European Archives of Oto-Rhino-Laryngology (2019) 276:1191–1196
https://doi.org/10.1007/s00405-019-05319-6

HEAD & NECK

Rising incidences of Warthin's tumors may be linked to obesity: a single-institutional experience

Lorenz Kadletz[1] · Stefan Grasl[1] · Christos Perisanidis[2] · Matthäus C. Grasl[1] · Boban M. Erovic[3]

Received: 25 October 2018 / Accepted: 29 January 2019 / Published online: 7 February 2019

Abstract

Purpose Recently, there has been an increase in the number of reported Warthin's tumors, but few risk factors have been described for this benign tumor. Yet, smoking is the only evidently identified risk factor. Obesity and the metabolic syndrome are causally linked to or a risk factor for a variety of diseases. Therefore, we analyzed whether metabolic syndrome, including obesity, might influence the incidence of Warthin's tumors.

Methods In this retrospective study, we evaluated 197 patients with Warthin's tumor. We assessed the tumor size, the body mass index (BMI), comorbidities related to the metabolic syndrome, and cigarette and alcohol consumption. Additionally, we evaluated several blood parameters and their influence.

Results Warthin's tumor patients had a significantly higher BMI in comparison to patients with other benign parotid gland tumors (29.1 versus 26.2, $p < 0.0001$). The rate of metabolic syndrome-associated comorbidities was higher in Warthin's tumor patients (62.4% versus 35.2%, $p < 0.0001$).

Conclusion Our results might be the first step to recognize obesity and its consequences as a co-driver in the formation of Warthin's tumors. Nevertheless, further studies are requested to validate our results and to answer the question whether obesity or the metabolic syndrome are integrally linked to Warthin's tumors.

Keywords Warthin's tumor · Obesity · Etiology · Risk factor · Incidence

Introduction

Tumors of the parotid gland are rare, and the vast majority are of benign origin [1, 2]. Two different histologic subtypes, pleomorphic adenoma (PA) and Warthin's tumor (WT), compose the plethora of all benign lesions located in the parotid gland. These account for over 95% of all tumors [3]. Until now, the PA is reported to be the most frequent neoplastic formation and represents 52–94% of all benign parotid gland tumors [1, 4].

According to recent relevant literature, WT is the second most common tumor of the parotid gland, with a median age of disease onset at 60 years [5]. WTs tend to show a bilateral or multilocular growth in contrast to PAs. Recently, Luers and coworkers described the rising incidences of WTs in the past 25 years in comparison to PAs [4]. The results of this study show an increase of WT from 24% of all parotid gland tumors in 1990 to 48% in 2014. We were also able to observe an increasing trend in the incidence of WT at our institution [6].

Currently, tobacco smoking is the major risk factor that is associated with the development of a WT [7, 8]. However, smoking behavior might not serve as a single explanation for the rising incidences of WTs. According to the available data about smokers in Austria published by the federal statistical office "Statistics Austria" (http://statistik.at/web_en/statistics/index.html), there has not been a dramatic change in relative (23.5% in 1972 versus 24.3% in 2014) and absolute numbers (1,770,000 in 1972 and 2,075,000 in 2014) of smokers in Austria. Therefore, it is necessary to evaluate other factors that might influence the development of WTs.

✉ Boban M. Erovic
b.erovic@ekhwien.at

1 Department of Otorhinolaryngology and Head and Neck Surgery, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria

2 Department of Maxillofacial Surgery, University of Athens, Athens, Greece

3 Institute of Head and Neck Surgery, Evangelical Hospital, Vienna, Austria

The typical modern, western lifestyle has led to increasing numbers of obese patients. It is well established that patients with metabolic syndrome have a higher risk of developing cardiovascular, inflammatory or malignant diseases [9]. It is estimated that there are more than 600 million obese patients worldwide [10]. Obesity is intrinsically linked with metabolic syndrome [11]. Metabolic syndrome is defined as a cluster of visceral obesity, dyslipidemia, hyperglycemia, and hypertension [12].

Since WT, obese and metabolic syndrome patient's numbers have been increasing over the last decades, we hypothesized about a potential association between these diseases. To achieve this, we aimed to investigate several factors that are linked to the metabolic syndrome and obesity in patients with WTs.

