



Time intervals from first symptom to diagnosis for head and neck cancers: An analysis of linked patient reports and medical records from the UK

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ABSTRACT

Background: England has significantly higher mortality risks due to Head and Neck Cancer (HNC) compared with other European countries. Early diagnosis is important as it is likely to increase early-stage diagnosis and improve survival and better quality of life. This study sought to improve understanding of the intervals from first symptom recognition to diagnosis for HNC and investigate associations between patient-reported symptoms and socio-demographic factors.

Methods: People within 3 months of diagnosis, completed a researcher-administered questionnaire and data were extracted from primary and secondary care clinical records.

Results: Eighty (mean age 62.9 [SD 11.7] years; 66% men) were interviewed. The appraisal interval was longer than a month for 39% of participants and the help-seeking interval was longer than a week for 44%. The median diagnostic interval was 92 (IQR; 34–172) days. Appraisal intervals of > 1 month were associated with male gender, ulceration and persistent throat pain. The only symptom that associated with a help-seeking interval of > 1 week was ulceration. Participants who reported red/white patches in the mouth and ulceration were associated with a reduced likelihood of a diagnostic interval of > 3 months. A higher proportion of participants with a diagnostic interval of > 3 months were diagnosed with advanced disease (78%) than those with an interval < 3 months (68%).

Conclusion: These data improve understanding of the intervals from first symptom recognition to HNC diagnosis and provide preliminary evidence to identify targets to reduce overall time to diagnosis.

1. Introduction

Taken as a group, head and neck cancers (HNC) account for 4% of all cancers arising in Europe [1] and are the eighth leading cause of cancer death worldwide [2]. England has significantly lower age- and sex-standardised survival rates than other Northern and Central European countries, especially for laryngeal cancer, with over half (54%) diagnosed with regional or metastatic disease at diagnosis [1]. Five-year survival is significantly better for localised (69%) than for regional (34%) or metastatic (8%) disease [1]; it is thus important to understand the pathway to diagnosis and any factors which may influence its duration.

{Walter, 2012, The Andersen Model of Total Patient Delay: a systematic review of its application in cancer diagnosis}The revised Andersen model of total patient delay [3] is a theoretical framework for

defining intervals between detection of a bodily change and diagnosis. It divides the time from initial symptom to diagnosis into three intervals: i) *Appraisal Interval*: the time from detection or awareness of a bodily change to perceiving a reason to discuss symptoms with a health care professional (HCP); ii) *Help-seeking Interval*: the time from perceiving a reason to discuss symptoms with a HCP to the first consultation with a HCP about these symptoms; and iii) *Diagnostic Interval*: the time between first appointment with a HCP and a diagnosis of cancer being established.

There is evidence that HNC patients with longer diagnostic intervals present with advanced-stage tumours at diagnosis more commonly than those with shorter intervals and prolonged diagnostic intervals lead to poorer outcomes, greater disease-related and treatment-related morbidity and adverse psychological adjustment [4–8]. Hence, early diagnosis is important as it is likely to have benefits for patients in terms of

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earlier-stage diagnosis, improved survival and improved quality of life [7].

To date, many studies have found no evidence of a relationship between the diagnostic intervals for HNC and gender, age, education, socioeconomic status, tobacco and/or alcohol use, tumour stage, or primary site [8–21]. There is limited evidence that longer intervals were associated with primary education only [22], lower occupational social class [22], socioeconomic status (in India) [23] and for patients living in the most deprived of wards in the UK [8]. However, most data come from outside the UK and studies have methodological concerns related to retrospective studies and recall bias, and not patient reported intervals. There is a need for studies to inform understanding about longer patient intervals [24] based on the Aarhus checklist [25], which promotes greater precision and transparency in definitions and methods for studies examining the relationship between time intervals and cancer diagnosis [7].

The aim of this study was to improve understanding of the intervals from first symptom recognition to HNC diagnosis and to investigate the intervals by patient reported symptoms and sociodemographic factors.

2. Materials and methods

This cross-sectional observational cohort study used prospectively collected data from a patient questionnaire and a retrospective review of clinical records. This approach allowed triangulation of data to determine intervals [25]. The approach to data collection, analysis and reporting is based on the Aarhus checklist [25].

2.1. Patient recruitment

Patients were identified from ear, nose and throat (ENT) and maxillofacial clinics within one NHS Trust in Northeast England. To minimise recall bias participants had to have had a HNC diagnosis within three months. Informed consent to access and link clinical records was obtained by a researcher following an initial approach by a clinical nurse specialist.

2.2. Data collection

The researcher-administered patient-reported questionnaire included questions about participants' symptoms, demographic characteristics (age, gender and relationship status), socio-economic status (education, living status, and employment status), smoking status and alcohol consumption. Participants were asked to recall the estimated date when they: i) experienced the first cancer-related sign/symptom; ii) decided to seek help from a HCP; iii) first contacted a HCP. Where data on the day of month or the month of year were missing, the mid-point was used. Participants were asked to categorise how long they felt something was wrong with them before recognising significance (appraisal interval) and how long after that before seeing a HCP (help-seeking interval). Index of Multiple Deprivation (IMD) was derived from the respondent's postcode and coded into the quintiles of the lower-layer super output areas (LSOA) [26].

