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Lateral cystic neck masses in adults: a ten-year series and comparative analysis of diagnostic modalities

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Running Title

Lateral cystic neck masses in adults

Funding and Conflict of Interest

Nothing to declare

Ethical declaration

There was no direct patient interaction during this study. The proportionate review sub-committee of the Bromley research ethics committee externally reviewed the proposal for the project and approved it for completion on 3rd October 2019. Further information is available on request.

Research ethics committee reference number – 19/LO/1603

Abstract

Background

In adults the solitary lateral cystic neck mass (LCNM) remains a diagnostic challenge with little solid material to target for cytology and few clues on imaging modalities to suggest underlying malignancy.

Methods

A retrospective review of patients presenting with LCNM to a tertiary academic head and neck centre over a 10-year period.

Results

25/157 cystic lesions were subsequently malignant on paraffin section histopathology, with the youngest patient being 42. In the age >40 cohort, 30% of males and 10% of females were diagnosed with malignancy. The ipsilateral palatine tonsil was the most common primary site (50%). 85% demonstrated integrated human papillomavirus infection. Age, male sex and alcohol were significant risk factors on univariate analysis. Ultrasound guided fine needle aspiration cytology and MRI represented the most accurate pre-open biopsy tests.

Conclusion

We advocate a risk stratified, evidence based work up in these patients to optimise timely diagnosis.

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Key Words

Squamous Cell Carcinoma of Head and Neck

Lateral cystic neck masses

Branchioma

Lymphatic Metastasis

Papillomavirus Infections

1 Introduction

The solitary lateral cystic neck mass (LCNM) in adults remains a diagnostic challenge for head and neck surgeons. The majority of published studies report a benign congenital cyst as the most common diagnosis in the absence of any other signs or symptoms of head and neck cancer, however the rates of malignancy vary widely (9-72%), with a direct positive correlation with increasing age.[1–8] Diagnostic uncertainty creates significant anxiety for patients and reliance on inaccurate investigations may result in delayed or inappropriate management for concealed malignant disease in, for example, the oropharynx or thyroid.

A number of series have been published in an attempt to quantify the diagnostic accuracy of investigations, although often focussing on a single diagnostic modality. Ultrasound (US) can examine the thickness of the cyst wall and the presence of solid elements to help guide fine needle aspiration cytology (USgFNAC) or core needle biopsy (CNB).[9] Computerised tomography (CT) and magnetic resonance imaging (MRI) are useful to examine potential primary tumour sites and assess the anatomy surrounding the cystic mass for surgical planning, although their ability to differentiate benign and malignant neck masses is often limited.[10,11] Fluorine-18 fluorodeoxyglucose (^{18}F-FDG) positron emission tomography-CT (PET/CT) is gaining popularity in the work-up of cystic neck nodes[12] but limitations include incidental false-positive findings in other organ systems in up to 33% of head and neck cancer patients, and significant doses of ionising radiation; a cost-benefit advantage has not been proven.[13] Fine needle aspiration cytology (FNAC) is useful in the diagnosis of solid neck masses but is often limited in lesions extensively affected by cystic degeneration due to a paucity of cellular material to target, with

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resultant poor diagnostic accuracy[14] For cystic neck masses the sensitivity and specificity yields improve as more viable solid material is obtained (Open biopsy>CNB>FNAC). The sensitivity for FNAC, CNB and frozen section (FS) has been quoted as 59%, 83% and 93% respectively while specificity has been reported as 83%, 100% and 92% respectively.[15] Although open biopsy obtains the greatest diagnostic accuracy, there are historic concerns regarding neck contamination and potential spillage/dissemination of cancer cells.[16,17] Evidence suggests however that tumour seeding from the head and neck is a very rare occurrence.[18,19]

We present our 10-year experience of investigating LCNM in adults, representing the largest published series of this clinical presentation to date. These numbers allow both a comparative analysis of diagnostic accuracy for a wide range of investigative modalities and regression analysis of variables that may increase the risk of a subsequent malignant diagnosis. Finally, we suggest a management algorithm to help stratify investigations for patients with these lesions and minimise time to diagnosis.

