Treatment modality: a predictor of continued tobacco use after treatment in patients with laryngeal cancer

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Abstract

Background: Laryngeal cancer patients who continue to smoke after treatment are at an elevated risk of mortality and morbidity. This study aimed to identify factors associated with continued tobacco use following treatment in patients with laryngeal cancer.

Methods: A smoking behaviour questionnaire, a self-report measure, was sent to 112 patients who were diagnosed with laryngeal cancer during 2006–2011 at the Brighton and Sussex University Hospitals, Brighton, UK. Patient demographics, tumour and treatment-related variables, comorbidity and socio-economic status were obtained from the medical records.

Results: Eighty-one per cent of patients responded to the survey; 22 per cent of these reported continued tobacco use after treatment. Treatment modality was found to be a predictor of post-therapeutic smoking (odds ratio: 4.9, $p = 0.01$); patients who received less invasive therapy (transoral laser microsurgery) were more likely to smoke after treatment.

Conclusions: The findings of this preliminary study suggest that treatment modality influences smoking behaviour in patients with laryngeal cancer, which may have important implications for the design of anti-smoking interventions.

Key words: Laryngeal Neoplasms; Smoking; Compliance; Preventive Measures

Introduction

Laryngeal cancer is the most common malignancy of the head and neck, accounting for 2.4 per cent of all malignancies worldwide.[1] Despite relatively early diagnosis and advances in the management of laryngeal cancer, overall survival rates have not improved over the past 30 years.[1,2] Non-improvement of laryngeal cancer survival has led to a shift in thinking in recent years, focusing research into preventive work.[3,4]

Given that smoking is the main aetiological factor of cancer of the larynx,[5,6] smoking cessation programmes are the subject of most preventive work, of which primary prevention is the main goal. An area that has not been extensively investigated is tertiary prevention, i.e. the prevention of disease progression and recurrence, and further morbidity.

Continued tobacco use following diagnosis of laryngeal cancer has been estimated to range from 26 to 61 per cent.[7,8] More recent observational studies suggest that the figure is approximately closer to 30 per cent.[3,9] Continued tobacco use is associated with deleterious health consequences, including decrease in disease-specific survival time and effectiveness of non-surgical treatment.[10,11] Furthermore, continued tobacco use increases the risk of recurrence,[10] second primary malignancies,[12] radiotherapy-induced morbidity[13] and peri- and post-operative complications.[13] There is a large body of evidence that strongly supports the need to provide formal smoking cessation programmes to patients who are newly diagnosed with laryngeal cancer.[9] To deliver effective smoking cessation programmes, a comprehensive understanding of the predictors of continued tobacco use after diagnosis of laryngeal cancer is useful. This information can be used to target high-risk individuals who would benefit most from smoking cessation interventions.

Studies investigating the correlates of smoking behaviour following diagnosis of laryngeal cancer are limited and out of date, while existing findings are inconsistent. In a smoking cessation intervention study in head and neck cancer patients, Gritz *et al.* reported that patients who were heavy smokers

(smoking >40 cigarettes per day), and thus more nicotine-dependent, were at a higher risk to continue smoking after treatment.[8] In contrast, Ostroff *et al.* reported that disease stage, treatment modality and tumour site were associated with post-therapeutic smoking, but the number of pack-years was a poor predictor.[6] Similar cross-sectional studies suggest that late-stage disease and more invasive treatments are associated with continued tobacco use.[3,6,8,9] Allison *et al.* showed that patients who received radiotherapy alone were 2.7 times more likely to continue to smoke than patients who received combination therapy, which included major surgery and radiotherapy.[3]

However, all studies failed to include patients treated with transoral laser microsurgery. Given that in recent years transoral laser microsurgery has become the first-line treatment for early laryngeal cancer in the UK,[14] the limited literature available regarding the predictors of post-therapeutic smoking is no longer applicable to current clinical practice.

The aims of this study were twofold: (1) to examine the prevalence and patterns of continued tobacco use in patients with laryngeal cancer following treatment and (2) to identify the factors associated with post-therapeutic smoking.