The primary care clinical electronic records were accessed for consenting participants and data were extracted by research nurses using a bespoke proforma. Data included the number of co-morbidities, date of first consultation with a HNC-related sign/symptom and the number of consultations following first consultation with a HNC-related symptom. Hospital clinical records data were also extracted into a bespoke proforma and included date of diagnosis (from the pathology report or GP records if hospital records were missing), type of cancer (categorised as: laryngeal and hypopharyngeal cancer; nasopharyngeal; oral and oropharyngeal or other) and stage at diagnosis. Stage at diagnosis was categorised as limited (grades 1 and 2) or advanced (grades 3 and 4).

2.3. Estimation of intervals

To estimate the intervals, the route to diagnosis was tracked backwards and data were triangulated between patient-report, primary care and hospital clinical records. Appraisal interval and help seeking interval, were estimated from patient-reported dates. If only a month was stated, the 15th of that month was chosen, if only a year was stated, the 1st of July in that year was chosen. Participants' categorical classification of these intervals were collapsed to a dichotomous variable based on the time interval category greater than the median. Where the respondent date of first contact with a HCP was missing (6, 7.5%), the date of first contact from the GP medical records was used to derive the help-seeking interval.

The diagnostic interval was derived from the date of first consultation with a HNC-related sign/symptom from the primary care clinical record. If the primary care date was missing, or the first visit was with a dentist, the patient-reported date for first health care provider visit was used. Where the first contact was as an emergency at hospital, the date of first hospital appointment was used. The date of diagnosis was based on the date of the pathology report from the hospital clinical record. Primary care records were used to establish diagnosis date if the hospital clinical record was missing (2, 2.5%). The diagnostic interval was further dichotomised using the median as the defined time point beyond which the interval is classified as 'long interval'.

2.4. Data analysis

Descriptive statistics are presented as mean (standard deviation (SD)) and median (Inter-quartile range (IQR)) or n (%) for all socio-demographic, clinical and symptom data. The intervals were compared group with Cox regression analyses, hazard ratios (HR) and 95% confidence intervals are presented. To measure the association level of categorical time intervals, univariate logistic regression analyses were used to calculate odds ratios (OR) and 95% confidence intervals as appropriate. Reference groups were chosen as follows: for ordinal variables the first category was chosen as the reference; for other variables, the category with the largest number was chosen as the reference. To assess the relationship between clinical outcomes (stage at diagnosis) and the intervals, logistic regression were used to investigate the interval and diagnosis with advanced disease. Those significant at the 5% was considered to indicate statistical significance. All analyses were undertaken on SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp).

3. Results

During the study recruitment period (August 2013 to December 2015), 232 people were diagnosed with HNC. Eighty patients participated in the questionnaire giving an overall 34% recruitment rate. Data were extracted from 78 (98%) hospital clinical records and from 70 (88%) primary care clinical electronic records.

Participant's sociodemographic characteristics are shown in [Table 1](#). The mean age was 62.9 [11.7] years and two thirds were male (53, 66%). A third of participants resided in the most deprived 20% IMD quintile (25, 31%). The majority were either current or ex-smokers (61, 76%) and drank alcohol (62, 77%).

Only a third of participants reported having an isolated first symptom (26, 33%). Reporting of synchronous first symptoms were common, with 17% reporting two symptoms, 16% reporting three and 23% reporting four or more, 11% reported no symptoms. [Table 2](#) shows the type of symptoms reported by participants. 'Lump in the neck', 'difficulty swallowing', 'hoarseness', and 'pain' were the most common symptoms. Only a fifth had no co-morbidities. The most common diagnoses were oral cancer (23, 29%) and oropharyngeal cancer (23, 29%), followed by hypopharyngeal and laryngeal cancer (20, 25%) and

Table 1
Characteristics of the participants.

	Mean (sd) or n (%)
Age	62.9 (11.7)
Gender	
Male	53 (66%)
Female	27 (34%)
Highest Education level	
No formal qualifications	35 (46%)
GCSE	14 (17%)
A Level/Btec/HND	10 (13%)
Degree or higher	7 (9%)
Other	10 (13%)
Missing	4
Relationship status	
Single	11 (14%)
Partner	49 (61%)
Widowed	7 (9%)
Separated/Divorced	13 (16%)
Working status	
Employed	24 (30%)
Unemployed	13 (16%)
Retired	40 (50%)
Other	3 (4%)
Living status	
Owner occupier/Mortgage	45 (58%)
Renting	27 (34%)
Other	6 (8%)
Missing	3
IMD Quintile	
1 (Most deprived 20% of LSOAs)	25 (31%)
2	17 (21%)
3	15 (19%)
4	11 (14%)
5 (Least deprived 20% of LSOAs)	12 (15%)
Smoking status	
Smoker	37 (46%)
Ex-smoker	24 (30%)
Never smoked	19 (24%)
Alcohol	
No alcohol	16 (20%)
Ex-drinker	2 (3%)
Current drinker	62 (77%)

nasopharyngeal cancer (10, 12%). Four (5%) participants had an unknown primary cancer location. The majority of participants had advanced disease at diagnosis (57, 73%).

