

## Abstract

### Objective

To investigate the recovery trajectory and predictors of outcome for swallowing difficulties following head and neck cancer treatment in a large prospective cohort.

### Materials and methods

Data from 5404 participants of the Head and Neck 5000 study were collected from 2011-2014. Patient-reported swallowing was measured using the EORTC HN35, recorded at baseline (pre-treatment) and 4 and 12 months post-baseline. Mixed-effects linear multivariable regression was used to investigate time trends, compare cancer sites, and identify associations between clinical, socio-demographic and lifestyle variables.

### Results

2458 participants with non-recurrent oral (29%) oropharyngeal (46%) and laryngeal (25%) cancer were included in the analysis. There was a clinically significant deterioration in scores between baseline and four months for swallowing (11.7 points; 95% CI 10.7-12.8) and trouble with social eating (17.9 points; 95% CI 16.7-19.2), but minimal difference between baseline and 12 months. Predictors of better swallowing and social eating were participants with larynx cancer, early-stage disease, treatment type, age, gender, co-morbidity, socio-economic status, smoking behaviour and cohabitation.

### Conclusion

Swallowing problems persist up to a year after head and neck cancer treatment. These findings identify disease and demographic characteristics for particularly vulnerable groups, supporting the need for holistic interventions to help improve swallowing outcomes. People diagnosed with head and neck cancer at risk of severe eating and drinking problems following treatment can be identified earlier in the pathway, receive more accurate information about early and late post-treatment side-effects, which can inform shared decision-making discussions.

Key words: Head and neck cancer; swallowing; social eating; patient-reported outcomes; predictors

## 1 Introduction

2 Dysphagia is a top priority concern for head and neck cancer (HNC) survivors [1].  
3 Swallowing difficulty can result from the tumour itself or from treatment side-effects and  
4 adversely impacts both health and quality of life (QoL) [2]. Clinicians need to understand  
5 prevalence and anticipated trajectory for recovery to provide survivors with realistic  
6 expectations regarding post-treatment outcomes beyond survival. This information may  
7 assist in the shared decision-making process during treatment planning. In addition,  
8 identifying predictors of swallowing outcome allows for timely identification of those most at  
9 risk, in order to provide accurate information and advice, and plan for early intervention. At  
10 an organisational level, understanding acute and long-term treatment effects is essential for  
11 providing adequate resources, to ensure survivorship needs are met.

12 Reported prevalence of dysphagia after HNC treatment varies widely in the published  
13 literature with conservative estimates suggesting between 50-60% of survivors are affected  
14 [3]. Most published studies are single institutional data sets. While these have identified  
15 tumour stage, subsite of disease, age, gender and treatment modality as potential explanatory  
16 variables of dysphagia [1, 4, 5] small sample sizes, and the biases inherent in studying only  
17 survivors from one centre, are important limitations. Publications from the USA population-  
18 based Surveillance Epidemiology and End Results program showed that older survivors and  
19 those treated with radiotherapy +/- chemotherapy have the highest risk of dysphagia, with  
20 prevalence estimated as 20-24% for laryngeal and oropharyngeal cancer [6, 7]. Limitations  
21 of these data are that dysphagia was recorded by clinicians using *The International*  
22 *Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) [8]. It is well  
23 documented that survivors' own reports of swallowing difficulties do not correlate strongly  
24 with clinician rated scales [9]. Moreover, patient-reported swallowing difficulties may be

25 influenced by additional factors beyond disease characteristics or type of treatment, which  
26 tend to be what is available in large datasets such as SEER.

27 A further limitation in the existing evidence relates to knowledge of the trajectory of  
28 swallowing recovery. A small number of longitudinal studies describe this, with follow up  
29 periods ranging from 6 to 24 months. These report on survivors following Intensity  
30 Modulated Chemoradiotherapy (CRT) [10, 11], accelerated radiotherapy [12], or a  
31 combination of post-radiotherapy and post-CRT [13, 14]. All identify a significant  
32 deterioration in swallowing from pre- to post-treatment. However, there is disagreement  
33 about the subsequent trajectory, with three studies reporting little recovery following  
34 treatment [10, 12, 13], whereas others [11, 14] report some improvement, but without a return  
35 to pre-treatment status.

