

Main Article

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Bilateral Warthin's tumour of the parotid gland: a 16-year retrospective analysis and systematic review

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Abstract

Objective. Warthin's tumours are the second most common benign parotid tumours in the UK. The World Health Organization states that 5–14 per cent of patients have bilateral Warthin's tumours. This study aimed to: assess the presence of contralateral Warthin's tumours in patients who underwent surgery over the past 16 years at a head and neck unit in England, and perform the first systematic literature review on bilateral Warthin's tumours.

Methods. A retrospective analysis was conducted on patients diagnosed with Warthin's tumour based on histology between 2005 and 2020. Additionally, a systematic review (International Prospective Register of Systematic Reviews ('PROSPERO') registration number: CRD42022326846) was performed using PubMed and the Cochrane Library.

Results. Among 290 patients diagnosed with Warthin's tumours based on histology following surgery, 24.5 per cent had bilateral Warthin's tumours. The systematic review identified 157 papers, with 14 meeting the inclusion criteria.

Conclusion. This study revealed that 24.5 per cent of patients had bilateral Warthin's tumours, deviating from the suggested range. These findings are of interest to surgeons discussing the disease with patients.

Introduction

Warthin's tumour, also known as papillary cystadenoma lymphomatosum, adenolymphoma and lymphomatous adenoma, is a benign growth in the parotid gland; it is the second most prevalent type of benign tumour of the parotid gland following pleomorphic adenoma.¹ According to the World Health Organization (WHO) Classification of Head and Neck Tumours, Warthin's tumour accounts for 2–15 per cent of all primary epithelial tumours within the parotid gland.¹

Warthin's tumours typically manifest as painless, slowly expanding, solid lumps in men aged 50–70 years, with a higher incidence in smokers. The tumours, on average, measure 2–4 cm upon detection.²

While Warthin's tumours are predominantly unilateral, the WHO records that bilateral Warthin's tumours appear in 5–14 per cent of patients.³ However, there is substantial divergence in the medical literature concerning the percentage of bilateral Warthin's tumours. Bilateral Warthin's tumours may occur synchronously or metachronously, more often the former.^{3–5}

Historically, the male-to-female ratio of Warthin's tumour has been reported to be as high as 10:1, but more recent estimates suggest a ratio of 5:1, and even as low as 2:1.^{6,7}

Clinical assessment, imaging and cytology inform the diagnosis of Warthin's tumour, but histology is the only definitive confirmation. Of Warthin's tumours, 0.3 per cent undergo malignant transformation, with malignant lymphoma being the typical alteration and epithelial malignancy being extraordinarily uncommon.⁸ Unless there is diagnostic ambiguity or symptomatic complications, Warthin's tumour tends to be a sole parotid lump, which is managed conservatively.

Investigations

In the UK, ultrasonography with fine needle aspiration cytology (FNAC) was previously the 'gold standard' for initial Warthin's tumours diagnosis.⁹ However, ultrasound-guided core biopsy has now emerged as the principal diagnostic technique for assessing patients with salivary gland tumours, especially when malignancy is suspected. Core biopsy shows higher sensitivity and specificity than FNAC, and has shown impressive sensitivity and specificity, 92–94 per cent and 99–100 per cent respectively, for diagnosing Warthin's

tumour.^{10,11} The parotid mass undergoes histological examination to confirm the diagnosis.

If there is clinical suspicion of deep lobe involvement or malignancy before surgery, a magnetic resonance imaging (MRI) scan is the preferred investigation; however, if that is contraindicated, a computed tomography (CT) scan with contrast may be considered. An MRI scan is also employed for disease surveillance.¹² Challenges with all imaging methods include differentiating malignant from benign tumours and visualising the facial nerve.⁹ Dynamic contrast-enhanced MRI, a novel form of MRI, is being explored as a diagnostic tool for Warthin's tumours, with promising results.¹³

Management

With its slow growth and low malignant transformation rate (0.3 per cent), Warthin's tumour management is predominantly conservative (watch and wait). Surgical intervention might be contemplated if there is diagnostic ambiguity, facial nerve involvement, facial pain or aesthetic concerns.^{8,14} However, bilaterality does not favour the decision to operate. The surgical approach depends on the tumour location. For superficial lobe Warthin's tumour, a superficial parotidectomy or extra-capsular dissection is often performed. Extra-capsular dissection is typically chosen for benign parotid superficial lobe tumours measuring less than 4 cm.¹⁵ If Warthin's tumours are situated in the deep lobes, a total or near total parotidectomy may be performed, depending on tumour location. Warthin's tumours can also present at the parotid gland tail, where a partial parotidectomy may be carried out.

