older than 50 years of age we believe radiotherapy is the best treatment option and best results are found with stereotactical radiotherapeutic techniques. A potential confounding factor might be however, that

tumours treated with this techniques are generally smaller than tumours treated with other radiotherapeutic techniques. Therefore, for younger patients, rather, the use of surgical debulking may be a viable treatment option. We believe that careful planning of the tumour allows an experienced skull base surgeon to safely debulk gross tumour mass with safe margins from delicate neurovascular structures such as cranial nerves. Subsequent follow-up of residual tumour is mandatory, and in case of growth/morbidity imposed by this residual re-debulking or radiotherapy can be considered.

Please note that we could not identify a difference in tumours of different C classes, or C_{1-4} and D classes. Therefore, the treatment protocol as presented should be considered for both C and D tumours.

Carotid body paraganglioma

Shamblin class 1 tumours

The results of our study combined with the results of the systematic review show that local control can be expected in up to 100% post surgery. Although not often found, there is still a theoretical risk of cranial nerve damage associated with surgery of these tumours. Therefore, also for these smaller tumours we advise to adopt an initial wait and scan strategy for these tumours as well. In case of tumour growth, surgery is advised.

Shamblin class 2 tumours

The results of our studies show that local control is achieved in 98% of cases post surgery. The risk of cranial nerve damage is 18% which mainly concerns n. X and XII deterioration. Moreover, potential serious complications such as strokes and pneumonias are found in 1%. The chance of local control found post radiotherapy is about 100% and no CND was found post radiotherapy of these tumours. It is important to notice however that sample sizes are small and follow-up ranges were relatively short with respect to evaluation of radiotherapy for these tumours. Therefore, the main advise in management of these tumours is to establish an initial wait and scan management strategy, and in case of tumour growth, surgical management by an experienced surgeon should be considered. More research on the potential use of radiotherapy for these tumours is required.

Shamblin class 3 tumours

The results of surgical management of these tumours show that local control is found in 94% of cases. Nonetheless, the risk of CND for these tumours is considerable and

found in 32% of cases. Furthermore, there seems to be an enhanced risk of complications found in the management of these tumours 10%, mainly in the form of strokes. Nonetheless there is a potential risk associated with radiotherapy for these tumours as well. Therefore, initial management should always be by means of a wait and scan strategy. We believe surgery should be applied with great caution for these tumours and should solely be conducted by an experienced head and neck surgeon. Furthermore, in case surgical intervention is applied, our meta analysis illustrates that routine ECA and ICA clamping should not be conducted as this is associated with an enhanced risk of strokes. Although literature is sparse on this matter and our own clinical experience is limited, we believe radiotherapy should be considered a viable option as well as this rendered excellent local control and no complications in the issued follow-up period. Particularly in the case of multifocal disease radiotherapy should be considered for these tumours.

Vagal body paraganglioma

Our studies illustrate that surgical management of these tumours is associated with unacceptable morbidity rates particularly in the form of n. X paresis, which is in turn associated with aspiration pneumonias in up to 44% of cases. Furthermore, there seems to be an enhanced risk of strokes post surgery for these tumours. Complementary, local control is achieved in about 100% of cases and there were no irradiation induced cranial nerve damages described for these tumours. Please note however, that evidence for these rare tumours is based on small sample sizes with often an unsatisfactory follow-up rate. Therefore also for these tumours we highly recommend an initial wait and scan strategy as first management strategy. In case of present cranial nerve damage however, we believe initial radiation therapy should be conducted.

