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Presenting symptoms and long term survival in Head and Neck cancer.

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Objectives;

To assess how type and number of symptoms are related to survival in head and neck cancer patients.

Design; Patients were followed-up for over 10 years from the Scottish Audit of Head and Neck Cancer; (national cohort of head and neck cancer patients in Scotland 1999 – 2001). September 2013, cohort was linked to national mortality data. First, second and third presenting symptoms were recorded at diagnosis.

Setting; National prospective audit - Scotland

Participants; A subset of 1589 patients, from the original cohort of 1895, who had cancer arising from one of the four main subsites; larynx, oropharynx, oral cavity and hypopharynx.

Main outcome measures; Median survival in relation to patients' presenting symptoms.

Results; 1146 (72%) males and 443 (28%) females, mean age at diagnosis 64 years (13 – 95). There was a significant difference in survival in relation to the number of the patient's presenting symptoms; one symptom had a median survival of 5.3 years compared with 1.1 years for three symptoms. Patients who presented with weight loss had a median survival of 0.8 years, compared to 4.2 years if they did not ($p < 0.001$). Patients who presented with hoarseness had a median survival of 5.9 years compared to 2.6 years without ($p < 0.001$). There was no significant difference in long term survival for patients who presented with an ulcer, compared to those that did not ($p = 0.105$).

Conclusions.

This study highlights the importance of patients' presenting symptoms, giving valuable information in highlighting appropriate "red flag" symptoms and subsequent treatment planning and prognosis.

INTRODUCTION

Patients who have head and neck cancer present with symptoms which may include hoarseness, dysphagia, pain, neck lump and ulceration. Such “red flag symptoms”, are used as the basis for national cancer referral guidelines. At the time of diagnosis in this cohort of patients, the SIGN guidelines were used¹⁻³.

It has been previously demonstrated, in other subsites, that symptoms can help predict prognosis. Furuta et al demonstrated that patients who had lung cancer, and presented with breathlessness and chest pain, had a worse prognosis⁴; The presence of fever, chills and night sweats have been used within lymphoma staging for many years⁵. In the 1990's Piccirillo et al highlighted that symptom severity in larynx cancer offered additional prognostic information not provided by the TNM classification⁶. To date there have been very few reports on the quantitative assessment of presenting symptoms and subsequent survival in head and neck cancer⁷.

The Scottish Audit of Head and Neck Cancer (SAHNC) in 1999-2001 recorded the presenting symptoms of the patients recruited and provides an opportunity to assess the long-term survival profile of patients' symptoms with respect to subsite.

The aim of this study was to assess how the type and number of symptoms are related to survival in a large cohort of head and neck cancer patients and discuss potential factors.

Materials and Methods

Patients and Data Linkage

The SAHNC recruited 1895 patients between 1st September 1999 and 31st August 2001. Methods have previously been described⁸⁻¹¹. Data were recorded on all new HNC patients diagnosed in Scotland. Quality assurance processes were carried out including cross-checking the incident data with medical and pathology results. This paper assesses a subset of 1589 patients, with the index cancer arising from one of the four main subsites; larynx, oropharynx, oral cavity and hypopharynx. The cohort was linked to the

National Records of Scotland (NRS) mortality data as at 30th September 2013 by ISD Scotland. Records were linked using the Howard Newcombe principle¹². Information governance and data linkage approvals were obtained from the NHS Privacy Advisory Committee (now known as the Public Benefits and Privacy Panel).

Determinants included in analysis

Determinants included age, sex, smoking behaviour, alcohol consumption, patient performance status, site, Stage, symptoms at presentation and treatment modality.

Symptoms were recorded at the time of diagnosis by the treating clinician, with key symptoms being recorded in numerical order, with the patient's principal symptom recorded first. This was in an 'open structure basis' with the clinician being able to record up to three symptoms they considered of relevance. Each different symptom was given a numerical code for entry into the database. There were therefore no suggestions of symptoms to be recorded or pre-determined checklist for the treating clinician to use.

Stage was determined using the Tumour, Node and Metastases (TNM) Classification of Malignant Tumours¹³, and the cohort was grouped accordingly into Stage I/ II/ III/ IV. Anatomical site was classified using the International Classification of Disease version 10¹⁴, and the cohort was grouped into 4 categories –larynx (C32), oral cavity (C02–C04, C05.0, C06, C14), oropharynx (C01, C05.1–, C09, C10), hypopharynx (C12, C13).

