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Introduction

Persistent hoarseness, as a symptom of laryngeal cancer, is one of the most frequent referrals made in the "urgent suspicion of cancer" (USOC) category in Scotland. This is equivalent to the "2 week wait" category in England. The Scottish Referral Guidelines (SRG) make no exclusions on age of patients with hoarseness, unlike the NICE guidelines (1) which stipulate that referrals are only received for patients 45 years or older. Hoarseness as a presentation of laryngeal cancer is important. Most head and neck cancers present in advanced stages, yet hoarseness as a presenting symptom can be a marker of early stage disease (2). The vast majority of patients referred with hoarseness can be safely reassured and discharge following examination and while much is currently published on the risk of having laryngeal cancer (3,4), examining other factors in relation to laryngeal health and focusing on the lower risk benign group is an understudied area.

There are around 2500 cases of laryngeal cancer diagnosed in the UK each year (5).Laryngeal cancer overwhelmingly presents in older patients – three quarters of all diagnoses are in patients aged over 60 years (2). It is well documented that tobacco and alcohol are the main causative factors for larynx cancer. Compared to oropharyngeal cancer, the human papilloma virus does not appear to be a major cause (6). Laryngeal cancer is more common in males than females (a ratio of 4.5 men to 1 woman) and is more commonly diagnosed in patients of a lower socioeconomic group (7).

Head and neck cancer pick up rates from USOC clinics are between 8-10%. Evidence shows that compliance with referral guidelines at these appointment slots is only 56%. Many non-compliant referrals arise when intermittent hoarseness is referred as USOC (8).

The aim of this study was to assess which demographic and comorbidity factors contributed to a higher or lower laryngeal cancer risk in patients referred with hoarseness.

Methods

All “urgent suspicion of cancer” hoarseness referrals were audited within a one-year period (April 2015 – April 2016) in NHS Greater Glasgow and Clyde. Data were anonymised prior to analysis. Demographic data, comorbidity relating to laryngeal health and diagnoses were collated. This database was chosen as it is currently the most complete referral database in our healthboard, and for this analysis the orignal referrals were further scrutinised for the benign factors related to laryngeal health outlined in table one.

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Data are presented descriptively for cancer and non-cancer patients. Univariate analysis was performed on each possible predictor and results are shown as odds ratios with 95% confidence intervals. A logistic regression model was then fitted to determine the independent predictors of cancer. Predictors of cancer were analysed using logistic regression. Goodness of fit tests (deviance, Pearson and Hosmer-Lemeshow) were performed for the final multivariate model, all values were greater than 0.05 and the model was deemed adequate. All analyses were done using Minitab (version 18) at a 5% significance level.

The Scottish index of multiple deprivation (SIMD) (9) was used to gather deprivation data. Quintiles were selected for analysis, whereby one denotes the most deprived category and five the most affluent.

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409 (59%) either had current or previous reflux disease. 196 (28%) had a preceding diagnosis of asthma. 171 (24%) had recently had an upper respiratory tract infection. 14 (2%) admitted to using drugs recreationally. 426 (61%) patients had a body mass index greater than 25.

The diagnoses of cancer (53 patients) and pre-malignant laryngeal dysplasia (carcinoma in situ) (8 patients) were considered together in this analysis (61 patients). All other diagnoses accounted for the remaining 637 patients. The mean duration of hoarseness in the cancer patients was 9 weeks, and for patients without cancer was 17 weeks. The diagnoses are seen in figure one.

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lump was associated with three times more likelihood of head and neck cancer, than patients without a neck lump.

Examination of demographic background reveals five significant variables that had an impact on the presence of cancer. The patients' age had an odd ratio of 1.02. For each year that passes with age, there is a 2% increase in cancer risk. The next significant variable shown is gender; men in this dataset were four times more likely to have cancer than women.

Another significant variable associated with the presence of cancer was alcohol intake above recommended limits. Each unit consumed was associated with a 3% likelihood of cancer. The same significant odds ratio was seen with smoking. The highest demographic odds ratio in the table is seen with recreational drug use (OR = 4.94). Although there was a relatively small sample of recorded recreational drug users within the sample, (5/74 (6.7%) cancer patients and 9/622 (1.4%) non cancer patients), comparison using Fisher's exact test was significant p = 0.011.