36 Head and Neck 5000 (HN5000) is an ongoing prospective clinical cohort study that has  
37 collected longitudinal data on in excess of 5000 participants. This allows large longitudinal  
38 analysis which can address gaps in knowledge around patient-reported swallowing and social  
39 eating over time. Specifically, we used this data to: (1) assess temporal trends in swallowing  
40 and social eating over the first year after diagnosis; (2) compare swallowing and social eating  
41 outcomes across HNC sites; and (3) identify factors associated with swallowing and social  
42 eating outcomes in the first year.

## 43 [Methods](#)

44 The HN5000 protocol and participant characteristics have been reported elsewhere [15, 16].  
45 People at 76 UK centres were invited to participate if they were  $\geq 16$  years and diagnosed  
46 with a new primary HNC or an unknown primary tumor likely to be HNC. Those who lacked  
47 capacity to provide informed consent or were deemed by their clinical team to be too  
48 vulnerable for participation were ineligible. The anonymized analysis dataset (version 2.1)

49 included 5404 individuals who consented to participate April 2011-December 2014. We  
50 limited consideration to oral cavity (ICD-10 C01-06), oropharynx (ICD-10 C10), or larynx  
51 (ICD-10 C32) cancers, treated with curative intent and not recorded as having recurred in the  
52 year post-recruitment (n=3259) (Supplementary figure s1).

### 53 Outcome measures

54 Participants completed a baseline health and lifestyle survey (prior to treatment starting) and  
55 surveys at 4 and 12 months post-baseline. These included the European Organization for  
56 Research and Treatment of Cancer Quality of Life Questionnaire-H&N35 (EORTC QLQ-  
57 H&N35), a disease-specific module of 35 questions in seven subscales relevant to HNC [17].  
58 We limited consideration to the swallowing and trouble with social eating sub-scales. These  
59 items cover the ability to swallow drinks and food; choking events; enjoying food; and eating  
60 with family and others. For each sub-scale, participants' responses were linearly transformed  
61 into a score in the range 0-100, treating missing data as recommended [18]. Higher scores  
62 represent more severe symptoms.

### 63 Clinical information

64 Clinical information abstracted from medical records included: ICD10 tumour site [19];  
65 TNM-stage (using the American Head and Neck Society system 3<sup>rd</sup> Edition)[20]; laterality of  
66 primary tumor; comorbidities (classified using the Adult Comorbidity Evaluation (ACE-  
67 27))[21]; and received treatment (at 4 months). Serological human papilloma virus status  
68 was defined as positive where HPV16E6 was >1000 median fluorescence intensity [22].

### 69 Socio-demographic and lifestyle data

70 Some socio-demographic variables were abstracted from clinical notes at baseline (age,  
71 gender, ethnicity). Others variables (e.g. marital status, smoking status) were collected in the

72 baseline survey. A deprivation category, based on the English Index of Multiple Deprivation  
73 2010 [23], was assigned according to the individual's home address postcode.

#### 74 Statistical analysis

75 Analyses were performed using STATA version 15. To be in the study population,  
76 individuals had to have completed the swallowing and/or trouble with social eating subscales  
77 at baseline (Supplementary figure s1). Chi-square tests were used to compare socio-  
78 demographic and clinical characteristics between those who completed these subscales  
79 (n=2458) and those who did not (n=801).

80 Mean swallowing and trouble with social eating outcome scores were computed for each time  
81 point (baseline, 4 months, 12 months) for the study population, by cancer site (oral cavity,  
82 oropharynx and larynx) and by clinical, socio-demographic and lifestyle subgroups.

83 Differences between subgroups of 5–9.9, 10–19.9 and  $\geq 20$  points were considered as  
84 'minimally', 'moderately' and 'largely' clinically significant, respectively [24]. The  
85 percentages over time and by site who scored  $>5$  on each subscale – which indicates a  
86 perceived need for supportive care [25] were also computed; cutoff scores have been  
87 suggested to be helpful in clinical practice for identifying patients who may require attention.