Materials and methods

Participants

Between January 2006 and December 2011, 148 consecutive patients with histologically confirmed laryngeal cancer were evaluated at the Brighton and Sussex University Hospitals, Brighton, UK. To be eligible for the study, patients were required to be originally diagnosed, followed and treated at the Brighton and Sussex University Hospitals. Patients were excluded from the study if they had died ($n = 20$), refused therapy ($n = 1$), had a concomitant malignant diagnosis ($n = 1$), had evidence of recurrent laryngeal cancer ($n = 8$) or had missing data ($n = 6$).

Ethical considerations

The study was undertaken with institutional review board approval by the Brighton and Sussex University Hospitals ethics committee. Written informed consent was obtained from all study participants.

Procedures

One hundred and twelve eligible patients were sent a smoking behaviour questionnaire, a self-report measure, together with a cover letter explaining the study, to identify the patient's current smoking status. Information regarding past tobacco use (lifetime use, 12 months preceding the diagnosis of laryngeal cancer and 12 months following treatment) and current tobacco use was obtained via the questionnaire. Each patient's smoking status was based on the information provided by the questionnaire, and was categorised as either: current smokers, defined as patients who had reported any

tobacco use in the past 7 days; ex-smokers, defined as patients who had reported any lifetime tobacco use, but had not used tobacco in the past 7 days; and non-smokers, defined as patients who had reported no lifetime tobacco use. Participants were given three weeks to respond to the questionnaire.

Variables

The questionnaire elicited information about smoking frequency during the aforementioned time periods and was quantified in terms of pack-years. Variables including patient demographics (age, gender and ethnicity), tumour site (supraglottis, glottis or subglottis), tumour staging (T-staging system), treatment modality (transoral laser microsurgery, radiotherapy or combined therapy or laryngectomy), comorbidity and socio-economic status were abstracted from each patient's medical records. These variables were included in the pool of potential predictors of smoking behaviour, based on previous research on tobacco use among patients with head and neck cancer.[3,6,8,9,15] Comorbidity was assessed using the Charlson comorbidity index, which assigns values between 1 and 6 to 19 major disease categories, and adds them up into a pooled score that predicts patient survival.[16] Patients were categorised into three groups according to their Charlson comorbidity index score: no comorbidity (score: 0), moderate comorbidity (score: 1–2) and severe comorbidity (score: ≥ 3). Socio-economic status is not routinely collected in cancer registries in the UK. Thus, the Townsend Deprivation Index, an ecological measure of area deprivation, was used to assess the socio-economic status of patients, based on each patient's postcode and data from the 2011 UK census.[17,18]

Statistical analysis

Chi-square tests were used to determine the relationships between categorical variables and smoking status; continuous variables were evaluated using the Student's *t*-test. Multiple logistic regression analysis was conducted to identify factors independently associated with continued tobacco use following treatment. Odds ratios with corresponding 95 per cent confidence intervals were reported for statistically significant predictors. Non-smokers were excluded from the statistical analyses. All *p* values represented were two-sided and statistical significance was declared at $p < 0.05$. Statistical analysis was undertaken using IBM SPSS Statistics 19.0 (IBM United Kingdom Limited, Portsmouth, UK).

Results

Patient characteristics

Ninety-one of 112 (81 per cent) eligible patients responded to the smoking behaviour questionnaire. Table I summarises the demographic and clinical profile of the 91 study participants. The average age of the participants at diagnosis was 67 years (range: 41–89 years); patients were predominantly men (90 per cent) and

TABLE I
BASELINE CHARACTERISTICS OF THE PATIENT
COHORT ($N = 91$)

Variable	Category	N (%)
Age (years)*		67.0 ± 1.1
Gender	Men	82 (90.1)
	Women	9 (9.9)
Ethnicity	White	85 (93.4)
	Non-white	6 (6.6)
Socio-economic status	Affluent	29 (31.9)
	Non-affluent	62 (68.1)
Comorbidity	No comorbidity	52 (57.1)
	Moderate	29 (31.9)
	Severe	10 (11.0)
Site	Supraglottis	14 (15.4)
	Glottis	77 (84.6)
	Subglottis	0 (0)
Tumour stage	T_1	32 (35.1)
	T_2	24 (26.4)
	T_3	17 (18.7)
	T_4	18 (10.8)
Treatment	Laser surgery	29 (31.9)
	Radiotherapy	39 (42.9)
	Combination therapy and/or laryngectomy	23 (25.2)
Time since treatment (in months)*		27 ± 1.9
Smoking	Current smokers	20 (22.0)
	Ex-smokers	63 (69.2)
	Non-smokers	8 (8.8)
Lifetime tobacco use (in pack-years)*†		40.3 ± 3.4

