Going beyond extracapsular dissection in cystadenolymphomas of the parotid gland

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ABSTRACT

Background: The aim of this study was to evaluate the potential for reducing surgical invasiveness in parotid cystadenolymphomas by means of capsular dissection based on the experience made in our department and on various aspects of these lesions gained from the relevant literature.

Methods: All patients treated for cystadenolymphomas with extracapsular or capsular dissection at a tertiary referral center between 2000 and 2017 were examined retrospectively. A literature review of various aspects and of different treatment strategies for this lesion was also performed.

Results: 629 patients were included in the study. 499 had solitary tumors (79.3%) and 130 had unilateral multicentric lesions (20.7%). 595 patients were managed by means of ED, while 34 patients underwent a CD. Our analysis detected an overall occurrence rate of ipsilateral metachronous tumors of 2.06% (13/629), all after extracapsular dissection, with a mean follow-up of 104.1 months. No statistical difference could be found between ED and CD in the overall occurrence rate of ipsilateral metachronous tumors or in the complication rate. No cases of a malignancy arising from a preexisting Warthin tumor could be detected in our study sample.

Conclusion: A clear potential for reducing surgical invasiveness could be shown. A reliable imaging diagnosis, appropriate patient counseling and high compliance with close follow-up are the basic prerequisites for an acceptable outcome.

Introduction

Cystadenolymphoma (or Warthin' tumor, WT) is the second most common benign lesion in the parotid gland [1]. Since it was first described at the turn of the 20th century, it is still not clear whether this lesion is a true neoplasm or a tumor-like lesion. The lesion is composed of an epithelial and a stromal component. The epithelial component of the tumor appears to originate from the intralobular intercalated or interlobular salivary gland duct epithelium [2], possibly in response to an unknown inflammatory stimulus. The stromal component contains lymphoid cells showing various degrees of reactivity including germinal centers as seen in lymph nodes [3]. This lesion appears to be fundamentally different from a pleomorphic adenoma, the most common benign tumor of the parotid gland, which shows several particular features such as pseudopodia, an incomplete capsule or even lack of a capsule [4].

It is therefore reasonable to assume that the optimal therapy probably also requires an approach which sets itself apart from a "one-size-fits-all" treatment. The aim of surgical management of WTs should be to confirm the benign nature of the diagnosis, remove suspicious, obvious and symptomatic lesions as well as to achieve an acceptable postoperative quality of life. In the era of minimal invasive surgery, the trend is moving from complete parotidectomy to more sparing approaches such as superficial parotidectomy or even extracapsular dissection (ED), the latter being propagated more and more in the literature [5,6]. The aim of this study was to evaluate the potential for further reducing surgical invasiveness in WTs by means of "capsular" dissection (CD) based on the preliminary experience made in our department and on an investigation of various aspects of these lesions gained from the relevant literature.

Materials and methods

This study was conducted at an academic tertiary referral center

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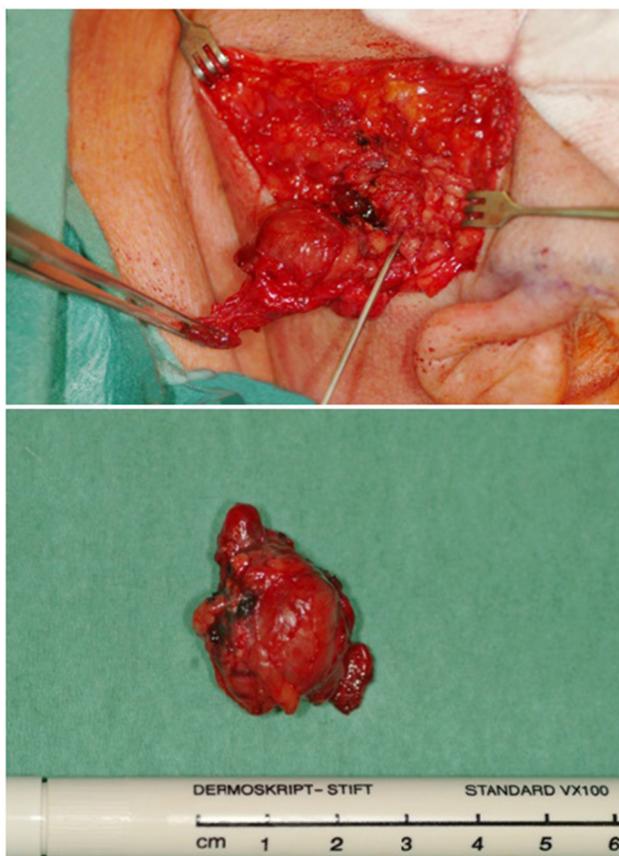[1] These authors contributed equally to this manuscript

Fig. 1. Extracapsular dissection: Removal of a tumor with a cuff of healthy tissue, without intending to identify the main trunk or branches of the facial nerve.