Six variables had an odds ratio < 1. This indicates that these variables are associated with not having cancer. The lowest odds ratios were found with the presence of cough (OR=0.2) and having intermittent hoarseness (OR=0.2). Any patient history associated with the presence of an upper respiratory tract infection had a 72% less chance of cancer, than those without.

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All significant independent variables from the univariate logistic regression were added to the multiple logistic regression model. The adjusted odd ratios and 95% confidence intervals were calculated for the logistic regression model and are displayed in table three. The variable that had the lowest odds ratio were patients who had a preceding viral illness (OR= 0.32), with the risk of being diagnosed decreased by 68%.

The highest odd ratio was persistent hoarseness, which implies that patients are nearly 5.75 times as likely to have cancer compared to a patient without persistent hoarseness.

Discussion

Summary

This study contains a large sample of consecutive hoarseness referrals, referred to an ENT clinic under the referral pathway “urgent suspicion of cancer”. It adds to the evidence base for future UK referral guidelines for suspected head and neck cancer (1). The results support persistent hoarseness, increasing age, male gender, smoking, increasing alcohol intake, weight loss and recreational drug use as features associated with an increased laryngeal cancer risk. It also identifies features that can reassure a patient about their risk of laryngeal cancer: intermittent hoarseness, a long duration of symptoms, globus sensation, recent upper respiratory tract infection and high body mass index.

Strengths and limitations

This study contains 698 consecutive hoarseness referrals over a one-year time period, in Scotland’s largest health board and one of the largest health boards in the United Kingdom. Scotland has one of the highest laryngeal cancer rates in comparison to the rest of the UK (5), and is an ideal site for such a study, analysing factors related to “urgent suspicion of cancer” in hoarseness referrals.

This paper adds to recent evidence published regarding primary care risks for laryngeal cancer (11). This present dataset contains information gathered from the primary care referral and the secondary care consultation, together with information surrounding laryngeal health. This study also analyses factors that are negatively associated with cancer. The number of patients in this study without cancer, outweigh the patients with cancer, and therefore these symptoms although frequently referred as “urgent suspicion of cancer” can be used to provide some reassurance to both the referrer and patient regarding the urgency of referral.

This study is retrospective in nature, which is a weakness. Even with scrutiny of clinical records, there are some missing values, such as completion of alcohol consumption and occupational history.

Literature comparison

Demographic factors are noticeably missing from laryngeal cancer referral criteria, with the exception of the age cut off in the NICE guidelines (1). The SRG make no distinction with age (12). This study would support the age cut off in the current NICE guidelines, and also supports the addition of smoking, alcohol intake and recreational drug use to the referral criteria. While this adds increased information to a referral to secondary care, it is clear that this information is pertinent to the likelihood of cancer. It is interesting that socioeconomic status has not impacted upon the presence of laryngeal cancer in this study, a finding made in all cases of head and neck cancer urgent referrals (13). As previously mentioned in the introduction, head and neck risk calculators are available, and are being updated (3,4). This study does not purport to be any form of risk calculator but rather an indepth analysis of the most frequent red flag symptom seen in otolaryngology clinic. In this regard however, the analysis could be useful for different clinic formation such as a low risk speech and language therapy led voice clinic or perhaps for further remodelling of available risk calculators.

Recreational drug use in this study contained opioid and cannabis use. Current literature does not prove a causal link between cannabis products and head and neck cancer (14,15) but evidence is starting to emerge that use of cannabis leads to development of laryngeal cancer, at younger ages (16). Weight loss at disease presentation, a factor that is seen as a later stage symptom of head and neck cancer, is associated with shorter survival (17).

Factors that decreased the likelihood of laryngeal cancer were intermittent hoarseness, coughing, globus sensation and preceding viral illness. Previous evidence examining globus patients does not associate the sensation with cancer risk, and suggests it can be managed with simple reassurance alone (18).

In this study, approximately one third of referrals were referred to ENT as persistent hoarseness, had intermittent hoarseness. Four of these patients had laryngeal

cancer, 3 of which had other red flag symptoms of head and neck cancer meriting referral. One patient however, had no other symptoms apart from intermittent hoarseness although was a long term smoker. It is therefore possible that if presenting symptom alone is relied on, cancer patients could be missed, which is why we stress the importance of additional demographic information (such as smoking).