MULTIFOCAL TUMOUR PRESENCE

In the case of multifocal tumour presence in case of an enhanced risk of metachronous tumour presence due to and SDHx mutation, extra attention for functional preservation is required. Particularly bilateral cranial nerve damage should be prevented at all cost. Since treatment induced cranial nerve damage sequelae might remain up to 1 year post treatment, careful planning of treatment is required. Moreover, the management strategy is mainly based on the risk of CND for the particular tumour per treatment modality. Therefore, we believe that for Fisch class A and B tumours as well as Shamblin class 1 tumours, primary surgical management is still a viable option. For the remaining tumours, a wait and scan strategy should be adopted and treatment should be avoided to induced iatrogenic morbidity, In the case of tumour growth or present partial

cranial nerve damage we believe radiotherapy should be initiated. It should be kept in mind however that late complications of radiotherapy can be expected, and therefore sequential treatment of synchronous HNPGL should be planned with an interval of at least 12 months. Surgery is generally not advised in the presence of multifocal tumour growth of tumours other than previously classified "low risk tumours" due to risk of CND. Surgery could be considered however in case of readily present (tumour induced) complete cranial nerve paralysis. However, please note that post surgery of Fisch class C and D tumours we found a mean CN damage rate of 1.58 implying that on average more than 1 nerve is affected post surgery. Therefore, even in the case of present cranial nerve paralysis of C and D tumours, surgery is not advised.

In case of bilateral high risk tumour presence, a careful risk profile of each tumour should be constituted. It should first be evaluated whether there is a presence of cranial nerve damage. In case of cranial nerve damage, the tumour associated with the paralysis should be treated first with radiotherapy. Hereby, we aim to halt further cranial nerve function deterioration, and potentially cranial nerve function recovery is induced. We believe that in case of contralateral tumour growth (without cranial nerve function deterioration), the tumour inducing CND should still be treated first. In case there is no present cranial nerve deterioration, tumour growth should be evaluated. In case of unilateral tumour growth, the growing tumour should be treated first. In case both tumours grow, the smallest/lowest classified tumour should be treated first as this renders the highest chance of at least unilateral functional preservation.

In case of younger patients (referring to patients younger than 50 years of age), the above mentioned suggestions for multifocal tumour management should be handled with great caution since the long term results of radiotherapy remain uncertain for these tumours and potential detrimental sequalae can be expected up to thirty years post treatment. Therefore, we believe patients younger than 50 should not generally not be treated with radiotherapy. We believe for these patients tumour debulking should be considered, with careful follow-up of the residual tumour. Hereby, we believe treatment induced complications can be reduced to a minimum and radiotherapy can be prevented or at least be postponed with highest chances of functional preservation. However, more research is required to evaluated the applicability of this treatment strategy, particularly for younger patients.

SUGGESTIONS FOR FUTURE RESEARCH

Many attempts have been made to describe the risk of the above mentioned treatment modalities for HNPGL, yet large (multicentre) studies are missing. Therefore, we believe future research should mainly be focussed on the cooperation between larger centres

sharing their data rendering larger samples. Potentially even allowing for prospective trials in which several treatment modalities can be compared and sub-group analysis' can be performed.

Particularly the aspect of hereditary tumour syndrome presence and its implications for the safety of an initial wait and scan management strategy is highly needed. Hereby, the potential enhanced risk of tumour induced complications during such a wait and scan session can be further investigated. Furthermore, the current work did not stratify treatment results of surgery or radiotherapy per genetic subclass. Potentially in case of tumour presence radiotherapy should be considered a less viable treatment option due to enhanced tumour growth?

Furthermore, more information is required on the long term effects of radiotherapy for HNPGL. Currently radiotherapy is advised for a large portion of the HNPGL, however this is mainly based on the enhanced risks of surgery for HNPGL of higher tumour class. We believe a large study is required that evaluates the long term complications of HNPGL, stratified per tumour class.

Furthermore, in the current study the aspect of tumour debulking has been suggested as a treatment for Fisch class C and D tumours. We believe this treatment option is a promising alternative when radiotherapy is less attractive (e.g.in case of younger patients). Whether or not this alternative can prevent (or sufficiently postpone) radiotherapy due to the absence of residual tumour growth requires further research.

Moreover, evaluating the potential of surgical debulking, particularly in the case of jugulotympanic paraganglioma, the effects of surgery on pulsatile tinnitus and conductive hearing loss requires future research. Potentially, surgical debulking is a safe treatment option for patients suffering from this.