Fig. 2. Capsular dissection: Removal of a tumor around its capsule without any cuff of healthy tissue around it, following the same surgical principles as in a cyst of the neck or a lymph node.

specializing in salivary gland pathologies (Department of Otorhinolaryngology, Head and Neck Surgery, University of Erlangen–Nuremberg, Erlangen, Germany). The records of all patients treated for WTs of the parotid gland by means of ED and CD between 2000 and 2017 were examined. An ED was defined as the removal of a tumor with a cuff of healthy tissue, without intending to identify the main trunk or branches of the facial nerve [2] (Fig. 1). This surgical modality was indicated in cases of single mobile lesions or conglomerates of lesions with preoperative imaging signs of a WT located within the superficial lobe of the parotid gland (Fig. 1). A "capsular" dissection (CD) was defined as the removal of a WT around its capsule without any cuff of healthy tissue around it, following the same surgical principles as in a cyst of the neck or a lymph node (Fig. 2). Approval was obtained from the institutional review board of our hospital.

Preoperatively, all patients were evaluated by means of a clinical examination (inspection, palpation) as well as ultrasonography of the head and neck with particular attention given to the parotid region, and in some carefully selected cases by magnetic resonance imaging. Preoperatively, the function of the facial nerve was assessed clinically using the House-Brackmann grading system [7] and by electromyography of the facial nerve.

Data concerning the occurrence rate of ipsilateral metachronous tumors after ED in comparison with CD as well as postoperative complications in our study sample were selected. For further evaluation of the potential for reducing surgical invasiveness in such lesions, a review of the relevant literature on several topics concerning these tumors was performed. First of all, reliability of the clinical (age, gender, smoking), imaging (ultrasound, magnetic resonance imaging) and image-guided invasive (core needle biopsy) diagnostic criteria for these tumors were examined. Additionally, a review of the literature on the

histopathologic features of WTs (capsule characteristics) with a potential therapeutic relevance was performed. A further research in the relevant literature was carried out to investigate the potential for malignant transformation in these lesions. Statistical analysis was performed using the chi-square test with 95% confidence intervals. SPSS software version 21 for Windows (SPSS, Chicago, IL), was used for the analysis. A p-value of < 0.05 was considered statistically significant.

Results

A total of 629 patients were included in the study (427 men, 202 women; male–female ratio: 2.11). Their mean age was 59.9 years (25–93 years). Out of these 629 cases, 499 had solitary tumors (79.3%) and 130 had unilateral multicentric lesions (20.7%). Our analysis detected an overall occurrence rate of ipsilateral metachronous tumors of 2.06% (13/629), all after ED, with a mean follow-up of 104.1 months. 595 patients were managed by means of ED, while 34 patients underwent a CD. No statistical difference in the overall occurrence rate of ipsilateral metachronous tumors could be found between ED and CD (x^2:0.759, p = 0.384). Similarly, no statistical difference in the complication rates (especially permanent facial nerve palsy or Frey' syndrome) could be found between ED and CD (x^2:1.12, p = 0.29). No cases of a malignancy arising from a preexisting Warthin tumor could be detected in our study sample.

Discussion

The aim of surgical management of WTs is to confirm the benign nature of the diagnosis, remove suspicious, obvious and symptomatic

lesions as well as to achieve an acceptable postoperative quality of life [6,8]. Our personal experience in over 17 years of performing ED in cystadenolymphomas showed both an acceptable surgical and an outstanding postoperative functional outcome: only 2.2% of our patients had to undergo revision surgery, and permanent facial palsy was seen in only 1% of our cases. This is in agreement with relevant literature reports [9–12] and points to the fact that avoidance of identification of the facial nerve or its branches seems to be surgically quite acceptable with a stable place in the management of these lesions. The aim of the present study was to investigate whether surgical invasiveness in the management of cystadenolymphomas could be further reduced by means of capsular dissection, drawing conclusions from our personal experience and well as from data from the relevant literature on various diagnostic and histopathologic aspects of this entity.