3.1. Intervals

The median total interval from first symptom to diagnosis was 111 (IQR: 69, 209) days; 25% had a total interval for more than 7 months. This is based on the 76 participants who were able to report a date of first symptom.

The median appraisal interval was 24 (IQR: 0-52, n = 76) days. Table 3 shows the median (IQR) appraisal intervals and the hazard ratios by sociodemographic and clinical characteristics. Generally there were no associations seen between measured variables and the appraisal interval. Only for gender, was there moderate evidence against the null with female participants reporting shorter intervals than males (HR: 1.69 (1.03–2.77), p = 0.038).

When participants were asked how long they felt that something was wrong before realising that this was something they might need help with, 13 (16%) reported this was less than 1 week, 11 (14%) as 1–2 weeks, 23 (29%) as 2 weeks to 1 month, 17 (21%) as 1 month to 3 months, and 14 (18%) as more than 3 months; 2 did not think anything was wrong. Table 4 summarises these data on appraisal interval dichotomised at one month by respondent characteristics. In this analysis an association with gender persisted with men more likely than women to have an appraisal interval > 1 month (OR: 3.10, (1.01, 9.00), p = 0.030). The appraisal interval was > 1 month for 73% of those

Table 2
Symptoms reported by participants and clinical characteristics.

	n (%)
Respondent reported symptoms	
Red or red and white patches in the mouth	10 (13%)
Ulceration of mouth and throat	11 (14%)
Mouth swelling	9 (11%)
Unexplained tooth mobility	7 (9%)
Persistent, particularly unilateral, pain in the throat for more than four weeks	21 (26%)
Pain on swallowing	21 (26%)
Difficulty swallowing	22 (28%)
Hoarseness	22 (28%)
Sudden difficulty in breathing	7 (9%)
Weakness or drooping of part of the face	1 (1%)
Ear problem, for example pain, discomfort, unusual sensations	16 (20%)
Lump in the neck	30 (38%)
Other symptom/symptoms	17 (21%)
Number of co-morbidities	
0	15 (19%)
2-Jan	24 (30%)
3+	41 (51%)
Diagnosis	
Hypopharyngeal and Laryngeal cancers	20 (25%)
Nasopharyngeal cancer	10 (12%)
Oral cancer	23 (29%)
Oropharyngeal cancer	23 (29%)
Unknown primary cancer location	4 (5%)
Stage at diagnosis	
TMN	
Stage 1	10 (13%)
Stage 2	11 (14%)
Stage 3	20 (26%)
Stage 4	37 (47%)
Missing	2
Limited or advanced	
Limited	21 (27%)
Advanced	57 (73%)
Missing	2

with ‘ulceration’ compared to 33% without the symptom (OR: 5.33 (1.29, 22.02, p = 0.021) and for 57% of those with ‘persistent throat pain’ compared to 32% without the symptom (OR: 2.81 (1.01, 7.80), p = 0.048). There were no statistically significant differences for any of the other variables.

It proved impossible to estimate the help-seeking interval from self-reported dates as only eight participants could provide an exact date when they perceived a reason to discuss symptoms. On the basis of categorical responses, just over half (44, 56%) reported a help-seeking interval of less than 1 week, 15 (19%) as 1–2 weeks, 8 (10%) as 2 weeks to 1 month, 4 (5%) as 1 month to 3 months, and 6 (8%) as more than 3 months; one participant did not think anything was wrong. The categorical response was missing for two participants and for these reported were. Overall, 35/80 (43%) were estimated to have a help-seeking interval longer than one week. We examined the dichotomised help-seeking interval by respondent characteristics (data not shown). The only variable that was statistically significant was the symptom ‘Ulceration.’ This was associated with an increased likelihood of a help-seeking interval of > 1 week; 73% of participants with ulceration reported an interval of > 1 week compared to 39% without that symptom (OR = 4.15 (1.01, 17.03, p = 0.048).

When asked which HCP the respondent first had contact, the majority stated it was their GP (68, 85%), 3 (4%) a practice nurse, 6 (8%) a dentist and 2 (3%) a hospital doctor. The median diagnostic interval was 92 (IQR; 34-172) days (Table 3). There were no statistically significant differences for any of the variables.

The diagnostic interval was dichotomised as less than or greater than the median, which was approximately 3 months. Table 4 summarises this dichotomised interval by respondent characteristics. Participants diagnosed with hypopharyngeal/laryngeal cancers and

Table 3
Time spent in each interval of the diagnostic process by sociodemographic and clinical characteristics.

