Available online at www.sciencedirect.com

ScienceDirect

British Journal of Oral and Maxillofacial Surgery 57 (2019) 425–429

BRITISH Journal of Oral and Maxillofacial Surgery

www.bjoms.com

Watchful waiting in carefully selected metachronous cystadenolymphomas of the parotid gland: a reliable option?

K. Mantsopoulos *[,1], M. Goncalves [1], M. Koch, H. Iro

Department of Otorhinolaryngology, Head and Neck Surgery, University of Erlangen–Nuremberg, Erlangen, Germany

Accepted 14 December 2018
Available online 20 April 2019

Abstract

The aim of this study was to evaluate the potential of watchful waiting in the treatment of metachronous cystadenolymphomas, taking the experience of our department into consideration. All patients suspected of having a metachronous cystadenolymphoma, and who had a minimum follow-up time of 12 months, were studied (n = 26). Data about the growth rate, number of lesions, and symptoms of inflammation were recorded. Mean (range) follow-up was 36 (13–94) months. Metachronous tumours developed in three cases on the ipsilateral side, in 22 cases on the contralateral side, and on both sides in one case. The mean rate of growth /lesion was 15% /year (range: 22%–158%). There were no signs of local inflammation. The extreme variability in the behaviour of metachronous cystadenolymphomas points to the need for an individualised approach, accurate investigation of the sonographic characteristics, and continuous watchful waiting in affected patients.

Keywords: Parotid gland; Benign tumours; Warthin tumour; Cystadenolymphoma; Watchful waiting

Introduction

Cystadenolymphomas (or Warthin tumours) are the second most common benign lesions in the parotid gland,[1] accounting for up to 30% of all parotid tumours. Interestingly, there is controversy about whether the lesion is a true benign neoplasm or a tumour-like lesion.[2] Consequently, the ideal form of management remains a matter of debate.[3]

According to the relevant published papers, the aim of surgical management of cystadenolymphomas should be to confirm the benign nature of the diagnosis, to remove concerning and symptomatic lesions, and to secure an acceptable quality of life postoperatively.[3,4] For a harmless lesion at extremely low risk of malignancy, several working groups have proposed active surveillance as a possible strategy in carefully selected cases, provided that there is a reliable diagnosis of cystadenolymphoma.

We have followed a watchful waiting strategy only for metachronous lesions that appeared after primary surgical excision and histological verification of the diagnosis. The aim of the present study was to evaluate our experience with this approach for carefully selected cases of metachronous cystadenolymphoma of the parotid gland, and to provide information about the growth rate, imaging characteristics, clinical features, and their impact on the management of these lesions.

Material and methods

This study was conducted at an academic tertiary referral centre that specialises in diseases of the salivary glands (Department of Otorhinolaryngology, Head and

* Corresponding author at: Department of Otorhinolaryngology, Head and Neck Surgery, University of Erlangen–Nuremberg, Waldstrasse 1, 91054 Erlangen, Germany. Tel.: +49 (0)9131-8533156; Fax: +49 (0)9131-8533833.
E-mail address: konstantinos.mantsopoulos@uk-erlangen.de (K. Mantsopoulos).
[1] These authors contributed equally to this manuscript.

https://doi.org/10.1016/j.bjoms.2018.12.018

Table 1
Details of patients and characteristics of tumour growth.

Case No.	Age (years)	Sex	Laterality	Primary operation	Lesions (start)	Lesions (end)	Mean growth rate / year (%)
1	76	M	C	TP	1	1	0
2	70	M	B	ED	1	7	157.7
3	58	M	C	TP	3	4	3.8
4	68	M	I	ED	1	1	25.4
5	68	F	C	ED	1	1	8.3
6	62	F	C	ED	1	1	13.0
7	63	F	C	ED	1	1	5.6
8	57	M	C	PSP	1	1	0
9	76	M	C	ED	2	2	−22.4
10	45	M	C	TP	1	2	6.9
11	74	M	C	TP	1	1	8.0
12	50	F	C	ED	1	3	23.2
13	66	M	C	ED	1	1	15.9
14	75	M	I	ED	1	1	0
15	54	M	C	TP	1	1	−18.9
16	76	F	C	ED	1	1	−5.8
17	34	F	C	TP	1	1	−4.4
18	52	M	C	TP	1	1	0
19	57	F	C	TP	1	2	93.5
20	68	F	C	ED	1	1	25.0
21	64	M	C	TP	1	1	35.8
22	59	M	C	ED	1	1	3.6
23	76	M	C	ED	1	1	39.4
24	64	F	C	ED	1	2	14.1
25	49	M	I	ED	1	1	16.9
26	51	M	C	TP	1	2	17.5

M = male, F = female, I = ipsilateral, C: = contralateral, B = bilateral, TP = total parotidectomy, PSP = partial superficial parotidectomy, ED = extracapsular dissection.
No patient had any symptoms.