Treatment modality was grouped into five categories: i) surgery only; ii) radiotherapy only; iii) surgery combined with radiotherapy; iv) chemotherapy only, chemotherapy combined with surgery, chemotherapy combined with radiotherapy, and chemotherapy combined with both surgery and radiotherapy; and v) no treatment.

Measurement of symptom

First, second and third presenting symptom were recorded at diagnosis and included hoarseness, pain/discomfort, lump in neck, dysphagia, ulceration, weight loss, swelling, other/unknown. Variables for the number of symptoms each patient had were created, and additional binary "yes/no" variables for

each presenting symptom were created. An interaction test confirmed a relationship between symptom and anatomical site, and therefore the analysis was performed for all patients and each anatomical site (larynx, oral cavity, oropharynx and hypopharynx). If the resultant group was small, for example hoarseness in oral cancer subgroup, they were placed in "other/unknown" category.

Statistical analysis

Five-year and 12-year disease-specific survival were calculated using the Kaplan-Meier method with 95% confidence intervals (CIs), and the log-rank test was used to determine the differences between the survival curves. Age- and Stage- adjusted Cox proportional hazard models were used to determine the differences in survival with 95% CIs.

Results

Patient Demographics

The study cohort of 1589 included larynx, oral cavity, oropharynx or hypopharynx cancer with all other subsites within the head and neck being excluded. The cohort consisted of 1146 (72%) males and 443 (28%) females. The mean age was 64 years (13 – 95 years). Table 1 shows the patient demographics for the study cohort. Larynx cancer was the most common subsite with 603 patients (38%), followed by oral cavity with 534 patients (34%), oropharynx with 330 patients (21%), then hypopharynx with 122 patients (7%). The majority of patients were current or previous smokers. Stage at presentation varied among the subsites, with half of the larynx cancer and oral cavity cancer patients presenting with Stage I or II cancer whereas two-thirds of the oropharynx and hypopharynx cancer patients presented with Stage III or IV disease.

Survival

Table 2 demonstrates the disease specific 5- and 12-year survival for all patient variables. Table 3 demonstrates the median survival for all patient variables. There was a significant difference in survival across subsites, with larynx patients having 71% 5-year survival and 63% 12-year survival compared to hypopharynx patients with 32% 5-year survival and 24% 12-year survival. There was a significant difference in survival at both 5 and 12-years depending on how many symptoms a patient presented with. If only one symptom was reported median survival was 5.3 years compared with 1.1 years for three symptoms. All head and neck cancer patients who presented with hoarseness had a significantly ($p < 0.001$) better survival than those who did not have hoarseness at both 5 and 12 years, with the median survival of a patient presenting with hoarseness being 5.9 years compared to 2.6 years for a patient without hoarseness. Patients presenting with a neck lump only had a median survival of 1.3 years versus 4.8 years for those without a neck lump at presentation. There was no significant difference in long term survival for those patients presenting with an ulcer, compared to those that did not, with

median survival being 4.2 years in patients presenting with an ulcer compared to 3.5 years for those not presenting with an ulcer. Patients that presented with weight loss had a significantly shorter median survival of 0.8 years, compared to 4.2 years if they did not have weight loss. Patients that presented with dysphagia had a significantly shorter median survival of 1.3 years compared to 4.3 years for those that didn't have dysphagia.

Symptoms

Table 4 demonstrates a frequency histogram for the number of symptoms and type of symptoms present at diagnosis for each subsite. The most commonly presenting symptom for those diagnosed with larynx cancer was hoarseness (82%), for oral cavity was ulceration (51.5%); for oropharyngeal cancer was pain (60.9%) and for hypopharyngeal cancer was weight loss (23.8%).

Larynx Cancer patients

Table 5 demonstrates the median survival of patients diagnosed with larynx cancer. Patients who presented with 0-1 symptoms had a median survival of 7.7 years compared to 1.95 years if they presented with 3 symptoms. A patient with hoarseness who presented with larynx cancer had a median survival of 7 years compared to 2.2 years for those who didn't have hoarseness.

Patients that had weight loss as a presenting symptom had a median survival of 1.3 years, which after adjustment for age and Stage in multivariate analysis was still a significant factor ($p=0.003$).

Oral Cavity Cancer Patients

Table 5 demonstrates the median survival of patients diagnosed with oral cavity cancer. Patients who presented with 1 symptom had a median survival of 4.6 years compared to those with 3 symptoms that had a median survival of only one year. Patients who presented with an ulcer had a median survival of 4.9 years compared to only 2.8 years for those who didn't. Patients presenting with weight loss had a median survival of 0.6 years, compared to 4 years for those without weight loss.