	Appraisal Interval				Diagnostic interval			
	n	Median (IQR)	Hazard ratio	P-value (diff)	n	Median (IQR)	Hazard ratio	P-value (diff)
Overall	76	24 (0–52)			80	92 (34–172)		
Age				0.560				0.575
< 65 years	43	30 (0–61)	1.00		44	105 (35–161)	1.00	
> =65 years	33	0 (0–31)	1.15 (0.72–1.81)		36	66 (34–181)	0.88 (0.55–1.38)	
Gender				0.038				0.374
Male	50	31 (0–62)	1.00		53	78 (30–147)	1.00	
Female	26	0 (0–30)	1.69 (1.03–2.77)		27	120 (51–258)	0.81 (0.51–1.29)	
Education				0.888				0.833
No formal qualifications	31	30 (0–31)	1.00		35	91 (33–229)	1.00	
GCSE	14	31 (0–59)	0.98 (0.52–1.85)		14	137 (85–174)	1.00 (0.53–1.89)	
A Level/Btec/HND	10	0 (0–62)	1.10 (0.54–2.26)		10	61 (33–120)	1.22 (0.60–2.48)	
Degree or higher	7	8 (0–106)	0.68 (0.28–1.64)		7	56 (19–147)	1.46(0.64–3.2)	
Other	10	0 (0–30)	1.12 (0.54–2.33)		10	66 (27–127)	1.34 (0.66–2.72)	
Relationship status				0.697				0.869
Partner	47	30 (0–59)	1.00		49	91 (33–147)	1.00	
Single	9	0 (0–31)	1.46 (0.71–3.02)		11	90 (44–212)	0.77 (0.39–1.52)	
Widowed	7	31 (0–62)	0.86 (0.39–1.91)		7	44 (30–258)	1.04 (0.47–2.31)	
Separated/Divorced	13	28 (0–31)	0.93 (0.49–1.76)		13	125 (85–174)	0.88 (0.47–1.62)	
Working status				0.624				0.926
Retired	37	13 (0–31)	1.00		40	65 (33–164)	1.00	
Employed	24	31 (0–60)	0.89 (0.53–1.50)		24	104 (28–135)	1.35 (0.62–1.73)	
Unemployed	12	0 (0–31)	0.97 (0.50–1.89)		13	90 (71–203)	1.04 (0.55–1.97)	
Other	0	0 (0–731)	0.38 (0.09–1.66)		3	147 (138–273)	0.69 (0.21–2.25)	
Living status				0.353				0.175
Owner occupier/Mortgage	43	30 (0–62)	1.00		45	66 (33–132)	1.00	
Renting	25	28 (0–31)	0.96 (0.57–1.60)		27	120 (71–244)	0.68 (0.42–1.11)	
Other	6	19 (0–30)	1.85 (0.77–4.48)		6	153 (133–287)	0.56 (0.24–1.31)	
Number of co-morbidities				0.816				0.887
0	15	13 (0–59)	1.00		15	66 (35–174)	1.00	
1-2	23	30 (0–45)	0.81 (0.42–1.58)		24	77 (37–140)	1.00 (0.52–1.92)	
3+	38	24 (0–61)	0.85 (0.46–1.55)		41	105 (33–198)	0.69 (0.49–1.63)	
IMD Quintile				0.841				0.564
1	23	0 (0–31)	1.00		25	80 (35–203)	1.00	
2	16	31 (0–61)	0.48 (0.42–1.51)		17	85 (40–125)	1.06 (0.57–1.99)	
3	15	0 (0–30)	0.56 (0.41–1.63)		15	147 (33–307)	0.74 (0.39–1.42)	
4	11	31 (0–92)	0.29 (0.33–1.39)		11	105 (27–198)	1.07 (0.52–2.19)	
5	11	30 (0–90)	0.42 (0.40–1.53)		12	91 (37–132)	1.48 (0.73–3.02)	
Smoking status				0.517				0.945
Smoker	35	31 (0–62)	1.00		37	119 (36–164)	1.00	
Ex-smoker	24	10 (0–38)	1.30 (0.76–2.20)		24	78 (40–186)	0.99 (0.58–1.66)	
Never smoked	17	0 (0–31)	1.33 (0.74–2.40)		19	56 (30–135)	1.09 (0.62–1.90)	
Alcohol				0.986				0.405
No alcohol	15	0 (0–62)	1.01 (0.57–1.79)		16	112 (36–197)	1.00 (0.57–1.73)	
Ex-drinker	2	46 (30–62)	0.89 (0.22–3.67)		2	54 (29–78)	2.66 (0.64–11.15)	
Current drinker	59	28 (0–45)	1.00		62	88 (35–174)	1.00	
Diagnosis				0.297				0.158
Hypopharyngeal/ Laryngeal	19	28 (0–31)	0.91 (0.49–1.69)		20	173 (60–265)	0.48 (0.26–0.88)	
Nasopharyngeal	10	0 (0–31)	1.18 (0.56–2.48)		10	133 (105–164)	0.59 (0.28–1.24)	
Oral	21	20 (0–92)	0.55 (0.29–1.06)		23	66 (29–147)	0.72 (0.41–1.24)	
Oropharyngeal	22	22 (0–31)	1.00		23	44 (30–104)	1.00	
Unknown	4	46 (16–92)	0.61 (0.21–1.80)		4	128 (75–502)	0.45 (0.15–1.34)	
Respondent reported symptoms No/Yes								
Red or red and white patches in the mouth	68	29 (0–38)	1.00	0.764	70	105 (40–174)	1.00	0.128
	8	4 (0–62)	0.89 (0.42–1.88)		10	32 (28–71)	1.69 (0.86–3.32)	
Ulceration of mouth and throat	68	24 (0–38)	1.00	0.928	69	105 (41–174)	1.00	0.619
	8	16 (0–62)	0.88 (0.42–1.85)		11	30 (25–90)	1.19 (0.60–2.35)	
Mouth swelling	69	30 (0–45)	1.00	0.414	71	104 (40–174)	1.00	0.584
	7	0 (0–61)	1.39 (0.63–3.05)		9	33 (28–142)	1.22 (0.60–2.45)	
Unexplained tooth mobility	69	30 (0–45)	1.00	0.877	73	104 (36–164)	1.00	0.563
	7	0 (0–62)	1.06 (0.49–2.33)		7	56 (30–258)	1.26 (0.58–2.75)	
Persistent, particularly unilateral, pain in the throat for more than four weeks	57	8 (0–31)	1.00	0.606	59	91 (36–147)	1.00	0.871
	19	31 (0–62)	0.87 (0.51–1.48)		21	90 (30–229)	0.96 (0.58–1.59)	
Pain on swallowing	57	20 (0–45)	1.00	0.989	59	92 (36–147)	1.00	0.826
	45	31 (0–61)	0.99 (0.59–1.68)		21	90 (33–244)	0.95 (0.57–1.57)	
Difficulty swallowing	56	17 (0–31)	1.00	0.169	58	104 (40–164)	1.00	0.699
	20	31 (0–62)	0.68 (0.39–1.18)		22	76 (30–212)	1.10 (0.67–1.81)	