CONCLUSIONS AND IMPLICATIONS OF THIS THESIS

In conclusion, the studies described in this thesis contribute to the understanding of risks associated with different treatment modalities of HNPGL of different tumour class. Hereby we aid the constitution of individualized treatment protocols of patients suffering (multifocal) HNPGL. However, enhanced knowledge of risk factors for tumour induced complications for example in a wait and scan period is mandatory to better depict timing of treatment. Moreover, further research with large trials constituted via the cooperation of multiple centres is required to allow for proper sub-group analysis' evaluating treatment outcome stratified per tumour class.

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CHAPTER 11

Summary

After a general introduction on head and neck paraganglioma and their diagnostic work up and introduction to the treatment paradigm, the first part of this thesis (chapter 2) discusses the feasibility of a wait and scan period as initial management strategy.

Part 1: the evaluation of a wait and scan management strategy for head and neck paraganglioma

In chapter 2 due to the high risk of treatment induced morbidity of all available treatment modalities the feasibility of a wait and scan period to preserve potential harmful treatment modalities for those tumours with an enhanced risk of inducing morbidity. To this end a retrospective cohort study was conducted in which tumour growth rates were measured and clinical predictors for tumour induced morbidity were evaluated. In a large series resembling 59 jugulotympanic-, 71 carotid body-, and 29 vagal body tumours we found that 44% of head and neck paraganglioma show tumour growth and that the median growth rate these tumours is only 0.44mm per year. Furthermore, a significant inverse correlation between growth rates and age at presentation was described. Ultimately seventeen tumours induced 20 complications. Six of these tumours were growing, and growth rates were higher than in tumours not inducing complications. From these results we can conclude that a wait-and-scan strategy is a feasible strategy for HNPGL. Nonetheless the management strategy could not prevent tumour-induced complications in 16% of non-growing tumours.

Part 2: Evaluation of different treatment modalities for head and neck paraganglioma of different sub-site and class

In chapter 3 we systematically analyzed the available literature on treatment of jugulotympanic paraganglioma. Out of 18 articles, resembling 83 patients treated with radiotherapy and 299 with surgery, an individualized risk profile was constituted regarding local control-, cranial nerve- and complication rates, post surgery for tumors of class A and B, and post surgery or radiotherapy for C1-4 tumors, and C1-4De/Di tumors. For class A and B tumors excellent local control was found post surgery and risk of cranial nerve damage was negligible. For class C1-4 tumours, local control was 80-95% post surgery (84% post radiotherapy), cranial nerve damage rates were as high as 71-76%, whereas no cranial nerve deficits were found post radiotherapy. Additionally, for class C1-4De/Di tumours, local control rates were variable post surgery (38-86%), but lower when compared to radiotherapy (98%), moreover, cranial nerve damage/ complication rates were found in 67-100% and only in 3% post radiotherapy. With this study, an individual risk profile is constituted for surgery and radiotherapy, stratified per Fisch class. For class A and B tumours surgery is a suitable treatment option. For

class C and D tumours radiotherapy results in lower complication rates and similar or better local control rates when compared to the surgical group

In chapter 4, the risk profile was further investigated as we evaluated treatment outcomes in our own population, resembling 66 C1-4 and 15 C1-4De/i tumors. In this cohort-study we analyzed results of surgery (n = 17), radiotherapy (n=29) and the use of tumor-debulking strategies (n=19). Furthermore, predictors of lesser treatment outcomes were evaluated. In this study we found complete local control after tumour debulking which was significantly higher when compared to the surgical group (80%). This did not differ significantly from the radiotherapy group (90%). Moreover, there were significantly less complications in the radiotherapy group (27%)when compared to surgery (63%) and the combined treatment group (44%). Therefore, in line with chapter 3, we conclude that radiotherapy should be the treatment of choice for the elderly. For younger patients tumour debulking should be considered, with potential radiotherapy in case of residual tumour growth.