88 Mixed-effects linear multivariable regression was used to investigate time trends, compare  
89 cancer sites, and identify associations between socio-demographic, clinical and attitudinal  
90 variables and swallowing and trouble in social eating. These models allow for inclusion of  
91 all surveys completed by each individual, taking within-subject correlations into account and  
92 producing robust error estimates [26]. Separate models were built for swallowing and trouble  
93 with social eating. We assessed bivariate associations between each potential predictor  
94 variable (listed in Table 1) and the outcome (adjusted for time-point). Variables significant at  
95 the 5% level (and time-point and cancer site) were included in initial multivariable models,  
96 with Wald tests used to reduce these models. The final models included variables that

97 remained significant at the 5% level when adjusted for other variables and, in terms of  
98 interpretation, provide estimates of the effect of each variable over all time points (ie over 12  
99 months). We used Akaike's Information Criterion (AIC) and Bayesian Information Criterion  
100 (BIC) to compare models with (i) random intercept and random slope with those including  
101 random intercept only and (ii) different covariance structures. There was little difference  
102 between models so we fitted the least complex models: random intercept with structured  
103 covariance. We excluded people with missing data if <3% of individuals had missing data for  
104 the variable; if  $\geq 3\%$  was missing, we included an "unknown" category of the variable.

## 105 Ethics

106 Participants provided written informed consent. The study was approved by the National  
107 Research Ethics Committee (South West Frenchay Ethics Committee, reference  
108 10/H0107/57, November 5, 2010), and the research and development departments for  
109 participating NHS Trusts.

## 110 Results

### 111 Participants

112 In total 2458 participants with non-recurrent oral cavity, oropharynx or larynx tumours  
113 provided data on swallowing and/or social eating at baseline (Figure 1). These participants  
114 had lower levels of deprivation, less comorbidity and a higher prevalence of HPV16 E6  
115 positivity than the 801 participants who did not complete either subscale.

116 Twenty nine percent of the study population had oral cavity, 46% oropharyngeal and 25%  
117 laryngeal cancer (Table 1). One quarter has stage I disease, 17% stage II, 13% stage III, and  
118 43% stage IV. Bilateral disease was present in 10%. Forty-five percent had no  
119 comorbidities, one third had mild decompensation, and 20% moderate/severe  
120 decompensation. Three-quarters were male and half were aged 50-64 years.

121 Participants with laryngeal cancer were older, more often male, less often had tertiary  
122 education and more often had moderate/severe decompensation than those with cancers at  
123 other sites (Supplementary table s1). Those with oropharyngeal cancer more often had stage  
124 IV and HPV positive disease and received CRT.

## 125 Swallowing

126 The mean swallowing score at baseline was 13.4 (standard deviation (sd)=21.1)(Table 2); this  
127 was worse at 4 months (mean=24.1, sd=27.7); and improved slightly at 12 months though  
128 was not back to baseline levels (mean=15.5, sd=21.0). This pattern was consistent across all  
129 tumour sites (Figure 2). At each time-point, the mean score was highest for oropharyngeal  
130 cancer, and lowest for laryngeal cancer; this difference was most pronounced at 4 months. In  
131 terms of unmet needs, at baseline 46% overall scored >5, rising to 66% at 4 months and  
132 falling slightly to 58% at 12 months (Table 2).

133 Supplementary table S2 summarises mean swallowing scores by socio-demographic and  
134 clinical factors at each time-point.

135 In the multivariable mixed linear regression model, swallowing symptom scores were, on  
136 average, 11.7 points higher/worse (95%CI 10.7 to 12.8) at 4-month than at baseline, and 3.4  
137 points higher (95%CI 2.3 to 4.5) at 12 months than at baseline (Table 3). Over 12 months,  
138 after adjusting for other variables, there was no difference in swallowing scores between oral  
139 cavity and oropharynx tumours; those with laryngeal tumours had scores that were, on  
140 average, 4.2 points lower/better (95%CI -6.6 to -1.9) than those with oral cavity tumours.  
141 The 65+ age group had better swallowing scores than those aged <50. Scores were worse in  
142 those with non-white ethnicity, who were not married or cohabiting, and who lived in the  
143 most deprived areas. Compared to never smokers, current smokers (at baseline) had, on



144 average over 12 months, a 7.6 point worse score (95%CI 5.1 to 10.1). Scores were better in  
145 those who reported consuming alcohol at baseline than those who did not.