(continued on next page)

Table 3 (continued)

	Appraisal Interval				Diagnostic interval			
	n	Median (IQR)	Hazard ratio	P-value (diff)	n	Median (IQR)	Hazard ratio	P-value (diff)
Hoarseness	54	0 (0–31)	1.00	0.842	57	92 (36–142)	1.00	0.813
	21	31 (0–61)	0.95 (0.57–1.58)		22	91 (33–229)	0.84 (0.57–1.55)	
Sudden difficulty in breathing	70	29 (0–59)	1.00	0.383	73	91 (35–147)	1.00	0.503
	6	0 (0–31)	1.46 (0.63–3.39)		7	212 (25–302)	0.77 (0.35–1.68)	
Weakness or drooping of part of the face	75	28 (0–59)	1.00	0.434	79	91 (33–164)	1.00	0.471
	1	1 (0–0)	2.21 (0.30–16.17)		1	302 (302–302)	0.48 (0.07–3.50)	
Ear problem, for example pain, discomfort, unusual sensations	59	0 (0–45)	1.00	0.947	63	92 (35–174)	1.00	0.868
	16	30 (0–47)	0.98 (0.56–1.71)		16	95 (32–188)	0.95 (0.54–1.66)	
Lump in the neck	48	29 (0–62)	1.00	0.244	50	97 (40–212)	1.00	0.733
	28	17 (0–31)	1.33 (0.82–2.14)		30	91 (30–138)	1.08 (0.68–1.72)	
Other symptom/symptoms	61	20 (0–31)	1.00	0.577	63	92 (35–174)	1.00	0.706
	15	30 (0–62)	0.85 (0.48–1.51)		17	65 (30–164)	0.92 (0.52–1.56)	

nasopharyngeal cancer were most likely to have a diagnostic interval of > 3 month ($p = 0.006$). Participant who reported 'red or red/white patches in the mouth' (OR: 0.20 (0.39, 1.00, $p = 0.051$) and ulceration (OR: 0.17 (0.03, 0.85, $p = 0.031$) were associated with a reduced likelihood of a diagnostic interval of > 3 months.

In addition, 19% reported seeing a GP/dentist three or more times about the health problem later diagnosed as cancer. Using data extracted from the primary care clinical electronic records (67/70), 29 (43%) had three or more contacts with their GP from their first contact with HNC symptoms before referral.

There was no evidence in the study data for an association between any of the intervals dichotomised at the median and the stage at presentation. For the appraisal interval, 70% of those with an interval of > 1 month were diagnosed with advanced disease compared to 75% of those with an interval < 1 month ($p = 0.629$). For the help-seeking interval, 77% of those with an interval of > 1 week were diagnosed with advanced disease compared to 70% of those with an interval < week ($p = 0.466$). For the diagnostic interval, 78% of those with an interval of > 3 months were diagnosed with advanced disease compared to 68% of those with an interval < 3 months ($p = 0.368$).

4. Discussion

4.1. Summary of main findings

To the authors' knowledge, this is the only study of the diagnostic pathway for HNC to recruit patients within a short time after diagnosis and triangulate patient-report data with medical records.

In this study the estimated median interval between first symptom and diagnosis was around four months, and the median appraisal interval was about one month. The median help-seeking interval was short (< 1 week). There was some evidence that men had a longer appraisal interval and that 'ulceration' was a symptom associated with a longer appraisal interval, conversely this symptom alongside presence of red red/white patches' was associated with a shorter diagnostic interval. So a non-healing mouth ulcer is poorly recognised by patients as a potentially serious symptom but is well recognised by professionals. This reflects findings from large population awareness surveys [27]. In addition, we found that it is most common to have multiple symptoms by time of presentation.