Aim

This study aimed to examine and evaluate the presence of contralateral Warthin's tumours among patients with positive histology results following surgical excision over the past 16 years at a high-volume head and neck unit in Kent, England. We conducted the first (to the best of our knowledge) systematic literature review on bilateral parotid Warthin's tumour, which aimed to enhance our comprehension of the prevalence, sex ratio and age at which this disease occurs.

Materials and methods

We conducted a single-centre retrospective analysis of patients diagnosed with Warthin's tumour based on histology following surgery between 1 January 2005 and 31 December 2020. A total of 290 patients (178 males and 112 females) underwent surgical excision of what was subsequently confirmed on histology to be a Warthin's tumour.

The study included patients with positive histology results following surgical excision. The data were digitally retrieved from the histology database. Contralateral Warthin's tumours were evaluated using ultrasound-guided FNAC, and MRI or CT scanning, with some doctors opting for surgical management or a histological diagnosis.

Search strategy, inclusion and exclusion criteria

The systematic review was conducted as per the standard outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') statement. This study was registered with the International Prospective Register of

Systematic Reviews ('PROSPERO') (registration number: CRD42022326846).

We carried out searches using the PubMed database and the Cochrane Library, to identify published studies describing patients, at any age, who were diagnosed with bilateral Warthin's tumour. The search terms (including Medical Subject Headings (MeSH terms)) and Boolean operators for PubMed were: (("Warthin tumour"[All Fields] OR "adenolymphoma"[MeSH Terms] OR "adenolymphoma"[All Fields] OR ("Warthin"[All Fields] AND "tumor"[All Fields]) OR "Warthin tumor"[All Fields]) OR ("Bilateral"[All Fields] AND ("Warthin tumour"[All Fields] OR "adenolymphoma"[MeSH Terms] OR "adenolymphoma"[All Fields] OR ("Warthin"[All Fields] AND "tumor"[All Fields]) OR "Warthin tumor"[All Fields])) OR ("lymphoma"[MeSH Terms] OR "lymphoma"[All Fields] OR "lymphomatous"[All Fields]) AND ("cystadenoma, papillary"[MeSH Terms] OR ("cystadenoma"[All Fields] AND "papillary"[All Fields]) OR "papillary cystadenoma"[All Fields] OR ("papillary"[All Fields] AND "cystadenomas"[All Fields]) OR "papillary cystadenomas"[All Fields])) OR "cystadenolymphoma"[All Fields]) AND "Bilateral"[All Fields]).

Screening, data extraction and quality assessment

An initial search was conducted using the abovementioned search strategy; discrepancies in terms of inclusion and exclusion decisions were discussed, and refinement of the application of these criteria was undertaken. The full screening process was independently carried out by two authors (RHKN and AG), with any conflicts being resolved by our co-first author (ZS). The full texts of potentially relevant articles for the review were retrieved and independently reviewed by RHKN and AG.

Eligibility criteria during data screening incorporated studies written in English language that described the prevalence of bilateral Warthin's tumour, and were not non-human studies, systematic reviews, literature reviews, or conference papers or abstracts. The systematic review identified 157 papers, with 14 meeting the inclusion criteria (Figure 1).

All data screening and extraction processes were implemented in MicrosoftTM Excel[®] software. In this study, we extracted: (1) first author's last name and publication year; (2) study timescale; (3) study country; (4) total sample size of the Warthin's tumour patient cohort; (5) number of bilateral Warthin's tumours; and (6) sex ratio. We used the 13-item Case Report ('CARE') guideline to evaluate the quality of case series studies, and the Newcastle-Ottawa Quality Assessment Scale for case-control and cohort studies.

Statistical analyses

IBM SPSS[®] software was used for all statistical comparisons. A *p*-value of less than 0.05 was considered statistically significant.