Neck Surgery, University of Erlangen–Nuremberg, Erlangen, Germany). The records of all patients treated for cystadenolymphomas of the parotid gland between 2000 and 2017 were examined. Metachronous cystadenolymphoma was defined as a lesion with sonographic features that are compatible with those of a cystadenolymphoma (sharp margins, homogeneous, hypoechoic lesion with distal sound enhancement and well-perfused intralesional septation) after resection and histological verification of a cystadenolymphoma on the same or contralateral side. All patients included were being managed by means of watchful waiting (because of the clinical and sonographic suspicion of a metachronous tumour) for a minimum follow-up time of 12 months after identification of the lesion. Approval for the study was obtained from the institutional review board of our hospital. Information was obtained about the growth rate based on the maximal diameter, progression in the number of lesions over time, as well as the local symptoms (discomfort, tension, or signs of inflammation) of a metachronous tumour.

Results

Our primary survey detected 967 operations for cystadenolymphomas during the period of the study, and a total of 26 patients with metachronous lesions who were being managed by watchful waiting were included in the study (17 men, 9 women; male:female ratio 1.89, mean (range) age 62 (34–76) years), and mean (range) follow-up 36 (13–94) months).

In 20/26 cases the number remained constant during follow up, in four a metachronous tumour appeared during the course of watchful waiting, in one case three metachronous lesions were detected and, in one single case, six new lesions were detected on both sides. Consequently, at the end of the observation, a total of 42 lesions had been detected (1.62 lesions/patient). The mean (SD) rate of growth/lesion was 15.4 (35)% /year (range: −22.4%–157.7%). This diameter-based mean growth rate corresponds to an approximate mean doubling of volume of each lesion every five years.

There was no change in the sonographic pattern of the metachronous lesions detected during follow-up. In two cases, rapid growth of the metachronous lesion led to a revision operation, which verified the diagnosis of a cystadenolymphoma. No signs of local inflammation could be detected in the course of follow-up in the cases of our study cohort (Details of each patient are shown in Table 1).

Discussion

The ideal strategy for the management of cystadenolymphomas should consider the aspect of a still unclear significance;[2] the biological behaviour (the possibility of a metachronous tumour[5] and rare malignant transformation);

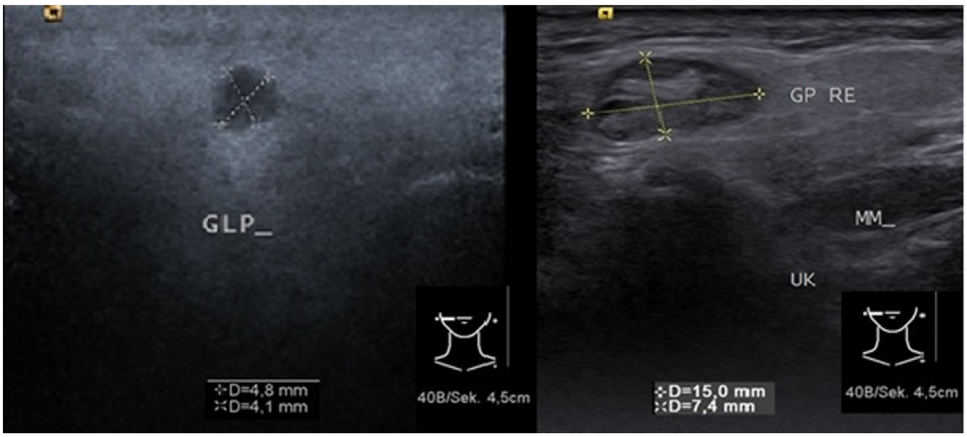

Fig. 1. Left: Sonographic picture of a lesion in the right parotid gland 12 months after surgery and verification of a cystadenolymphoma on the same side. Right: The same lesion, 55 months later, with a significant increase in growth and intralesional septations (GLP: parotid gland, MM: master muscle, UK: mandible).