Oropharynx Cancer Patients

Table 5 demonstrates the median survival of patients diagnosed with oropharyngeal cancer. Patients who presented with 1 symptom had a significantly better median survival of 3.3 years, compared to those with 3 symptoms who had a median survival of only 1.0 year. Patients who presented with a neck lump had a median survival of 1.8 years compared to 2.6 years for those without a neck lump.

Hypopharynx Cancer Patients

Table 5 demonstrates the median survival of patients diagnosed with hypopharyngeal cancer. There was no significant difference in median survival by the number of symptoms they presented with: patients with 1 symptom had the same median survival as patients who presented with 3 symptoms – 1.1 years. However, it should be noted that the numbers of hypopharynx patients were much smaller than the other subsites.

Age and Stage adjusted analysis.

Table 6 reports the age and stage adjusted analysis for each symptom and subsite. The number of symptoms a patient presented with was significantly related to survival after adjustment for age and stage in larynx, oral cavity and oropharynx subsite. Number of symptoms did not impact on survival for hypopharynx patients. Weight loss was the only symptom that was a significant predictor of survival after adjustment for age and stage in all four subsites.

Discussion

This prospective series of head and neck cancer patients demonstrates the importance of number and type of symptoms at the time of diagnosis. Red flag symptoms may indicate more serious underlying pathology. Red flag symptoms in the NICE guidelines for suspected head and neck cancer include hoarseness, neck lump, pain or discomfort and ulceration. There was a significant difference in survival in relation to the number of the patient's presenting symptoms; one symptom had a median survival of 5.3 years compared with 1.1 years for three symptoms, which was still significant for the subsites of larynx, oral cavity and oropharynx after adjustment for age and stage. Any head and neck cancer patient who presented with hoarseness had a median survival of 5.9 years compared to 2.6 years without. There was no significant difference in long term survival for patients who presented with an ulcer, compared to those that did not ($p=0.105$). Patients presenting with dysphagia survived 1.3 years compared to 4.3 years for those that did not. Patients who presented with weight loss had a median survival of 0.8 years, compared to 4.2 years if they did not ($p<0.001$), even after adjustment for age and stage at all subsites.

Symptoms as a predictor of prognosis

Cancer symptoms (type, duration, severity) and the performance status of the patient are clinical elements that represent the severity of the cancer in the patient. Using symptoms as a predictor of prognosis is not a new idea to head and neck cancer, however to date symptoms have failed to make it into any formal staging system or help direct treatment and predict prognosis. Over 50 years ago Jackson and Norris discussed the prognostic significance of "increasing degrees of dyspnea, stridor, hoarseness and dysphagia, with persistent pain on swallowing and progressive cachexia" in a review article about laryngeal cancer¹⁵. Piccirillo et al highlighted that symptom severity in larynx cancer offered additional prognostic information that the TNM classification did not have. It was suggested that the addition of symptoms to the Staging provided an index of the biological behaviour of the tumour that cannot simply be discerned from anatomy alone. Our results would support this finding, as we found that the number of symptoms a patient presented

with was significant for both 5 and 12 year survival, after adjustment for Stage and age, in laryngeal, oral cavity and oropharynx cancer. Interestingly there was no significance in patients with hypopharyngeal cancer, highlighting the very poor prognosis of patients diagnosed with this disease, no matter how many symptoms they present with. However, it should be noted that we did have small numbers of hypopharyngeal cancer compared to the other subsites.

Our results also highlight that patients with specific symptoms, and confirmed head and neck cancer at a specific subsite, have an added indicator of prognosis. In our cohort patients who presented with hoarseness, and diagnosed with larynx cancer specifically, had a median survival of 7 years, demonstrating the “good” prognosis associated with hoarseness. In stark contrast weight loss was a significant predictor of poor prognosis in all four subsites in this series, even after adjustment for age and stage. The median survival for a patient with weight loss was only 0.8 years, the worst median survival for all the symptoms examined. Weight loss has previously been shown to be an independent prognostic factor in palliative care patients¹⁶. The significance of weight loss has been reported previously in patients with recurrent oral cavity and oropharyngeal cancer,¹⁷ however this is the first study in head and neck cancer to highlight its significance in median survival. At present the MDT decision making process focuses on the TNM staging of the primary tumour. However, there is now increasing evidence that specific types and number of symptoms are of prognostic value. There is an argument for using this information not only in the decision making process in treatment planning, but also in informed discussions with patients. To develop this concept a more rigorous approach of symptom recording, using an agreed symptom group, reflecting prognosis, could be implemented and recorded and the relationship with outcome noted.