First of all, our first preliminary experience showed, encouragingly, that capsular dissection could be sufficient for WTs from an oncological perspective, as no metachronous ipsilateral lesions could be detected after management of the first 34 cases using this surgical modality. Moreover, capsular dissection was followed by an excellent functional outcome, without any cases being complicated by postoperative facial nerve palsy. The potential functional advantage of capsular dissection over extracapsular dissection and other more extensive surgical modalities lies in the fact that dissection around the capsule of the tumor leads to reducing the possibility of hitting a branch of the facial nerve and thus to a minimization of the risk of iatrogenic facial palsy. Reasonably, implementation of this surgical procedure presumes a thorough preoperative work-out of each case, leading to a reliable preoperative diagnosis of WT.

For this reason, we aimed at detecting, with the help of the relevant literature, the extent to which the existing diagnostic tools (patient's history, clinical examination, ultrasound, MRI, core needle biopsy) allow a reliable preoperative diagnosis of these lesions. First of all, it is well known that epidemiologic features (male gender [13,14], predilection in the fifth and sixth decades of life [13,15]) as well as information about a patient's background (nicotine consumption [16], signs of inflammation in the parotid region [17], surgical excision of a WT on the contralateral side in the past [13]) provide the first suspicion of such a lesion. In the course of the clinical examination, palpation of a soft, fleshy, partly cystic mass mainly localized in the caudal part of the parotid region strengthens the working hypothesis of a WT [18]. Additional use of the combination of certain sonographic or sonoelastographic characteristics (ovoid, sharply delineated, homogeneous, hypoechoic lesion with a mainly superficial caudal localization [13], well-perfused intralesional septations, possibly total anechoic or cystic with a distal sound enhancement, multifocal or bilateral presence, sonoelastographic "half-half" sign [19]) allow a diagnosis in over 93% of cystadenolymphomas [6,20]. Relevant radiologic literature reports point to the fact that combined consideration of MRI features (hyperintense components on T1-weighted images, mild contrast enhancement, and an apparent diffusion coefficient of no more than $1.016 \times 10^{-3}\, mm^2/s$) and demographic characteristics can achieve a high diagnostic accuracy for these lesions [21–23]. Last but not least, an ultrasound-guided fine- or core-needle biopsy in these easily accessible lesions seems to have great diagnostic potential [24–26]. Interestingly, in our study group no cases of a presumed Warthin's tumor removed either with extracapsular of capsular dissection were found later to be a malignant tumor.

From a histopathological point of view, several literature reports point to the fact that WTs are always sharply demarcated by an intact capsule [3,27]. Kuzenko et al. describe extensive fibrosis at the periphery of these lesions with a dense collagen zone and a myofibroblastic spindle cell proliferation [3]. When studying 21 cases, Daguci et al. was able to detect that the stroma component determines a thin but always stable capsule in the periphery of these lesions, which separates them completely from the other parenchyma [28]. Several reports explain the encapsulation of these lesions through their development from heterotopic salivary gland ductal epithelium within preexisting intraparotid lymph nodes, structures which are always sharply delineated [27,29]. It seems that reduction of the minimum surgical extent from an extracapsular to a capsular dissection following the same surgical principles as in a cyst of the neck or a lymph node does not clash with the capsular features of these lesions. This pathologic data tallies with our preliminary surgical experience in the CD of cystadenolymphomas: Performing dissection at the level of the capsule of a WT did not seem to have a negative impact on the occurrence rate of ipsilateral metachronous tumors. It should be pointed out that CD has been performed in carefully selected cases in our department for the past 3–4 years, and for that reason the average follow-up time in the CD group was shorter than in the ECD group (25 months vs. 108 months). This should be regarded as a limitation of the interpretation of the study results.