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2 Materials and Methods

2.1 Case identification and review

All patients presenting with a solitary LCNM to our tertiary academic head and neck centre between 2009 and 2019 inclusive were identified. We retrospectively reviewed operating theatre records, electronic patient records and the head and neck cancer registry to collect demographic data, reports/outcome of investigations, histopathology reports and final diagnosis. Exclusion criteria included; <18 years old, midline lesions, primary skin lesions (basal cell carcinoma, sebaceous cyst), multiple synchronous pathological lymphadenopathy and an obvious primary tumour on oral inspection, flexible endoscopy. Cases were also excluded if there was an obvious primary thyroid lesion on US later confirmed by thyroid excision histology. Human papillomavirus (HPV) testing of tissue potentially from primary oropharyngeal malignancies became routine midway through the study period, and included in-situ hybridisation and immunohistochemistry for p16 protein, requiring both for viral confirmation.

2.2 Literature review

To identify comparable case series we searched the MEDLINE electronic database for English-language articles between January 1990 to July 2020 using the following search terms: lateral neck cyst and lateral cervical cyst. We identified additional references by screening bibliographies of identified series.

2.3 Data analysis

Likelihood ratios predicting the presence of malignancy based on a positive result in

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each investigative modality were calculated, given a positive test result (sensitivity/1-specificity) and a negative test result (1-sensitivity/specificity). Further, the accuracy of each test i.e. the overall probability that a patient is correctly classified as having benign or malignant disease was calculated (Sensitivity × Prevalence + Specificity × (1 − Prevalence)). All analysis was performed using Microsoft Excel and IBM SPSS, Statistics 22 for Microsoft Windows (SPSS, Chicago, Illinois).

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3 Results

3.1 Overview

558 cases were identified from our initial case search. Following application of inclusion criteria and removal of duplicates a total of 164 cases were identified, with final histopathological diagnosis available for 157 patients (Table 1). This comprised 25 cases with a final diagnosis of malignancy and 132 benign cysts. The histopathological diagnosis was confirmed from either the primary tumour or cystic node. 2/25 malignant cases had a diagnosis of differentiated thyroid carcinoma (DTC) both of which were diagnosed by cyst excision. The other 23 malignancies were squamous cell carcinoma (SCC). In these cases a primary tumour was visualised on panendoscopy in 9 cases. In the remaining 14 cases clinicians performed tonsillectomies and guided biopsies of the high-risk sites (postnasal space (PNS) and tongue base (BOT)) and identified a further 8 tumours. In the subsequently confirmed benign group on cyst examination (n=132), rigid endoscopy was performed 24 times at the time of the initial excision and biopsies of high-risk sites were performed in 16 cases including 5 tonsillectomies, all without yield of malignant tissue.

For the SCC cases the ipsilateral palatine tonsil was the most common site of primary tumour (13/23), followed by cancer unknown primary (CUP) disease (6/23). BOT and hypopharynx were the site of primary disease in two cases each. No contralateral primary tumour to a cystic node was identified. Importantly, of 13 malignant cases tested for HPV, 11 were determined positive. The number of neck cysts presenting per year remained stable for the whole study period.

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3.2 Age Distribution

There were no cases of malignancy under the age of 40. The rate of malignancy increased with age, but didn't rise above 31% as a proportion of total cases per decade age group (Figure 1).

3.3 Risk Factors

Univariate logistic regression was performed to identify variables associated with malignancy (Table 2). Three significant risk factors were identified: increasing age by year (OR 1.06, $p \leq 0.001$), male sex (OR 3.89, $p \leq 0.010$) and heavy alcohol intake (OR 4.63 $0 \leq 0.017$). Smoking was not an associated risk factor in this disease presentation as a whole, however both patients discovered to have hypopharyngeal malignancy had heavy smoking and alcohol intake.