Value of Red Flag Symptoms

One of the difficulties with red flag symptoms in head and neck cancer is that there are symptoms which are frequently experienced by many patients who have non malignant issues, such as benign pathology or functional conditions. In comparison, colorectal cancer has a much stronger evidence base with

regards to GPs and presenting symptoms. The higher predictive value of symptoms in patients referred for investigation when compared to the predictive value on first presentation to primary care demonstrates that the GP is able to identify, in part, those patients who are likely to harbour a colorectal cancer. It also demonstrates that if there is a higher relative rise from the predictive value in the general population to those presenting to the GP that patients are also capable of identifying which symptoms matter for colorectal cancer¹⁸. This is certainly not the case for head and neck cancer, with many published reports identifying that patients don't know the risk factors and symptoms for head and neck cancer¹⁹.

Red Flags in Head and Neck Cancer

In 2015 NICE published "Suspected cancer: recognition and referral." This UK guideline document (NG12)³ offers "evidence based advice on the recognition of, and referral for, suspected cancer". Despite such guidelines, to date there has not been any publication showing an improvement in head and neck cancer detection rates^{20 21}. The key questions are therefore: is the correct group of symptoms being used, and of these symptoms are they sufficiently refined?

From this study it would appear that the 2015 NICE guidelines have failed to address a number of other important "red flag" symptoms that should warrant an urgent suspicion of cancer (USOC) referral. Patients who presented with dysphagia, and were subsequently diagnosed with cancer of any subsite, the median survival was only 1.4 years, with the survival decreasing to less than a year (0.9 yr) if they were diagnosed with hypopharyngeal cancer. Dysphagia as a symptom was not present in the 2005 or the 2015 NICE guidelines for USOC referrals. Tikka et al highlighted the significant association of dysphagia with head and neck cancer and this study adds further evidence to the need for this symptom to be included as a "red flag" needing a USOC referral.²² The presence of pain in the form of sore throat or otalgia, was present as a "red flag" symptom in the 2005 NICE guidelines, but was removed in the updated 2015 version. Pain as a symptom at diagnosis in this

series was associated with a 2.3 year median survival, compared to 4.8 years median survival for those without pain. This significant difference in median survival would suggest that pain should be reintroduced to the “red flag” symptoms requiring urgent referral, a finding also highlighted by Tikka et al²². Weight loss is a very common symptom in patients with cancer and is not specific to head and neck cancer. However this study highlights the poor prognostic significance of weight loss as a presenting symptom. Weight loss was an independent prognostic factor for survival at all four subsites after adjustment for age and stage. Weight loss has not been a “red flag” symptom for head and neck cancer in the NICE guidelines of 2005 or 2015, but it may be that unexplained weight loss should be considered for inclusion in future “red flag” symptoms.

The second issue is to refine the chosen head and neck red flag symptoms to yield a higher proportion of head and neck cancer. Currently patients who present with persistent unexplained hoarseness for over three weeks need a 2 week referral for urgent suspicious of cancer (USOC). Our study highlights that a patient who presents with hoarseness, and is subsequently diagnosed with a squamous cell carcinoma of the head and neck, has a median survival of 5.9 years; if they are subsequently diagnosed with laryngeal squamous cell carcinoma the median survival is 7 years, arguably a very good prognosis. Given this prognosis it could be suggested that the referral USOC for hoarseness should be voice ‘never normal’ for over six weeks, excluding most of the ‘non-structural’ dysphonic patients from the USOC clinics.

The “evidence” for the “red flags” in laryngeal and oral cancer was based on one publication²³, highlighting a significant failing in the development of these guidelines. However, it may be that there simply isn’t the evidence base at present to develop true “evidence based “ guidelines and this is an area that requires further research.

Strengths and limitations of the study

The main limitation of this study was the accuracy of the recording of the symptoms. As this was designed to simply describe the study cohort at

diagnosis multiple clinicians were involved and symptom recording was as reported by the patient, not based on an interrogation using a pre-determined agreed list of symptoms. Although this potential inaccuracy could be used as an argument for not using symptoms as a prognostic tool, compared to an “objective” TNM Stage, this could be addressed by using an agreed symptom checklist. This is supported by Picirillo who demonstrated, in a series of larynx cancer patients, that symptom staging was just as reliable as the anatomical staging⁶.

A strength of this study is the large number of patients which were included in the original head and neck audit, and furthermore the long term survival data which we have in relation to the patients. Furthermore, the applicability of the findings are twofold; firstly it could be used to help direct symptom presentation for the early detection of head and neck cancer and secondly could be used to help build prognostic models and treatment planning discussions with the patient.