[6] coexisting conditions (age and smoking); and the compliance of the patient. Resection is the traditional treatment for these tumours[7] and should aim at histological verification of the benign nature of the disease while removing all symptomatic lesions and securing the best possible postoperative quality of life.[8]

Previous publications have reported completely acceptable surgical results (in terms of the rate of metachronous lesions) when less invasive, gland-sparing techniques (such as extracapsular dissection) were used,[3] but several working groups underlined the appreciable incidence of coexisting conditions in these patients, and propagated a "watchful-waiting" approach when there was a suspicion of a cystadenolymphoma.[9,10] The main disadvantage of this conservative strategy is that lack of histological verification of a cystadenolymphoma carries the risk of a false working hypothesis.[11–13] In an attempt to overcome this, some authors have suggested that fine-needle aspiration cytology (FNAC) could provide an accurate diagnosis and lend sufficient support to the strategy of active surveillance.[14] However, FNAC relies on the only moderate sensitivity of lesions of the salivary gland, and bears a higher risk (up to 10 times) of iatrogenic inflammation on the grounds of a cystadenolymphoma.[15] For these reasons, in our department we choose to follow a "wait-and-scan" strategy only for carefully selected metachronous lesions.

After resection of a cystadenolymphoma, we examine the patient clinically by palpation, and by ultrasound, annually for at least five years. Metachronous lesions were suspected only on the basis of the tumour-specific ultrasound findings (clear margin; homogeneous, hypoechoic lesion situated mainly superficially and caudally with well-perfused intralesional septations; totally anechoic or cystic with distal sound enhancement; and multifocal or bilateral).

At first, during follow-up, it is not easy to distinguish a small, potential metachronous cystadenolymphoma from an intraparotid inflamed lymph node, as both lesions have clear margins, are homogeneous and hypoechoic, and are situated mainly superficially and caudally. At this stage, hilar perfusion of an intraparotid lymph node may be absent or can be misinterpreted as a solitary well-perfused septation of a metachronous cystadenolymphoma.[16] In addition, it is well known that small cystadenolymphomas rarely show an anechoic or cystic pattern with distal sound enhancement on ultrasound.[17] This differential diagnostic pitfall is shown in Fig. 1, which shows the sonographic picture of a small, ovoid, homogeneous, hypoechoic lesion with clear margins, 4.8×4.1 mm, positioned centrally in the residual ipsilateral parenchyma on the right side 12 months after primary resection. At that time, this lesion gave the impression of a swollen intraparotid lymph node of no further clinical or therapeutic relevance. Fifty-five months later, the same lesion had increased considerably in size with a growth rate of 15×7.4 mm, and had well-perfused intralesional septations, which directed the diagnosis towards an ipsilateral metachronous cystadenolymphoma. This confirms the theory that cystadenolymphomas develop on the basis of heterotopic salivary gland ductal epithelium within pre-existing intraparotid lymph nodes,[18] and points out the importance of long-term follow-up and a constantly high degree of suspicion long after resection of a cystadenolymphoma.

Remarkably, the growth rate of metachronous lesions can vary considerably over time: some tumours remain asymptomatic over a long period of time and may shrink, whereas others develop shortly after operation and there is a rapid, clinically concerning, progression in size during follow-up. In our group metachronous lesions showed a mean (SD) tendency for a slow yearly increase in size of 15.4 (35) %, with their general behaviour being characterised by this variable. Fig. 2 shows a study case with a lesion size of 11.6×8.7 mm eight months after extracapsular dissection of a cystadenolymphoma, and a growth to 21.9×10.3 mm over a period of 54 months.

As rapid growth of a secondary lesion is generally thought to herald malignant transformation, we decided in this case (case 2), as well in case 19 (Table 1), to do a