4.2. Comparison with the literature

A systematic review [28] found an average patient interval of 3.5 to 5.4 months, whilst data from the 2016 Cancer Patient Experience Survey [29] showed that 21% of HNC patients had presented to a health care professional 3 months after noticing symptoms. This study found that 18% reported an appraisal interval of more than 3 months, hence

the combined appraisal and help seeking interval observed is in line with other studies. Data from the English National Audit of Cancer Diagnosis in Primary Care [30] found laryngeal and oropharyngeal cancers had the longest median patient intervals compared to other cancers 34.5 (95% CI: 30–57) and 30 (95% CI 21–34) days, respectively, which is in line with our study. In our study, the median diagnostic interval was 3 months, consistent with the average professional delay is approximately 3 to 5 months reported in a systematic review [28].

With regard to the association between HNC symptoms and intervals, previous work indicates [31] that a non-healing ulcer or sore was the first thing patients noted but was something that they believed would probably would get better by itself. Most would have sought advice earlier if they had been more aware of oral cancer; the lay public do not necessarily relate this symptom to cancer [31]. It has been found that those who reported an intraoral symptom were more likely to have taken three months or more to present to a healthcare professional than those who had not [32]. There is evidence to suggest that patients are self-managing these symptoms, or simply ignoring them.

Amongst our respondents, 19% reported seeing a GP/dentist three or more times about the health problem later diagnosed as cancer. This is consistent with the findings from the 2016 Cancer Patient Experience Survey (18%) [29]. However, the proportion increased to 43% using data from the primary care clinical electronic records, indicating that patients do not necessarily relate symptoms presented with their GP as related to cancer [31]. The symptoms such as a sore throat or hoarseness, maybe managed in other ways by their GP e.g. antibiotics, blood tests. In six other cancers, investigation in primary care was associated with later referral for specialist assessment and this effect was independent of the nature of symptoms [33]. In other cancers a substantial proportion of patients whose symptoms mandated urgent referral were investigated in primary care [33].

The NICE guidelines [34] state that GPs should consider a suspected cancer pathway referral for laryngeal cancer in people aged 45 and with persistent unexplained hoarseness, for unexplained ulceration in the oral cavity lasting for more than 3 weeks. In this study, the presence of hoarseness and ulceration were associated with shorter diagnostic intervals. The guidelines were updated after these data were collected and the referral criteria for red and white patches altered, removing the requirement that the lesion be accompanied by pain, or bleeding or swelling, or both; in this study the presence red/white patches in the mouth were associated with shorter diagnostic intervals.

Studies have found that longer professional intervals increased the risk of being diagnosed with advanced head and neck tumours [5,35,36], whereas another found no relationship [37]. The findings in our study were compatible with such an association, but we were under-powered to confirm this relationship.

Table 4
Time spent in each interval (> median) of the diagnostic process by sociodemographic and clinical characteristics.

