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Longitudinal study to assess impact of smoking at diagnosis and quitting on 1-year survival for people with non-small cell lung cancer

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ABSTRACT

Objectives: To update the prevalence of smoking in people as they were diagnosed with non-small cell lung cancer (NSCLC) and to see whether smoking status at baseline and quitting are independently associated with 1-year survival.
Design: A real-world cohort study following patients from diagnosis for up to 1 year or until death.
Setting: UK multi-centre study (28 sites) based in secondary and primary care.
Participants: 1124 patients with newly diagnosed NSCLC between 2010-2016.
Main outcome measures: Smoking status was validated at diagnosis and at every routine and emergency hospital visit. Cancer treatments were offered according to local multi-disciplinary team decisions following UK guidelines and smoking cessation treatments offered according to local practice /availability. Survival analysis and Cox Proportional Hazards Modelling examined the associations of a) smoking at baseline and b) quitting smoking, on survival at 1 year.
Results: 77% of never smokers, 60% of ex-smokers and 57% of current smokers, were alive at 1 year ($p = 0.01$). After adjusting for age, stage, EGOG, surgery and gender, ex smokers (adjusted HR 1.96, 95% CI 1.16–2.31) and current smokers (aHR 2.04, 1.19–3.48) were both more likely to die within one year.

23% of smokers with NSCLC quit within 3 months of diagnosis. At 1 year, 69% of those who quit were alive versus 53% of those who continued to smoke ($p < 0.01$). After adjusting the risk of dying was lower (aHR 0.75), in those who quit smoking, although this was not statistically significant ($p = 0.23$).
Conclusions: This is the largest prospective study that validates smoking in NSCLC; it shows a third of people are smoking at the time of diagnosis. Smokers have lower 12-month survival than never and ex -smokers. Quitting smoking was associated with 25% reduction in mortality which may be clinically important although not statistically significant, after adjusting for other factors.

1. Introduction

Lung Cancer (LC) is responsible for over 30,000 deaths [1] in the UK and over 46,000 new cases in 2015 [2]. Despite advances in treatment and diagnosis ten-year survival remains only 14% for men and 17.5% for women [3].

Smoking is a risk factor for 80% of LC in the UK [4] but there are no large cancer data sets recording smoking status over time or validating self-reported smoking. Pilot point prevalence data of 400 consecutive UK patients suggest almost half were still smoking at the time of LC diagnosis [5], given the large numbers diagnosed each year, this presents a significant population. In 2012, Park et al reported slightly lower rates of smoking of 14–39% but in patients with LC selected to undergo surgery [6]. In other countries, smoking status at baseline is associated with differences in survival; among 5229 Non-Small Cell Lung Cancer (NSCLC) patients attending the Mayo clinic, the median survival differed significantly from 1.4 years in never smokers to 1.3 years in ex-smokers, and 1.1 years in current smokers but this effect was not observed in small cell lung cancer (SCLC) [7]. Parson's meta-analysis in 2010, suggested that continued (reported) smoking in LC was

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independently associated with higher mortality than in never smokers, with those who quit smoking after diagnosis having 33% higher overall survival compared to continued smokers, with up to 70% alive at 5 years [8]. The benefits of quitting smoking in LC have been less well studied. A retrospective analysis of 284 patients with limited SCLC found that patients who reported quitting at, or just after, diagnosis reduced their risk of death by 45% (HR = 0·50, 95% CI 0·38-0·79) compared to continued smokers [9]. Following telephone smoking cessation advice to 250 patients newly diagnosed with LC, the 102 patients who had reportedly quit by the time of last contact had a median survival of 29 months compared to 20 months in continued smokers [10]. A study in Japan, indicated 1.07 year median survival difference between current smokers (7.18 years) versus those who had quit 3 years pre diagnosis (8.25years) [11]. A survival effect that is similar or greater to the survival gains obtained with chemotherapy [2]. However, none of these studies validated smoking status biochemically and self-reported point prevalence at diagnosis and never during follow-up. Moreover, many had limited follow-up and/or missing data resulting in possible selection, reporting, recall and observational biases.

