Int. J. Oral Maxillofac. Surg. 2019; 48: 1138–1144
https://doi.org/10.1016/j.ijom.2019.01.017, available online at https://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Clinical Paper
Head and Neck Oncology

Simultaneous occurrence of benign and malignant tumours in the ipsilateral parotid gland—retrospective study

H. Lu[1,2,a], W. Xu[1,2,a], Y. Zhu[1,2], L. Liu[1,2], S. Liu[1,2], W. Yang[1,2]
[1]Department of Oral Maxillofacial–Head and Neck Oncology, Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [2]Shanghai Research Institute of Stomatology and Shanghai Key Laboratory of Stomatology, Shanghai, China

H. Lu, W. Xu, Y. Zhu, L. Liu, S. Liu, W. Yang: Simultaneous occurrence of benign and malignant tumours in the ipsilateral parotid gland—retrospective study. Int. J. Oral Maxillofac. Surg. 2019; 48: 1138–1144.

Abstract. The simultaneous occurrence of benign and malignant tumours in the ipsilateral parotid gland is extremely rare. The cases of five patients with synchronous multiple parotid gland tumours consisting of diverse combinations of benign and malignant histological types are presented here. In addition, all published cases of this entity identified in the PubMed, Embase, and Web of Science databases up to January 2018 were reviewed. It is concluded that clinical vigilance should be raised when multifocal tumours are indicated by imaging examinations, in the presence of unmovable, painful, and rapid growth or symptoms of facial nerve palsy. In such cases, resected specimens should be sectioned meticulously, especially for tiny lesions, during histopathological sampling. Based on the possibility of the co-existence of benign and malignant neoplasms, it is necessary for clinicians to pay attention to this entity in order to have a favourable outcome.

Key words: parotid gland tumours; synchronous; multiple; literature review.

Accepted for publication 3 January 2019
Available online 22 February 2019

According to the World Health Organization classification of tumours, updated in 2017, salivary gland tumours comprise a heterogeneous group of tumours in terms of histological and clinical behaviour[1]. Most parotid gland tumours originate from the secretory acini and ductal units, presenting morphological and cell type diversity. Hence the diagnosis, therapeutic regimen, and prognosis will vary, making tumour management challenging.

Although the occurrence of single neoplasms is most common, synchronous unilateral or bilateral multifocal tumours of the parotid gland of the same histological type are occasionally seen, particularly Warthin's tumour (WT)[2]. Furthermore, combinations of tumours of different histological types have been reported sporadically in the world literature, with the combination of WT associated with pleomorphic adenoma (PA) being the most common. Tanaka and Chen first described the appearance of synchronous bilateral multiple parotid gland tumours – WT associated with mucoepidermoid carcinoma

[a] Hao Lu and Wanlin Xu contributed to this work equally.

0901-5027/0901138 + 07

(MEC) – in 1953[3]. Since then, only sporadic cases of synchronous unilateral benign and malignant parotid gland tumours have been reported. A lack of awareness of this potential finding has led to a number of patients undergoing a secondary procedure, with exposure to the associated risks[4,5].

The aim of this retrospective study was to present and discuss the clinicopathological characteristics and treatment outcomes of synchronous unilateral benign and malignant parotid gland tumours managed by the surgical and medical team of a tertiary referral centre over a period of 18 years. A literature review was conducted to summarize the morphological diversity of this rare entity for future reference.

Methods

Study population

Approval for the study was obtained from the Institutional Review Board of Shanghai Ninth Hospital Affiliated to Shanghai Jiao Tong University School of Medicine. The records of 2197 consecutive patients suffering from parotid gland tumours, treated in the Department of Oral and Maxillofacial–Head and Neck Oncology between January 2000 and January 2018, were searched. Patients younger than 18 years of age, with metastatic disease at presentation (i.e. breast ductal carcinoma), or with different benign types of synchronous multifocal unilateral tumours of the parotid gland were excluded.

All patients were evaluated and managed by a multidisciplinary head and neck oncology team. Demographic and clinical data, histopathological parameters, and other relevant data were extracted from the medical records by two surgeons independently, using the same standard form.