With respect to carotid body paraganglioma, the main subject of debate is not so much which treatment modality to consider, as it is also uncertain which surgical resection technique should be used. To evaluate the treatment outcomes of different surgical techniques, in chapter 5, we systematically evaluated the literature on this matter. We summarized the clinical outcome of 139 class 1, 228 class 2 and 201 class 3 patients, subtracted from 27 studies. A meta-analysis on routine ICA and ECA clamping techniques evaluated its association with clinical outcome. We found that Cranial nerve damage (3%, 17% and 39%) and complication rates (0%, 1%, 10%) were significantly related to Shamblin class (class 1, 2, 3, respectively). For class 3 tumours an increased risk of complications was found associated with routine ICA manipulation/ reconstruction, mainly in form of a stroke. Moreover, a trend towards enhanced risk of routine ECA ligation was described. Therefore, it is concluded that for class 1 and 2 tumours surgery seems a viable treatment option. For class 3 tumours, morbidity in terms of cranial nerve deficit and complications is considerable, particularly the use of ICA manipulation/reconstruction and potentially ECA ligation seems to be accompanied by high a stroke incidence.

Having found considerable risks associated with surgery of larger class carotid body paraganglioma, in chapter 6 we evaluated our own surgical results in a retrospective cohort study, evaluating treatment outcomes. Subsequently, and acknowledging the risk of surgery for these tumors (particularly in multifocal disease), we also evaluated the risk of 7 patients treated with radiotherapy for these tumors. This was complemented by a systematic literature search evaluating the results of radiotherapy for 118 carotid body paraganglioma (not stratified per Shamblin class), as described in 10 carefully selected studies. Thirteen class 1, 25 class 2 and 16 class 3 tumours were included. Post surgery, local control rates were similar for all Shamblin tumours (range

90-100%). Cranial nerve damage rates increased per tumour class (0%, 8% and 18% respectively) and complication rates were low (0% 4% and 6% respectively). The complications constituted amongst others a stroke. Post radiotherapy no complications and 100% local control was found after median follow-up of 11 years (range 4-30). In the systematic review, constituted of 10 cohort-studies resembling 118 patients with median follow-up of 9.5 years (range: 1-34), local control as found in 96-100%. Furthermore, no irradiation induced cranial nerve damage and 1 potentially irradiation induced meningeoma was found. Therefore, it has been concluded that post post surgery, the risk of complications in class 2 and 3 tumours is low, yet, complications are potentially severe. In case patients are not fit for surgery, radiotherapy should be applied.

In chapter 7, a systematic literature search was executed, evaluating the treatment results for vagal body paraganglioma in 17 studies, resembling 177 patients treated with surgery and 78 with radiotherapy. Compared to surgical results, post radiotherapy, there were significantly higher local control (95% vs. 100% resp.), and significantly less cranial nerve damage (97% vs. 0% resp.) and complication rates (29% vs. 0%). Therefore, it is concluded that surgery is not the preferred treatment option for vagal body paraganglioma. Local control after radiotherapy is high but long-term side effects are not well documented. The risk of cranial nerve damage caused by radiotherapy seems small when compared to the risk of iatrogenic nerve damage post surgery.

These results are complimented in chapter 8 by a retrospective cohort-study comparing the results of surgery versus radiotherapy for a total of 16 clinical patients. Out of 16 patients 11 were treated with radiotherapy. Post surgery and radiotherapy local control rates were 100% at 20 months (range 15-38) and 11 years (Range 3-29) follow-up respectively. Significantly less cranial nerve damage was found post radiotherapy when compared to surgery (27% versus 80%). All post-treatment cranial nerve damages were N. X lesions. In conclusion it is stated that surgery inevitably renders n. X lesion and poses an additional risk for surrounding cranial nerves. Radiotherapy has rendered new cranial nerve damage or worsening of cranial nerve damage function in 27% of cases. Considering these risks associated with treatment, it seems wise to adopt an initial wait and scan protocol and to treat these tumours as little as possible.