Materials and methods

Patients

This retrospective study was performed at the Medical University of Vienna. All patients that underwent parotid gland surgery because of a WT in the period between 2000 and 2015 were included. In the case of bilateral WTs, data were obtained from reports at the time of the first performed surgery. Moreover, the incidence rates of WT between the years 1960 and 2015 in comparison to all other benign parotid gland neoplasms were analyzed. Patients with other benign parotid gland tumors served as a reference group. Patients with insufficient medical reports were excluded from the analysis. Approval was obtained from the institutional research board (EK1926/2015).

Clinical data

Hospital medical records were analyzed for sociodemographic characteristics. Moreover, medical reports were surveyed for the size and weight of the patients. Consecutively, the body mass index (BMI) was calculated. According to the WHO, a BMI > 25 was classified as overweight and > 30 as obese. Each patient's medical history was investigated for comorbidities that are associated with metabolic syndrome (e.g., coronary heart disease, peripheral vascular disease stroke, diabetes), smoking behavior (cigarettes per day), and alcohol consumption (never, occasionally or daily). Heavy smoking was defined as more than ten cigarettes per day. Also, tumor size was obtained from histopathological and medical imaging findings. The largest transversal diameter was taken into consideration for statistical analysis. Since the modern, western lifestyle affects multiple metabolic and inflammatory processes, we analyzed the patient's laboratory findings for the levels of the following parameters: high- and low-density lipoprotein (HDL&LDL), total serum cholesterol, triglyceride, glycated hemoglobin (HbA_{1c}), gamma-glutamyl transpeptidase, aspartate transaminase, alanine transaminase, fibrinogen, C-reactive protein, and erythrocyte sedimentation rate after 1 and 2 h.

Statistics

Descriptive statistics were used to analyze data. Mean, median, minimum, and maximum were calculated for all numeric variables. Moreover, we compared all assessed variables between WT patients and all other patients with benign lesions located in the parotid gland. Categorical variables were compared with a Fisher's exact test. Since BMI and all blood parameters are normally distributed, an independent *t* test was used to evaluate a possible difference between both groups. If more than two groups were compared, a one-way ANOVA analysis was performed. To measure a potential correlation between two variables within the WT patient population, the Pearson correlation coefficient R was calculated. SPSS software (Version 21.0; SPSS, Inc., Chicago, IL) and Prism GraphPad software (GraphPad Software, Inc., La Jolla, CA) were used to analyze the data.

Results

The incidence of Warthin's tumors and patient data

A total of 919 patients with benign parotid gland tumors underwent surgery at the General Hospital of Vienna between the years 1960 and 2015 (Fig. 1). Three hundred eighty (41.3%) out of 919 patients were diagnosed with a WT (Fig. 2). It was possible to observe a steady increase

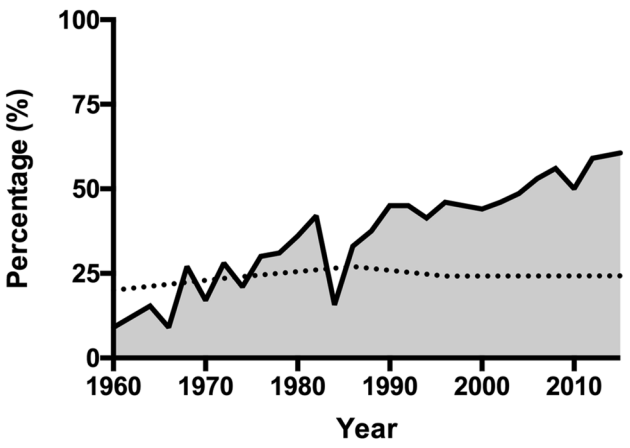

Fig. 1 The percentage share of Warthin's tumor patients compared with benign parotid gland tumors over time. The dotted line shows the percentage of smokers in Austria

