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HEAD AND NECK

The growth rate and the positive prediction of needle biopsy of clinically diagnosed Warthin's tumor

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Abstract

Purpose This study reports the clinical course, including the growth rate, of Warthin's tumor (WT) and evaluates the positive prediction of needle biopsy for WT.

Methods The medical records of 182 patients clinically diagnosed with WT were retrospectively reviewed. Tumor growth rates were measured in patients who underwent serial radiologic exams with minimum 6-month time intervals, and the positive prediction value (PPV) of needle biopsy was evaluated in comparison with surgical pathology in patients who underwent surgical excision of the tumors.

Results Serial radiologic exams were available for growth rate measurement in 31 tumors (size 0.7–9.1 cm) from 25 patients. Among these, 24 tumors increased in size, and 7 were stable. The median follow-up duration was 23.5 months [interquartile range (IQR) 14.8–51.9], and the tumor growth rate ranged from −0.36 to 2.26 cm per year (median 0.26, IQR 0.07–0.44). Needle biopsy results were available for comparison with postoperative pathology specimens in 147 patients. The PPV was 97.7% for fine-needle aspiration biopsy and 100% for core-needle biopsy. There were no reports of inflammation, facial nerve paralysis, or admission event during the follow-up.

Conclusions WT glows slowly and can be predicted by needle biopsy. Therefore, parotid masses diagnosed as Warthin's tumor can be treated or left untreated based on the patient's needs and clinical decision-making.

Keywords Warthin's tumor · Growth rate · Fine-needle aspiration biopsy · Core-needle biopsy · Conservative management

Introduction

Papillary cystadenoma lymphomatosum, more commonly known as Warthin's tumor, is the second most common benign tumor of the parotid gland, after pleomorphic adenoma [1], and is characterised by its bilaterality, multifocality and its association with other malignancies and with smoking [2, 3].

While the preferred management of Warthin's tumor is a matter of some debate, surgery is generally considered the preferred treatment. Among all head-and-neck sites, the major salivary glands are associated with the greatest FNA inaccuracy rates [4]. A study showed that false-negative rate for malignant tumors was 32% [5]. For this reason, surgeons generally opt for surgery for patients with parotid tumor rather than observation awaiting diagnosis. While there have been case reports about facial paralysis caused by large Warthin's tumors [6, 7] and a study showed that Warthin's tumor presents with a high rate of systemic inflammation such as cellulitis and inflammatory bouts [8], but reports of complications and malignant transformation occurring during the observation of Warthin's tumor are rare [9]; nevertheless, only a few attempts have been made to observe progress without surgery [10, 11].

In determining the optimal treatment strategy for Warthin's tumor, it is essential to know whether the preoperative biopsy testing is accurate. It is also necessary to be familiar with the growth patterns and complications of

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an untreated tumor. However, due to the low incidence of Warthin's tumor, there are not enough published studies to provide sufficient evidence, and we lack sufficient knowledge in these areas.

From this perspective, the purpose of this study was to evaluate the growth rate of the tumor, the complications that may happen in unoperated patients during the follow-up period and how well the preoperative needle test could predict the actual final diagnosis.

Materials and methods

Patients

The medical records of 182 patients diagnosed with Warthin's tumor from January 2004 to May 2018 at a single tertiary hospital were retrospectively reviewed. The diagnosis was confirmed by surgery or FNAB and/or core-needle biopsy (CNB). The patient's age at the initial scan, gender, the radiologic images, any complications during follow-up period, and information as to whether patient had undergone surgery, as well as related pathologic reports, were reviewed. Smoking status of the patients was investigated at the time of initial diagnosis. Active smoker, ex-smoker, and never smoker, depending on whether they were smoking at the time of diagnosis.

Growth rate measurement

The size of the tumor was reviewed from the radiologist's report. Using the three-dimensional size, the longest axis of the tumor was measured; in the follow-up images, the same axis was used to measure the subsequent difference in length. The growth rate was measured by dividing the difference in the length by the time interval between the two radiological tests. A change was considered significant when the difference between the initial size and the final size was greater than 20%. A less than a 20% change was considered as not significant.

Evaluate predictive value of FNAB and CNB

To assist in assessing the predictive power of FNAB and CNB tests, reports of 'suggestive Warthin's tumor' or 'consistent with Warthin's tumor' were regarded as confirmed Warthin's tumor, and if differential diagnoses other than Warthin's tumor were made or the conclusion was non-diagnostic, they were classified as uncertain. This classification was analyzed with postoperative pathology results to measure the positive predictive value (PPV).