Results

Of the 290 cases, 71 had bilateral or contralateral Warthin's tumours, yielding a prevalence rate of 24.48 per cent over the 16-year period in our case series study. Among the 290 cases, there were 178 males and 112 females, resulting in a sex ratio of 1.6:1. Thirty-nine males and 32 females were diagnosed with bilateral Warthin's tumour. Table 1 illustrates that there was no significant difference between males and females

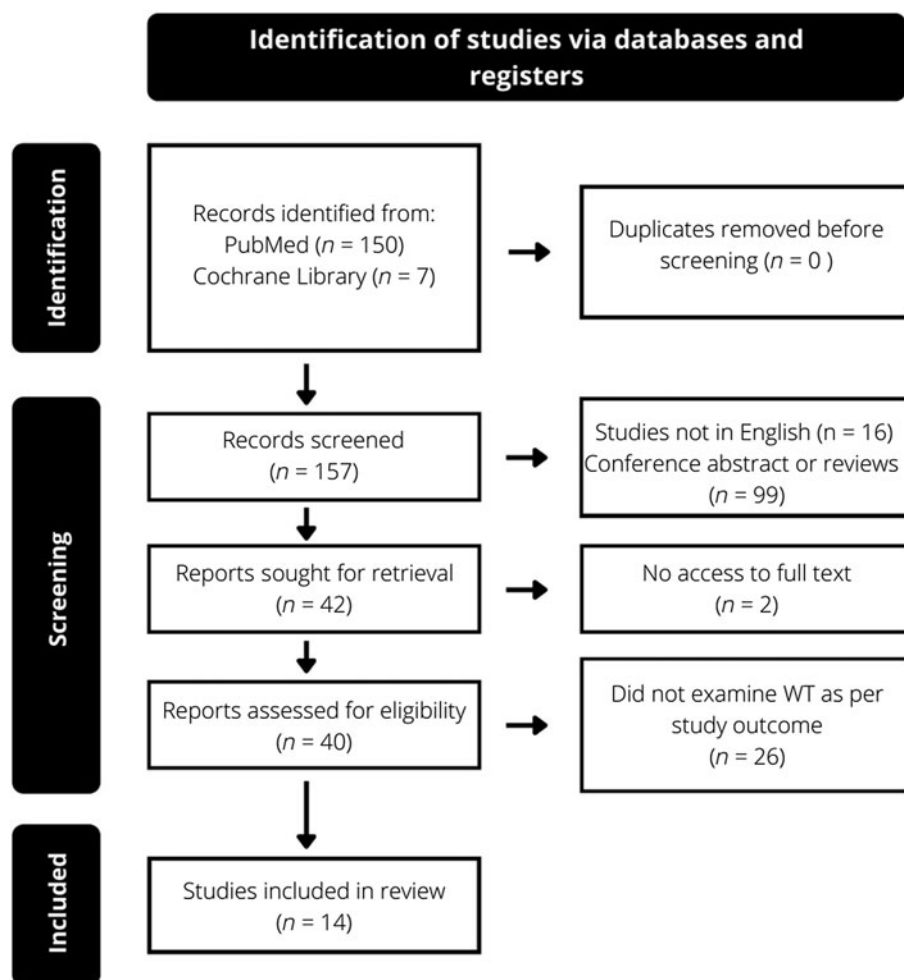


Figure 1. Identification of studies via databases and registers. WT = Warthin’s tumours

Table 1. Bilateral versus unilateral Warthin’s tumour divided by sex

Sex	Unilateral	Bilateral	Total
Male	139	39	178
Female	80	32	112
Total	219	71	290

Data represent numbers of cases

in terms of unilateral and bilateral tumours, as the chi-square test *p*-value was 0.199 (*p* < 0.05). Eight of the patients underwent contralateral parotidectomies.

Throughout the analysed study period, an increasing number of patients were diagnosed with Warthin’s tumours in both unilateral and bilateral forms, as depicted in Figure 2. The average age at diagnosis for both unilateral and bilateral Warthin’s tumours was higher for females compared to males in our cohort. The mean values for both groups are summarised in Table 2. Regarding age distribution, our data revealed that most patients diagnosed with Warthin’s tumour were aged 60–70 years. Furthermore, Figure 3 shows that the peak diagnostic age for Warthin’s tumours ranged between 50 and 80 years.

As seen in Table 3, 14 papers from 1980 to 2019 were included in our systematic review.^{3,16–28} These papers included patients with at least one histological diagnosis of Warthin’s tumours. The largest study had 1084 patients and the smallest had 25 patients. There was significant variation in the reported bilateral nature of the disease and the sex ratio. There was variation even among studies conducted within the same country.