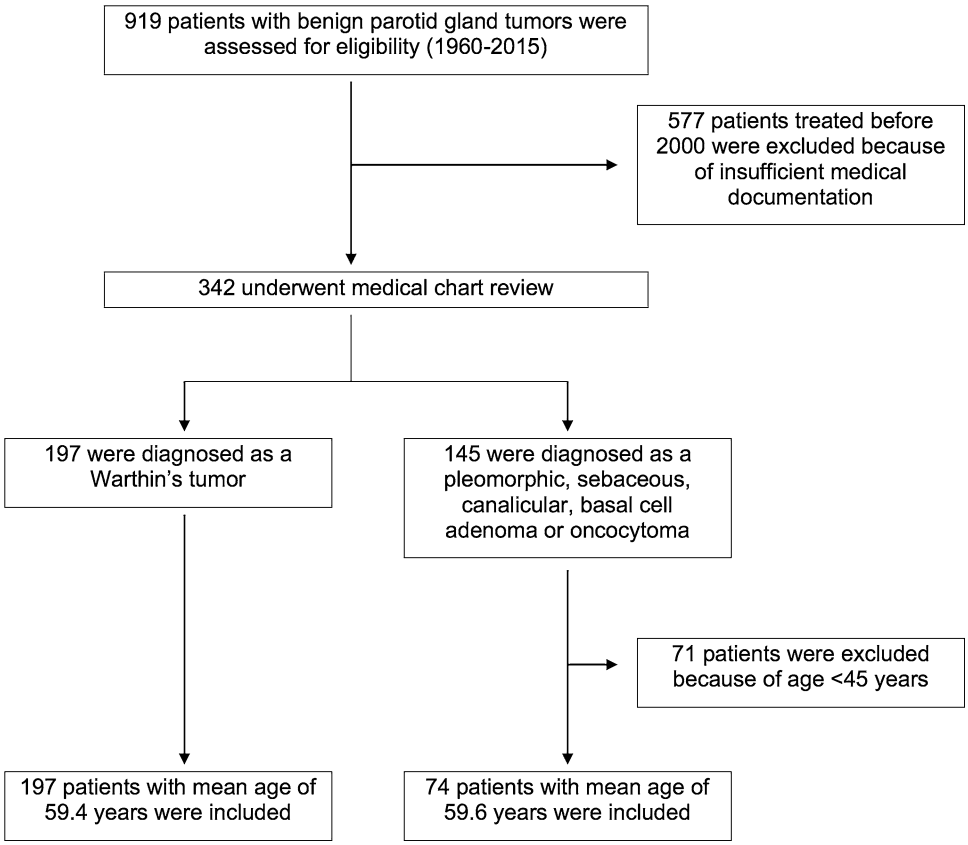

Fig. 2 Flowchart of study enrollment, showing the design of the study, including patients that were eligible for further analysis

of incidences of WTs. The percentage of diagnosed WTs increased from 9.1% in the early 1960s to over 50% in the 2000s. In 2015, 60.6% of all parotid gland tumors were diagnosed as WT. Most of our patients had a PA of the parotid gland ($n = 514$, 55.9%). Ten patients (1.2%) were either diagnosed as basal cell adenoma or oncocytoma, three patients (0.3%) as sebaceous adenoma, and two patients (0.2%) as canalicular adenoma. WT patients had a mean age of 59.4 years (range, 18.6–87.6 years), whereas all other patients had a mean age of 51.0 years at the time of surgery (range, 18.1–89.5 years). Male patients were more frequently diagnosed with a WT ($n = 217/380$, 57.1%), in contrast to other benign tumors where the percentage of males was 40.8% ($n = 220/539$).

The medical charts of those patients treated in the years between 2000 and 2015 were analyzed for sociodemographic, clinical, and blood parameters (Table 1). Therefore, it was possible to assess the data of 197 WT patients and 145 patients with other benign neoplasms of the parotid gland.

Comparison of patients with Warthin's tumor and benign parotid gland tumors

First, smoking behavior and alcohol consumption were evaluated. The WT patients included a higher percentage of heavy smokers. A total of 136 (69.0%) patients smoked

Table 1 Demographic and clinical data of Warthin's tumor patients in comparison to other benign parotid gland tumor patients treated between the years 2000 and 2015

	Warthin's tumor	Benign parotid gland tumors
Total no. of patients	197	145
Sex		
Female	79 (40.1%)	86 (59.3%)
Male	118 (59.9%)	59 (40.7%)
Age (years)		
Mean	60.1	47.0
Median	60.0	45.1
Range	36.1–87.3	18.1–84.4
Smokers		
> 10 cigarettes/day	136 (69.0%)	43 (29.7%)
< 10 cigarettes/day	26 (13.2%)	16 (11.0%)
Non smokers	35 (17.8%)	86 (59.3%)
Alcohol consumption		
Daily	22 (11.2%)	12 (8.3%)
Occasionally	144 (73.1%)	78 (53.8%)
Never	31 (15.7%)	55 (37.9%)

more than ten cigarettes per day. In comparison, only 43 patients (29.7%) of the other group were excessive smokers ($p < 0.0001$). Daily alcohol consumption could be assessed in 22 patients with WT (11.2%) and 12 patients (8.2%) of the other group ($p = 0.4655$).