3.4 Investigations

We performed over 740 investigations in our series, histopathology apart, although some investigations may have been performed prior to referral to our unit and therefore not obtainable. Choice of investigation was dependent on primary clinician preference and departmental guidelines at the time of clinical review, although these were subject to numerous changes over the 10-year series. The diagnostic parameters of each investigation individually and in combination were analysed, and prior to open biopsy. As stand-alone investigations ultrasound guided FNAC (USgFNAC) and PET/CT demonstrating the highest specificity (92.25%) and sensitivity (65.38%) respectively (Table 3). At this initial stage in the management pathway, USgFNAC alone and the combination of USgFNAC with MRI provided the greatest accuracy (80.25% and 80.49% respectively). However once proceeding to open biopsy, frozen

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section had a sensitivity and specificity of 72.73% and 100% respectively, with an accuracy of 95.64%.

Further analysis on time to diagnosis was performed for all patients, grouping investigations by the number performed for each patient (Table 4). Interestingly, there was no significant correlation between number of investigations and time to diagnosis.

3.5 Outcome data

Four deaths were noted in the positive malignancy cases, with both hypopharyngeal SCC patients succumbing to disease within a year of diagnosis. Another patient died four years after treatment of metastatic recurrence and the other patient died of breast cancer without receiving any treatment. The five-year overall survival (5yr OS) in the oropharyngeal primary and unknown primary group was 87.5% (n=21).

3.6 Published series

We have summarised important demographics and comparisons between the present study and other large series in the literature (Table 5).

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4 Discussion

In this series we have reported outcomes from a 10-year cohort of patients presenting to our tertiary head and neck centre with unilateral solitary cystic masses. The aim was to guide our stratification of investigations and provide tailored advice for our patients about their risk of malignancy. We failed to find any malignancies in patients under 40. Alcohol and smoking were not significant risk factors for malignancy in this group and the number of investigations performed did not appear to adversely lengthen the time to diagnosis. We also provide novel data for the accuracy of combinations of different investigations in LCNM.

Despite routine p16 testing only being introduced midway through our series, of those tested 85% were positive demonstrating integrated HPV infection. This is likely to account for why the traditional risk factor of smoking was not of significance and therefore disagree with the approach of utilising this information in a risk-based approach to management.[20] Age over 40 (OR 1.06 per year of age, $p \leq 0.001$), male gender (OR 3.89, $p \leq 0.010$) and alcohol intake (OR 4.63 $p \leq 0.0170$) were significant variables on univariate analysis and should be considered when counselling patients, supporting several recent studies.[7,8,15] The youngest malignancy in our cohort was 42 years.

The number of investigations performed did not appear to affect the timeframe of the patient pathway, in addition to resource considerations this study provides important outcome data on individual and combined imaging modalities to help organise the most efficient and accurate test order. The highest overall accuracy (i.e. the weighted average of the sensitivity and specificity) is found with USgFNAC (80.25%; 95% CI: 73.16-86.17%). Adding cross-sectional imaging in the form of an

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MRI to the ultrasound improves the sensitivity (from 25.00% to 40.75%), increases the positive likelihood ratio (from 3.22 to 3.49), reduces the negative likelihood ratio (from 0.81 to 0.67) but doesn't significantly affect the accuracy (80.49%; 95% CI: 73.59-86.25%). We therefore recommend an initial investigation order set of USgFNAC and MRI in these cases as a minimum prior to proceeding to an open biopsy. We can reassure patients that this combination of modalities give the highest pre-biopsy accuracy, together with the highest chance of subsequently confirming disease in the event of a positive test.

FNAC sensitivity varies widely in the literature, and results obtained from cystic lesions demonstrate significantly lower accuracy. Tabet et al. performed a comprehensive cytopathological analysis of 135 cystic lesions, resulting in a PPV of 92%, and a sensitivity of 59%,[15] both significantly higher than the present series. However, with a malignancy rate in their studied cohort of 72%, this represented a detection rate far in excess of other published series. Their reasoning that this may be due to the tertiary nature of their unit appears to be contradicted by our study, but more likely represents the inclusion of partially necrotic lesions within their cohort. However, we believe inclusion of purely cystic lateral neck masses provides a more clinically relevant cohort to help guide management of this distinct clinic presentation group. Indeed a previously published series of 2,702 general head and neck aspirates from our unit[21] reports sensitivity, specificity, positive predictive value (PPV), NPV, and accuracy rates of 89.5%, 98.5%, 97.3%, 94.0%, and 95.1%, respectively, demonstrating the difficulty of pre-biopsy tests when dealing with purely cystic lateral neck masses.