The multivariate analysis found the variables with the highest risk of cancer were persistent hoarseness, weight loss and recreational drug use. This was similar to the univariate analysis. The only difference in these two analyses was that in the multivariate analysis male gender was also a high-risk variable for cancer. The multivariate analysis also found the two variables with a decreasing risk to cancer, which were longer symptom duration and preceding viral illness.

Implications for future practice

There are many causes of hoarseness and deciding which patients need 2WW or USOC referral can be difficult. Understandably, the “urgent suspicion of cancer” and 2WW pathways are becoming overwhelmed with increasing numbers of referrals every year. Improvement of national guidelines based on evidence is now paramount to ensure those patients that have the highest risk of laryngeal cancer are seen in the timeliest fashion. Enriching the guidelines with patient demographic information such as smoking status, alcohol status, weight loss, neck lump and recreational drug use would ensure hoarseness is referred via the appropriate referral pathway.

Persistent hoarseness can be identified by enquiring if the voice ever returns to normal. Factors that should reassure patients and clinicians are fluctuating hoarseness, the presence of a cough, the presence of globus sensation and high body mass index. Globus sensation is often described as a sensation of something sticking in the throat, but preserved swallowing ability. The longer the duration of these symptoms, with no progression, is also reassuring with regard to laryngeal cancer risk. Although none of the above factors are included in referral criteria, when

a patient with hoarseness is assessed in primary care, asking about such symptoms may help reassure primary care colleagues and the patient that “urgent suspicion of cancer” referral is not required.

If we adopt these demographic data to referral processes, other practice implications that may follow are potentially a reduction in the number of USOC referrals and an increase in cancer pick up rate from the referrals received.

Conclusion

Overall, the predominant factor to increase the likelihood of cancer was persistent hoarseness. The analysis also determined intermittent hoarseness as the predominant factor to decrease the likelihood of laryngeal cancer. Cancer referral guidelines, when being revised, must take into account emerging evidence about presenting symptoms and the increased or decreased risk such symptoms have with laryngeal cancer.

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Dear Editor

We would like to thank the reviewers for their insightful comments and hope that the adjustments to this paper has addressed any shortcomings. Thank you for your consideration

Reviewer: 1

Comments to the Author

The paper conveys useful and practical information on demographic referral that could be incorporated in the referral pathway not previously mentioned in the literature.
Considering the ever increasing urgent referrals from GP adapting demographic data to referral processes, could potentially a reduction in the number of USOC referrals and an increase in cancer pick up rate from the referrals received.
I would recommend for publication

Thank you

Reviewer: 2

Comments to the Author
This is a retrospective cohort study of patients seen in urgent suspicion of cancer clinics in the year 2015-2016.
Introduction:
-The last sentence of the first paragraph is misleading. There are now papers published in the literature that mention the duration and characteristics of hoarseness in relation to head and neck cancer, providing OR and guidance for referral criteria (I would advise the authors to perform a more thorough review of the literature on this topic with suggested readings of the following papers:

Gao et al., 2019 Two week wait referral criteria - heading in the right direction? Laryngol Otol. 2019 Aug;133(8):704-712.
Tikka T, Pracy P, Paleri V. Refining the head and neck cancer referral guidelines: a two-centre analysis of 4715 referrals. Clin Otolaryngol. 2016; 41(1): 66- 75.
Tikka T, Paleri P, MacKenzie K. External validation of a cancer risk prediction model for suspected head and neck cancer referrals. Clinical Otolaryngol. 2018; 43(2): 714- 717
Lau K, Wilkinson J, Moorthy R. A web-based prediction score for head and neck cancer referrals. Clin Otolaryngol. 2018. [Epub ahead of print].
Tikka et al., 2020. Head and neck cancer risk calculator (HaNC-RC)-V.2. Adjustments and addition of symptoms and social history factors. Clin Otolaryngol. 2020 Jan 27. doi: 10.1111/coa.13511. [Epub ahead of print]

*Thank you. We have now updated the sentence to the more correct "*The vast majority of patients referred with *hoarseness* can be safely reassured and discharge following examination and while much is currently published on the risk of having laryngeal cancer (3,4), examining other factors in relation to laryngeal health and focusing on the lower risk benign group is an understudied area." *We have also updated the references accordingly.*

Methods

- The data analysis is based on a relatively old, over 5 years database. Why did the authors select such an old database? There is increase risk here of recall and data collection bias.