Moreover, we wanted to gain insight into the comorbidities of our patient cohort. In particular, we evaluated diseases that are associated with metabolic syndrome. A total of 123 patients (62.4%) with WTs were diagnosed with diseases associated with metabolic syndrome, compared to only 28 (19.3%) patients in the control group ($p < 0.0001$). Since the prevalence of metabolic syndrome increases with age and WT patients had a higher mean age, we excluded all young patients (< 45 years) from both groups. Thus, of the remaining 74 patients with benign parotid gland tumors, 26 (35.1%) had a patient's history of diseases associated with metabolic syndrome. A total of 188 patients with a WT were older than 45 years and 122 patients (64.9%) suffered from a disease associated with the metabolic syndrome. Fisher's exact test also showed a statistically significant difference in the prevalence between WT and other parotid gland tumors ($p < 0.0001$).

Evaluation of the BMI revealed a higher BMI in patients with WTs. Patients with a WT had a mean BMI of 29.1 (range, 19.1–50.9) in comparison to a mean BMI of 26.2 (range, 14.9–45.7) in the control group. An independent *t* test revealed a significant difference in BMI between patients with a WT and other parotid gland tumors ($p < 0.0001$). Additionally, 75 WT patients (39.9%) were classified as overweight and 74 (39.4%) patients as obese. We could observe a similar percentage of overweight patients (37.8%, $n = 28$) in the control group, but only 13.5% ($n = 10$) had a BMI > 30.

Furthermore, we evaluated the above blood parameters in both groups. Detailed results of this analysis are shown in Table 2. We could detect statistically significant differences for HDL and triglyceride.

Table 2 Statistical analysis of differences in body mass index and blood parameters between Warthin's tumor and other benign parotid gland tumor patients (> 45 years)

	Warthin's tumor Mean (± SEM)	Benign tumors Mean (± SEM)	*p* value
BMI	29.1 (± 0.4)	26.18 (± 0.6)	< 0.0001
HDL (mg/dL)	50.3 (± 1.6)	63.10 (± 4.4)	0.0009
LDL (mg/dL)	130.1 (± 5.8)	134.10 (± 7.1)	0.7490
Total cholesterol (mg/dL)	213.3 (± 5.0)	208.2 (± 7.7)	0.5887
Triglyceride (mg/dL)	171.5 (± 11.0)	119.4 (± 8.0)	0.0088
HbA_{1c} (%)	6.7 (± 0.3)	6.6 (± 0.3)	0.7773
GGT (U/L)	46.2 (± 5.1)	32.35 (± 3.9)	0.2514
ASAT (U/L)	26.5 (± 1.5)	24.9 (± 2.0)	0.4466
ALAT (U/L)	25.3 (± 1.1)	24.2 (± 1.7)	0.2534
Fibrinogen (mg/dL)	389.3 (± 8.2)	339.5 (± 12.6)	0.0979
CRP (mg/dL)	0.9 (± 0.1)	0.5 (± 0.2)	0.0891
ESR after 1 h (mm/h)	12.1 (± 0.9)	10.3 (± 1.6)	0.3206
ESR after 2 h (mm/h)	25.5 (± 1.6)	21.1 (± 2.3)	0.0955

SEM standard error of the mean, *BMI* body mass index, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, HbA_{1c} glycated hemoglobin, *GGT* gamma-glutamyl transpeptidase, *ASAT* aspartate transaminase, *ALAT* alanine transaminase, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate

Influence of parameters on the size of Warthin's tumor

Subsequently, we wanted to evaluate whether these parameters affect tumor size. The mean tumor size of all WT patients was 23.8 mm (range, 5–55 mm). Since WT patients presented with a higher BMI, we wanted to determine whether higher BMI affects tumor size. Therefore, WT patients were stratified into three groups: (1) normal weight, (2) overweight, and (3) obese. Normal weight patients had a mean tumor size of 18.0 mm (range, 5–35 mm), whereas overweight WT patients had a mean tumor size of 23.0 mm (range, 7–53 mm). Obese patients showed the highest mean tumor size (27.7 mm; range, 12–55 mm). One-way ANOVA analysis detected a significant difference between these three groups ($p = 0.0299$). To evaluate a direct link between BMI and tumor size, Pearson's correlation coefficient R was calculated. However, it was not possible to detect a direct correlation between BMI and tumor size ($r = 0.4195$, $p < 0.0001$).

Also, we evaluated the effect of elevated blood test parameters on tumor size. Among the tested parameters, only patients with elevated fibrinogen levels had a significantly larger tumor size ($p = 0.0457$). It was not possible to detect a direct correlation between any blood test parameter and tumor size. These results are shown in Table 3.