Conclusion

This study highlights the value of using patients’ symptoms throughout a patient’s journey, from when they first present in primary care with “red flag” symptoms to direct urgent referrals, and in specialist cancer units to support the diagnosis, treatment planning, prognosis and communication with patients. As many symptoms appear to be of prognostic value there is a need for more “symptom research” prior to the updating of national guidelines and involvement in staging systems.

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Studentship

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Table 1. Patient demographics by anatomical site.

	Larynx Frequency (n = 603)	%	Oral Cavity Frequency (n = 534)	%	Oropharynx Frequency (n = 330)	%	Hypopharynx Frequency (n = 122)	%
Sex								
Male	485	80.4	345	64.6	232	70.3	84	68.9
Female	118	19.6	189	35.4	98	29.7	38	31.2
Age								
<45	14	2.3	31	5.8	22	6.7	2	1.6
45 – 54	79	13.1	86	16.1	64	19.4	19	15.6
55 – 64	210	34.8	152	28.5	130	39.4	39	32.0
65 – 74	199	33.0	149	27.9	77	23.3	43	35.3
>= 75	101	16.8	116	21.7	37	11.2	19	15.6
Smoker								
Current	400	66.3	308	57.7	234	70.9	82	67.2
Previous	164	27.2	112	21.0	53	16.1	26	21.3
Never	31	5.1	93	17.4	36	10.9	12	9.8
Not recorded	8	1.3	21	2.9	7	2.1	2	1.6
Alcohol								
Current (problem)	152	25.2	168	31.5	114	35.6	37	30.3
Previous (problem)	67	11.1	61	11.4	52	15.8	17	13.9
Occasional drinker/never drank	287	47.6	256	47.9	140	42.4	60	49.2
Not recorded	97	16.1	49	9.2	24	7.3	8	6.6
WHO Status								
Normal activity	279	46.3	231	43.3	129	39.1	37	30.3
Strenuous activity restricted	161	26.7	133	24.9	93	28.2	45	36.9
Up and about >50% waking hours	50	8.3	35	6.6	33	10.0	15	12.3
Confined to bed/chair > 50% waking hours	37	6.1	35	6.6	22	6.7	9	9.4
Not recorded	79	12.6	100	18.7	53	16.1	16	13.1
Stage								
I	160	26.5	123	23.0	32	9.7	6	4.9
II	169	28.0	120	22.5	45	13.6	11	9.0
III	105	17.4	80	15.0	56	17.0	21	17.2
IV	157	26.0	160	30.0	188	57.0	82	67.2
Unknown	12	2.0	51	9.6	9	2.7	2	1.6
Treatment								
Surgery only	56	9.3	258	48.3	43	13.0	10	8.2
Radiotherapy only	346	57.4	61	11.4	55	16.7	28	23.0
Surgery and radiotherapy	166	19.2	140	26.2	99	30.0	28	23.0
Chemotherapy	49	8.1	34	6.4	95	28.8	40	32.8
No treatment	36	6.0	41	7.7	38	11.5	16	13.1

Table 2. Overall disease specific survival for patient variables at 5 and 12 years.