We chose this database as it is one of the most complete databases we have in our healthboard for USOC referrals, and indeed is the same "external validation" database of the risk nomogram above mentioned. In our health board this data cannot be generated by computer and the search had to be manually performed. The vast majority of data were collected the year following the referrals and more recently added to with benign factors to laryngeal health. We don't' believe that this suffers recall bias as all information was extracted from the original referrals. We have updated the methods section accordingly " This database was chosen as it is currently the most complete referral database in our healthboard, and for this analysis the original referrals were further scrutinised for the benign factors related to laryngeal health outlined in table one."

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The methodology prior to undergoing multivariate analysis is not mentioned. Was the sample size adequate to perform such analysis? (sample size calculation) and what goodness of fit test was done to validate the multivariate analysis output?

Thank you we have clarified with the following points from our colleagues in statistics.
There was no sample size calculation since the data is not a random sample from a prospective study. The analysis is based on data available from patients over a 1 year period so the data is those cases and the sample size results from the number of cases seen in the time period.

Goodness of fit was not something we were interested in for the model since the purpose of the multivariate model was to determine independent predictors and negative predictors of cancer and not to produce a predictive model.

The goodness-of-fit for the final multivariate model is:

Goodness-of-Fit Tests

Test	DF	Chi-Square	P-Value
Deviance	632	352.34	1.000
Pearson	632	669.89	0.144
Hosmer-Lemeshow	8	3.21	0.920

Since p>0.05 for each of these. The model is an adequate fit to the data.

*The following has now been added to the methods section. "*Goodness of fit tests (deviance, Pearson and Hosmer-Lemeshow) were performed for the final multivariate model, all values were greater than 0.05 and the model was deemed adequate*."*

Results

The results of the univariate analysis are in accordance with previous available papers in the literature (as mentioned previously) on the topic. Nevertheless, in the discussion these papers are not mentioned at all.

Thank you we will address this area below in the discussion comments.

The only new data from this study is the collection of data on the use of recreational drugs but with only 14 patients being users and only 5 of these being diagnosed with cancer, the numbers are too small for any meaningful and generalisable results. This is also demonstrated by the large 95% CI of the OR for recreational drugs.

Thank you, we note the large CI included in the paper indicates to the reader the uncertainly in the OR of 4.94 for recreational drug use. In the data 5 of 74 patients with cancer were recreational drug users and only 9 of 622 non cancer patients were. The numbers are small (due to the small number of drug users within the sample). A longer study may have increased the observed numbers but the difference is statistically significant (6.7% vs 1.4%, Fisher's exact p=0.011) and we believe this to be a result worth highlighting.

We have now highlighted this within the results section " Although there was a relatively small sample of recorded recreational drug users within the sample, (5/74 (6.7%) cancer patients and 9/622 (1.4%) non cancer patients), comparison using Fisher's exact test was significant p = 0.011.

There are major flaws in the multivariate analysis performed for this paper. Apart from the methodology gaps, 15 variables were included in the analysis for possible final inclusion. It is well known that for each variable assessed for possible inclusion in a multivariate analysis there should be at least 10 events. Therefore, this study should have at least 150 cancer cases

to allow for potential inclusion of all the significant variables from the univariate analysis. They finally included 9 variables which again makes the multivariate outcomes unstable due to the small number of events. -What method was used for variables elimination? (backward/forward/stepwise/manual?)

This study uses data from a fixed period of time, therefore we have no control over the number of cancer cases. There is varying information in the literature re. sample sizes for logistic regression e.g. Bujang MA, Sa'at N, Sidik TMITAB, Joo LC. Sample Size Guidelines for Logistic Regression from Observational Studies with Large Population: Emphasis on the Accuracy Between Statistics and Parameters Based on Real Life Clinical Data. Malays J Med Sci. 2018;25(4):122-130. doi:10.21315/mjms2018.25.4.12 state that:

"For observational studies with large population size that involve logistic regression in the analysis, taking a minimum sample size of 500 is necessary to derive the statistics that represent the parameters."