Discussion

Until now, pleomorphic adenoma has been reported to be the most frequent histologic subtype of benign parotid gland tumors [13, 14]. The incidence rate of pleomorphic adenomas varies between 52 and 94% [1, 4]. Most recently, Luers and colleagues were able to document increasing incidence rates of WT in their retrospective study over the past 25 years. It was possible to detect an increasing proportion of WT patients from 24% in 1990 to 48% in 2014 [4]. Other studies have reported an analogical gradient of WT incidences [15]. It was possible to detect similar findings in our cohort. Nowadays, WT patients represent the most common histologic subtype at our institution. However, this is a single-institution experience, and to date, there are no

Table 3 Statistical analysis of the influence of evaluated parameters on Warthin's tumor size

	Mean tumor size (mm)			*p* value	*r*
	Normal values	Pathologic values			
BMI (> 25, > 30)	18.0	23.0	27.7	0.0299	0.4195
HDL (55 mg/dL)	22.3	24.3		0.5967	−0.1887
LDL (160 mg/dL)	24.0	24.1		0.9778	−0.1432
Total Cholesterol (200 mg/dL)	22.9	25.0		0.2546	−0.2038
Triglyceride (150 mg/dL)	22.6	25.6		0.1235	0.0915
HbA_{1c} (6%)	23.0	27.5		0.2825	0.1205
GGT (60 U/L)	24.0	24.1		0.9834	0.1112
ASAT (50 U/L)	23.8	26.1		0.4879	0.0373
ALAT (50 U/L)	23.4	25.1		0.2422	0.1255
Fibrinogen (400 mg/dl)	22.8	26.1		0.0457	0.1267
CRP (0.5 mg/dL)	23.9	26.4		0.2350	0.0353
ESR after 1 h (10 mm/h)	22.7	24.6		0.3086	0.0133
ESR after 2 h (20 mm/h)	22.9	24.3		0.4675	0.0315

Values in brackets present the upper limit of the reference range for each parameter and are accordingly subdivided into normal and pathologic values

r Pearson correlation coefficient r, *BMI* body mass index, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *HbA_{1c}* glycated hemoglobin, *GGT* gamma-glutamyl transpeptidase, *ASAT* aspartate transaminase, *ALAT* alanine transaminase, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate

multicenter epidemiological studies that have addressed this matter.

Therefore, we wanted to analyze the potential causes for this development. Currently, the relevant literature postulates tobacco smoking as the main risk factor for WT development [16, 17]. Our results demonstrate that WT patients show a higher percentage of smokers than other benign parotid gland tumor patients. These findings underline that smoking is associated with an increased risk of developing a WT.

However, statistics about the smoking behavior in Austria report only a marginal change in the percentage of smokers (from 23.5% in 1972 to 24.3% in 2014). This corresponds to an increase of 1.2 in absolute terms, but it is now possible to detect 3.9 times as many WT patients compared to the 1970s. Even population growth might not serve as an explanation for the rising numbers of WT patients. In particular, only 1.2 times as many people live in Austria in 2015 compared to 1970. Thus, we hypothesized that other factors are responsible for the increasing incidence of WT patients at our institution. Since diet and lifestyle are adversely associated with increasing numbers of many diseases in Western countries over the past few decades, we wanted to assess the influence of these conditions on WT patients. In the USA, the prevalence of the metabolic syndrome is reported to affect more than one-third of the adult population [18]. It is well known that metabolic syndrome is linked to an impressive number of diseases, and inflammatory processes often contribute to them. In our study, WT patients showed a significantly higher percentage of patients with a history positive for diseases associated with metabolic syndrome. This difference remained statistically significant even after the exclusion of young patients in the control group. Moreover, we were able to detect a significantly higher BMI in patients with WTs in comparison to patients with other parotid gland neoplasms; the mean BMI of WT patients was 1.1 times higher. Due to the retrospective character of our study, it was not possible to examine nutritional habits of our patients. Only smoking and alcohol drinking are routinely assessed at our institution. This has to be further investigated in prospective studies.

Consecutively, we assessed the effects of our evaluated parameters on tumor size. Here, it was possible to observe a potential link between being overweight and obese with tumor size. However, delayed detection and diagnosis in more obese patients might serve as a possible explanation for these results, rather than a direct link to obesity. Thus, these results have to be evaluated very carefully since this might be a relevant bias for this association.