*Mean $\pm$ standard error. †$n = 83$ (excludes 8 non-smokers)

white (93 per cent). The median follow-up rate following treatment was 27 months (range: 1–68 months). Respondents ($n = 91$) and non-respondents ($n = 21$) were comparable with respect to age, gender, ethnicity, tumour site, tumour staging, treatment modality, comorbidity and socio-economic status; no statistically significant associations were found between the two groups.

Ninety-one per cent of the study participants ($n = 83$) reported any lifetime history of tobacco use; the remaining 9 per cent ($n = 8$) of respondents reported no lifetime tobacco use and were classified as non-smokers; 22 per cent of the patient cohort ($n = 20$) were categorised as current smokers, while 69 per cent ($n = 63$) were classified as ex-smokers.

Prevalence of continued tobacco use

Twenty patients reported having used tobacco in the past 7 days, representing 22 per cent of the patient cohort. Current smokers averaged 46.3 ± 7.0 pack-years ($\pm$ standard error) and started smoking at an average age of 19.8 ± 3.6 years. All current smokers reported having smoked in the 12 months preceding the diagnosis of laryngeal cancer and during the 12 months after treatment.

Predictors of post-therapeutic smoking

The associations between smoking status and potential predictors are illustrated in Table II; tobacco use after treatment was used as the primary smoking behaviour outcome. Non-smokers were excluded from the analyses.

No statistically significant associations were found between smoking status and demographic predictors, including age ($p = 0.098$), gender ($\chi^2 = 0.931$, $p = 0.335$), ethnicity ($\chi^2 = 0.145$, $p = 0.703$) and socio-economic status ($\chi^2 = 3.316$, $p = 0.061$). Disease variables, including tumour site ($\chi^2 = 0.640$, $p = 0.424$) and comorbidity ($\chi^2 = 2.509$, $p = 0.285$), and smoking history variables, including lifetime tobacco use ($p = 0.319$) and age at which smoking started ($p = 0.622$), did not show any statistically significant associations with smoking status.

Two variables showed statistically significant associations with continued tobacco use following treatment: tumour staging ($\chi^2 = 10.513$, $p = 0.015$) and treatment modality ($\chi^2 = 17.720$, $p < 0.0001$). With regard to tumour staging, patients with a more severe tumour stage were less likely to smoke following treatment: 43 per cent of patients who had T_1 laryngeal cancer in the study cohort continued to smoke following treatment; 20, 14 and 6 per cent of patients with T_2, T_3 and T_4 laryngeal cancer respectively, used tobacco after treatment. With regard to treatment modality, patients were less likely to smoke after treatment as treatment invasiveness increased: 52 per cent of patients who had their laryngeal cancer treated with transoral laser microsurgery continued to smoke following treatment; 15 and 5 per cent of patients treated with radiotherapy and combined therapy and/or laryngectomy respectively, used tobacco following treatment.

To determine the relative significance of disease-related and treatment-related factors as predictors of post-therapeutic smoking, logistic regression analysis was conducted, with smoking status as the outcome variable. Predictors in the logistic regression model included tumour staging and treatment modality, based on the results of the independent t-tests and chi-square analyses (Table III). Logistic regression analysis showed that treatment modality is an independent predictor of post-treatment tobacco use, when tumour staging is accounted for. Patients who underwent transoral laser microsurgery were 4.9 times more likely to continue to smoke after treatment than those patients who received radiotherapy or combined therapy and/or laryngectomy respectively ($p = 0.01$). Conversely, when controlling for treatment modality, tumour staging was not a statistically significant correlate of smoking status.