Statistical analysis and literature review

Descriptive statistics were employed for patient and disease characteristics. All statistical analyses were performed using the statistical software package IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA).

The relevant literature was searched through the PubMed, Embase, and Web of Science databases using the following key words: (''parotid gland'' OR ''salivary gland'') and (''tumor'' OR ''cancer'' OR ''carcinoma'' OR ''neoplasm'' OR ''malignant''); up to January 1; 2018. The reference lists of retrieved articles; including review articles; were also reviewed to guarantee the sensitivity of the search process.

Results

Demographics, tumour characteristics, and treatment

Among the 2197 patients with parotid gland tumours who were treated in the department between January 2000 and January 2018, five (0.23%) were found to have synchronous multiple unilateral parotid tumours of benign and malignant histological types. The median age of the cohort was 55 years and the average age was 54.8 years (range 36–68 years), which is in keeping with the age of patients with single malignancies in the salivary glands in general[1].

The mean interval from initial symptoms to diagnosis (latency time) was 50.6 months (range 1–120 months). None of the patients had previously experienced salivary lesions or trauma. Details of the patients and the tumour characteristics are presented in Table 1.

The treatment modality was individualized based on the site of origin, tumour stage, histological grade, and other risk factors (i.e. margin status, perineural invasion). Four patients underwent complete superficial parotidectomy and one patient underwent total parotidectomy combined with ipsilateral modified radical neck dissection (MRND) and immediate cable grafting (the great auricular nerve), because the marginal branch was invaded by the tumour (lymphoepithelial carcinoma).

With regard to the histological examination, two patients had WT associated with acinic cell carcinoma (AcCC), one had PA associated with lymphoepithelial carcinoma, one had basal cell adenoma associated with MEC, and one had basal cell adenoma associated with basal cell adenocarcinoma. The multifocal lesions were not interconnected at all; a typical preoperative magnetic resonance image (MRI) is shown in Fig. 1. The mean size of the tumour was 2.6 cm (range 1.5–4.2 cm), and none of the microscopic resection margins were positive or close to 5 mm. Perineural invasion was observed in two cases (40%), while lymphovascular invasion and lymph node involvement were not seen in any patient. The mean duration of follow-up was 70.8 months (range 26–99 months).

Literature review

In total, 20 articles reporting 28 cases of simultaneous benign and malignant neoplasms were identified and included in the subsequent pooling analysis[3–22]. Some information in these reports was rather lim-

Table 1. Clinical characteristics of patients with simultaneous occurrence of benign and malignant tumours in the ipsilateral parotid gland in this series.

Patient	Sex	Location	Size, cm[a]	Symptoms	Interval time	Benign tumour	Malignant tumour	Treatment	Follow-up period (months)	Prognosis
1	F	Superficial lobe	4.2 × 3.0	Parotid swelling + rapid growth for 4 months	10 years	PA	LYC	TP + MRND + cable grafting	99	No recurrence
2	M	Superficial lobe	3.0 × 2.5	Parotid swelling + rapid growth + fixed tumour + pain	3 years	WT	AcCC	SP + chemotherapy	26	Died
3	M	Superficial lobe	2.5 × 2.5	Parotid swelling	2 years	WT	AcCC	SP + radiotherapy	51	Died
4	F	Superficial lobe	1.5 × 1.0	Parotid swelling	1 month	BCA	MEC	SP + radiotherapy	96	No recurrence
5	F	Superficial lobe	2.1 × 1.5	Parotid swelling + pain	6 years	BCA	BCAC	SP + radiotherapy	82	No recurrence

AcCC, acinic cell carcinoma; BCA, basal cell adenoma; BCAC, basal cell adenocarcinoma; F, female; LYC, lymphoepithelial carcinoma; M, male; MEC, mucoepidermoid carcinoma; MRND, modified radical neck dissection; PA, pleomorphic adenoma; SP, superficial parotidectomy; TP, total parotidectomy; WT, Warthin's tumour.