In the case of the patient of multiple tumors of the parotid, usually, not all of the tumors could be sampled by FNAB and/or CNB. Once Warthin's tumor was proven by biopsy, other tumors were assumed to be Warthin's tumors if their radiological findings were similar [12].

Study protocol

The study protocol was reviewed and approved by the Institutional Review Board of Seoul National University Bundang Hospital, and a waiver of informed consent was granted due to the retrospective design of the study (IRB No. B-1808/489-103).

Results

Tumor growth rate

Of 182 patients, 25 patients (21 males, 4 females) who underwent two or more CT or MRI scans at intervals of at least 6 months were able to be evaluated for tumor growth rate. The follow-up period of the patients ranged from 6 to 144 months (median 23.5 months, IQR 14.8–51.9). Of these patients, 5 had multiple tumors, with 31 tumors in total (range 0.7–9.1 cm, median 1.8 cm) (eTable 1 in the supplement). There were no complications (such as facial nerve paralysis) found in any patients at the time of diagnosis or during follow-up.

As shown in Fig. 1, the tumor size increased during the follow-up period (adjusted R^2 0.187, $P = 0.009$). Twenty-four tumors (77.4%; 18 patients) underwent a significant size increase of more than 20%, while seven tumors of seven patients were stable. No tumor underwent significant size decrease. Overall, the growth rate ranged from −0.36 to 2.26 cm per year; the median growth rate was 0.26 cm per year (IQR 0.07–0.44).

There was no significant correlation between growth rates and gender, initial size, tumor multiplicity or age at the time of the initial scan.

Predictive value of FNAB and CNB

Of the 182 patients with Warthin's tumor, 147 patients underwent surgery, and these were reviewed to evaluate the predictive value of FNAB and CNB. Three of these 147 patients afterwards underwent further surgical treatment for contralateral Warthin's tumors.

Of the 147 patients who underwent surgery, 23 patients were excluded from the analysis, because they underwent surgery without preoperative biopsy or underwent biopsy in other institutes. Sixty-eight patients underwent FNAB, 53 patients received CNB, and 3 patients received both (Fig. 2).

In the preoperative FNAB and CNB, patients who were diagnosed as 'suggestive of Warthin's tumor' or

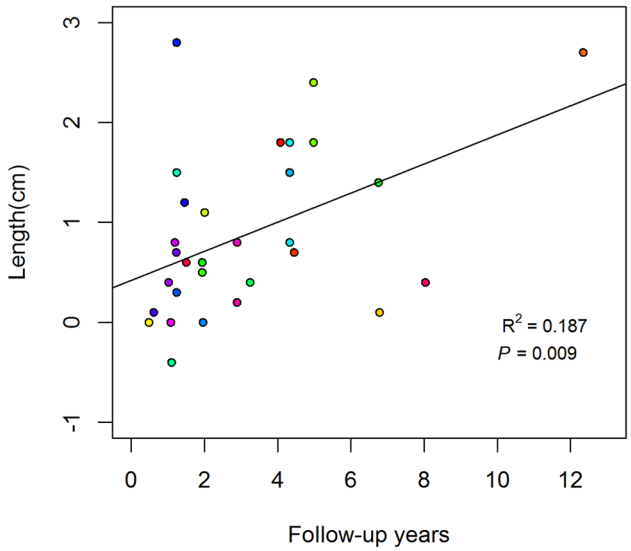

Fig. 1 Changes in the length of the long axis of 31 tumors during follow-up. Note the positive correlation between the duration of the observation and the tumor growth ($P=0.009$)

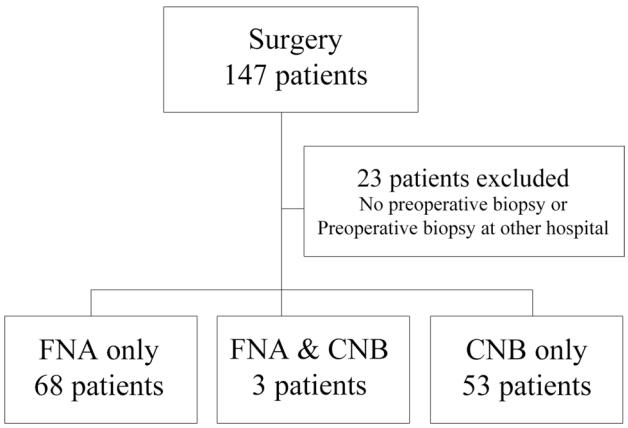

Fig. 2 Schematic diagram showing how the pre-operative test was performed in the 147 patients undergoing surgery. Of these, 23 patients were excluded, 68 underwent fine-needle aspiration (FNA) biopsy only, 53 had core-needle biopsy (CNB) only and 3 patients had both FNA and CNB