Adding PET/CT imaging to the USgFNAC/MRI combination significantly reduced the accuracy of the result in our series (60.74%; 95% CI: 52.80%-68.29%).

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PET/CT however does have the highest sensitivity (70.83%), albeit with the lowest specificity (37.97%) and therefore a higher risk of false alarms and incidental findings, as well as a high radiation dose (about 25 mSv compared with about 6 mSv for a CT Thorax). These findings are consistent with other published series, the most comparably being Sokoya et al[22] who similarly published a 10-year retrospective series reporting a sensitivity and negative predictive value (NPV) for detecting malignancy by PET/CT in unknown primary head and neck squamous cell carcinoma of 73.1% and 68.9%, respectively.

With its low specificity in this clinical scenario of LCNM, we propose PET/CT should be reserved until after malignancy has been confirmed, optimising the use of this resource and minimising the risk of false alarms for patients who often then require further invasive investigations to rule out co-existing pathology e.g. colonoscopy of lower GI tract. This timing will allow further imaging of the potential primary sites (if no evidence was found on primary examination) in keeping with international recommendations.[23]

Should the above investigations fail to diagnose malignancy, open biopsy is the gold standard for diagnosis. We emphasise that adding further pre-biopsy investigations to USgFNAC and MRI does not aid surgical planning and may actually reduce the accuracy of the diagnostic test battery. In the cases where frozen section was utilised, it was found to be a highly accurate adjunct during open biopsy. Ugo Fisch et al eloquently demonstrated how operating on the neck can change the lymphatic drainage.[24] This was important at a time when radical surgery was used as the sole treatment modality, which made Frozen section especially important. Frozen section of a lymph node was popularised in the setting of CUP to confirm the diagnosis while the neck was open and avoid delaying definitive surgery.

In modern times the use of frozen section in neck cysts remains controversial. In our series, the use of frozen section is insufficient to completely exclude malignancy (sensitivity 73%), which led to false reassurance and delayed treatment in 3 of 11 subsequently confirmed cancer patients on paraffin histopathology, consistent with other published work.[7]

Based on our findings, we propose a diagnostic algorithm for the management of LCNM (Figure 2). Several authors including Franzen et al have suggested performing a panendoscopy, biopsies and tonsillectomy on anyone over the age of 40 prior to cyst excision.[7] In their series they reported a malignancy rate of up to 80% in the older age group, which justifies this approach. We found a much lower malignancy rate of 10% for females over 40 and 30% for males over 40. We therefore believe the excess morbidity and time delay (25% will remain CUP) does not justify a blanket biopsy approach in the absence of a clinically evident primary lesion. This would affect the utility of subsequent PET/CT imaging. From our series half the patients with a subsequently confirmed malignant cystic node had an identifiable primary on rigid endoscopy. We therefore recommend a rigid endoscopy in patients over the age of 40 at the time of cystic mass excision (intermediate-high risk). If a primary lesion is clinically evident at this more detailed mucosal examination, it is biopsied, and we abandon the planned cyst excision. In the absence of a primary lesion but with subsequently confirmed malignancy and negative PET/CT, formal ipsilateral tonsillectomy and tongue base mucosectomy forms the second procedure as part of standard of care modern CUP management. In our series 50% of the malignancies were in the ipsilateral palatine tonsil.

Several studies have demonstrated no impact on survival when excision biopsy is performed on a solitary neck node prior to radical radiotherapy.[25–27] Indeed

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the combined 5yr OS in this series including the oropharyngeal and unknown primary cases was 87.5%, comparing favourably with our published outcomes for all HPV+ve and -ve SCC (83% and 53% respectively)[28] which is reassuring. However, we hope that optimisation of investigation strategy will help improve our pre-open biopsy diagnostic rate and potentially help to reduce the overall pathway time by reducing uncertainty regarding investigations.