With these caveats, the 2011 NICE guidelines for treating LC include recommendations to "investigate the benefits of smoking cessation on pulmonary complications, quality of life and survival". [12] We could not find any studies investigating these questions as primary outcomes. We wanted to update and validate the prevalence of smoking in people with LC as the number of adult smokers continues to decline in the UK to inform us of potential scale of impact of smoking cessation strategies in LC. We also wanted to see whether smoking status at baseline and quitting following diagnosis, particularly in the more common and potentially curative NSCLC, have any independent effects initially on survival.

2. Methods

2.1. Ethics

The study had loco regional ethical approval and was registered NCT01192256 and UKCRN 9851.

2.2. Patient population

1124 patients from 33 hospitals in England and Wales (UK) were recruited within 1 month of a clinical or histological diagnosis of NSCLC agreed at local hospital Multi-Disciplinary Team (MDT) meetings and prior to the commencement of any definitive treatment (except analgesia). Patients who were visibly distressed following diagnosis were not approached on the discretion of the attending physician. Of those approached, 74% agreed to participate in the study; of those who did not agree the main reason cited verbally was time pressures. We excluded those patients whose survival was less than one month or had no follow-up visit.

Patients were categorized as current smokers if they reported smoking within 30 days of diagnosis or during follow-up or had an exhaled carbon monoxide (eCO) > 10 parts per million (ppm) (Smokerlyzer piCO, Bedfont, UK and MicroCO, CareFusion, UK) at any timepoint. Patients were categorized as ex-smokers if they had smoked more than 100 cigarettes in their lifetime but not smoked within 30 days prior to diagnosis or follow-up visit and had eCO < 10 ppm throughout. Patients were categorized as never smokers if they had smoked less than 100 cigarettes in their lifetime, none within 30 days of diagnosis and had eCO < 10 ppm throughout. [13] For this study quitters were defined as those who were smoking at diagnosis but who quit within 3 months of diagnosis and remained abstinence with eCO < 10 ppm for the remaining study duration and did not report any cigarette use during the follow-up period.

2.3. Assessments & data collection

The following routine data were recorded at baseline and corroborated from cancer databases: age, gender, cyto/histological diagnosis, Tumour Nodes Metastases (TNM) staging, Eastern Cooperative Oncology Group (ECOG) Performance Status, presence of co-morbidities. We recorded self-reported smoking status, exhaled eCO, and a generic health related quality of life score (EQ5D). Smokers completed Fagerstrőm Test for Nicotine Dependence (FTND), pack-year history and any cessation dates.

Everyone received standard treatment for their LC according to NICE guidelines [12] and local practice and smokers were referred to local smoking cessation services. They were offered visits at 1, 3, 6 and 12-months post LC diagnosis and wherever possible, to coincide with standard clinical follow-up. At each time-point we recorded smoking status, EQ5D, ECOG, TNM status and frequency, duration and severity of any treatment complications.

Participants had eCO recorded at every routine hospital LC clinic visit and also if they attended the hospital or community smoking cessation teams. They were followed for 12 months or until death. Date and cause of death were recorded from clinical databases.

2.4. Patient & public involvement

Patients were involved in initial trial design and conduct from onset. Patient representatives helped develop and review study documents and procedures to ensure they would be understandable and agreeable during the study and not burden participants unnecessarily. The follow-up periods and undertaking of assessment were agreed based on patient experiences.

2.5. Primary outcome

To estimate smoking prevalence at diagnosis of NSCLC and compare survival at 12 months according to baseline smoking status, after adjusting for TNM stage and other factors.

2.6. Secondary outcome

To compare survival at 12 months in those smokers who quit (validated sustained cessation) versus those who continued to smoke, after adjusting for TNM stage and other factors.

2.7. Statistical analysis

Groups were compared with Mann-Whitney and Chi square. Univariate survival analyses were conducted using Kaplan-Meier methods to evaluate the association of smoking status at diagnosis.

The association of quitting at diagnosis was evaluated using Cox Proportional Hazards models. Univariate Cox Proportional Hazards models identified significant variables for the saturated multivariate model. Saturated models with and without the omitted variables were compared using the log rank test to create the final saturated model. The association of the omission of each variable in the final saturated model was evaluated using the log rank test to confirm a final reduced model.

The final reduced model was assessed for proportionality. To mitigate the deviation from proportionality, the final reduced model was stratified. The specification, proportionality and goodness of fit of the final reduced stratified model were assessed using formal tests and/or plots. All analyses were conducted in Stata SE 14.1.