Part 3: management of multifocal head and neck paraganglioma disease

In chapter 9 we compared the complication-free survival of patients suffering multifocal disease and those suffering multifocal tumor presence. A large retrospective cohort study was conducted of all patients suffering HNPGL and the main outcome measure was complication free survival , analyzed using Kaplan-Meier survival analysis. Doing

so we found a significantly worse complication free survival in 58 patients suffering 159 tumours when compared to 120 patients suffering unifocal disease. No significant difference was found in complication free survival between unilateral versus bilateral tumour presence or the number of tumours found. Using univariate regression analysis, we found that when managed only with a wait and scan strategy, this was a negative predictor of complications. Using binary logistic regression, we found that the number of surgical procedures required for disease control is an independent predictor of complications in patients suffering multifocal disease. In conclusion we state that a significantly reduced complication free-survival can be expected for patients suffering multifocal tumours. Mainly the treatment modality chosen to manage these tumours are associated with complication-free survival, and radical tumour removal with sacrifice of cranial nerves should be avoided.

In the current thesis the impact of different treatment modalities of different tumour types of different tumour class' has been studied and discussed. The impact of radiotherapy and various surgical techniques have been evaluated. Hereby, this thesis contributes to the management of head and neck paraganglioma, as it aids the constitution of individualized treatment regimens.

SAMENVATTING

In hoofdstuk 1 wordt een algemene introductie gegeven over hoofd-/halsparagangliomen (HHPGL) en wordt het dilemma in behandeling van deze tumoren ingeleid. Hierna spitst het eerste deel van het proefschrift zich toe op de toepasbaarheid van een wait-en-scan beleid als initiële behandelstrategie voor deze tumoren.

Deel 1: De toepasbaarheid van een wait-en-scan beleid als initiële behandelstrategie voor hoofd-/halsparagangliomen.

Door de hoge morbiditeit geassocieerd met behandelingen van deze tumoren is in hoofdstuk 2 onderzocht of deze potentiële schade berokkenende therapieën patiënten bespaard kunnen blijven door een wait-en-scan beleid te voeren. Hiermee hopen we behandeling alleen in te zetten voor patiënten met een verhoogd risico op morbiditeit ten gevolge van uitbreiding van de tumor. Hierop is een retrospectieve cohort studie uitgevoed waarin groeisnelheden van deze tumoren zijn geëvalueerd en klinische voorspellers voor tumor geïnduceerde morbiditeit zijn geëvalueerd. In een grote serie van 59 jugulotympanicum-, 71 carotid body-, and 29 vagale paragangliomen is gevonden dat groei plaatsvindt in ongeveer 44% van de tumoren en dat de mediane groeisnelheid van deze tumoren ongeveer 0.44mm per jaar is. Verder is een significante inverse correlatie gevonden tussen groeisnelheid en leeftijd van presentatie gevonden. Uiteindelijk is gevonden dat 17 tumoren 20 complicaties hebben berokkend. Zes van deze tumoren lieten groei zien en de groeisnelheden waren hoger dan bij tumoren waarbij geen complicaties zijn gevonden. Uit deze resultaten wordt geconcludeerd dat een wait-en-scan beleid een toepasbare behandelstrategie is voor HHPGL. Desalniettemin werd in 16% van de niet groeiende tumoren toch een complicatie waargenomen.

Deel 2: Evaluatie van verschillende behandelstrategieën voor hoofd-/halsparagangliomen van verschillende lokalisatie en tumor klasse

In hoofdstuk 3 is een systematische literatuuranalyse uitgevoerd. Uit 18 artikelen werden resultaten van radiotherapie voor 83, en voor chirurgie in 299 patiënten van verschillende Fisch klasse beschreven. Hiermee is een geïndividualiseerd risicoprofiel opgesteld wat betreft uitkomstmaten lokale controle, hersenzenuwuitval en complicaties per Fisch klasse. Voor Fisch klasse A en B tumoren is excellente locale controle gevonden na chirurgie en was het risico op hersenzenuwuitval nadien kleiner dan 1%. Voor klasse C1-4 tumoren is locale controle gevonden in 80-95% na chirurgie en hersenzenuwuitval is beschreven in 71-76% van de gevallen. Na radiotherapie is locale controle in gevonden 84% en is geen hersenzenuwuitval gevonden na bestraling. Voor klasse C1-4De/Di