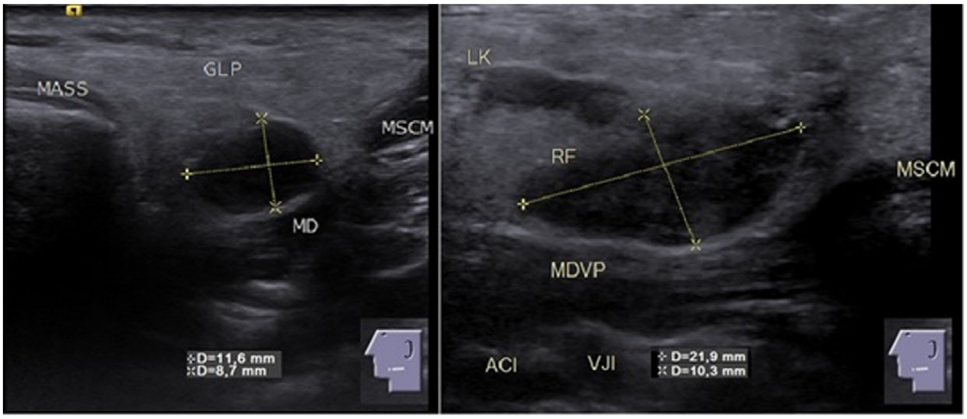

Fig. 2. Left: Sonographic picture of a lesion in the left parotid gland eight months after extracapsular dissection and verification of a cystadenolymphoma on the same side. Right: The same lesion 55 months later, with a considerable increase in growth (GLP: parotid gland, MASS: masseter muscle, MD: digastric muscle, MSCM: sternocleidomastoid muscle, LK: lymph node, MDVP: posterior belly of the digastric muscle, ACI: internal carotid artery, VJI: internal jugular artery).

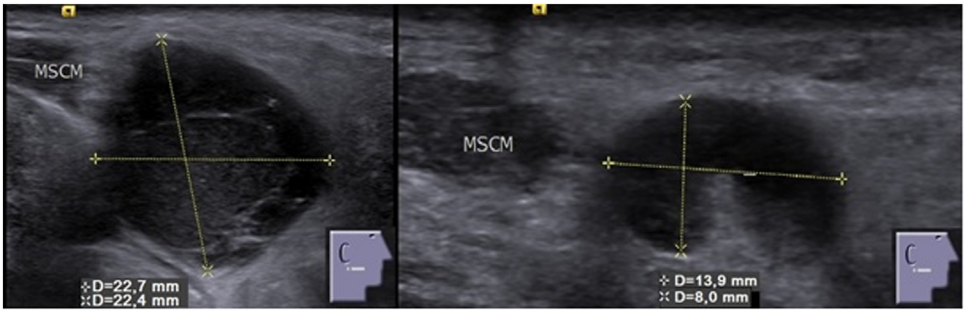

Fig. 3. Left: Sonographic picture of a lesion in the right parotid gland 18 months after extracapsular dissection and verification of a cystadenolymphoma on the same side. Right: The same lesion, 14 months later, with a large reduction in growth (MSCM: sternocleidomastoid muscle).

revision operation, which remarkably verified the diagnosis of cystadenolymphoma. In contrast, Fig. 3 shows another metachronous lesion, 22.7 × 22.4 mm in size, 16 months after primary surgery, which had reduced to 13.9 × 8.0 mm 14 months later. This variable, but generally slow, growth rate was also reported by Schwalje et al, who detected a mean (SD) growth rate of 8% (96) %.[18] Undoubtedly this variation in the behaviour of metachronous lesions intensifies confusion about the differential diagnosis: whereas a reduction in size is not an exclusion criterion for a metachronous lesion, a slow increase in size over time is not a pathognomonic indication of a secondary cystadenolymphoma either. The progression in the number of lesions seems to follow the same pattern: the tendency for an increase in the number of metachronous lesions could be detected with a relatively slow yearly rate (8.5% in total). Although a reduction in the number of lesions leads the diagnosis retrospectively in the direction of parotid lymphadenitis, an increase in the number of lesions could correspond to a further metachronous cystadenolymphoma, the new appearance of an intraparotid lymph node, or other histological entities.

This non-uniform pattern of behaviour corresponds to the theory of the heterogeneous pathogenesis of cystadenolymphoma, with morphologically similar lesions being either polyclonal and possibly reactive, or clonal and unquestionably neoplastic.[2] Our clinical observations have led us to conclude that an individualised approach is probably more justified, and should take the patient's age; coexisting conditions; preferences; and compliance (as well as imaging findings at follow-up and tumour-related symptoms) into consideration. Indication for further resection could possibly arise in the case of local symptoms such as discomfort and tension from a growing lesion, signs of inflammation,[17] or suspicion of a false working hypothesis.