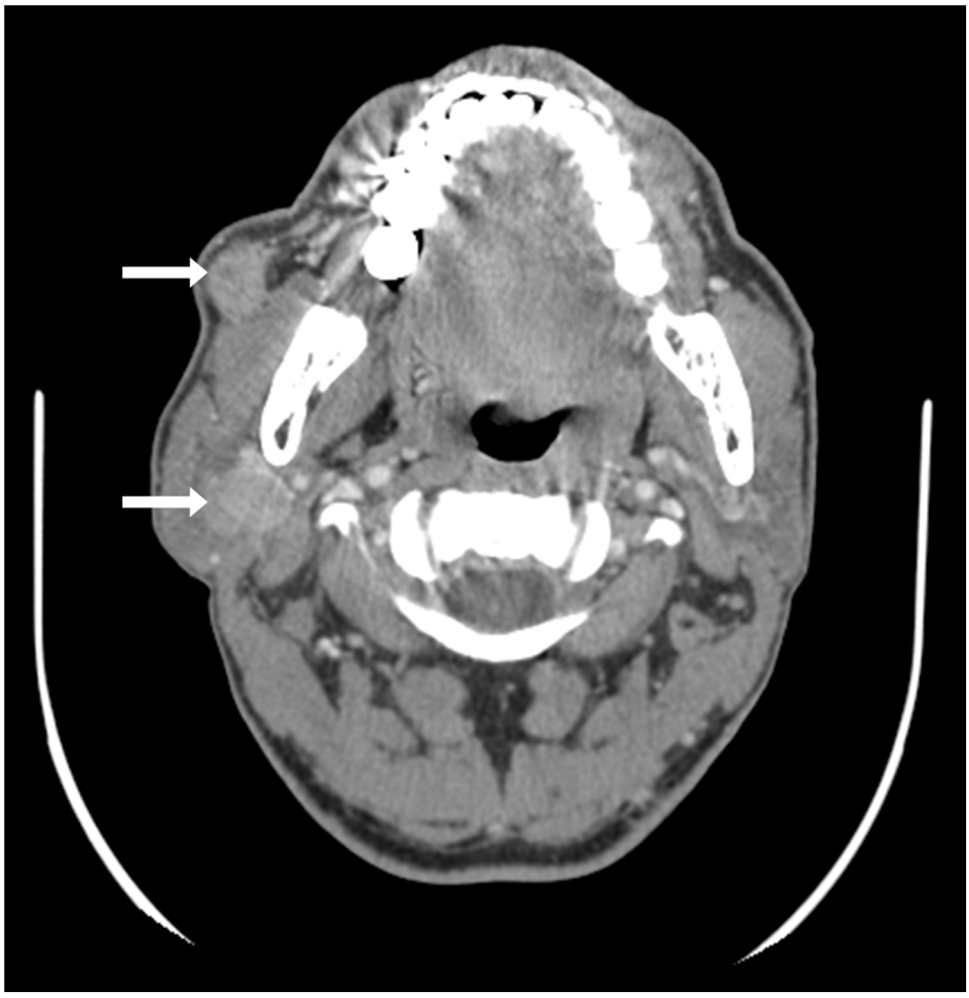

Fig. 1. Typical preoperative magnetic resonance image showing the simultaneous occurrence of benign and malignant tumours in the ipsilateral parotid gland (arrows indicate the tumours).

ited. The demographic data and clinical manifestations for all cases are presented in Table 2.

A male predominance was observed (male to female ratio of 1.4:1), and the mean age was 62 years. With regard to the location, the superficial lobes were usually affected. Patients commonly complained of a non-tender, mobile, growing parotid mass discovered incidentally. Fast growing tumours appeared in two cases and two patients felt pain in the affected parotid region. The mean time interval from the initial discovery to treatment was 30 months, ranging from 1 month to 120 months.

Histopathologically, the most common benign lesion was WT ($n = 20$), followed by PA ($n = 9$), sebaceous lymphadenoma ($n = 2$), basal cell adenoma ($n = 2$), and myoepithelioma ($n = 1$). Meanwhile, malignant neoplasms were classified as follows: MEC ($n = 11$), AcCC ($n = 8$), adenoid cystic carcinoma ($n = 3$), salivary duct carcinoma ($n = 3$), adenocarcinoma ($n = 3$), carcinoma ex pleomorphic adenoma ($n = 2$), lymphoepithelial carcinoma ($n = 1$), basal cell adenocarcinoma ($n = 1$), and squamous cell carcinoma ($n = 1$). Various combinations were presented, the most common being WT and MEC ($n = 8$), followed by WT associated with AcCC ($n = 5$), WT associated with adenocarcinoma ($n = 2$), WT associated with carcinoma ex pleomorphic adenoma ($n = 2$), PA associated with MEC ($n = 2$), PA associated with AcCC ($n = 2$), and others ($n = 12$). Due to the incomplete information and diverse therapeutic regimens presented by the authors, other clinical features and survival rates were not calculated.