	5-year survival percent (95% CIs)	5-year p-value	12-year survival percent (95% CIs)	12-year p-value
Overall	61.4 (58.8, 63.9)		54.1 (51.3, 56.9)	
Age				
Less than 45	80.0 (68.0, 87.9)	<0.001	70.0 (57.0, 79.7)	<0.001
45 to 54	68.4 (62.0, 74.0)		60.2 (53.2, 66.4)	
55 to 64	64.3 (59.9, 68.5)		58.4 (53.6, 62.9)	
65 to 74	58.2 (53.2, 63.0)		50.6 (45.0, 56.0)	
75 and over	48.6 (41.9, 54.9)		38.7 (31.0, 46.3)	
Anatomical site				
Larynx	71.2 (67.2, 74.7)	<0.001	63.6 (59.1, 67.7)	<0.001
Oral cavity	63.2 (58.6, 67.4)		54.2 (49.2, 59.0)	
Oropharynx	49.1 (43.1, 54.8)		45.1 (39.0, 51.0)	
Hypopharynx	32.9 (23.4, 42.6)		24.1 (15.1, 34.3)	
Stage				
I	90.2 (86.2, 93.1)	<0.001	82.7 (77.3, 86.9)	<0.001
II	73.6 (68.4, 78.2)		63.7 (57.4, 69.3)	
III	61.6 (54.9, 67.6)		51.3 (44.1, 58.1)	
IV	38.1 (33.7, 42.4)		33.6 (29.2, 38.1)	
Unknown	44.3 (31.4, 56.5)		37.3 (24.6, 50.1)	
Number				
0-1 symptom	71.4 (69.0, 74.4)	<0.001	63.0 (59.1, 66.5)	<0.001
2 symptoms	54.1 (49.3, 58.7)		47.2 (42.0, 52.2)	
3 symptoms	39.9 (33.1, 46.6)		35.5 (28.6, 42.4)	
Hoarseness				
Yes	71.2 (67.1, 74.9)	<0.001	63.5 (58.9, 67.7)	<0.001
No	55.7 (52.3, 58.9)		48.5 (44.9, 52.0)	
Pain/discomfort				
Yes	51.6 (47.3, 55.8)	<0.001	44.4 (39.8, 48.9)	<0.001
No	67.5 (64.2, 70.5)		60.0 (56.5, 63.4)	
Lump in neck				
Yes	42.6 (34.4, 50.4)	<0.001	39.4 (31.2, 47.4)	<0.001
No	63.7 (61.0, 66.3)		55.8 (52.8, 58.7)	
Dysphagia				
Yes	44.4 (37.8, 50.7)	<0.001	40.8 (34.1, 47.4)	<0.001
No	64.9 (62.0, 67.5)		56.8 (53.7, 59.8)	
Ulceration				
Yes	65.5 (59.8, 70.6)	0.050	56.7 (50.3, 62.6)	0.105
No	60.4 (57.4, 63.2)		53.4 (50.2, 56.5)	
Swelling				
Yes	57.6 (48.3, 65.8)	0.206	51.9 (42.3, 60.7)	0.454
No	61.8 (59.1, 64.4)		54.3 (52.8, 58.9)	
Weight loss				
Yes	26.3 (18.2, 35.1)	<0.001	19.3 (10.9, 29.4)	<0.001
No	64.5 (61.8, 67.1)		57.0 (54.1, 59.9)	
Other/unknown				
Yes	51.3 (44.7, 57.4)	0.003	45.1 (38.2, 51.8)	0.002
No	63.5 (60.7, 66.2)		56.0 (52.8, 58.9)	

Table 3. Overall Median Survival.

	Median survival in days (95% CIs)	Median survival in years (95% CIs)
Overall	1321 (1185, 1492)	3.6 (3.2, 4.1)
Age		
Less than 45	5029 (3278,	13.8 (9.0,
45 to 54	2646.5 (1834, 3233)	7.2 (5.0, 8.9)
55 to 64	1602 (1257, 1959)	4.4 (3.4, 5.4)
65 to 74	1019.5 (828, 1340)	2.8 (2.3, 3.7)
75 and over	613 (437, 820)	1.7 (1.2, 2.2)
Anatomical site		
Larynx	2144 (1817, 2448)	8.9 (5.0, 6.7)
Oral cavity	1357.5 (1113, 1667)	3.7 (3.0, 4.6)
Oropharynx	836.5 (607, 1052)	2.3 (1.7, 4.6)
Hypopharynx	387 (317, 501)	1.1 (0.9, 1.4)
Stage		
I	3815 (3222, 4088)	10.4 (8.8, 11.2)
II	1926 (1569, 2378)	5.3 (4.3, 6.5)
III	1295.5 (945, 1760)	3.5 (2.6, 4.8)
IV	447 (383, 543)	1.2 (1.0, 1.5)
Unknown	477.5 (293, 964)	1.3 (0.8, 2.6)
Number		
0-1 symptom	1951 (1715, 2263)	5.3 (4.7, 6.2)
2 symptoms	960 (730, 1300)	2.6 (2.0, 3.6)
3 symptoms	413 (353, 586)	1.1 (1.0, 1.6)
Hoarseness		
Yes	2164 (1864, 2528)	5.9 (5.1, 6.9)
No	960.5 (822, 1140)	2.6 (2.3, 3.1)
Pain/discomfort		
Yes	841 (651, 1031)	2.3 (1.8, 2.8)
No	1745.5 (1418, 1982)	4.8 (3.9, 5.4)
Lump in neck		
Yes	461 (339, 651)	1.3 (0.9, 1.8)
No	1485 (1312, 1698)	4.1 (3.6, 4.6)
Dysphagia		
Yes	486 (383, 690)	1.3 (1.0, 1.9)
No	1565.5 (1363, 1833)	4.3 (3.7, 5.0)
Ulceration		
Yes	1523 (1198, 1899)	4.2 (3.3, 5.2)
No	1295.5 (1084, 1418)	3.5 (3.0, 3.9)
Swelling		
Yes	1256 (686, 1871)	3.4 (1.8, 5.1)
No	1333 (1195, 1508)	3.6 (3.3, 4.1)
Weight loss		
Yes	294 (245, 376)	0.8 (0.7, 1.0)
No	1537.5 (1341, 1749)	4.2 (3.7, 4.8)
Other/unknown		
Yes	1006 (841, 1302)	2.8 (2.3, 3.6)
No	1388.5 (1271, 1665)	3.8 (3.5, 4.6)