Our findings are contrary to some of the published literature about differences between WT and PA. In 2006, Teymoortash and coworkers detected no differences in the incidence of concomitant diseases or blood parameters when comparing WT and PA [19].

However, based on their published data, the percentage of WT and PA patients with diseases associated with the metabolic syndrome (hypertension, diabetes, coronary heart disease) seems to be comparable to our cohort (WT 56.8% vs. PA 28.6%). Further studies are required to exemplify the

molecular pathogenesis of WTs and to prove a causal link between WTs and obesity.

In conclusion, smoking remains a key risk factor for the development of WTs. However, rising incidences cannot be solely explained by tobacco smoking. In this retrospective study, we were able to detect a possible link between metabolic syndrome, and in particular for the overweight, with the increasing incidences of WT patients. It should be emphasized that this work is intended as a hypothesis-generating study.

Acknowledgements This study was presented at the 60th Annual Meeting of the Austrian Society of Oto-Rhino-Laryngology—Head and Neck Surgery, Villach, Austria, September, 2016.

Funding No third party funding was obtained for this study.

Compliance with ethical standards

Conflict of interest All authors state to have no conflict of interest.

References

1. Upton DC, McNamar JP, Connor NP, Harari PM, Hartig GK (2007) Parotidectomy: ten-year review of 237 cases at a single institution. Otolaryngol Head Neck Surg 136:788–792
2. Pinkston JA, Cole P (1999) Incidence rates of salivary gland tumors: results from a population-based study. Otolaryngol Head Neck Surg 120:834–840
3. Tweedie DJ, Jacob A (2009) Surgery of the parotid gland: evolution of techniques, nomenclature and a revised classification system. Clin Otolaryngol 34:303–308
4. Luers JC, Guntinas-Lichius O, Klussmann JP, Küsgen C, Beutner D, Grosheva M (2016) The incidence of Warthin tumors and pleomorphic adenomas in the parotid gland over a 25 year period. Clin Otolaryngol 41:793–797
5. Patel DK, Morton RP (2016) Demographics of benign parotid tumours: Warthin's tumour versus other benign salivary tumours. Acta Otolaryngol 136:83–86
6. Kadletz L, Grasl S, Grasl MC, Perisanidis C, Erovic BM (2017) Extracapsular dissection versus superficial parotidectomy in benign parotid gland tumors: the Vienna Medical School experience. Head Neck 39:356–360
7. Pinkston JA, Cole P (1996) Cigarette smoking and Warthin's tumor. Am J Epidemiol 144:183–187
8. Witt RL, Iacocca M, Gerges F (2015) Contemporary diagnosis and management of Warthin's tumor. Del Med J 87:13–16
9. Nikolopoulou A, Kadoglou NPE (2012) Obesity and metabolic syndrome as related to cardiovascular disease. Expert Rev Cardiovasc Ther 10:933–939
10. Ng M, Fleming T, Robinson M et al (2014) Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the global burden of disease study 2013. Lancet 384:766–781
11. Flegal KM, Carroll MD, Kit BK, Ogden CL (2012) Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. JAMA 307:491–497
12. Alberti KG, Zimmet P, Shaw J, IDF Epidemiology Task Force Consensus Group (2005) The metabolic syndrome: a new worldwide definition. Lancet 366:1059–1062
13. Andreasen S, Therkildsen MH, Bjørndal K, Homøe P (2016) Pleomorphic adenoma of the parotid gland 1985–2010: a Danish nationwide study of incidence, recurrence rate, and malignant transformation. Head Neck 38(Suppl 1):E1364–E1369
14. Zhan KY, Khaja SF, Flack AB, Day TA (2016) Benign parotid tumors. Otolaryngol Clin N Am 49:327–342
15. Mantsopoulos K, Koch M, Klintworth N, Zenk J, Iro H (2015) Evolution and changing trends in surgery for benign parotid tumors. Laryngoscope 125:122–127
16. Yoo GH, Eisele DW, Askin FB, Driben JS, Johns ME (1994) Warthin's tumor: a 40-year experience at The Johns Hopkins hospital. Laryngoscope 104:799–803
17. de Ru JA, Plantinga RF, Majoor MHJM et al (2005) Warthin's tumour and smoking. B-ENT 1:63–66
18. Ford ES, Giles WH, Dietz WH (2002) Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA 287:356–359
19. Teymoortash A, Krasnewicz Y. Werner JA (2006) Clinical features of cystadenolymphoma (Warthin's tumor) of the parotid gland: a retrospective comparative study of 96 cases. Oral Oncol 42:569–573