	n	Appraisal interval			Diagnostic interval		
		> 1 month (%)	Odds ratio (95% CI)	P-value (diff)	> 3 months (%)	Odds ratio (95% CI)	P-value (diff)
Overall	80	31 (39%)			41 (51%)		
Age							
Interval < =	49	62.3 (12.7)	0.99 (0.95, 1.03)	0.676	63.2 (10.7)	0.98 (0.94, 1.02)	0.311
Interval >	31	61.2 (10.0)			60.6 (12.5)		
Gender							
Male	53	25 (47%)	3.10 (1.01, 9.00)	0.030	24 (45%)	0.49 (0.19, 1.26)	0.138
Female	27	6 (22%)	1.00		17 (63%)	1.00	
Education				0.719			0.504
No formal qualifications	35	13 (37%)	1.00		18 (51%)	1.00	
GCSE	14	6 (43%)	1.27 (0.36, 4.48)		10 (71%)	2.36 (0.62, 8.98)	
A Level/Btec/HND	10	5 (50%)	1.69 (0.41, 6.98)		4 (40%)	0.63 (0.15, 2.63)	
Degree or higher	7	3 (43%)	1.27 (0.25, 6.59)		3 (43%)	0.71 (0.14, 2.64)	
Other	10	2 (20%)	0.42 (0.08, 2.30)		4 (40%)	0.63 (0.15, 2.63)	
Relationship status				0.891			0.379
Partner	49	19 (39%)	1.00		25 (51%)	1.00	
Single	11	4 (36%)	0.90 (0.23, 3.50)		5 (46%)	0.80 (0.22, 2.97)	
Widowed	7	2 (29%)	0.63 (0.11, 3.59)		2 (29%)	0.38 (0.07, 2.17)	
Separated/Divorced	13	6 (46%)	1.35 (0.40, 4.64)		9 (69%)	2.16 (0.59, 7.96)	
Working status				0.823			0.772
Employed	24	11 (46%)	1.41 (0.51, 3.94)		14 (58%)	1.71 (0.62, 4.76)	
Unemployed	13	4 (31%)	0.74 (0.19, 2.83)		6 (46%)	1.05 (0.30, 3.68)	
Retired	40	15 (38%)	1.00		18 (45%)	1.00	
Other	3	1 (33%)	0.83 (0.07, 9.99)		3 (100%)	-	
Living status				0.555			0.171
Owner occupier/Mortgage	45	18 (40%)	1.00		20 (44%)	1.00	
Renting	27	11 (41%)	1.03 (0.39, 2.73)		15 (59%)	1.82 (0.69, 4.78)	
Other	6	1 (17%)	0.30 (0.03, 2.79)		5 (83%)	5.25 (0.68, 57.90)	
Number of co-morbidities				0.195			0.564
0	15	8 (53%)	1.00		6 (40%)	1.00	
1-2	24	6 (25%)	0.29 (0.07, 1.15)		12 (50%)	1.50 (0.41, 5.54)	
3+	41	17 (42%)	0.62 (0.19, 2.04)		23 (44%)	1.92 (0.58, 6.68)	
IMD Quintile				0.963			0.779
1	25	10 (40%)	1.00		11 (44%)	1.00	
2	17	7 (41%)	1.05 (0.30, 3.68)		8 (47%)	1.13 (0.33, 3.90)	
3	15	5 (33%)	0.75 (0.20, 2.86)		9 (60%)	1.91 (0.52, 7.01)	
4	11	5 (46%)	1.25 (0.30, 5.23)		7 (64%)	2.23 (0.52, 9.60)	
5	12	4 (33%)	0.75 (0.18, 2.17)		6 (50%)	1.27 (0.32, 5.06)	
Smoking status				0.692			0.387
Smoker	37	16 (43%)	1.00		22 (60%)	1.00	
Ex-smoker	24	9 (38%)	0.79 (0.28, 2.25)		11 (46%)	0.58 (0.21, 1.63)	
Never smoked	19	6 (32%)	0.61 (0.19, 1.94)		8 (42%)	0.50 (0.16, 1.52)	
Alcohol				0.543			0.674
No alcohol	16	8 (50%)	1.82 (0.60, 5.51)		10 (63%)	1.67 (0.54, 2.15)	
Ex-drinker	2	1 (50%)	1.82 (0.11, 30.51)		0 (0%)	-	
Current drinker	62	22 (36%)	1.00		31 (50%)	1.00	
Diagnosis				0.125			0.006
Hypopharyngeal/ Laryngeal	20	6 (30%)	1.21 (0.32, 4.61)		15 (75%)	8.50 (2.15, 33.62)	
Nasopharyngeal	10	3 (30%)	1.21 (0.26, 6.27)		8 (80%)	11.33 (1.86, 69.08)	
Oral	23	13 (57%)	3.68 (1.06, 12.77)		9 (39%)	1.82 (0.52, 6.37)	
Oropharyngeal	23	6 (26%)	1.00		6 (26%)	1.00	
Unknown primary cancer location	4	3 (75%)	8.50 (0.74, 98.21)		3 (75%)	8.50 (0.74, 98.21)	
Respondent reported symptoms (No/Yes)							
Red or red and white patches in the mouth	70	27 (38%)	1.00	0.931	39 (56%)	1.00	0.051
	10	4 (40%)	1.06 (0.27, 4.11)		2 (20%)	0.20 (0.39, 1.00)	
Ulceration of mouth and throat	69	23 (33%)	1.00	0.021	39 (57%)	1.00	0.031
	11	8 (73%)	5.33 (1.29, 22.02)		2 (18%)	0.17 (0.03, 0.85)	
Mouth swelling	71	27 (38%)	1.00	0.710	38 (54%)	1.00	0.263
	9	4 (44%)	1.30 (0.32, 5.28)		3 (33%)	0.43 (0.10, 1.87)	

(continued on next page)

Table 4 (continued)

	n	Appraisal interval			Diagnostic interval		
		> 1 month (%)	Odds ratio (95% CI)	P-value (diff)	> 3 months (%)	Odds ratio (95% CI)	P-value (diff)
Unexplained tooth mobility	73	27 (37%)	1.00	0.306	39 (53%)	1.00	0.225
	7	4 (57%)	2.72 (0.47, 10.93)		2 (29%)	0.35 (0.06, 1.92)	
Persistent, particularly unilateral, pain in the throat for more than four weeks	59	19 (32%)	1.00	0.048	30 (51%)	1.00	0.904
	21	12 (57%)	2.81 (1.01, 7.80)		11 (52%)	1.06 (0.39, 2.88)	
Pain on swallowing	59	20 (34%)	1.00	0.139	30 (51%)	1.00	0.904
	21	11 (52%)	2.15 (0.78, 5.90)		11 (52%)	1.06 (0.39, 2.88)	
Difficulty swallowing	58	20 (35%)	1.00	0.206	31 (53%)	1.00	0.524
	22	11 (50%)	1.90 (0.70, 5.14)		10 (46%)	0.73 (0.27, 1.94)	
Hoarseness	57	24 (42%)	1.00	0.403	29 (51%)	1.00	0.770
	22	7 (42%)	0.64 (0.23, 1.82)		12 (55%)	1.16 (0.43, 3.11)	
Sudden difficulty in breathing	73	27 (37%)	1.00	0.306	37 (51%)	1.00	0.745
	7	4 (57%)	2.27 (0.47, 10.93)		4 (57%)	1.30 (0.27, 6.21)	
Weakness or drooping of part of the face	79	31 (39%)	1.00	1.00	40 (51%)	1.00	
	1	0 (0%)	0.00		1 (100%)	-	
Ear problem, for example pain, discomfort, unusual sensations	63	24 (38%)	1.00	0.965	33 (52%)	1.00	0.865
	16	6 (38%)	0.98 (0.31, 3.01)		8 (50%)	0.91 (0.30, 2.73)	
Lump in the neck	50	23 (46%)	1.00	0.089	26 (52%)	1.00	0.862
	30	8 (28%)	0.43 (0.16, 1.14)		15 (50%)	0.92 (0.37, 2.28)	
Other symptom/symptoms	63	22 (35%)	1.00	0.181	33 (52%)	1.00	0.697
	17	9 (53%)	2.10 (0.71, 6.20)		8 (47%)	0.81 (0.28, 2.36)	