The relatively higher risk of ipsilateral metachronous tumours after parenchyma-sparing forms of parotid surgery as well as the occurrence rate of cystadenolymphomas (as high as 10%) on the contralateral side in a group of patients, with a large number of age-related and smoking-related coexisting diseases, points to the need for individualised management of these cases. Our analysis showed extreme variability in the behaviour of metachronous cystadenolymphomas, and points to the importance of accurate investigation of the clinical aspects and the imaging characteristics of all lesions that develop after primary verification of a cystadenolymphoma. Undoubtedly, metachronous lesions should only be managed conservatively on the basis of diagnostic expertise, sufficient counselling of patients, good

compliance, and long-term follow-up after the primary resection.

Conflict of interest

We have no conflicts of interest.

Ethics statement/confirmation of patients' permission

Approval was obtained from the institutional review board of our hospital. No consent was required from patients.

References

1. Gao M, Hao Y, Huang MX, et al. Salivary gland tumours in a northern Chinese population: a 50-year retrospective study of 7190 cases. *Int J Oral Maxillofac Surg* 2017;**46**:343–9.
2. O'Neill ID. New insights into the nature of Warthin's tumour. *J Oral Pathol Med* 2009;**38**:145–9.
3. Mantsopoulos K, Goncalves M, Koch M, et al. Extracapsular dissection for warthin tumors despite the risk of ipsilateral metachronous occurrence. *Laryngoscope* 2018;**128**:2521–4.
4. Mantsopoulos K, Koch M, Goncalves M, et al. Investigation of the surgical strategies for unilateral multifocal cystadenolymphomas of the parotid gland. *Oral Oncol* 2018;**82**:176–80.
5. Peter Klussmann J, Wittekindt C, Florian Preuss S, et al. High risk for bilateral Warthin tumor in heavy smokers — review of 185 cases. *Acta Otolaryngol* 2006;**126**:1213–7.
6. Bell D, Luna MA, Weber RS, et al. CRTC1/MAML2 fusion transcript in Warthin's tumor and mucoepidermoid carcinoma: evidence for a common genetic association. *Genes Chromosomes Cancer* 2008;**47**:309–14.
7. Mantsopoulos K, Goncalves M, Koch M, et al. Going beyond extracapsular dissection in cystadenolymphomas of the parotid gland. *Oral Oncol* 2019;**88**:168–71.
8. Mantsopoulos K, Scherl C, Iro H. Investigation of arguments against properly indicated extracapsular dissection in the parotid gland. *Head Neck* 2017;**39**:498–502.
9. Thangarajah T, Reddy VM, Castellanos-Arango F, et al. Current controversies in the management of Warthin tumour. *Postgrad Med J* 2009;**85**:3–8.
10. Chapnik JS. The controversy of Warthin's tumor. *Laryngoscope* 1983;**93**:695–716.
11. Mantsopoulos K, Velegrakis S, Iro H. Unexpected detection of parotid gland malignancy during primary extracapsular dissection. *Otolaryngol Head Neck Surg* 2015;**152**:1042–7.
12. McGurk M, Thomas BL, Renehan AG. Extracapsular dissection for clinically benign parotid lumps: reduced morbidity without oncological compromise. *Br J Cancer* 2003;**89**:1610–3.
13. Mantsopoulos K, Koch M, Iro H. Extracapsular dissection as sole therapy for small low-grade malignant tumors of the parotid gland. *Laryngoscope* 2017;**127**:1804–7.
14. Vlantis AC, Ng SK, Mak CK, et al. If cytology of Warthin tumor is accurate, can management be conservative? *Ear Nose Throat J* 2016;**95**:185–8.
15. Fakhry N, Antonini F, Michel J, et al. Fine-needle aspiration cytology in the management of parotid masses: evaluation of 249 patients. *Eur Ann Otorhinolaryngol Head Neck Dis* 2012;**129**:131–5.
16. Mantsopoulos K, Psychogios G, Agaimy A, et al. Inflamed benign tumors of the parotid gland: diagnostic pitfalls from a potentially misleading entity. *Head Neck* 2015;**37**:23–9.
17. Bruneton JN, editor. *Applications of sonography in head and neck pathology*. Berlin: Springer-Verlag; 2002. p. 110.
18. Schwalje AT, Uzelac A, Ryan WR. Growth rate characteristics of Warthin's tumours of the parotid gland. *Int J Oral Maxillofacial Surg* 2015;**44**:1474–9.