From a tumorbiologic point of view, our attempt for reduction of the surgical invasiveness by WTs requires a thorough investigation of the potential for malignancy in these specific lesions: In general, the malignant transformation of WTs is reported to be about 0.3% and is, consequently, extremely rare [30] – in a series of 629 cases we did not detect any malignancies. Most commonly, this concerns non-disseminated malignant lymphomas involving the lymphoid stroma of WTs [31–33]. In contrast, the epithelial component of this lesion seems to be far more rarely involved in a malignant process: The presence of the CRTC1/MAML2 fusion gene in benign Warthin's tumors suggests that some of these lesions may be prone to transformation to a mucoepidermoid carcinoma [34]. Squamous metaplastic changes in the oncocytic epithelium can be observed in up to 7.5% of all WTs and could theoretically represent the first stage in the process towards malignant transformation, but without ending in malignancy in the vast majority of cases [35]. A malignant change in a WT could be suggested clinically in some cases by a recent history of rapid enlargement of a longstanding mass [36,37]. In any case, the potential for malignancy seems to be extremely low and should be considered mainly in cases of clinical symptoms or suspicious imaging features.

The high reliability of the diagnosis, the stable and sharp demarcation of the lesions with an intact capsule as well as the extremely low potential for malignancy offer ideal circumstances for further reducing the surgical invasiveness in WTs by means of capsular dissection. Dissection of the tumor around its capsule further reduces the risk of hitting and thus injuring the facial nerve or its branches. Interestingly, for these harmless lesions with an extremely low risk of malignancy, several working groups have proposed active surveillance as a possible strategy in carefully selected cases, provided there is a reliable diagnosis of cystadenolymphoma. In our department, a "wait-and-scan" strategy is adopted for older patients with severe morbidities after histologic verification of the cystadenolymphoma by means of fine needle aspirating cytology or core needle biopsy as well if there is suspicion of metachronous lesions appearing after primary surgical excision and histologic verification of a cystadenolymphoma. It should, however, be pointed out that expertise in diagnostics, appropriate counseling, and the optimization of patient selection as well as close follow-up are important prerequisites for reducing invasiveness in the management of these lesions.

Conflicts of interest

None declared

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] Handra-Luca A. HBME1 expression in Warthin tumour: relationships to CK5/6, P63, BCL2 and WT1 expression and histogenesis. J Clin Pathol 2017;70:458–60.

[3] Kuzenko YV, Romanuk AM, Dyachenko OO, Hudymenko O. Pathogenesis of Warthin's tumors. Intervent Med Appl Sci 2016;8:41–8.

[4] Dulguerov P, Todic J, Pusztaszeri M, Alotaibi NH. Why do parotid pleomorphic adenomas recur? A systematic review of pathological and surgical variables. Front Surg 2017;4:26.

[5] Iro H, Zenk J. Role of extracapsular dissection in surgical management of benign parotid tumors. JAMA Otolaryngol Head Neck Surg 2014;140:768–9.

[6] Mantsopoulos K, Goncalves M, Koch M, Iro H. Extracapsular dissection for warthin tumors despite the risk of ipsilateral metachronous occurrence. Laryngoscope 2018.

[7] House JW, Brackmann DE. Facial nerve grading system. Otolaryngol–Head Neck Surg: Off J Am Acad Otolaryngol-Head Neck Surg 1985;93:146–7.

[8] Mantsopoulos K, Koch M, Goncalves M, Iro H. Investigation of the surgical strategies for unilateral multifocal cystadenolymphomas of the parotid gland. Oral Oncol 2018;82:176–80.

[9] Iwai H, Yamashita T. Local excision procedure for Warthin's tumor of the parotid gland. Otolaryngol Head Neck Surg 2005;132:577–80.

[10] Iwai H, Yamashita T. Surgical procedure for Warthin's tumor in the parotid gland. Nihon Jibiinkoka Gakkai Kaiho 2005;108:679–83.

[11] Skolnik EM, Friedman M, Becker S, Sisson GA, Keyes GA. Tumors of the major salivary glands. Laryngoscope 1977;87:843–61.

[12] Mantsopoulos K, Koch M, Klintworth N, Zenk J, Iro H. Evolution and changing trends in surgery for benign parotid tumors. Laryngoscope 2015;125:122–7.

[13] Patel DK, Morton RP. Demographics of benign parotid tumours: Warthin's tumour versus other benign salivary tumours. Acta Otolaryngol 2016;136:83–6.

[14] Tian Z, Li L, Wang L, Hu Y, Li J. Salivary gland neoplasms in oral and maxillofacial regions: a 23-year retrospective study of 6982 cases in an eastern Chinese population. Int J Oral Maxillofac Surg 2010;39:235–42.

[15] Pinkston JA, Cole P. Cigarette smoking and Warthin's tumor. Am J Epidemiol 1996;144:183–7.