'consistent with Warthin's tumor', without any differential diagnosis, were regarded as having a confirmed diagnosis. Preoperatively, with FNAB, 43 of 68 patients, and 50 of 53 patients with CNB, were able to be diagnosed as Warthin's tumor. When compared to the postoperative results of pathology, only one patient underwent FNAB was diagnosed with mucoepidermoid carcinoma. Positive predictive value of FNAB was 98% (42/43) and CNB was 100% (50/50), respectively (Table 1).

Table 1 Positive predictive value (PPV) of fine-needle aspiration biopsy (FNAB) and core-needle biopsy (CNB)

	Warthin's tumor (postoperative result)		Total	PPV (%)
	Present	Not present		
FNAB	42	1	43	98
CNB	50	0	50	100

Note that positive prediction value was measured only in patients diagnosed with 'suggestive Warthin's tumor' or 'consistent with Warthin's tumor' in the preoperative needle biopsy

Table 2 Patients' age at diagnosis and tumor multiplicity according to smoking status

	Active smoker ($n=17$)	Ex- or never-smoker ($n=7$)	P value
Age at diagnosis, average	52.2 ± 8.4	72.2 ± 10.6	0.002
Tumor multiplicity, n	4 (23.5%)	0 (0.0%)	0.272

In the case of active smokers, the age at which the tumor was diagnosed was statistically low ($P=0.002$, two-sample t test). All four patients who had multiple tumors were active smokers, but there was no statistical significance ($P=0.272$, Fisher's exact test). Note that 1 patient was excluded, because their smoking history was unknown

Smoking status

The smoking history of the patients was also investigated. At the time of diagnosis, 17 patients were active smokers, 6 patients were ex-smokers, 1 patient had never smoked, and 1 patient's smoking history was not investigated (eTable 2 in the supplement). In conclusion, 23 of 24 patients (95.8%) had a smoking history.

Comparisons in the two groups are shown in Tables 2 and 3. The only factor found to have a significant correlation to smoking status was age at diagnosis ($P=0.002$). Active smokers tended to be diagnosed with Warthin's tumor earlier than ex-smokers or never-smokers. All four patients who had multiple tumors were active smokers, but there was no statistical significance ($P=0.272$). Whether or not the patient was smoking at the time of diagnosis was not statistically related to the initial size of the tumor ($P=0.771$). Tumors of the active smokers appeared to grow faster and showed a high percentage of tumors with increased size, but these were not statistically significant ($P=0.266$, 0.208, respectively).

Table 3 Initial size, growth rate, and size change of tumors according to smoking status

	Tumors of active smokers ($n=23$)	Tumors of ex- or never- smoker ($n=7$)	P value
Initial size (cm)			
Average	3.3 ± 2.3	3.0 ± 1.9	0.771
Growth rate (cm)			
Median	0.26	0.16	0.266
IQR	0.12–0.48	0.00–0.40	
Size change			
Increase (≥ 20%)	19 (82.6%)	4 (57.1%)	0.208
Stable	4 (17.4%)	3 (42.9%)	
Decrease (≤ 20%)	0 (0.0%)	0 (0.0%)	

Smoking status and the initial size of the tumors was not statistically related ($P=0.771$, two-sample t test). Tumors of active smokers appeared to grow faster and showed a high percentage of tumors with increased size, but these were not statistically significant. ($P=0.266$, Mann–Whitney U test, $P=0.208$, two-sample t test, respectively). Note that one tumor of a patient was excluded, because their smoking history was unknown

Discussion

Warthin's tumor has low incidence and is a benign tumor, but to date, there has been no in-depth discussion of the best treatment strategy for this condition, with the choice of surgery and observation being a matter of debate [10, 13]. When a reliable diagnosis is difficult to obtain, observation as treatment for patients with Warthin tumor is controversial [14].