In sample size estimation, it is well understood that a smaller sample size is needed to detect large effect size. In other words, sample size lower than 500 is sufficient if the aim of the analysis is to determine factors which are highly associated with an outcome. (*This was the aim of our study)*

However, the common problem in research is that the effect size is unknown most of the times. Hence, to purposely estimate a lower sample size with the assumption that the estimated effect sizes are large can introduce bias. To overcome the problem, researchers need to be able to estimate an almost accurate effect sizes based on literature. Besides that, the majority of multivariable analysis such as logistic regression will involve stepwise analysis, resulting in only independent variables with large effect size to be remained in the result (1–2). Therefore, a lower rule of thumb such as EPV of 10 and 20 are still relevant and this subject to in a case for medium to large effect size.

There are additional publications that look at the number of events (cases of cancer) per variable in logistic regression:

Another famous sample size guideline proposed that the minimum required sample size should be based on the rule of event per variable (EPV). According to Concato et al. and Peduzzi et al., the concept of EPV of 10 is acceptable for both logistic regression and cox regression.

Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996;49(2):1373–1379. doi: 10.1016/S0895-4356(96)00236-3.

Concato J, Peduzzi P, Holford TR, Feinstein AR. The importance of event per variable (EPV) in proportional hazard analysis: I. Background, goals and general strategy. J Clin Epidemiol. 1995;48(12):1495–1501. doi: 10.1016/0895-4356(95)00510-2.

-The authors mentioned that they considered significant all variables with a p value <0.05, nevertheless in table 2, a variable with p value 0.09 is also marked as being significant (variable: symptom duration).

Thank you - This has been removed from the multivariate analysis and the table updated accordingly.

-Two more variables that appear significant from the p-value output have OR that includes the value of 1 in the 95% CI output from table 2 (variables: age, recreational drugs). This makes the variables not statistically significant. The authors should repeat the analysis to check why this mistake appears after removing the non-significant variable (symptom duration).

- the odds ratios in table 2 are rounded to 2 decimal places. The effect of age is that for each year older someone gets, the odds of cancer increase by a factor of 1.02:

Age as a univariate predictor:

Odds Ratios for Continuous Predictors

	Odds Ratio	95% CI
Age	1.0225	(1.0033, 1.0421)

Age drops out of the multivariate model (see below), as does symptom duration.

All the odds ratios and p-values in the Table 2 are correct – We have ensured all data displays 2 decimal places as below.

Multivariate Model: the following univariate variables were included in the multivariate model and stepwise selection was used to get the final model:

Univariate Odd Ratios			
Variable (Level A, Level B)	**Odds Ratio**	**Confidence interval (95%)**	**P Value**
Intermittent Hoarseness (Yes vs No)	0.20	(0.09,0.47)	<0.001
Persistent Hoarseness (Yes vs No)	4.97	(2.12, 11.65)	<0.001
Cough (Yes vs No)	0.20	(0.05, 0.85)	0.005
Neck Lump (Yes vs No)	2.90	(1.31, 6.40)	0.015
Sensation of Lump in Throat (Yes vs No)	0.25	(0.06, 1.03)	0.018
Weight Loss (Yes vs No)	3.75	(1.99, 7.08)	<0.001
Symptom Duration (Weeks)	0.98	(0.98, 1.00)	0.018
Age (Years)	1.02	(1.00, 1.04)	0.019
Gender (Male vs Female)	4.05	(2.40, 6.80)	<0.001
Smoker (Yes/Ex vs No)	2.79	(1.40, 5.50)	0.001
Alcohol Intake (High/Ex Alcoholic vs Low/No)	2.79	(1.50, 5.21)	0.002
Preceding Viral Illness (Yes vs No)	0.29	(0.13, 0.65)	<0.001
Recreational Drug Use (Yes vs No)	4.94	(1.61, 15.14)	0.012

Final model using stepwise selection:

Odds Ratios for Categorical Predictors

Level A	Level B	Odds Ratio	95% CI	p-value
Persistent Hoarseness				
Yes	No	5.7465	(2.2685, 14.5566)	<0.001
Neck Lump				
Yes	No	3.6169	(1.3624, 9.6023)	0.015

Weight Loss				
Yes	No	4.3791	(2.0917, 9.1682)	<0.001
Gender				
Male	Female	4.3469	(2.4131, 7.8305)	<0.001
Preceding Viral Illness				
Yes	No	0.3780	(0.1595, 0.8962)	0.016
Recreational Drug Use				
Yes	No	3.6143	(1.0439, 12.5130)	0.051

Odds ratio for level A relative to level B

Discussion:

- Literature review is not thorough enough

We have now included the following segment in the discussion

"As previously mentioned in the introduction, head and neck risk calculators are available, and are being updated (3,4). This study does not purport to be any form of risk calculator but rather an indepth analysis of the most frequent red flag symptom seen in otolaryngology clinic." In this regard however, the analysis could be useful for different clinic formation such as a low risk speech and language therapy led voice clinic or perhaps for further remodelling of available risk calculators.