Table 1
Baseline group characteristics for never, ex and current smokers at the time of diagnosis.

	Never smokers (n = 64)	Ex-smokers (n = 696)	Current smokers (n = 364)	p-value
Mean Age (years)	68.7 (11.3)	70.3 (8.6)	66.0 (9.4)	Never vs Ex p = 0.91 Never vs Current p = 0.02 Current vs Ex p < 0.01
% male	34.4	61.9	58.2	p < 0.01
% Stage I or II	25.0	22.0	21.7	p = 0.84
Mean ECOG	0.83	0.95	1.09	p = 0.13
% surgery	14.1	16.4	12.1	p = 0.17
% chemotherapy	61.0	61.4	57.1	p = 0.65
% radiotherapy	29.7	31.0	32.7	p = 0.89
% receiving BSC	18.8	12.4	16.2	p = 0.12

3. Results

3.1. Primary outcomes

- Record prevalence and characteristics of smoking at diagnosis in a large UK cohort
- Determine if smoking at diagnosis independently influence survival at 12-months

We had data on 1124 patients, mean (SD) age = 68.9 (9.3) years; 59% male, Stage I&II NSCLC = 248 (22% total).

364 (32%) were smoking at the time of their LC diagnosis. 11 people (3%) reported not smoking but had eCO > 10 ppm.

Current smokers at baseline diagnosis were younger than both never-smokers (p = 0.02) and ex-smokers (p < 0.01). In the never-smokers group there were fewer males (p < 0.01) (Table 1).

76.6% of never smokers (95% CI 64.2–85.2), 60.3% of ex-smokers (95% CI 56.6–63.9), and 56.9% of current smokers (95% CI 51.6–61.2) (at baseline) were alive at 1 year (X2 = 9.15, P = 0.01) (Fig. 1). Of those deceased, median survival was 185 days for never smokers, 150 days for ex-smokers and 135 days for smokers.

Entering all the variables into a Cox Proportional Hazards Model led to a violation of the proportionality assumption. This was overcome by stratifying the model by E-COG. Therefore it was not possible to estimate the effect of E-COG but it was possible to adjust the effects of the other variables for E-COG.

After adjusting for age, sex, stage, surgery and E-COG, the risk of dying was statistically significantly higher for ex smokers (hazard ratio 1.96, 95% CI 1.16–3.31, p = 0.01) and for current smokers (2.04, 1.19–3.48 p < 0.01) than for never smokers. Table 2.

The stratified model appeared to be correctly specified (linktest p = 0.42) and there was no evidence of deviation in either the global test (p = 0.33) or in visual inspection of the log-log plot of survival. Inspection of the Nelson-Aalen cumulative hazard against the Cox-Snell residuals indicated the model fitted the data well.

3.2. Secondary outcome

- Record prevalence and characteristics of smokers with NSCLC who quit within 3 months of diagnosis
- Determine if quitting smoking within 3 months of diagnosis independently influence survival at 12-months

71 of 364 (20%) smokers quit within 3 months of their diagnosis of NSCLC. The quitters had more earlier stage NSCLC, more received surgery and more were alive at 1 year, see Table 3.

70.4% of those who quit (95% CI 58.3–79.6) and 53.6% (95% CI 47.7–59.1) of continued smokers were alive at 1 year (X2 = 7.00, P < 0.01) (Fig. 2). Of those deceased, median survival was 130 days (CI 108–155) for continued smokers and 184 days (CI 164–264) for those who quit ($p < 0.01$).

Entering all the variables into a Cox Proportional Hazards Model led to a violation of the proportionality assumption. This was overcome by stratifying the model by E−COG and stage. Therefore it was not possible to estimate the effects of E−COG and stage but it was possible to adjust the effects of the other variables for E−COG and stage.