Surgeons concerned that the preoperative FNAB or CNB results may not be accurate, and worry about the possibility of malignant transformation of the tumor [9] and the facial paralysis in the patient that may occur during the growth of the tumor [6, 7]. In fact, research shows that the most common reason for elective surgery is for a definitive pathologic diagnosis to rule out a malignancy, with the second reason being an increase in tumor size [11]. A study reports that Warthin's tumor was the most common false-negative diagnosis of acinic cell carcinoma and squamous cell carcinoma [15].

On the other hand, there are also rational reasons for adopting conservative management. First, Warthin's tumor has a low rate of malignant transformation [9], and second, facial nerve paralysis during surgery is always a possibility [16]. Indeed, some studies have concluded that conservative treatment may the justifiable option [10, 11, 17, 18]. One study has revealed that the most common reason for avoiding surgery was the desire to avoid the risks of surgery [11].

Amid this controversy, a good understanding of the disease is essential in managing the patient conservatively, and this includes knowing how reliable the results of FNAB or CNB are in making the diagnosis of Warthin's tumor.

The reported sensitivity or specificity of FNAB or CNB of the salivary gland mass has differed according to researchers, but overall, the studies have shown a high positive predictive value for these tests. For FNAB, a study has shown a specificity of 98.6% and a positive predictive value of 88.9% [19], and in the case of CNB, two studies have shown a specificity of 99% and a positive predictive value of nearly 100% [19, 20]. The implications of these results are that not all parotid tumors can be initially accurately diagnosed by clinical means, but once diagnosed by FNAB or CNB, there is a high probability of diagnostic matching. In our study, we observed similar results, in that the FNAB of Warthin's tumor showed a positive predictive value of 97.7%, while CNB of Warthin's tumor showed a positive predictive value of 100%. Thus, if the diagnosis of Warthin's tumor is made preoperatively, the results of these needle biopsy tests can be fully relied upon.

From our results, it was also possible to estimate the growth rate of Warthin's tumor diagnosed using FNAB or CNB. In this study, of 25 tumors of increasing size, the growth rate was − 0.36 to 2.26 cm (median 0.26, IQR 0.07–0.44) per year. The difference in the growth rate of a tumor varied from person to person, and even varied among multiple tumors in the same patient. Our result differs from that of a tertiary center in the United States [12], and the difference may be due to the fact that both studies reviewed small numbers of patients. In addition, it is possible that patients whose tumor size did not change or in fact decreased may have discontinued attending the hospital. Genetic and epidemiologic factors also may have affected the outcome [21].

As was the case in the study reported previously [11], no patients of this study experienced complications during the follow-up period. There were studies in which Warthin's tumor was associated with inflammation; Warthin's tumor presents with a high rate of symptomatic inflammation [8], and parotitis following fine-needle aspiration was more common in patients with Warthin's tumor [22]. However, in this study, there was no patients who had inflammation after needle biopsy and during the follow-up period in unoperated patients.

The association of Warthin's tumor with smoking with is already well known, and indeed 23 patients (95.8%) had a smoking history, with 2 patients either not knowing their smoking history or denying smoking. An interesting result was that the age at diagnosis was significantly lower in the active smoker group ($P=0.002$), as shown in Table 2. This result may be a supplementary evidence of a matched case–control study which revealed the risk of Warthin's tumor decreased sharply after smoking cessation [23]. In this study, there seemed to be a relationship between smoking

status and significant size change or growth rate of tumor, but this was not of statistical significance. The reason may be due to the small number of patients in this study.

There are obvious limitations to this study. As described above, this study targets a small number of patients and tumors and cannot give an entire picture of Warthin's tumor. In addition, because this study is retrospective, there is the possibility of selection bias, and there is the selection bias arising from patients being encouraged to choose surgical treatment when the size of the tumor was large. Moreover, the sensitivity or specificity (i.e., the accuracy) of tests other than PPV was not evaluated. Because the parotid gland needle biopsy can show various pathology results, there was a problem as to which results could be defined as a 'true negative' for Warthin's tumor.

Further prospective studies such as a cohort study are needed to evaluate the tumor growth rate more accurately, to understand the natural course of the tumor, and to determine when tumors should be surgically removed.

Conclusion

In this study, we showed that the growth rate of Warthin's tumor ranged from − 0.36 to 2.26 cm per year (median 0.26, IQR 0.07–0.44) and varied from patient to patient. There were no complications during follow-up. Based on high positive predictive value of needle biopsy (FNAB 97.7%, CNB 100%), parotid masses diagnosed with Warthin's tumor can be treated or left untreated based on patients' needs and clinical decision-making.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Consent is not required because of retrospective study. This study is granted exemption from IRB review.

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