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5 Limitations

The retrospective nature of this series means interpretation must be considered in this context. Recommended investigations were subject to intra-departmental changes and clinician preference over the course of the 10-year study period and may introduce selection bias for the investigations selected. Half of the 139 total MRI scans performed in our cohort were excluded from analysis due to indeterminate reports that failed to indicate a likelihood of malignancy from the cystic lesion appearance (when combined with a negative oropharynx for radiological primary lesion). We believe these omissions have only underscored the potential final test metrics for MRI, especially specificity and NPV, and we still advocate this modality as an important anatomical baseline and oropharyngeal screen prior to cystic mass excision. Core needle biopsy has been advocated by a number of large series and guidelines[23,29] as a second line investigation but has not been included in this series due to the paucity of cases where it was utilised. Safety appears supported by published series and seeding risk similarly rare.[21,30] It remains a viable alternative second line to FNA, although in our experience the limitation of solid material to target in these cystic lesions is not improved by use of a wider calibre core biopsy needle and should not delay progression through the diagnostic pathway to open biopsy. HPV +ve cases increased in the second half of the collection period but is likely due to increased testing rather than prevalence. The number of oropharynx SCC cases remained stable throughout the study period from 2008-2018.

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6 Conclusion

The most common causes of a LCNM are benign cysts of branchial origin. However 16% of patients with this presentation will harbour a malignancy (30% males and 10% females over 40), most commonly HPV-positive SCC from the ipsilateral oropharynx. Following a thorough history and physical examination, we recommend USgFNAC and MRI as initial investigations that provide the highest accuracy, and then a risk stratified approach based on age, gender and alcohol intake. The traditional head and neck risk factor of smoking is not indicative. With a low specificity and PPV, PET/CT imaging should be reserved for confirmed malignant cases without an identified primary lesion to image potential high-risk sites. If a solitary, indeterminate - high-risk cystic lesion is confirmed, we advise early excision of the mass for paraffin section histology, combined with an upper aerodigestive tract examination.