Discussion

Salivary gland tumours constitute a significant part of head and neck neoplasms. The considerable diversity of histological features, biological behaviour, and responsiveness to therapy of these entities make management challenging. Synchronous multifocal unilateral tumours of the same histological type may occasionally be seen, specifically WT. However, synchronous tumours including benign and malignant histological types in the unilateral parotid gland are extremely rare and only 28 cases have been reported in the literature worldwide.

This study is novel in describing synchronous multiple unilateral tumours of the parotid gland. The new series presented included four different types of synchronous multiple unilateral benign and malignant tumours of the parotid gland. Furthermore, 18 combinations of synchronous multiple unilateral benign and malignant tumours were identified through the literature review. WT was the most commonly described benign neo-

Table 2. Summary of cases of simultaneous occurrence of benign and malignant tumours in the ipsilateral parotid gland identified in the literature review.

Case	First author Year Country	Age (years)	Sex	Location	Size, cm[a]	Symptoms	Interval time	Benign tumour	Malignant tumour	Treatment	Follow-up period (months)	Prognosis
1	Ochal-Choinska[4] 2016 Poland	61	M	Both lobes	5.7 × 4.0	Parotid swelling	10 years	WT	CXPA	Subtotal + RT	60	No recurrence
2	Srivastava[5] 2010 USA	52	M	Both lobes	2.7 × 1.6	Parotid swelling + rapid growth for 1 year	5 years	WT	MEC	TP	NA	NA
3	Roh[6] 2007 Republic of Korea	71	M	Superficial lobe	2.5 × 2.5	Parotid swelling	1 year	WT	adenoCA	TP + MRND + RT 180 cGy/21 fractions	24	No recurrence
4	Tanaka[7] 2007 Japan	67	M	Superficial lobe	3.5 × 3.0	Parotid swelling	1 year	WT + PA	SDC	SP + RT 50 Gy	12	No recurrence
5	Ethunandan[8] 2006 UK	NA	NA	NA	NA	NA	NA	WT	AcCC	NA	NA	NA
6	Yu[9] 2004 China	NA	NA	NA	NA	NA	NA	PA	AdCC	NA	NA	NA
7	Zeebregts[10] 2003 Netherlands	NA	NA	NA	1.5 × 1.5	NA	NA	PA	AcCC	NA	NA	NA
8	Shukla[11] 2003 India	68	F	Superficial lobe	7.0 × 5.0	Parotid swelling + pain for 12 months + tinnitus for 2 months	8 years	SL	SCC	Parotidectomy	NA	NA
9	Curry[12] 2002 USA	67	F	Superficial lobe	8.0 × 5.0	Parotid swelling	1 year	PA	SDC	Parotidectomy + RT 65 Gy	12	No recurrence
10	Curry[12] 2002 USA	51	F	Both lobes	7.0 × 4.5	Parotid swelling	6 months	WT	MEC	Parotidectomy + RT 65 Gy	36	No recurrence
11	Mayorga[13] 1999 Spain	78	F	Superficial lobe	3.0 × 3.0	Parotid swelling	2 months	SL	AcCC	TP	13	No recurrence
12	Misselevich[14] 1997 Israel	44	F	Superficial lobe	4.5 × 3.5	Parotid swelling	NA	PA	AcCC	Partial parotidectomy	42	No recurrence
13	Seifert[15] 1997 Germany	73	M	NA	3.0 × 4.0	Parotid swelling	NA	WT	MEC	NA	NA	NA
14	Hanada[16] 1995 Japan	71	F	Both lobes	2.0 × 2.0	Parotid swelling	1 year	ME	AdCC	Subtotal parotidectomy	12	No recurrence
15	Gnepp[17] 1989 USA	60	M	NA	NA	NA	NA	WT	MEC	NA	NA	NA