tumoren, werd locale controle bereikt in een range van 38-86%, terwijl dit 98% was na radiotherapie. Daarbij werd hersenzenuwuitval gezien na chirurgie in 67 tot 100% van de gevallen, terwijl dit na bestraling 3% was. Hiermee is een geïndividualiseerd risicoprofiel opgesteld voor chirurgie en radiotherapie als behandelmodaliteiten voor jugulotympanicum tumoren van verschillende Fisch klasse en werd geconcludeerd dat voor klasse A en B tumoren chirurgie een prima optie is, terwijl voor klasse C en D tumoren radiotherapie de beste op lijkt.

In hoofdstuk 4 is dit risicoprofiel verder onderzocht aan de hand van resultaten uit onze eigen klinische serie bestaande uit 66 klasse C1-4 tumoren en 15 C1-4De/Di tumoren. In dit cohort zijn de resultaten van chirurgie (n = 17), radiotherapie (n = 29) en tumor debulking (n = 19) geëvalueerd. Totale locale controle is gevonden in alle patiënten waarbij tumor debulking-strategieën zijn gebruikt, hetgeen statistisch significant hoger was dan bij patiënten waarbij poging tot radicale resectie was uitgevoerd waarbij locale controle 80% was. De resultaten waren vergelijkbaar met resultaten van radiotherapie; 90% locale controle. Verder werden significant minder complicaties gezien in de radiotherapiegroep in vergelijking met chirurgie (27 vs. 63% resp.) of in vergelijking met de debulking groep (44%). Om deze reden wordt in lijn met hoofdstuk 3 geconcludeerd dat radiotherapie de behandeling van keuze zou moeten zijn voor deze tumoren, ten minste bij ouderen. In geval van jongere patiënten dient chirurgische debulking overwogen te worden. Eventueel kan radiotherapie dan toegepast worden voor het tumor residu.

Wat betreft carotid body paragangliomen is de discussie over behandeling niet alleen welke modaliteit gekozen dient te worden, maar wordt ook ingegaan op de chirurgische techniek. Om uitkomsten van verschillende behandelingen te evalueren is in hoofdstuk 5 een systematische review uitgevoerd. Hier worden de resultaten van 139 klasse 1, 228 klasse 2 en 201 klasse 3 patiënten gepresenteerd, zoals beschreven in 27 studies. Vervolgens is een meta-analyse uitgevoerd naar de consequenties van routinematige ICA en ECA clamping technieken. Hierop is gevonden dat hersenzenuwschade en complicaties vaker voorkwamen bij oplopende Shamblin klasse (3%, 17% en 39%; en 0%, 1% en 10%). Voor klasse 3 tumoren is een toenemend risico op complicaties gevonden met routinematige ICA manipulatie/reconstructie. De voornaamste complicatie gevonden was een beroerte. Daarbij is een trend gevonden in toename van risico van routinematige ECA ligatie. Derhalve is geconcludeerd dat voor klasse 1 en 2 tumoren chirurgie een goede behandelingsoptie is. Voor klasse 3 tumoren is het risico op iatrogene morbiditeit in aanzienlijk, met name in het geval van ICA en mogelijk ook ECA manipulatie/reconstructie en wordt derhalve geconcludeerd dat chirurgie zeer spaarzaam toegepast dient te worden.

Naar aanleiding van het risicoprofiel beschreven voor chirurgie van grotere carotid body paragangliomen wordt in hoofdstuk 6 beschreven wat de resultaten zijn van