Discussion

The aims of this study were to examine the prevalence and predictors of continued tobacco use following treatment in laryngeal cancer patients. The results showed that 22 per cent of the patient cohort ($n = 20$) reported smoking 12 months following treatment and were currently smoking at the time of analysis. The smoking rate is comparable to other studies examining

TABLE II
ASSOCIATIONS BETWEEN SMOKING STATUS AND INDEPENDENT STUDY VARIABLES ($N = 83$)

Variable	Category	Current smokers N (%)	Ex-smokers N (%)	χ^2	p value
Age (years)*		66.0 ± 2.0	66.7 ± 1.3		0.098
Gender	Men	19 (22.9)	55 (66.3)	0.931	0.335
	Women	1 (1.2)	8 (9.6)		
Ethnicity	White	19 (22.9)	61 (73.5)	0.145	0.703
	Non-white	1 (1.2)	2 (2.4)		
Socio-economic status	Affluent	9 (10.8)	15 (18.1)	3.316	0.061
	Non-affluent	11 (13.3)	48 (57.8)		
Comorbidity	No comorbidity	11 (13.3)	36 (43.4)	2.509	0.285
	Moderate	5 (6.0)	22 (26.5)		
	Severe	4 (4.8)	5 (6.0)		
Site	Supraglottis	2 (2.4)	11 (13.3)	0.640	0.424
	Glottis	18 (21.7)	52 (62.6)		
	Subglottis	0 (0)	0 (0)		
Tumour stage	T_1 (30)†	13 (15.7)	17 (20.5)	10.513	0.015
	T_2 (20)†	4 (4.8)	16 (19.3)		
	T_3 (16)†	2 (2.4)	14 (16.9)		
	T_4 (17)†	1 (1.2)	16 (19.2)		
Treatment	Laser surgery (27)†	14 (16.9)	13 (15.7)	17.720	<0.0001
	Radiotherapy (33)†	5 (6.0)	28 (33.8)		
	Combination therapy (23)† and/or laryngectomy	1 (1.2)	22 (26.5)		
Time since treatment (in months)*		27.4 ± 4.7	28.0 ± 2.4		0.904
Lifetime tobacco use (in pack-years)*		46.3 ± 7.0	38.4 ± 3.9		0.319
Age at which smoking started*		19.8 ± 3.6	21.2 ± 2.9		0.622

*Mean $\pm$ standard error. †(N) Total number of patients (current smokers + ex-smokers)

the prevalence of post-therapeutic smoking in head and neck cancer.[3,6,15] Patients who continued to smoke following treatment were individuals who were longstanding, nicotine-dependent smokers with little motivation to quit smoking.[6,19]

Demographic-, smoking history-, disease- and treatment-related predictors of post-therapeutic smoking were examined in the patient cohort. The first observation that emerged from the study findings was that sociodemographic variables have negligible influence on a patient's smoking behaviour following treatment. The lack of association between demographic variables, including age, gender, ethnicity and socio-economic status, and post-therapeutic smoking is consistent with previous studies.[3,9,20]

With respect to disease- and treatment-related predictors of continued tobacco use, chi-square analysis showed significant associations between smoking behaviour and tumour staging ($\chi^2 = 10.513$, $p = 0.015$), and treatment modality ($\chi^2 = 17.720$, $p <$

0.0001). Patients who continued to smoke following treatment were likely to have less severe disease, in the form of lower tumour T stage, and undergone less invasive therapy for their laryngeal cancer. However, only treatment modality remained statistically significant following multiple logistic regression analysis (Table III).

The more invasive the treatment is, the more likely the patient will quit smoking following treatment. Although tumour staging may largely dictate treatment in laryngeal cancer, treatment modality is an independent correlate of smoking behaviour and does not simply reflect disease severity. This observation is supported by multivariate analysis and similar findings from other studies.[3,6,15]

Treatment modality has the greatest impact on smoking cessation; several reasons are suggested for this finding. Patients who undergo more extensive treatment may have an increased perception of the severity of the disease and thus, may be more motivated

TABLE III
LOGISTIC REGRESSION ANALYSIS FOR SMOKING STATUS OUTCOME AFTER TREATMENT WITH DICHOTOMISED VARIABLES

Predictor	Estimated coefficient	Standard error	p	Odds ratio	95% confidence interval
Treatment (code: 0 = laser; 1 = radiotherapy/ combination*)	1.60	0.64	0.01	4.94	1.62–17.21
Tumour stage (code: 0 = T_1/T_2; 1 = T_3/T_4)	0.82	0.78	0.29	2.27	0.50–10.4

*Combination therapy and/or laryngectomy

to quit smoking. Furthermore, transoral laser microsurgery is performed as a day-case procedure allowing patients to return to their employment and daily life immediately after surgery. The modest impact of transoral laser microsurgery on the patient's life, in conjunction with the optimal side-effect profile,[21,22] allows patients to minimise the seriousness of the diagnosis and thus be less committed to quitting.