Table 2 (*Continued*)

Case	First author Year Country	Age (years)	Sex	Location	Size, cm[a]	Symptoms	Interval time	Benign tumour	Malignant tumour	Treatment	Follow-up period (months)	Prognosis
16	Gnepp[17] 1989 USA	84	M	NA	NA	NA	NA	WT	AcCC	NA	NA	NA
17	Gnepp[17] 1989 USA	56	M	NA	NA	NA	NA	WT	AcCC	NA	NA	NA
18	Gnepp[17] 1989 USA	69	M	NA	NA	NA	NA	WT	SDC	NA	NA	NA
19	Gnepp[17] 1989 USA	66	M	NA	NA	NA	NA	WT	AdCC	NA	NA	NA
20	Janecka[18] 1983 USA	45	F	Superficial lobe	7.0 × 4.0	NA	10 years	PA	MEC	Subtotal parotidectomy	NA	NA
21	Janecka[18] 1983 USA	64	M	Both lobes	5.0	Parotid swelling + rapid growth	NA	WT	adenoCA	TP	24	Died
22	Janecka[18] 1983 USA	58	M	NA	NA	Parotid swelling	NA	WT	MEC	Subtotal parotidectomy	120	No recurrence
23	Pontilena[19] 1979 USA	45	F	Superficial lobe	1.0 × 1.0	Parotid swelling	10 years	PA	MEC	SP	NA	NA
24	Gadient[20] 1975 USA	60	M	Superficial lobe	1.8 × 1.6	Parotid swelling	1 week	WT	MEC	SP	72	No recurrence
25	Lumerman[21] 1975 USA	65	M	Superficial lobe	10.0 × 6.0	Parotid swelling + facial palsy + lymph nodes palpable	4 months	WT	MEC	TP + RND	96	Died
26	Turnbull[22] 1969 USA	36	F	NA	NA	NA	10 years	WT	CXPA	TP	NA	NA
27	Turnbull[22] 1969 USA	60	M	NA	NA	NA	NA	PA	adenoCA	NA	NA	NA
28	Tanaka[3] 1953 NA	NA	NA	NA	NA	NA	NA	WT	MEC	NA	NA	NA

AcCC, acinic cell carcinoma; AdCC, adenoid cystic carcinoma; adenoCA, adenocarcinoma; CXPA, carcinoma ex pleomorphic adenoma; F, female; M, male; ME, myoepithelioma; MEC, mucoepidermoid carcinoma; MRND, modified radical neck dissection; NA, not available; PA, pleomorphic adenoma; RND, radical neck dissection; RT, radiotherapy; SCC, squamous cell carcinoma; SDC, salivary duct carcinoma; SL, sebaceous lymphadenoma; SP, superficial parotidectomy; TP, total parotidectomy; WT, Warthin's tumour.

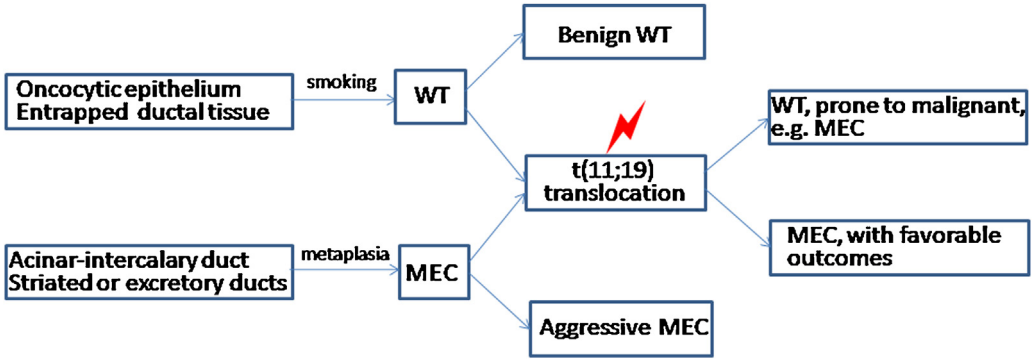

Fig. 2. Schematic diagram depicting the proposed mechanism of the genetic association between Warthin's tumour (WT) and mucoepidermoid carcinoma (MEC).

plasm (20/33 cases), followed by PA (9/33 cases). The most frequently observed malignant type was MEC (11/33 cases), followed by AcCC (8/33 cases). Hence, the most common histological combination of benign and malignant tumours was WT and MEC (8/33 cases).