146 Those who were HPV16 E6 positive had better swallowing scores than those HPV16 E6  
147 negative. Swallowing scores worsened with increasing stage and increasing comorbidity.  
148 Compared to those who had surgery only, score were worse for those who had radiotherapy  
149 only, chemotherapy/chemoradiotherapy and surgery and adjuvant therapy.

#### 150 Social eating

151 The mean trouble with social eating score was 16.9 at baseline (sd=25.0), rising to 33.6 at 4  
152 months (sd=31.8) and falling to 23.5 (sd=28.2) at 12 months (Table 4). At baseline, the mean  
153 score was highest/worst for oral cavity cancer, intermediate for oropharyngeal cancer, and  
154 lowest for laryngeal cancer. Scores were higher for all sites at 4 months and 12 months than  
155 at baseline and, at 4 months, were worst in those with oropharyngeal tumours (Table 3;  
156 Figure 3). At baseline, 51% overall scored >5; this rose to 74% at 4 months and declined to  
157 63% at 12 months (Table 2).

158 Supplementary table s3 shows mean trouble with social eating scores for each time-point by  
159 socio-economic and clinical subgroup.

160 In the multivariable mixed linear regression model, the trouble with social eating symptom  
161 score was, on average, 17.9 points (95%CI 16.7 to 19.2) worse at 4-months than at baseline,  
162 and 7.9 points (95%CI 6.6 to 9.2) worse at 12 months than at baseline (Table 4). Compared  
163 to oral cavity cancer, those who had oropharyngeal cancer had scores that were, on average  
164 over 12 months, 3.6 points better (95% -6.2 to -1.0) while those for laryngeal cancer were, on  
165 average, 12.6 points better (-15.4 to -9.8). Social eating scores were better for older  
166 participants, and worse for women, those not married/cohabiting, and those resident in the  
167 most deprived areas. The score for current smokers was, on average over 12 months, 10.5

168 points higher (95%CI 7.6 to 13.4) than for never smokers. Scores were worse for those with  
169 higher stage disease; those with comorbidities; and those who had radiotherapy,  
170 chemotherapy or chemoradiotherapy, or surgery plus adjuvant therapy, compared to surgery  
171 alone.

## 172 Discussion

173 This study reports on one of the largest HNC prospective multi-centre studies that includes  
174 patient reported swallowing outcome data. Results confirmed findings from smaller studies  
175 that swallowing and social eating deteriorates following treatment, with some improvement  
176 over time, and tumour site and treatment type are important variables for predicting outcome.  
177 Several factors not previously considered in the literature such as age, living circumstance,  
178 gender, smoking and socio-economic status were also found to independently impact on  
179 participants' reports of their swallowing.

## 180 Trajectory

181 In exploring the temporal trends over the first year, swallowing and social eating domains  
182 followed a similar pattern, with a moderately clinically significant deterioration between pre-  
183 treatment and four months, and minimal differences between baseline pre-treatment scores  
184 and 12 months (although scores at 12 months were below those at baseline). This trajectory  
185 confirms observations from other smaller longitudinal studies for IMRT and transoral  
186 surgical approaches [11, 27], on a swallowing-specific QOL questionnaire. In the current  
187 study, deterioration between baseline and four months was greater for social eating than the  
188 swallowing domain, with the largest differences observed in those treated with CRT and  
189 survivors presenting with advanced disease.