After adjusting for age, sex, stage, surgery and E−COG, the risk of dying was lower, though not statistically significantly so, for those that

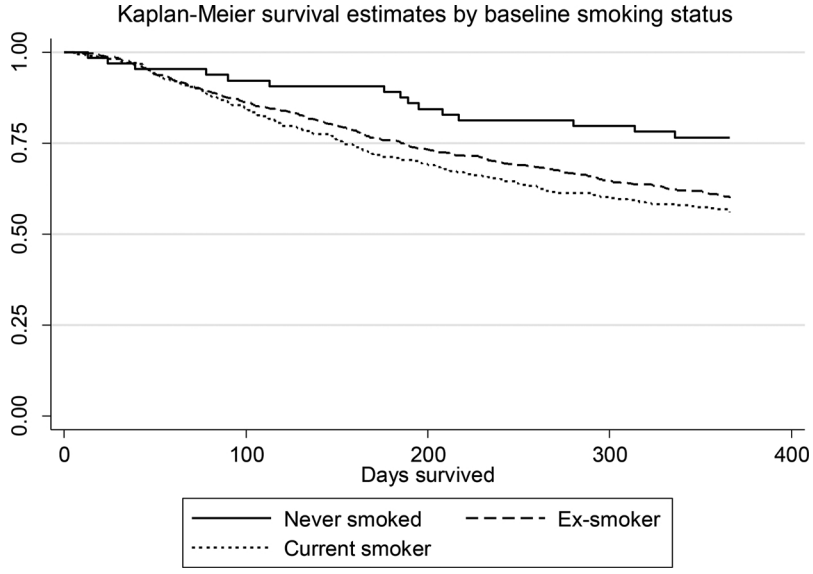

Fig. 1. Kaplan-Meier Survival curves for baseline smoking status at diagnosis of NSCLC (all stages).

Table 2
Univariate analysis of baseline variables and their effect on survival & Multivariate analysis of baseline variables and their effect on survival.

Univariate analysis of baseline variables and their effect on survival

Variable	Level	Hazard ratio	95% confidence interval	p-value
smoking	Never (baseline)	–	–	–
	Ex-	1.91	1.14-3.21	< 0.01
	current	2.18	1.29-3.71	< 0.01
Stage	I (baseline)	–	–	–
	II	1.07	0.62-1.83	0.82
	III	1.91	1.28-2.83	< 0.01
	IV	3.32	2.27-4.84	< 0.01
ECOG	0 (baseline)	–	–	–
	1	1.53	1.20-1.96	< 0.01
	2	2.41	1.83-3.18	< 0.01
	3&4	5.51	3.85-7.90	< 0.01
Surgery	No (baseline)	–	–	–
	Yes	0.34	0.23-0.49	< 0.01
Chemotherapy	No (baseline)	–	–	–
	Yes	0.98	0.74-1.39	0.93
Sex	Male (baseline)	–	–	–
	Female	0.81	0.67- 0.98	0.03
Age	–	1.00	0.99-1.00	0.85

Multivariate analysis of baseline variables and their effect on survival

Variable	Level	Adjusted Hazard ratio	95% CI	p value
Smoking status	Never smoked (baseline)	–	–	–
	Ex smoker	1.96	1.16 to 3.31	0.01
	Current smoker	2.04	1.19 to 3.48	< 0.01
Received surgery	No (baseline)	–	–	–
	Yes	0.65	0.43 to 0.97	0.03
Stage	I (baseline)	–	–	–
	II	1.05	0.61 to 1.80	0.87
	III	1.63	1.07 to 2.47	0.02
	IV	2.85	1.91 to 4.28	< 0.01
Sex	Male (baseline)	–	–	–
	Female	0.83	0.69 to 1.01	0.05
Age	–	0.99	0.98 to 1.00	0.51

Table 3
Characteristics of continued smokers Vs those who quit by 3 months.

	Quitters n = 71	Continuers n = 293	p-value
Age (years)	66.0 (9.7)	66.0 (9.4)	0.99
Sex % male	56.3	58.7	0.72
% Stage I or II	36.6	18.1	< 0.01
% receiving surgery	32.4	7.2	< 0.01
% alive 1 year	69.0	52.9	0.01

quit smoking (hazard ratio 0.75, 95% CI 0.46–1.20, p = 0.23) compared to those that continued to smoke. Table 4.

The stratified model appeared to be correctly specified (linktest p = 0.22) and there was no evidence of deviation in either the global test (p = 0.19) or in visual inspection of the log-log plot of survival. Inspection of the Nelson-Aalen cumulative hazard against the Cox-Snell residuals indicated the model fitted the data well.