In 2013, Xu *et al.*²³ reported a bilateral tumour rate of 40 per cent, with a male to female ratio of 7.3:1. In 2018, Xu *et al.*²⁷ performed a larger study, which showed a 0.65 per cent bilaterality and 11:1 male to female ratio. German studies conducted by Teymoortash *et al.*¹⁹ and Klussmann *et al.*²⁰ showed some consistency; however, Seifert *et al.*¹⁶ reported half the rate of bilateral Warthin’s tumours.

Discussion

The prevalence of bilateral Warthin’s tumour is not currently agreed upon. The WHO Classification of Head and Neck Tumours states that the prevalence of bilateral involvement can be between 5 and 14 per cent.¹ In our systematic review, the prevalence of reported bilateral Warthin’s tumours varied widely, from as low as 0.65 per cent to 40 per cent, as seen in Table 3. The mean reported prevalence was 12.5 per cent, which aligns with the WHO classification of tumours.¹

The primary finding from our study is the contralateral Warthin’s tumour rate of 24.5 per cent. This should prompt us to discuss the bilateral nature of this disease with patients who are diagnosed with Warthin’s tumours or who undergo resection of this tumour.

Additionally, our study found an increasing incidence of both unilateral and bilateral Warthin’s tumours over our 16-year study period, as seen in Figure 2, which may represent an increasing incidence in the general population. The incidence is difficult to assess from this study as a large cohort are not diagnosed histologically. Interestingly, the increasing rates of diagnosis may also be the result of an ageing

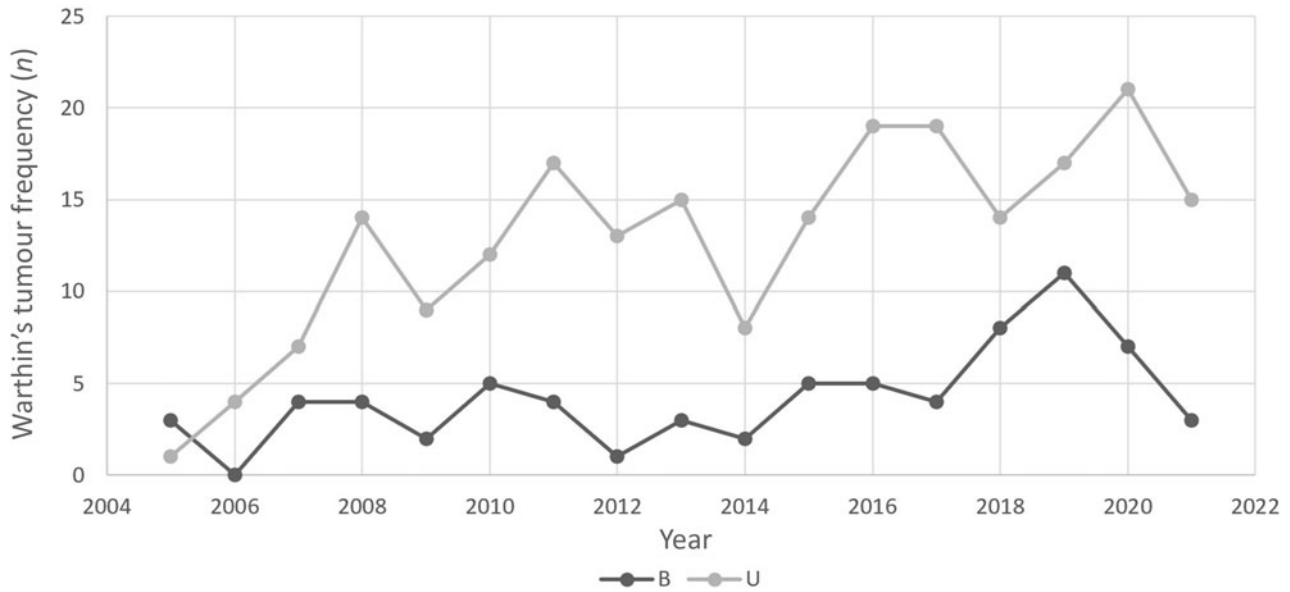


Figure 2. Trend of bilateral ('B') and unilateral ('U') tumour frequencies from 2005 to 2021.