[16] Peter Klussmann J, Wittekindt C, Florian Preuss S, Al Attab A, Schroeder U, Guntinas-Lichius O. High risk for bilateral Warthin tumor in heavy smokers–review of 185 cases. Acta Otolaryngol 2006;126:1213–7.

[17] 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.

[18] McGurk M, Combes J. Controversies in the management of salivary gland disease. Oxford University Press; 2012. p. 64.

[19] Klintworth N, Mantsopoulos K, Zenk J, Psychogios G, Iro H, Bozzato A. Sonoelastography of parotid gland tumours: initial experience and identification of characteristic patterns. Eur Radiol 2012;22:947–56.

[20] Renehan A, Gleave EN, Hancock BD, Smith P, McGurk M. Long-term follow-up of over 1000 patients with salivary gland tumours treated in a single centre. Br J Surg 1996;83:1750–4.

[21] Wang CW, Chu YH, Chiu DY, et al. JOURNAL CLUB: The Warthin tumor score: a simple and reliable method to distinguish Warthin tumors from pleomorphic adenomas and carcinomas. AJR Am J Roentgenol 2018;210:1330–7.

[22] Ikeda M, Motoori K, Hanazawa T, et al. Warthin tumor of the parotid gland: diagnostic value of MR imaging with histopathologic correlation. AJNR Am J Neuroradiol 2004;25:1256–62.

[23] Tartaglione T, Botto A, Sciandra M, et al. Differential diagnosis of parotid gland tumours: which magnetic resonance findings should be taken in account? Acta Otorhinolaryngol Ital 2015;35:314–20.

[24] Wan YL, Chan SC, Chen YL, et al. Ultrasonography-guided core-needle biopsy of parotid gland masses. AJNR Am J Neuroradiol 2004;25:1608–12.

[25] Brennan PA, Herd MK, Howlett DC, Gibson D, Oeppen RS. Is ultrasound alone sufficient for imaging superficial lobe benign parotid tumours before surgery? Br J Oral Maxillofac Surg 2012;50:333–7.

[26] Witt BL, Schmidt RL. Ultrasound-guided core needle biopsy of salivary gland lesions: a systematic review and meta-analysis. Laryngoscope 2014;124:695–700.

[27] Hansen T, Kirkpatrick CJ. Expression of podoplanin in Warthin tumours. Oral Maxillofac Surg 2010;14:223–6.

[28] Daguci L, Simionescu C, Stepan A, Munteanu C, Daguci C, Bataiosu M. Warthin tumor–morphological study of the stromal compartment. Rom J Morphol Embryol 2011;52:1319–23.

[29] Seifert G, Bull HG, Donath K. Histologic subclassification of the cystadenolymphoma of the parotid gland. Analysis of 275 cases. Virchows Arch A Pathol Anat Histol 1980;388:13–38.

[30] Thangarajah T, Reddy VM, Castellanos-Arango F, Panarese A. Current controversies in the management of Warthin tumour. Postgrad Med J 2009;85:3–8.

[31] Marioni G, Marchese-Ragona R, Marino F, et al. MALT-type lymphoma and Warthin's tumour presenting in the same parotid gland. Acta Otolaryngol 2004;124:318–23.

[32] Reiner M, Goldhirsch A, Luscieti PR, Pedrinis E, Kaplan E, Cavalli F. Warthin's tumor with Sjogren's syndrome and non-Hodgkin's lymphoma. Ear Nose Throat J 1979;58:345–50.

[33] Shikhani AH, Shikhani LT, Kuhajda FP, Allam CK. Warthin's tumor-associated neoplasms: report of two cases and review of the literature. Ear Nose Throat J 1993;72(264–269):272–1263.

[34] 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 Chromosom Cancer 2008;47:309–14.

[35] Seifert G. Carcinoma in pre-existing Warthin tumors (cystadenolymphoma) of the parotid gland. Classification, pathogenesis and differential diagnosis. Pathologe 1997;18:359–67.

[36] Damjanov I, Sneff EM, Delerme AN. Squamous cell carcinoma arising in Warthin's tumor of the parotid gland. A light, electron microscopic, and immunohistochemical study. Oral Surg Oral Med Oral Pathol 1983;55:286–90.

[37] Cobb CJ, Greaves TS, Raza AS. Fine needle aspiration cytology and diagnostic pitfalls in Warthin's tumor with necrotizing granulomatous inflammation and facial nerve paralysis: a case report. Acta Cytol 2009;53:431–4.