- In the discussion they mentioned that their results are related to laryngeal cancer. But this was not mentioned in the methodology. Did all patients have laryngeal cancer? Were there no patient with head and neck cancer of other subsites also affecting voice (i.e. recurrent laryngeal nerve infiltration?). And what about supraglottic cancer that might not present with hoarseness? The dataset only included patients with hoarseness as primary symptom so the results cannot be generalised to all laryngeal cancers.

This was an analysis of hoarseness referrals and the likelihood or not of having laryngeal cancer with hoarseness (intermittent or persistent). In figure one, 22 patients are shown to have vocal cord palsy (some of which were related to non head and neck malignancy, and while these patients were correctly picked up via referral, the main focus of interest here was looking at laryngeal cancer (which our guidelines are trying to predict). All patients in the analysis had laryngeal cancer which had affected their voice. The results are only generalised to laryngeal cancers that present with hoarseness, and importantly the low risk patients that do have voice change, but do not have cancer. A major focus of interest has been looking at this populous group of patients in more detail, and trying to identify reassuring factors related to them.

Recommendations:

The sample size and robustness of the analysis is not strong enough to allow for generalisable results. Authors may want to consider using their dataset to validate already published normograms.

We are unaware of any other papers analysing this amount of variables related to a large sample of hoarseness referrals. Our co authors include 2 statisticians who have considerable experience in medical statistics. As previously mentioned this dataset was used to validate the previously published nomograms, yet by further expansion of the dataset, we have identified further features not included in any nomogram (recreational drug use), and examined many reassuring factors not included in the nomograms (eg/ resolution of symptoms by time of attendance, presence of reflux, BMI, asthma etc) all of which are commonly seen in the more benign spectrum of patients that are referred USOC but don't have cancer.