Table 2. Average age at diagnosis of bilateral versus unilateral Warthin's tumour divided by sex

Laterality	Female	Male	Total
Bilateral	67.75	63.13	65.21
Unilateral	65.19	63.19	63.92
Total	65.92	63.18	64.24

Data represent mean patient age at diagnosis, in years

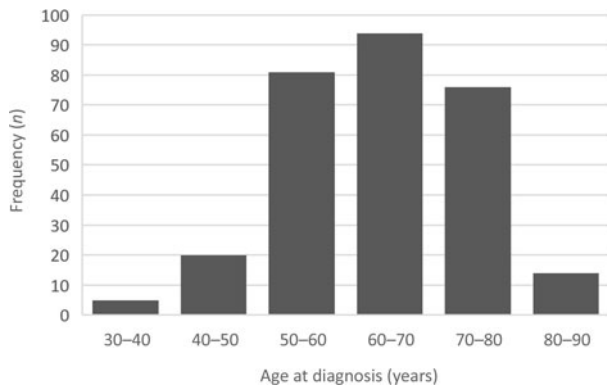


Figure 3. Frequencies of ages at diagnosis.

population. The increasing incidence of Warthin's tumours has been mentioned in earlier studies, possibly due to an increasing elderly population and improved diagnostic capability.^{6,7,27} The increase specifically in female patients may also be a result of an increase in the numbers of women smoking.¹⁷

The prevalence of bilateral Warthin's tumour varies in the literature. Three studies from Germany presented significantly different rates of bilateral Warthin's tumour prevalence, ranging from 7.5 per cent to 16.7 per cent.^{16,19,20} Franzen *et al.*²⁹ reported a bilaterality of 41 per cent in a German cohort, but this is not comparable to our study, as those authors specifically investigated only multiple parotid tumours

and excluded all solitary tumours. Only two studies in the systematic review presented higher bilaterality than our study: Xu *et al.*,²³ who reported 40 per cent, and Patel and Morton,²⁴ who reported 30 per cent. However, the sample size for both studies was small, at 25 and 41 patients respectively; therefore, their results are less likely to represent the population at large.

The significant variation reported is due to a lack of research into Warthin's tumours. This may be the result of a lack of interest in Warthin's tumours, as they are benign tumours and, in many cases, can be treated with a single operation. Even the origin of the tumour is not well understood. The current hypothesis is that it arises from proliferating salivary gland ductal cells that were entrapped in parotid lymph nodes. Therefore, Warthin's tumours are tumour-like lesions rather than adenomas.³⁰

The mean age at diagnosis for unilateral and bilateral Warthin's tumours in our study was 65.2 and 67.8 years old respectively. This is in accordance with the WHO classification of Head and Neck Tumours, which reports that Warthin's tumours are most often diagnosed in people aged 50–70 years.¹ Seifert *et al.*¹⁶ (1980) reported similar findings, with most Warthin's tumours, of 275 cases, being diagnosed in patients in their sixth decade of life. Xu *et al.*²⁷ reported, in a sample of 1084 patients, an average age at diagnosis of 56.48 years, with 82 per cent of cases being diagnosed in patients aged 50–70 years. Klussman *et al.*²⁰ also reported a median age at diagnosis of 60 years in 185 cases. It is interesting to note that there were 5 patients diagnosed at 30–40 years of age and 20 patients diagnosed at 40–50 years of age. Although Warthin's tumour tends to affect older people, it must still be considered as a diagnosis in younger patients presenting with a parotid gland mass.

Our study revealed a male-to-female ratio of 1.6:1. The majority of the papers included suggest a higher male dominance (Table 3). The highest reported male-to-female ratios were from: Maiorano *et al.*,³ who reported a 19:1 ratio in their Italian cohort; Xu *et al.*,²⁷ who reported 11:1 in their cohort of 1084 Chinese patients; and Lee *et al.*,²⁵ who reported 9:1 in 110 South Korean patients. In comparison, the lowest reported male-to-female ratios come from: Patel and

Table 3. Studies identified from systematic review reporting bilaterality of Warthin's tumours and sex ratios