The occurrence of concomitant neoplasms impacts the preoperative diagnosis and therapeutic regimen. Clinical examinations, imaging examinations, fine needle aspiration (FNA), and intraoperative frozen section biopsy should be performed to increase the accuracy of diagnosis for synchronous multifocal unilateral lesions. With regard to the clinical examination, a fixed tumour with pain, rapid growth, or symptoms of facial nerve palsy should be noticed. MRI is useful for precise local mapping of the different neoplasms, including the tumour size, location, nature, invasion, and nodal metastasis. FNA is also advocated to aid the diagnostic process before surgery. Finally, intraoperative frozen section biopsy may yield a definitive diagnosis with meticulous examination of the resected specimens, especially for tiny tumours, during histopathological sampling. Therefore, accurate preoperative examination and intraoperative assessment are warranted to optimize the treatment strategy and improve the final outcomes of patients with co-existing tumours.

Surgery is the cornerstone of treatment for these types of lesion. Basically, a complete resection with adequate free surgical margins is crucial. When it comes to high-risk malignancies, combined treatments including radical surgery, facial nerve reinnervation, and adjuvant radiotherapy are recommended. The prognosis of synchronous multiple unilateral tumours of benign and malignant types is similar to that of routine single malignant neoplasms of the same histopathological types.

Synchronous unilateral parotid tumours of different histological types account for less than 0.3% of all salivary gland neoplasms[17]. The aetiology and histogenesis of these entities remain controversial. On the one hand, there might be a possible association between the co-existing tumours with different histopathology. Srivastava and Nadelman[5] considered that the long-standing presence of benign tumours might lead to chronic sialadenitis, which was observed in the involved gland in several reported cases. Long-standing chronic sialadenitis could result in epithelial metaplasia, dysplasia, and eventually carcinoma. A similar viewpoint was presented in other cases[23]. On the other hand, the synchronous occurrence of benign and malignant tumours has also been considered to represent independent events[9,10,12,18,21], as the tumours are separated from each other and exist independently. However, this would not explain why metastatic nodules of adenocarcinoma were found in the synchronous unilateral tumours of WT in the case reported by Roh et al.[6]. Therefore, further study is needed to clarify the underlying pathogenesis.

Recent discoveries of genomic alternations in several salivary gland tumours have altered the current perception of some salivary gland tumours, and there may be a genetic association between the concomitant tumours[24]. Take the most common combination – WT associated with MEC – as an example: the t(11;19) translocation resulting in the fusion gene CRTC1/MAML2 transcript has been identified in both part of WT and MEC, which indicates a histogenetic link between a subset of these tumours (Fig. 2)[25]. The CRTC1/MAML2 fusion protein may disrupt intercellular communication including cell cycle and differentiation functions by activating both the cAMP-CERB target and Notch signalling target[26]. These genetic aberrations are recurrent and reproducible and might be pathognomonic for MEC due to the cytogenetic abnormality. The CRTC1/MAML2 fusion transcript is present in more than 50% of MEC and is more often detected in clinically indolent, low-to-intermediate grade MEC, with a lower risk of local recurrence and metastasis[27]. As for WT, the predominant hypothesis of pathogenesis is that these tumours arise from a hyperplasia of ductal tissue and oncocytic epithelium entrapped in lymph nodes stimulated by smoking[28]. The fusion gene transcript has also been detected in WT by multiple independent groups and indicates a histogenetic link between WT and MEC[25,29,30]. Although controversy exists, clonal oncocytic growth induced by CRTC1/MAML2 may make WT prone to malignancy such as MEC on the basis of metaplasia[30]. Moreover, Bell et al.[25] reported the fusion gene as an early or aetiological event in the development of tumours and/or malignant transformation based on research into WT and MEC. Hence, screening for direct evidence of molecular heterogeneity, along with analysis of the t(11;19) fusion gene, is necessary to determine the histogenetic link between these tumours.