onze eigen chirurgische serie. Daarbij is, gezien het risico op morbiditeit, gekeken naar de mogelijkheid van radiotherapie voor deze tumoren. Hiertoe zijn in onze eigen serie 7 patiënten bestraald, de resultaten hiervan zijn aangevuld door resultaten van een systematische literatuurstudie naar effectiviteit van bestraling voor deze tumoren. Hiertoe zijn resultaten van bestraling van 118 carotid body paragangliomen (niet gestratificeerd per Shamblin klasse), zoals beschreven in 10 zorgvuldig geselecteerde artikelen. Resultaten lieten zien dat voor 13 klasse 1, 25 klasse 2 en 16 klasse 3 tumoren, na chirurgie lokale controle vergelijkbaar is voor de verschillende tumorklassen (range 90-100%). Hersenzenuwuitval lijkt wel toe te nemen met Shamblin klasse (0, 8 en 18% respectievelijk) en het complicatierisico ook (0, 4 en 6%). Onder de complicaties werd tevens een beroerte waargenomen. In onze serie werd na radiotherapie voor alle patiënten locale controle bereikt zonder complicaties na een mediane follow-up van 11 jaar (range 4-30). In de aanvullende literatuurstudie werd na een mediane follow-up van 9.5 jaar (range 1-34) locale controle in 96% van de gevallen gevonden zonder hersenzenuwuitval. Mogelijk is een enkel radiatiegeïnduceerde meningeoom gevonden. Op basis van deze resultaten is geconcludeerd dat het risico op complicaties na chirurgie ook voor hogere klasse 2 en 3 tumoren, maar dat complicaties potentieel ernstig zijn. Derhalve dient in geval van een niet vitale patiënt radiotherapie als behandelmogelijkheid overwogen te worden.

In hoofdstuk 7 wordt een systematische literatuurstudie uitgevoerd waarbij de resultaten van chirurgie en radiotherapie voor vagale paragangliomen wordt beschreven. In 17 studies zijn 177 patiënten beschreven welke behandeld zijn met chirurgie, en 78 met radiotherapie. In vergelijking met chirurgie, werd na radiotherapie significant betere locale controle bereikt (100 vs. 95%), daarbij werd significant minder hersenzenuwuitval gevonden (0 versus 97%), en warden er minder complicaties beschreven (0 versus 29%). Derhalve wordt geconcludeerd dat chirurgie niet de behandeling van keuze dient te zijn voor deze tumoren. Alhoewel de lange termijn resultaten van radiotherapie nog niet volledig bekend zijn is dit toch de behandeling van keuze gezien het extreme hoge risico op complicaties na overige behandeling na chirurgie.

Deze resultaten zijn aangevuld met onze eigen serie in hoofdstuk 8, waarbij een retrospectieve cohortstudie is uitgevoerd welke tevens de resultaten van radiotherapie en chirurgie beschrijft. Na chirurgie en radiotherapie werd in locale controle beschreven in alle gevallen. Er werd significant minder hersenzenuwuitval gevonden na radiotherapie in vergelijking met resultaten na chirurgie (27% versus 80%). In alle gevallen van hersenzenuwuitval was minstens de n. X betrokken. Derhalve wordt geconcludeerd dat chirurgie onvermijdelijk leidt tot n. X laesie en een aanvullend risico voor overige hersenzenuwuitval gevonden wordt. Echter, het risico op n. X uitval na chirurgie is tevens aanzienlijk (27%). Derhalve wordt geadviseerd een afwachtend beleid te voeren voor deze tumoren.

Deel 3: management van multifocale hoofd-/halsparagangliomen

In hoofdstuk 9 wordt de complicatievrije overleving van patiënten welke lijden aan multifocale ziekte vergeleken met deze van patiënten welke aan een enkele tumor lijden. Als onderdeel hiervan is een grote cohortstudie uitgevoerd, waarbij de belangrijkste uitkomstmaat was de complicatievrije overleving. We hebben gevonden dat er een significant slechtere complicatievrije overleving is voor 58 patiënten welke aan 159 tumoren lijden, wanneer vergeleken met 120 patiënten met een enkele tumor. Er is geen verschil gevonden in complicatievrije overleving in geval van unilateraal of bilateraal voorkomen van meerdere tumoren of het aantal tumoren dat gevonden is. Met univariate regressieanalyse werd gezien dat wanneer alleen een wait-en-scan beleid gevoerd werd een verhoogde complicatievrije overleving gezien is. Na logistische regressie bleek dat het aantal chirurgische procedures uitgevoerd bij patiënten onafhankelijk geassocieerd is met een verlaagde complicatievrije overleving. Derhalve werd geconcludeerd dat een significante verlaagde complicatievrije overleving verwacht kan worden bij patiënten met multifocale tumorgroei, en met name de gekozen behandelmodaliteit van invloed is op de complicatievrije overleving. Met name radicale chirurgische resectie met opofferen van hersenzenuwen dient hierbij vermeden te worden.