Table 4. Frequencies of each symptom per anatomical site after grouping for survival analysis

	Larynx Frequency (n = 603)		Oral Cavity Frequency (n = 534)		Oropharynx Frequency (n = 330)		Hypopharynx Frequency (n = 122)	
		%		%		%		%
Number								
0-1 symptom	348	57.7	317	59.4	158	47.9	28	23.0
2 symptoms	170	28.2	165	30.9	104	31.5	57	46.7
3 symptoms	85	14.1	52	9.7	68	20.6	37	30.3
Hoarseness								
Yes	497	82.4	N/A*	N/A*	24	7.3	41	33.6
No	106	17.6	N/A*	N/A*	306	92.7	81	66.4
Pain/discomfort								
Yes	154	25.5	203	38.0	201	60.9	57	46.7
No	449	74.5	331	62.0	129	39.1	65	53.3
Lump in neck								
Yes	35	5.8	37	6.9	83	25.2	28	23.0
No	568	94.2	497	93.1	247	74.8	94	77.0
Dysphagia								
Yes	97	16.1	45	8.4	77	23.3	64	52.5
No	506	83.9	489	91.6	253	76.7	58	47.5
Ulceration								
Yes	N/A*	N/A*	275	51.5	54	16.4	N/A*	N/A*
No	N/A*	N/A*	259	48.5	276	83.6	N/A*	N/A*
Weight loss								
Yes	44	7.3	27	5.1	39	11.8	29	23.8
No	559	92.7	507	94.9	291	88.2	93	76.2
Swelling								
Yes	N/A*	N/A*	86	16.1	41	12.4	N/A	N/A
No	N/A*	N/A*	448	83.9	289	87.6	N/A	N/A
Other/unknown								
Yes	114	18.9	194	36.3	115	34.8	41	33.6
No	489	81.1	340	63.7	215	65.2	81	66.4

*Symptom included in "Other/unknown" due to low frequency of patients with the symptom for this anatomical site

Table 5. Median survival for each subsite and symptom.

	Larynx Median Survival in years (95% CI)	Oral Cavity Median Survival in years (95% CI)	Oropharynx Median Survival in years (95% CIs)	Hypopharynx Median Survival in years (95% CIs)
Number				
0-1 symptom	7.7 (6.7, 8.8)	4.6 (3.7, 5.7)	3.3 (2.3, 4.2)	1.1 (0.8, 2.0)
2 symptoms	4.2 (2.6, 5.8)	3.3 (1.7, 4.6)	2.4 (1.3, 3.9)	1.2 (0.8, 1.8)
3 symptoms		1.0 (0.6, 2.4)	1.0 (0.7, 1.7)	1.1 (0.7, 1.3)
Hoarseness				
Yes	7.0 (5.9, 7.9)	NA	1.7 (0.2, 4.8)	1.1 (0.7, 1.7)
No	2.2 (1.5, 2.8)	NA	2.3 (1.7, 3.0)	1.0 (0.8, 1.4)
Pain/discomfort				
Yes	2.9 (2.1, 4.8)	2.5 (1.6, 3.6)	2.3 (1.4, 3.2)	1.5 (0.9, 1.8)
No	6.6 (5.7, 7.8)	4.8 (3.7, 5.7)	2.3 (1.4, 3.6)	0.9 (0.7, 1.3)
Lump in neck				
Yes	1.7 (0.9, 2.3)	0.9 (0.4, 1.6)	1.8 (0.7, 3.6)	1.2 (0.7, 1.7)
No	6.0 (5.3, 7.1)	4.1 (3.5, 4.9)	2.6 (1.7, 3.3)	1.0 (0.9, 1.4)
Dysphagia				
Yes	2.7 (1.4, 4.1)	1.2 (0.5, 2.0)	1.1 (0.7, 2.1)	0.9 (0.8, 1.3)
No	6.3 (5.6, 7.4)	4.1 (3.5, 4.9)	2.7 (2.1, 3.6)	1.2 (0.9, 1.7)
Ulceration				
Yes	NA	4.9 (3.7, 6.2)	2.2 (1.2, 3.4)	NA
No	NA	2.8 (1.9, 3.7)	2.4 (1.6, 3.1)	NA
Weight loss				
Yes	1.3 (0.7, 2.2)	0.6 (0.2, 1.4)	0.7 (0.4, 1.1)	0.8 (0.5, 0.9)
No	6.3 (5.4, 7.5)	4.0 (3.5, 4.9)	2.8 (2.2, 3.6)	1.3 (1.0, 1.7)
Swelling				
Yes	NA	4.5 (2.0, 6.8)	3.1 (1.1, 7.5)	NA
No	NA	3.7 (2.9, 4.4)	2.3 (1.5, 2.8)	NA
Other/unknown				
Yes	2.8 (2.4, 5.1)	3.1 (2.0, 4.2)	2.8 (0.9, 4.8)	1.3 (0.5, 1.9)
No	6.4 (5.4, 7.4)	3.9 (3.1, 5.0)	2.2 (1.5, 2.9)	1.1 (0.8, 1.3)