This study is subject to a few limitations. First, the low incidence of this disease resulted in the identification of limited cases for the retrospective analysis. Second, there might be an interpretation bias concerning the non-standardized cases reported by different surgeons or pathologists. Further reports using a standardized pattern with long-term follow-up are required.

It is imperative that clinicians take note of the incidence of synchronous multiple lesions, in order to contribute to a better prognosis based on rigorous preoperative examination and tailored therapeutic regimens.

Funding

This work was supported by research grants from the Science and Technology Commission of Shanghai Municipality (16ZR1418800).

Competing interests

The authors have declared that no competing interests exist.

Ethical approval

Ethical approval was given by the Institutional Review Board of Shanghai Ninth Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (judgement reference number 113 (V1.0, 2018-1-3)).

Patient consent

Not required.

References

1. El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ. *WHO classification of head and neck tumours (IARC WHO classification of tumours)*. 4th ed. Geneva: World Health Organization; 2017.
2. Maiorano E, Lo Muzio L, Favia G, Piattelli A. Warthin's tumour: a study of 78 cases with emphasis on bilaterality, multifocality and association with other malignancies. *Oral Oncol* 2002;**38**:35–40.
3. Tanaka N, Chen WC. A case of bilateral papillary cystadenoma lymphomatosum (Warthin's tumor) of the parotid complicated with muco-epidermoid tumor. *Gan* 1953;**44**:229–31.
4. Ochal-Choinska A, Bruzgielewicz A, Osuch-Wojcikiewicz E. Synchronous multiple unilateral parotid gland tumors of benign and malignant histological types: case report and literature review. *Braz J Otorhinolaryngol*)2016;(April). http://dx.doi.org/10.1016/j.bjorl.2016.03.002. [in press].
5. Srivastava S, Nadelman C. Synchronous ipsilateral Warthin tumor encased by a separate mucoepidermoid carcinoma of the parotid gland: a case report and review of the literature. *Diagn Cytopathol* 2010;**38**:533–7.
6. Roh JL, Kim JM, Park CI. Synchronous benign and malignant tumors in the ipsilateral parotid gland. *Acta Otolaryngol* 2007;**127**:110–2.
7. Tanaka S, Tabuchi K, Oikawa K, Kohanawa R, Okubo H, Ikebe D, Noguchi M, Hara A. Synchronous unilateral parotid gland neoplasms of three different histological types. *Auris Nasus Larynx* 2007;**34**:263–6.
8. Ethunandan M, Pratt CA, Morrison A, Anand R, Macpherson DW, Wilson AW. Multiple synchronous and metachronous neoplasms of the parotid gland: the Chichester experience. *Br J Oral Maxillofac Surg* 2006;**44**:397–401.
9. Yu GY, Ma DQ, Zhang Y, Peng X, Cai ZG, Gao Y, Chen Y. Multiple primary tumours of the parotid gland. *Int J Oral Maxillofac Surg* 2004;**33**:531–4.
10. Zeebregts CJ, Mastboom WJ, van Noort G, van Det RJ. Synchronous tumours of the unilateral parotid gland: rare or undetected? *J Craniomaxillofac Surg* 2003;**31**:62–6.
11. Shukla M, Panicker S. Synchronous sebaceous lymphadenoma with squamous cell carcinoma—case report. *World J Surg Oncol* 2003;**1**:30.
12. Curry JL, Petruzzelli GJ, McClatchey KD, Lingen MW. Synchronous benign and malignant salivary gland tumors in ipsilateral glands: a report of two cases and a review of literature. *Head Neck* 2002;**24**:301–6.