190 Oropharyngeal cancer survivors scored consistently worse across swallowing and social  
191 eating, and their scores were particularly poor at 4 months. This is a similar finding to a

192 much smaller study using a swallowing-specific QOL questionnaire [28]. The oropharynx  
193 contains a number of crucial structures necessary for safe and efficient swallowing and it is  
194 not surprising that treatment results in significant dysphagia. The incidence of HNC in the  
195 United Kingdom has risen by a third since 1990, and is expected to increase by 50% over the  
196 next 20 years [29, 30], mainly due to HPV infection. HPV now accounts for 70% of  
197 oropharyngeal cancer, in contrast to a reported 41% prior to 2000 [31]. This sub-group are  
198 typically younger at diagnosis and have better survival outcomes. This means many  
199 survivors are living longer with profound functional deficits. There is an urgent need,  
200 therefore, to develop strategies to either minimise treatment toxicity or develop  
201 strategies/interventions to support survivors to manage these deficits. In terms of the first,  
202 current trials are addressing treatment de-escalation to reduce toxicity, and have included  
203 swallowing as the primary outcome [32]. As regards the latter, while function may be  
204 improved by swallowing exercises, there are challenges around adherence [33].

#### 205 Predictors of outcomes over the first year

206 Several predictors of outcome over 12 months were identified. As previously noted,  
207 survivors having combined treatments did worse than those having single modality treatment  
208 [1]. The addition of chemotherapy to treatment resulted in clinically significant deterioration,  
209 although the effect was small. Some evidence suggests that survivors treated by minimally  
210 invasive surgery and adjuvant treatment do better than those treated with CRT [27, 34].  
211 More recently, a randomised controlled trial found a statistically significant, but not clinically  
212 significant, difference on a swallowing-specific QOL questionnaire, with better results for  
213 IMRT than surgery, but no difference was found on EORTC swallowing and social eating  
214 domains [35]. A European trial is underway, to compare swallowing outcomes for IMRT and  
215 surgery for early oropharyngeal disease, using a comprehensive battery of tests [36].

216 Among the current study population, older people reported better swallowing and social  
217 eating scores. Intuitively, one might expect that older survivors would have poorer treatment  
218 tolerance or additional comorbidities, reduced reserve and age-related swallowing decline,  
219 resulting in poorer outcomes. Our previous findings on a small prospective cohort also found  
220 better swallowing-specific QOL outcomes for older adults [1]. It is possible that, as we age,  
221 we may be more accepting of lower functional status, alongside fewer demands on social  
222 eating, i.e. less frequent eating out [37]. However, difficulty with swallowing is still a  
223 priority concern in older survivors [38], indicating that this group should not be disregarded  
224 in terms of support.

225 Our analysis found that those who were single and living alone had poorer outcome across  
226 both domains. Families play an important role in supporting survivors with eating and  
227 drinking, adapting shopping habits, food preparation and presentation [39]. People with  
228 dysphagia who co-habit have better nutrition, have more cooked meals and eat more regularly  
229 than those who do not [40, 41]. The presence of others may also help with developing  
230 confidence with social eating. These observations, and our findings, suggest that HNC  
231 survivors living alone may be more vulnerable to poorer outcomes, and require additional  
232 healthcare support.

233 While we found no differences by gender for the swallow domain, females reported poorer  
234 social eating scores than males. Smaller HNC studies on swallowing or, more generally,  
235 QoL have either not identified gender as an important factor, have excluded it from their  
236 analysis or included only male participants [1, 28, 42]. Thus little is known about whether  
237 there are gender differences in functioning among HNC survivors. Elsewhere, females have  
238 been found to be at greater risk of poorer psychosocial outcomes following HNC treatment  
239 [43, 44]. Studies reporting on laryngectomy survivors suggested that females had poorer

240 outcomes and higher unmet needs [16, 42, 45]. Overall, our results suggest that living alone  
241 and being female places survivors at greater risk of poorer social eating outcomes.

242 Many HNC survivors are from poor socio-economic backgrounds, and have low levels of  
243 support and education [46, 47]. Levels of deprivation have not previously been considered in  
244 relation to swallowing or social eating outcomes, so this study is novel in that regard and  
245 found poorer functioning in people resident in the most, compared to the least, deprived  
246 areas. In general, people of lower socio-economic status have higher usage of takeaways and  
247 ready prepared meals [37]. Access to modified diet textures may be particularly problematic  
248 for survivors who depend on out-of-home meals. Furthermore, there is a financial burden  
249 associated with swallowing difficulties, with additional costs for the purchase of special  
250 foods, supplements and texture modifying equipment [48]. Many survivors with dysphagia  
251 need to adjust their eating behaviours such as having smaller amounts more often [49].  
252 Further work is needed to evaluate the true financial cost of living with dysphagia.