In contrast, the duration of radiotherapy and the significant morbidity irradiated patients may endure, including radiation-induced oral mucosa side effects (e.g. xerostomia, mucositis), may discourage post-therapeutic tobacco use.[6] Hence, patients who have received radiotherapy are more likely to cease smoking than patients who have undergone transoral laser microsurgery. In the case of combined therapy and/or laryngectomy, the longevity of the treatment and the post-operative morbidity of laryngectomy deter patients from post-therapeutic tobacco use. Furthermore, patients who undergo total laryngectomy are physically unable to inhale tobacco smoke orally; hence they report the lowest post-therapeutic smoking rate. In our study, only one patient (5 per cent) reported smoking after combined therapy and/or laryngectomy.

In addition to treatment invasiveness, treatment modality as a predictor of smoking cessation may be explained by the time patients are exposed to health-care professionals during their treatment course. Patients undergoing longer treatment courses are more likely to have prolonged contact with health-care professionals and receive more advice regarding smoking cessation. Also, longer periods of hospitalisation, required in patients undergoing laryngectomy, provide a period of enforced abstinence and facilitate tobacco withdrawal.

The study limitations must also be recognised. Current smoking status was assessed using a self-report questionnaire, a method that resembles the approach used in clinical practice, but that has been shown to be unreliable in certain populations.[23,24] False reporting of smoking behaviour may have occurred and consequently biased the data, as patients may be reluctant to report tobacco use due to 'feelings of guilt'.[23] However, studies have shown false reporting rates among the smoking population to be less than 3.5 per cent,[25] hence supporting the validity of assessing smoking behaviour by means of questionnaires. Biochemical verification of self-reported smoking status via cotinine assays is warranted in future studies.[23] One pitfall of the study was the limited sample size. Although the number of eligible patients was relatively large, only a small proportion of patients reported continued tobacco use following treatment, which is the outcome on which all statistical analyses are based. A larger sample is needed to confirm the study findings and improve the accuracy of such statistical analyses.

In conclusion, this preliminary study describes the predictors of post-therapeutic smoking in a sample of laryngeal cancer patients. We have provided evidence for the importance of treatment modality in determining the post-therapeutic smoking behaviour of laryngeal cancer patients; patients undergoing transoral laser microsurgery are at a significantly higher risk of continued tobacco use compared to patients receiving other treatment modalities. This information is valuable for designing and improving smoking cessation interventions for laryngeal cancer patients. Although for many patients the diagnosis of laryngeal cancer is sufficient to lead to smoking cessation, more than 20 per cent of patients will continue to smoke; few of these patients will enter a formal cessation programme.

The results of our study suggest that increasing anti-smoking interventions for patients who undergo transoral laser microsurgery may increase disease-related survival and decrease morbidity associated with post-therapeutic smoking. However, more data is needed; we are currently seeking to collaborate with other cancer centres to conduct a larger, multi-centre study to confirm and consolidate the study findings.

- **Previous studies have shown that treatment modality, tumour staging and pack-year history influence post-therapeutic smoking in patients with head and neck malignancies**
- **The present study investigated the factors associated with post-therapeutic smoking in patients who have received treatment for laryngeal cancer**
- **Treatment modality is a significant predictor of post-therapeutic smoking**
- **Patients who undergo transoral laser microsurgery, the least invasive form of treatment, are 4.9 times more likely to smoke than patients receiving more invasive therapies**
- **To our knowledge, this is the first study examining the predictors of post-therapeutic smoking in laryngeal cancer patients taking modern treatment strategies into account**

To our knowledge, this is the first study examining the predictors of post-therapeutic smoking including modern treatment strategies, such as transoral laser microsurgery, that have been adopted in clinical practice in the last 15 years.

Acknowledgements

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