13. Mayorga M, Fernandez N, Val-Bernal JF. Synchronous ipsilateral sebaceous lymphadenoma and acinic cell adenocarcinoma of the parotid gland. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999;**88**:593–6.
14. Misselevich I, Podoshin L, Fradis M, Boss JH. Salivary gland double tumor: synchronous ipsilateral pleomorphic adenoma and acinic cell carcinoma of the parotid gland. *Ann Otol Rhinol Laryngol* 1997;**106**:226–9.
15. Seifert G. Bilateral mucoepidermoid carcinomas arising in bilateral pre-existing Warthin's tumours of the parotid gland. *Oral Oncol* 1997;**33**:284–7.
16. Hanada T, Hirase H, Ohyama M. Unusual case of myoepithelioma associated with adenoid cystic carcinoma of the parotid gland. *Auris Nasus Larynx* 1995;**22**:65–70.
17. Gnepp DR, Schroeder W, Heffner D. Synchronous tumors arising in a single major salivary gland. *Cancer* 1989;**63**:1219–24.
18. Janecka IP, Perzin KH, Sternschein MJ. Rare synchronous parotid tumors of different histologic types. *Plast Reconstr Surg* 1983;**72**:798–802.
19. Pontilena N, Rankow RM. Coexisting benign mixed tumor and mucoepidermoid carcinoma of the parotid gland. *Ann Otol Rhinol Laryngol* 1979;**88**:327–30.
20. Gadient SE, Kalfayan B. Mucoepidermoid carcinoma arising within a Warthin's tumor. *Oral Surg Oral Med Oral Pathol* 1975;**40**:391–8.
21. Lumerman H, Freedman P, Caracciolo P, Remigio PS. Synchronous malignant mucoepidermoid tumor of the parotid gland and Warthin's tumor in adjacent lymph node. *Oral Surg Oral Med Oral Pathol* 1975;**39**:953–8.
22. Turnbull AD, Frazell EL. Multiple tumors of the major salivary glands. *Am J Surg* 1969;**118**:787–9.
23. Gunduz M, Yamanaka N, Hotomi M, Kuki K, Yokoyama M, Nakamine H. Squamous cell carcinoma arising in a Warthin's tumor. *Auris Nasus Larynx* 1999;**26**:355–60.
24. Weinreb I. Translocation-associated salivary gland tumors: a review and update. *Adv Anat Pathol* 2013;**20**:367–77.
25. Bell D, Luna MA, Weber RS, Kaye FJ, El-Naggar AK. CRTC1/MAML2 fusion transcript in Warthin's tumor and mucoepidermoid carcinoma: evidence for a common genetic association. *Genes Chromosomes Cancer* 2008;**47**:309–14.
26. Tonon G, Modi S, Wu L, Kubo A, Coxon AB, Komiya T, O'Neil K, Stover K, El-Naggar A, Griffin JD, Kirsch IR, Kaye FJ. t(11;19)(q21;p13) translocation in mucoepidermoid carcinoma creates a novel fusion product that disrupts a Notch signaling pathway. *Nat Genet* 2003;**33**:208–13.
27. Seethala RR, Dacic S, Cieply K, Kelly LM, Nikiforova MN. A reappraisal of the MECT1/MAML2 translocation in salivary mucoepidermoid carcinomas. *Am J Surg Pathol* 2010;**34**:1106–21.
28. Cope W, Naugler C, Taylor SM, Trites J, Hart RD, Bullock MJ. The association of Warthin tumor with salivary ductal inclusions in intra and periparotid lymph nodes. *Head Neck Pathol* 2014;**8**:73–6.
29. Enlund F, Behboudi A, Andrén Y, Oberg C, Lendahl U, Mark J, Stenman G. Altered Notch signaling resulting from expression of a WAMTP1-MAML2 gene fusion in mucoepidermoid carcinomas and benign Warthin's tumors. *Exp Cell Res* 2004;**292**:21–8.
30. Tirado Y, Williams MD, Hanna EY, Kaye FJ, Batsakis JG, El-Naggar AK. CRTC1/MAML2 fusion transcript in high grade mucoepidermoid carcinomas of salivary and thyroid glands and Warthin's tumors: implications for histogenesis and biologic behavior. *Genes Chromosomes Cancer* 2007;**46**:708–15.

Address:
Wenjun Yang
Department of Oral Maxillofacial–Head and Neck Oncology
Ninth People's Hospital
Shanghai Jiao Tong University School of Medicine
Shanghai
China. Fax: +86 21 63136856
E-mail: tianbingxiaojiang@126.com