4. Discussion

We report the largest prospective cohort study in a developed country where lung cancer is the biggest cancer killer. It validates smoking at multiple time points and offers standard cancer care throughout. It shows around a third of people are smoking at the time of a diagnosis of NSCLC. Never smoking was associated with better 12 month survival. Smokers are younger at diagnosis have lower 12-month survival rates. Quitting within 3 months was associated with increased 12-month survival (HR 0.75) compared to continued smoking. However, after controlling for stage, surgery, ECOG, gender and age, smoking was not independently associated with survival.

Amato showed a median survival advantage of 9 months in quitters compared to continued smokers [9] and a similar effect to 1.07 years that was found in longer term quitters by Tabuchi [11] and the meta-analysis by Parsons [8]. A retrospective analysis by Stevens of 269 patients with head and neck cancer showed that those who continued to smoke after diagnosis had a fourfold increase in the recurrence rate of those who never smoked and double that of those who stopped smoking. Survival was also the lowest in those who continued to smoke [14]. We are still collecting data to compare median survival.

The major confounder is that those smokers who quit had a higher proportion of early stage (I and II) lung cancer and a higher proportion of quitters had received surgery compared with continuers. Having a potentially curative NSCLC is more likely to motivate people to quit and more radical treatments and more contacts by more health care professionals should allow more opportunities for smoking cessation advice and smoking pharmacotherapy prescribing. Quitting smoking is associated with a 25% reduction in mortality and this maybe clinically important in a common disease with a very poor prognosis. However, our modelling shows that after adjusting for stage and surgery, quitting smoking was not a statistically significant predictor of survival and so could have occurred through chance. This may be due to sample size or because survival is overwhelmingly determined by receiving surgery. We also excluded those who died within one month as we could not accurately categorise them as quitters or continued smokers. We are investigating the role of smoking cessation specifically for early stage / operable disease with larger numbers and recording all cancer treatment complications by smoking status.

Some of the survival benefits could be explained by behaviour. It is possible that smokers delay seeking help either because they misinterpret their symptoms as being due to a ‘smokers’ cough’ or they feel

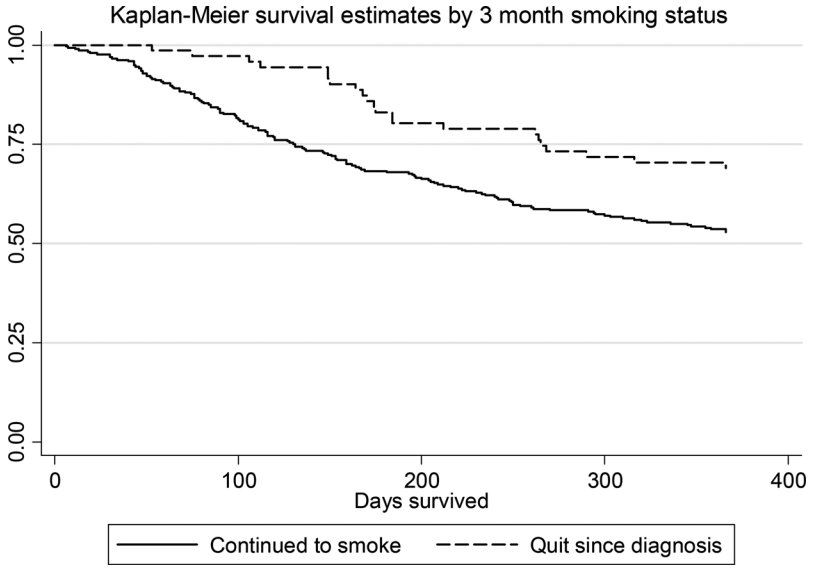

Fig. 2. Kaplan-Meier Survival curves for continued smokers versus quitters.

Table 4
Univariate analysis of quitting or continued smoking and effect on survival & multivariate analysis of quitting or continued smoking and effect on survival.

Univariate analysis of quitting or continued smoking and effect on survival

Variable	Level	Hazard ratio	95% confidence interval	p-value
smoking	Quitting	0.55	0.35-0.86	< 0.01
Stage	I (baseline)	–	–	–
	II	0.87	0.37-2.05	0.76
	III	1.50	0.78-2.87	0.23
	IV	2.54	1.36-4.75	< 0.01
ECOG	0 (baseline)	–	–	–
	1	1.15	0.76-1.73	0.51
	2	1.59	1.00-2.53	0.05
	3&4	2.83	1.53-5.21	< 0.01
Surgery	No (baseline)	–	–	–
	Yes	0.31	0.15-0.62	< 0.01
Chemotherapy	No (baseline)	–	–	–
	Yes	1.01	0.74-1.39	0.93
Sex	Male (baseline)	–	–	–
	Female	0.89	0.65-1.22	0.48
Age	–	1.00	0.98-1.02	0.95

Multivariate analysis of quitting or continued smoking and effect on survival.