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Figure legends

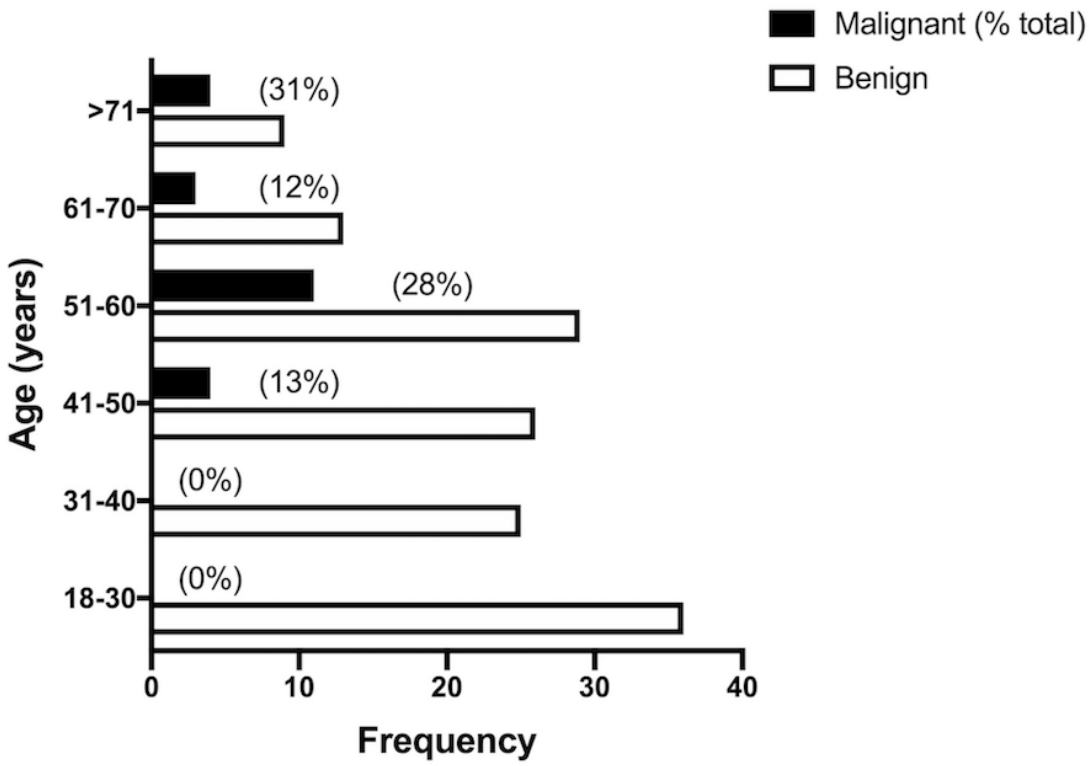

Figure 1 Squamous cell carcinoma (SCC) and benign cases arranged by age group. % total malignant cases per age group are in brackets.

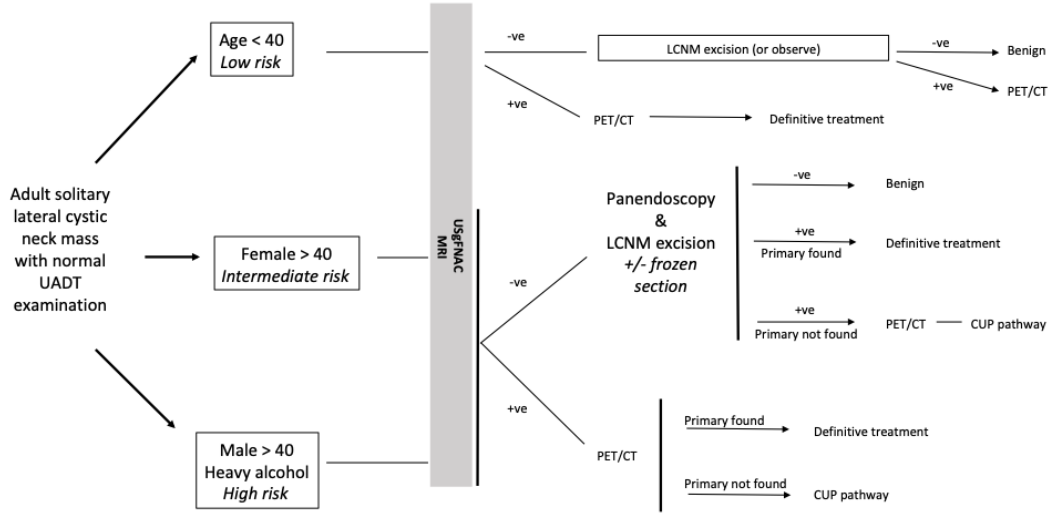

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Figure 2. Proposed investigation pathway for management of adult lateral cystic neck masses.

Table 1. Final pathological diagnosis; SCC = squamous cell carcinoma; DTC = differentiated thyroid cancer

Benign	n=132	Malignant	n=25
Branchial Cyst	126	SCC	23
Oncocytic cystadenoma	2	DTC	2
Schwannoma	2		
Mucocele	1		
Warthin's	1		

Table 2. Model estimates for univariate logistic regression. An asterixis indicates statistical significance of P<0.05

Variable	Frequency (malignant cases)	Odds Ratio (95% CI)	P-value
Age (years)	157 (25)	1.06 (1.03 – 1.09)	<0.001*
Gender			
Female	70 (5)	1	
Male	87 (20)	3.89 (1.38 – 10.95)	0.010*
Smoking			
Never	59 (7)	1	
Ex	36 (3)	0.68 (0.16 – 2.80)	0.624
Current	49 (10)	1.91 (0.67-5.45)	0.230
Missing	13 (5)		
Alcohol			
<14 units/wk	119 (11)	1	
>14 units/wk	16 (5)	4.63 (1.31-15.20)	0.017*
Missing	22 (9)		

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Table 3. Diagnostic test metrics. CT neck was only perfomed in 2 patients so was excluded from analysis. USgFNAC: ultrasound guided fine needle aspiration cytology, FS: frozen section, PPV: positive predictive value, NPV: negative predictive value, LR: likelihood ratio. N/A: insufficient data to compute. PPV, NPV and Accuracy are dependent on disease prevalence.