Table 6: Age- and Stage- adjusted hazard ratios for disease-specific survival

	Larynx HRs (95% CIs)	p-value	Oral Cavity HRs (95% CIs)	p-value	Oropharynx HRs (95% CIs)	p-value	Hypopharynx HRs (95% CIs)	p-value
Number								
0-1 symptom	1.0 (REF.)	0.004	1.0 (REF.)	0.015	1.0 (REF.)	0.001	1.0 (REF.)	0.533
2 symptoms	1.40 (1.01, 1.96)		1.32 (0.96, 1.80)		1.35 (0.94, 1.95)		1.15 (0.62, 2.15)	
3 symptoms	1.87 (1.28, 2.75)		1.88 (1.20, 2.95)		2.16 (1.44, 3.23)		1.45 (0.74, 2.83)	
Hoarseness								
Yes	0.80 (0.57, 1.12)	0.192	N/A*	N/A*	1.88 (1.09, 3.22)	0.023	0.88 (0.53, 1.46)	0.613
No	1.0 (REF.)		N/A*		1.0 (REF.)		1.0 (REF.)	
Pain/discomfort								
Yes	1.21 (0.89, 1.65)	0.219	1.27 (0.95, 1.69)	0.106	1.42 (1.00, 2.02)	0.048	1.31 (0.79, 2.18)	0.303
No	1.0 (REF.)		1.0 (REF.)		1.0 (REF.)		1.0 (REF.)	
Lump in neck								
Yes	1.36 (0.84, 1.65)	0.214	1.78 (1.09, 2.91)	0.021	0.82 (0.55, 1.22)	0.320	0.77 (0.42, 1.43)	0.408
No	1.0 (REF.)		1.0 (REF.)		1.0 (REF.)		1.0 (REF.)	
Dysphagia								
Yes	1.01 (0.71, 1.46)	0.936	1.60 (1.03, 2.48)	0.037	1.57 (1.10, 2.25)	0.014	1.11 (0.68, 1.83)	0.670
No	1.0 (REF.)		1.0 (REF.)		1.0 (REF.)		1.0 (REF.)	
Ulceration								
Yes	N/A*	N/A*	0.76 (0.57, 1.01)	0.060	1.28 (0.84, 1.93)	0.249	N/A*	N/A*
No	N/A*		1.0 (REF.)		1.0 (REF.)		N/A*	
Weight loss								
Yes	1.90 (1.24, 2.92)	0.003	2.39 (1.47, 3.39)	< 0.001	2.74 (1.73, 4.36)	< 0.001	2.65 (1.55, 4.52)	< 0.001
No	1.0 (REF.)		1.0 (REF.)		1.0 (REF.)		1.0 (REF.)	
Swelling								
Yes	N/A*	N/A*	1.02 (0.70, 1.49)	0.927	0.76 (0.46, 1.24)	0.269	N/A*	N/A*
No	N/A*		1.0 (REF.)		1.0 (REF.)		N/A*	
Other/unknown								
Yes	1.64 (1.18, 2.27)	0.003	1.20 (0.90, 1.59)	0.212	1.09 (0.78, 1.53)	0.610	0.87 (0.52, 1.48)	0.618
No	1.0 (REF.)		1.0 (REF.)		1.0 (REF.)		1.0 (REF.)	

*Symptom included in "Other/unknown" due to low frequency of patients with the symptom for this anatomical site