Figure one: Frequency of diagnoses

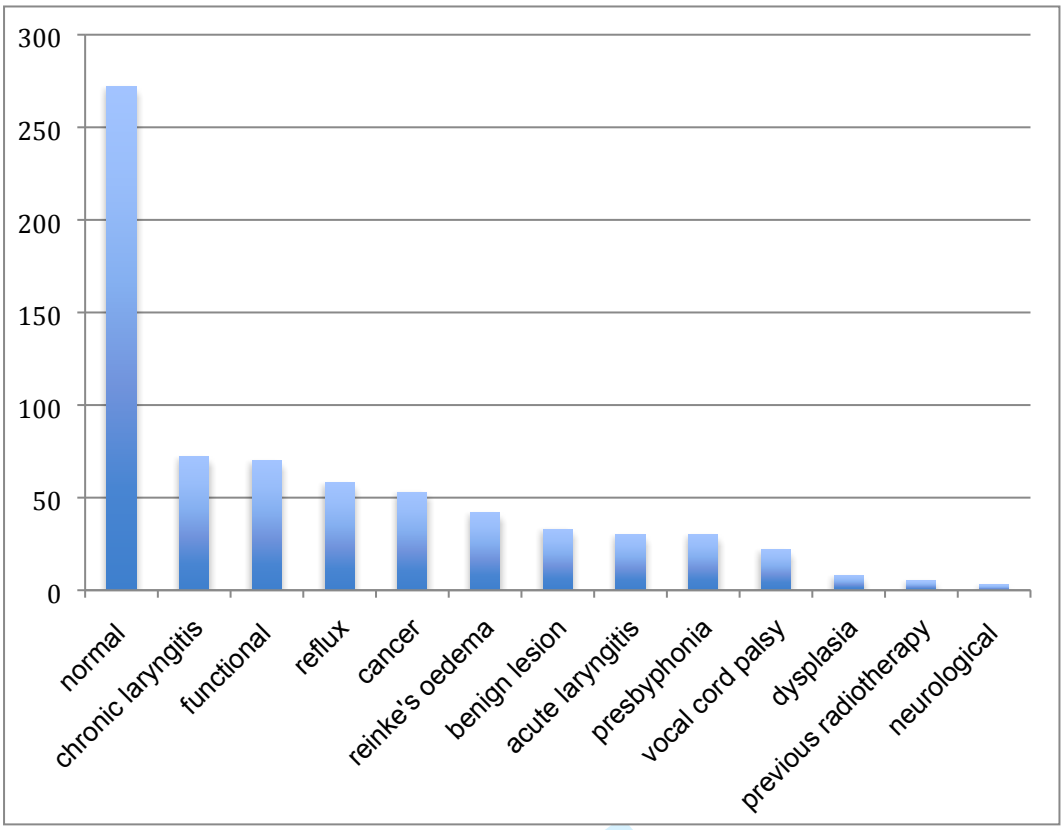

Table one: Categorical variables used in analysis

Categorical Descriptive Statistics					
		CANCER			
		Yes		No	
Patient Variable		Count	Percentage	Count	Percentage
Occupation	Academic	0	0%	2	0.3%
	Clerical	3	0.4%	39	5.9%
	Full Time Education	0	0%	4	0.6%
	Health/ Social Care	1	0.1%	36	5.2%
	Hospitality	0	0%	12	1.7%
	Manual Labour	5	0.7%	34	4.9%
	Retail	2	0.3%	15	2.1%
	Retired	55	7.9%	305	43.7%
	Singer	1	0.1%	3	0.4%
	Teacher	0	0%	11	1.6%
	Transport	0	0%	4	0.6%
	Unemployed	6	0.9%	76	10.9%
	Missing	2	0.3%	82	11.7%
Intermittent Hoarseness	Yes	4	0.07%	188	29.5%
	No	57	93.4%	449	64.3%
Persistent Hoarseness	Yes	57	93.4%	365	47.7%
	No	4	0.07%	580	83.1%
Cough	Yes	3	5%	509	27.1%
	No	73	10.5%	549	78.7%
Neck Lump	Yes	9	1.2%	28	4%
	No	66	9.5%	595	85.2%
Odynophagia	Yes	5	0.7%	15	2.1%
	No	70	10%	608	87.1%
Intermittent Dysphagia	Yes	1	0.1%	29	4.2%
	No	74	10.6%	594	85.1%
Persistent Dysphagia	Yes	10	1.4%	43	6.2%
	No	65	9.3%	580	83.1%
Intermittent Sore Throat	Yes	1	0.1%	20	2.9%
	No	74	10.6%	603	86.4%
Persistent Sore Throat	Yes	10	1.4%	58	8.3%
	No	65	9.3%	565	80.9%
Unilateral Sore Throat	Yes	2	0.3%	11	1.6%
	No	73	10.5%	612	87.7%
Haemoptysis	Yes	0	0%	4	0.6%
	No	75	10.7%	619	88.7%
Oral Mucosa of Tongue Swelling	Yes	1	0.3%	4	0.6%
	No	74	10.6%	619	88.7%
Oral Mucosa red/white patches	Yes	0	0%	1	0.3%
	No	75	10.7%	622	89.1%
Sensation of Lump in Throat	Yes	2	0.3%	62	8.9%
	No	73	10.5%	561	80.4%
Weight Loss	Yes	16	2.3%	42	6%
	No	59	8.5%	581	83.2%
Gender	Male	53	7.6%	232	33.2%
	Female	22	3.2%	390	55.9%
	Missing	0	0%	1	0.1%