4.3. Strengths and limitations

The key strength of this study is that both patient report and clinical record data were triangulated. Gomez [5] recommended that researchers should aim to enhance reliability by validating interval data collected from the patient against information in clinical records. The analyses and reporting were performed in accordance with the Aarhus statement [25]. We defined the date of first symptom/s using patient-reported date and symptoms rather than the primary care-reported date. We recruited patients within a short time period after diagnosis to maximise the accuracy of recall. Patients were recruited in secondary care from ear, nose and throat (ENT) and maxillofacial clinics; this had the benefit of ensuring recruited patients included those referred by a dentist and who presented as an emergency.

Our main limitation is the recruitment rate. Only 80 (34%) of the 232 people were diagnosed with HNC during the study period participated. This was in part due to changes in research staff with gaps in employment covering the recruitment time. Thus this is not truly a consecutive sample, although consecutive patients were recruited when the researcher was in post. Also, the challenges of busy practice meant that some otherwise eligible patients may not have been approached by the clinical team. It is possible that some were unwilling to undertake the research-led questionnaire because they were coping with a serious illness or undergoing treatment, as found in other cancer groups [38,39].

There were some missing GP and hospital data due to unavailable records. To minimize this problem, we used the patient reported dates to calculate the diagnostic interval where these data were missing. Where the respondent only provided the month and year of their first consultation with health care professional this was coded as the 15th day of that month, hence there may be a two week under or over estimation of the intervals.

Multiple tests were conducted and the possibility that reported associations are false-positives should be acknowledged.

4.4. Implications for policy and practice

Oral cancer awareness can be successfully enhanced [40–43], however there seems to be little impact on reducing the primary care interval [44]. In our study there was some suggestion that the appraisal

interval was longer for those with ulceration, which is a common symptom and has been suggested as a suitable target for an awareness initiative [31]. To date none of the national ‘Be Clear on Cancer’ campaigns have focussed on oral cancer [45]. There may be mileage in future campaigns highlighting mouth ulceration as a potential cancer symptom.

The updated NICE guidelines [34] in 2015 imply that certain presentations, if identified by a GP, should be referred to a dentist for assessment before they are reviewed by a specialist. In this study 7/69 (10%) were referred to a dentist by their GP. However, this guidance [34] may expose patients to increased risk of delayed referral because there is no clear referral pathway between doctors and dentists for suspected cancer [46]. Data suggest that men, people who are older, or have lower socioeconomic status are least likely to use primary dental care services [47] which are the same groups at greatest risk of developing oral cancer [48].

The analysis only focused on patient-reported symptoms before first presentation with a health care professional. The impact of subsequent symptoms on time to diagnosis requires further study [38]. Symptoms are seen by GPs at an earlier stage of development than in secondary care, and time allows the clinician to observe whether relatively undifferentiated symptoms develop more specific characteristics or resolve spontaneously [33]. The NICE criteria [46] were developed using a ‘risk threshold’, whereby if the risk of symptoms being caused by cancer is above a certain level then action (investigation or referral) is warranted. A 3% positive predictive value (PPV) was used to determine the threshold, with the large majority not having the disease. GPs may use investigations as means of increasing the probability of cancer prior to making a decision about referral. Investigations may form a part of this temporising approach while also being part of a safety-netting strategy [49]. Policy initiatives should include more widespread knowledge of these symptoms in applying the decision support tools and significant event analyses [50] and case-note review studies [51] are required to further establish the circumstances surrounding longer primary care intervals [33].

5. Conclusion

These data improve understanding of the intervals from first symptom recognition to HNC diagnosis and provide preliminary

evidence to identify targets to reduce overall time to diagnosis. There may be mileage in future awareness campaigns highlighting mouth ulceration as a potential cancer symptom to reduce the appraisal and help-seeking interval. This study has demonstrated the application of the Aarhus statement [25] for calculating the intervals for HNC patients' first experienced symptom to diagnosis through patient report and routinely available health service data.

Conflict of interest statement

None declared.

Ethics approval and consent to participate

We gained appropriate ethics approval from the NRES Committee London - Surrey Borders (REC Reference: 13/LO/0398; IRAS project ID: 123447) and clinical governance approvals. The study was performed in accordance with the Declaration of Helsinki.

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Authors' contributions

We confirm that all the authors meet the following three conditions: 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published.

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