TEST	USgFNAC	MRI	PET/CT	USgFNAC*MRI	USgFNAC*PET	MRI*PET	ALL IMAGING	FS
Sensitivity	25.00%	24.00%	65.38%	40.75%	64.29%	62.96%	66.67%	72.73%
95% CI	10.69 to 44.87	9.36 to 45.13	44.33 to 82.79	22.39 to 61.20	44.07 to 81.36	42.37 to 80.60	46.04 to 83.48	39.03 to 93.98
Specificity	92.25%	82.98%	37.97%	88.32%	60.58%	61.31%	59.12%	100.00%
95% CI	86.21 to 96.22	69.19 to 92.35	27.28 to 49.59	81.73 to 93.18	51.88 to 68.82	52.62 to 69.51	50.40 to 67.44	92.60 to 100.00
PPV	41.18%	42.86%	25.76%	40.74%	25.00%	24.29%	24.32%	100.00%
95% CI	22.59 to 62.68	22.65 to 65.77	19.98 to 32.52	26.46 to 56.77	19.09 to 32.01	18.32 to 31.45	18.71 to 30.99	N/A
NPV	85.00%	67.24%	76.92%	88.32%	89.25%	89.36%	90.00%	95.06%
95% CI	81.98 to 87.59	61.39 to 72.60	64.68 to 85.85	84.61 to 91.23	83.22 to 93.28	83.46 to 93.32	83.83 to 93.98	88.00 to 98.06
+ve LR	3.22	1.41	1.05	3.49	1.63	1.63	1.63	N/A
95% CI	1.34 to 7.74	0.55 to 3.61	0.76 to 1.46	1.83 to 6.66	1.15 to 2.30	1.14 to 2.33	1.17 to 2.28	N/A
-ve LR	0.81	0.92	0.91	0.67	0.59	0.6	0.56	0.27
95% CI	0.65 to 1.01	0.71 to 1.18	0.50 to 1.66	0.49 to 0.92	0.35 to 0.99	0.36 to 1.01	0.32 to 0.98	0.10 to 0.72
Accuracy	80.25%	62.50%	44.76%	80.49%	61.21%	61.59%	60.37%	95.64%
95% CI	73.16 to 86.17	50.30 to 73.64	35.05 to 54.78	73.59 to 86.25	53.33 to 68.69	53.68 to 69.06	52.44 to 67.91	86.87 to 99.24

Table 4. Summary table for time to diagnosis against no. of investigations (excluding histopathology). One patient's 'time to diagnosis' was clasified as an outlier and removed from analysis. IQR: interquartile range

No. of investigations	n=	Malignancies in group (%)	Time to diagnosis (days)		
			Median	IQR	Range
2	19	1 (5%)	71	51 - 139	16 - 229
3	38	1 (3%)	62	41 - 102	12 – 359
4	48	5 (10%)	43	29 - 80	15 – 207
5	35	11 (31%)	71	47 - 90	19 – 149
6	16	7 (44%)	73	48 - 105	40 - 221

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Table 5. Comparison of published series on lateral cystic neck masses (present article in bold). Age = median (range)

Series	**Jones et al**	**Tabet et al**	**Franzen et al**	**Stefanicka et al**	**Gronlund et al**	**Koch et al**	**Gourin et al**
Country	**UK**	Canada	Germany	Slovakia	Denmark	Germany	USA
Year	**2021**	2019	2019	2019	2016	2018	2000
Patient number	**157**	135	133	111	135	131	121
Malignancy (%)	**25 (16%)**	83 (61%)	41 (30%)	11 (10%)	19 (14%)	12 (9%)	12 (10%)
Age	**48 (16-83)**	41-59 (not stated)	44 (5-91)	40 (18-77)	39 (3-80)	39 (3-69)	38 (18-69)
Youngest SCC diagnosis	**42**	(not stated)	>40	35	39	39	44

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