Smoker	Yes	40	5.7%	225	32.2%
	No	10	1.4%	187	26.8%
	Ex	25	3.6%	211	30.2%
Alcohol Intake	High	16	2.3%	50	7.2%
	Low	53	7.6%	518	74.2%
	Ex Alcoholic	0	0%	6	0.9%
	Missing	6	0.9%	49	7%
Resolved Hoarseness	Yes	0	0%	84	12%
	No	71	10.2%	469	67.2%
	Missing	2	0.3%	1	0.1%
Reflux	Yes	4	0.6%	36	5.2%
	No	37	5.3%	249	35.7%
	Treated	32	4.5%	337	48.2%
	Missing	2	0.3%	1	0.1
Asthma	Yes	15	2.1%	181	25.9%
	No	59	8.5%	442	63.3%
	Missing	1	0.1%	0	0%
Preceding Viral Illness	Yes	7	1%	164	23.5%
	No	67	9.6%	458	65.6%
	Missing	1	0.1%	1	0.1%
Recreational Drug Use	Yes	5	0.7%	9	1.3%
	No	69	9.9%	613	87.8%
	Missing	1	0.1%	1	0.1%
Scottish Index of Multiple Deprivation	Extremely Deprived	40	5.7%	256	36.7%
	Very Deprived	12	1.7%	137	19.7%
	Satisfaction	10	1.4%	77	11%
	Very Affluent	5	0.7%	84	12%
	Extremely Affluent	8	1.1%	69	9.9%
Body Mass Index	<19	14	2%	34	4.9%
	20-24.9	21	3%	156	22.3%
	25-29.9	21	3%	206	29.5%
	30-34.9	13	1.9%	133	19.1%
	35-39.9	0	0%	31	4.4%
	40>	3	0.4%	19	2.7%
	Missing	3	0.4%	43	6.2%

Table two: Univariate odd ratios

Univariate Odd Ratios

Variable (Level A, Level B)	Odds Ratio	Confidence interval (95%)	P Value
Occupation (Unskilled Labour vs Skilled Worker)	4.92	(0.64, 37.88)	0.054
Intermittent Hoarseness (Yes vs No)	0.20	(0.09,0.47)	<0.001
Persistent Hoarseness (Yes vs No)	4.97	(2.12, 11.65)	<0.001
Cough (Yes vs No)	0.20	(0.05, 0.85)	0.005
Neck Lump (Yes vs No)	2.90	(1.31, 6.4)	0.015
Odynophagia (Yes vs No)	2.90	(1.02, 8.21)	0.067
Intermittent Dysphagia (Yes vs No)	0.28	(0.04, 2.06)	0.124
Persistent Dysphagia (Yes vs No)	2.08	(1.00, 4.32)	0.067
Intermittent Sore Throat (Yes vs No)	0.41	(0.05, 3.08)	0.319
Persistent Sore Throat (Yes vs No)	1.50	(0.73, 3.07)	0.287
Unilateral Sore Throat (Yes vs No)	1.52	(0.33, 7.01)	0.605
Haemoptysis (Yes vs No)	-	-	1
Oral Muscosa or Tongue Swelling (Yes vs No)	2.09	(0.23, 18.96)	0.543
Oral Muscosa Red/White Patches (Yes vs No)	-	-	1
Sensation of Lump in Throat (Yes vs No)	0.25	(0.06, 1.03)	0.018
Weight Loss (Yes vs No)	3.75	(1.99, 7.08)	<0.001
Symptom Duration (Weeks)	0.98	(0.98, 1.00)	0.018
Age (Years)	1.02	(1.00, 1.04)	0.019
Scottish Index of Multiple Deprivation (Affluent vs Deprived)	0.64	(0.34, 1.20)	0.152
Gender (Male vs Female)	4.05	(2.40, 6.80)	<0.001
Smoker (Yes/Ex vs No)	2.79	(1.40, 5.50)	0.001
Alcohol Intake (High/Ex Alcoholic vs Low/No)	2.79	(1.50, 5.21)	0.002
Resolved Hoarseness (Yes vs No)	-	-	1
Reflux (Yes vs No/Treated)	0.94	(0.33, 2.73)	0.914
Asthma (Yes vs No)	0.62	(0.34, 1.12)	0.102
Preceding Viral Illness (Yes vs No)	0.29	(0.13, 0.65)	<0.001
Recreational Drug Use (Yes vs No)	4.94	(1.61, 15.14)	0.012

Table three: Odds Ratios on Multivariate Analysis

Multivariate Odd Ratios		
Variable	**Odds Ratio**	**Confidence interval (95%)**
Persistent Hoarseness (Yes vs. No)	5.75	(2.27, 14.56)
Neck Lump (Yes vs.No)	3.62	(1.36, 9.60)
Weight Loss (Yes vs. No)	4.38	(2.09, 9.17)
Gender (Male vs. Female)	4.35	(2.41, 7.83)
Preceding Viral Illness (Yes vs. No)	0.38	(0.16, 0.90)
Recreation Drug Use (Yes vs. No)	3.61	(1.04, 12.51)