In dit proefschrift is de impact van verschillende behandelmodaliteiten op patiënten met HHPGL van verschillend type en tumor klassen beschreven. De impact van radiotherapie en verschillende chirurgische technieken zijn geëvalueerd. Hiermee draagt het huidige proefschrift bij aan het management van HHPGL, en geeft het inzichten voor het opstellen van geïndividualiseerde behandelingen.

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Dit proefschrift heb ik niet alleen geschreven. Een aantal mensen wil ik dan ook graag bedanken voor hun bijdrage, zowel inhoudelijk als op een andere manier.

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CURRICULUM VITAE

Thijs Theo Gerrit Jansen werd geboren op 19 juli 1987 in Malden. Op vier jarige leeftijd verhuist hij met zijn oudere zus Noortje en jongere zusje Sophie naar Nijmegen. Hij behaalt in 2005 zijn Atheneumdiploma aan het Montessoricollege in Nijmegen en start nadien aan de Roosevelt Academy in Middelburg, een University College van de Universiteit van Utrecht. Hier is hij lid van het herendispuut Erodios en in 2008 behaalt hij zijn bachelor in Science, met aandacht voor de pre-medical track. In 2008 start hij het Selective Utrecht Medical MAster-programma waarbinnen hij wordt opgeleid tot arts en klinisch onderzoeker. Tijdens zijn reguliere coschap in het Gelreziekenhuis in Apeldoorn komt hij voor het eerst in aanraking met de Keel-, Neus-, en Oorheelkunde. Vele wetenschappelijke en klinische stages volgde. Hij start fundamenteel onderzoek in het experimenteel lab van de Universiteit van Utrecht, onder leiding van dr. Klis, naar de ototoxiciteit van aminoglycoside-antibiotica en lis-diuretica bij muizen. Deze resultaten zijn gepubliceerd en vervolgonderzoek is ingezet. Simultaan wordt onderzoek opgestart bij dr. H.D. Vuyk, KNO-arts en aangezichtschirurg, naar de lange termijn effecten van rhinoplastieken. Zijn keuze-coschap volgt Thijs binnen de KNO aan de Medizinische Hochschule in Hannover onder leiding van prof. dr. Lenarz en prof. Lesinski-Schiedat. Hij zet een onderzoekslijn op tussen de KNO-afdelingen van het UMC-Utrecht en de medische faculteit in Hannover, waar ook wetenschappelijke publicaties uit voortkomen. Na de afronding van zijn laatste stage als semi-arts bij de afdeling Heelkunde van het Diakonessenhuis Utrecht werd de artsenbul behaald in februari 2013.

In augustus 2013 begint Thijs aan het onderzoeksproject dat leidde tot dit proefschrift. Na 8 maanden voltijd onderzoek te hebben gedaan start hij in april 2014 met de opleiding tot KNO-arts. Het tweede jaar van zijn opleiding werd in het CWZ in Nijmegen onder leiding van dr. Engel doorlopen, en het vierde jaar in het VieCuri Medisch Centrum in Venlo onder leiding van dr. Dammeijer. Tijdens de opleiding en naast het promotietraject coördineert Thijs met dr. Kunst en prof. Marres de totstandkoming van de eerste nationale richtlijn hoofd-/halsparagangliomen. Daarbij werkt hij in samenwerking met oud collega de Sjoerd Jan de Vries aan een adviesrapport voor het landelijk KNO-bestuur, getiteld "de impact van de vergrijzing binnen de KNO", waarvan de resultaten in juni 2019 officieel gepubliceerd zullen worden. Op het moment van de verdediging van dit proefschrift is hij halverege het vijfde en laatste jaar van zijn opleiding.