253 In the present analysis, co-morbidities had a minimal clinically significant effect on both  
254 swallowing and social eating. Chronic obstructive pulmonary disease (COPD) is one of the  
255 most prevalent comorbidity present at HNC diagnosis [50]. COPD is also associated with  
256 dysphagia, increasing the risk of aspiration. Although this is of clinical concern, co-  
257 morbidities were reported as being minimally clinically significant for both swallowing and  
258 social contact. However, current smokers reported worse outcomes – and the difference for  
259 social eating between current and never smokers was of moderate clinical significance. The  
260 relationship between smoking and eating and drinking has received little attention. In a small  
261 scale study, symptom burden for current smokers was significantly higher on the EORTC,  
262 with adjusted regression models retaining swallowing, but not social eating [51]. A  
263 systematic review identified that continued smoking increases likelihood of late toxicities

264 such as osteoradionecrosis, dysphagia and laryngeal oedema [52], which could impact on  
265 patient reported outcomes.

### 266 Strengths

267 This study has numerous strengths. The HN5000 cohort provided a large sample, recruited  
268 from multiple centres, enabling a comprehensive and representative analysis of swallowing  
269 outcomes in the first year following diagnosis. The EORTC HN 35 is a commonly used and  
270 well-validated HRQOL questionnaire and provides an indication of clinical significance of  
271 differences over time or between groups. The analysis included a broad range of factors  
272 including clinical, demographic and lifestyle, not previously considered by other studies.

### 273 Weaknesses

274 Despite this large dataset, only 61% of eligible participants provided complete data at  
275 baseline [16]. Furthermore, participants with more co-morbidities, lower socio-economic  
276 status and HPV negative disease were under-represented. Questionnaires were collected at  
277 four months post diagnosis. At this time point, participants receiving aggressive radiotherapy  
278 will be experiencing acute treatment side-effects, whereas those treated with surgery alone  
279 will have benefitted from a longer recovery period. This study reports on outcomes up to  
280 twelve months. Beyond one year, patient reported outcomes may continue to change [52,  
281 53]. Finally, it is acknowledged that this study reports solely on patient reported swallowing,  
282 which is only weakly associated with swallowing impairment [55].

### 283 Clinical implications

284 These findings suggest a high prevalence of unmet supportive care needs according to cutoff  
285 figures and can assist clinicians to identify and predict patients at greater risk of developing  
286 eating and drinking problems. Initial case history taking should include details on disease  
287 characteristics, treatment intention as well as lifestyle factors and smoking behaviour. More

288 accurate patient information can be provided at diagnosis about likely early and late post-  
289 treatment outcomes. This can inform shared decision-making, where treatment options are  
290 available. Early and intensive rehabilitation aiming to prevent dysphagia may also be  
291 targeted at high risk patients. At an organisational level, local population demographics  
292 should be considered when planning rehabilitation services.

### 293 Further research

294 This study has identified people who are at higher risk of swallowing and social eating  
295 problems. Further work is required to more fully understand the needs of these groups,  
296 developing interventions to address both survivors' perceptions of dysphagia and its social  
297 consequences. Furthermore, these may be extended and integrated with other interventions  
298 such as smoking cessation programmes to further improve symptom burden [52].

### 299 Conclusions

300 Data from HNC5000, a large prospective cohort study confirmed that HNC survivors report a  
301 marked deterioration in swallowing and social eating from pre-treatment to four months  
302 following treatment, with some evidence of recovery by one year, but not to baseline status.  
303 Oropharyngeal cancer survivors had poorer outcomes in comparison to other HNC tumour  
304 sites. Predictors of outcome at one year included multi-modality treatment and age at  
305 presentation. Living alone, sex, smoking behaviour and low socio-economic status also  
306 contributed towards the predictive model. These novel findings identify particularly  
307 vulnerable groups, supporting the need for holistic dysphagia interventions to help improve  
308 outcomes.

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