Author(s)	Publication year	Study period	Location	Sample size (patients, n)	Bilateral Warthin's tumour (%)	Male to female ratio
Seifert <i>et al.</i> ¹⁶	1980	1965–1979	Germany	275	7.5	3:1
Ebbs & Webb ¹⁷	1986	1951–1984	UK	57	5.3	2.6:1
Chung <i>et al.</i> ¹⁸	1999	1988–1998	Singapore	73	9.6	4.6:1
Maiorano <i>et al.</i> ³	2002	1987–1998	Italy	78	6.5	19:1
Teymoortash <i>et al.</i> ¹⁹	2006	1998–2005	Germany	81	12.3	3.3:1
Klussmann <i>et al.</i> ²⁰	2006	1990–2000	Germany	185	16.7	2.3:1
Viguer <i>et al.</i> ²¹	2010	n/a	Spain	110	3.6	8.09:1
Chedid <i>et al.</i> ²²	2011	1979–2007	Portugal	70	5.7	1.7:1
Xu <i>et al.</i> ²³	2013	2009–2011	China	25	40	7.3:1
Patel & Morton ²⁴	2016	2001–2014	New Zealand	41	30	1.56:1
Lee <i>et al.</i> ²⁵	2019	2006–2016	South Korea	110	7.3	9:1
Sagiv <i>et al.</i> ²⁶	2017	n/a	USA & Israel	72	9.8	2.4:1
Xu <i>et al.</i> ²⁷	2018	1993–2010	China	1084	0.65	11:1
So <i>et al.</i> ²⁸	2019	2006–2017	USA	177	2	1.85:1
Current study	2024	2005–2021	UK	290	24.5	1.6:1

n/a = not applicable

Morton²⁴ with a ratio of 1.56:1 in a cohort from New Zealand; So *et al.*,²⁸ reporting 1.85:1 from their US cohort; and our study. There is considerable variation in the reported sex ratios. However, none of the previous studies showed a higher female to male ratio; this aligns with the WHO classification, which states that male sex is a risk factor for Warthin's tumour.¹

An interesting detail regarding the sex incidence ratios is their increasing female trend. Ebbs and Webb¹⁷ found that the proportion of affected females increased over their data collection period. Before 1965, all patients were male, between 1965 and 75 the ratio was 3:1, and between 1975 and 85 the ratio was 1.6:1. They purport that the reason for this was an increase in the prevalence of smoking in females. Lamelas *et al.*³¹ found the same in their cohort and gave a similar reason of increased smoking in females for the decreasing sex ratio. Furthermore, Franzen *et al.*,²⁹ in addition to their reported increase in the frequency of Warthin's tumour, identified that the incidence ratio between males and females decreased from 5:1 to 2:1 over their data collection period.

- According to World Health Organization, Warthin's tumours are bilateral in 5–14 per cent of cases; however, this systematic review shows a much wider range
- This study found contralateral Warthin's tumours in 24.5 per cent of 290 patients who underwent surgery, based on histology
- Frequency of Warthin's tumour has increased over the last 16 years
- A decreased sex ratio was also evident in our study, as has been mentioned previously, but there are large disparities in the data

The rate of contralateral tumours identified in our study has implications for clinical practice. Although Warthin's tumours rarely become malignant, they do cause distress to patients, with some patients presenting with facial swelling or pain. Xu *et al.*²⁷ recommend performing superficial bilateral parotidectomies for their patients in China; however, practice in the UK is much more conservative. Initial investigation of a Warthin's tumour should consist of a combination of clinical feature examination, imaging, and core biopsy or FNAC in

both parotid glands, to ensure that bilateral tumours are not missed. There have been reports of metachronous development of bilateral Warthin's tumour. Patients should be warned of this possibility, and be given advice on what symptoms and signs may suggest metachronous development of a Warthin's tumour. Clinicians may wish to follow up patients for this possibility; however, given its rarity, this may not be a practical solution.

Limitations

The limitations of this study include its retrospective design and the limited selection of data variables collected. Given its retrospective design, the study is at risk of recall bias and selection bias. This is somewhat mitigated by the selection of consecutive patients diagnosed with Warthin's tumour. The limited data collection was intentional, for practical reasons, but it does limit more detailed comparison and analysis in relation to the existing literature. Synchronicity, smoking, surgical complications and recurrence have been measured in some other studies. Furthermore, it can be suggested that our high bilateral tumour rate is the result of data only being collected on patients who underwent surgery, thus it may not be representative of all Warthin's tumours. Future studies should address these limitations by prospectively collecting consecutive patient data with more variables, as well as collecting data on confirmed Warthin's tumours that are not operated on.

Conclusion

In our cohort of patients, who had a histological diagnosis of Warthin's tumour following surgical resection, these tumours were contralateral in 24.5 per cent of cases, and over 30 per cent of cases occurred in female patients. Our systematic review indicates that the rates of bilateral occurrence varies widely. We also provide evidence that the frequency of Warthin's tumour has increased over the last 16 years, with a decrease in the sex incidence ratio over time. We hope that

the findings of this study and the systematic review can provide valuable insights for clinicians when discussing the bilateral nature and prevalence of Warthin's tumour with patients.

Competing interests. None declared

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