Variable	Level	Adjusted Hazard ratio	95% CI	p value
Smoking status	Continued after diagnosis (baseline)	–	–	–
	Quit at diagnosis	0.75	0.46 to 1.20	0.23
Received surgery	No (baseline)	–	–	–
	Yes	0.55	0.25 to 1.21	0.13
Sex	Male	–	–	–
	Female	0.94	0.68 to 1.30	0.71
Age	–	1.00	0.98 to 1.01	0.80

guilty or do not want to be admonished by health professionals. Although their younger age at diagnosis partially goes against this, we have shown that smokers have larger tumours at diagnosis compared to non-smokers [4]. We didn't specifically record estimates of symptom duration. Stopping smoking could be a marker of other healthy behaviours (e.g. higher treatment concordance) or simply a marker of other confounders such as higher social class that can influence mortality. The reverse causality might also be true as those receiving more radical (potentially curative) surgical treatments are more likely to see more health professionals and may be more motivated at a chance of cure which could lead to higher quit rates.

There are many clinically plausible explanations for why smokers with LC will have poorer survival than those who abstain. Observational studies in those receiving surgery for NSCLC report higher rates of local recurrence, secondary cancers, higher risk of early post-operative complications, [15] more longer-term post-operative complications [16] and higher overall mortality [17]. Similarly those who smoke while undergoing radiotherapy for LC report reduced quality of life, but also more treatment-related complications [18], higher rate of second primary cancers [19] and these are likely to worsen survival compared to non-smokers (median 14 vs 28 months) [20].

There are biologically plausible explanations why continuing to smoke directly adversely clinical affects outcomes. Continued exposure to carcinogens increases the rate of tumour growth in animal studies [21,22] and the development of secondary cancers in humans. [23] in vitro studies show tumours from smokers are more chemoresistant [24]. We also know that smoking lowers the immune system's innate response to malignant growths and metastatic development [25].

Finally, by inducing cytochrome P450 enzyme activity, smoking can increase the metabolism (and lead to lower tissues levels) of chemotherapy drugs [26]. Pre-clinical studies show that by increasing carboxy-haemoglobin levels, smoking impairs tumour oxygenation which in turn reduces the effectiveness of radiotherapy [27] or worsens radiotherapy complications [18].

Continued smoking can adversely affect outcomes by causing higher rates and more rapid progression of other illnesses often seen in people with LC. It is surprising that smoking status is not reported as a strong confounder in most trials of cancer therapies as it is in treatments for COPD or heart disease.

This large, multi-centre study reflects up-to date smoking prevalence reflecting demographics and current smoking habits in the UK. It reflects real-world LC care in a developed country and is generalisable to most UK settings. Smoking cessation was validated at different time points often through different services including smoking cessation teams, UK research nurses and specialist LC nurses. Our high rates of survival at 1 year is probably because most patients were recruited from clinics and those presenting acutely unwell as emergencies, were unwilling or unable to provide informed consent or had emergency treatments before consent.

This is an observational study so we cannot exclude other potential confounders such a smoking being associated with other positive health behaviours e.g. better medication concordance, more healthy diet, exercise etc. or smoking being strongly associated with lower socioeconomic status, itself an independent predictor of mortality. We did not record use of electronic nicotine delivery devices as they were not in widespread public use at the time of trial commencement [28]. Our one year survival rates of 57–77%, are higher that the UK national lung cancer figures [2,3]. This may be because we recruited almost exclusively from outpatient clinics where people gave informed consent in a controlled environment. We had very few participants recruited from inpatients or acute oncological emergencies where stage and therefore mortality are higher. We could not corroborate from routine data sources if all smokers had basic advice to quit from their clinical teams or appropriate cessation pharmacotherapies. We were also unable to monitor exposure to environmental tobacco smoke although typically this does not cause eCO > 10 ppm [12].

The majority of smoking patients with LC reported they were motivated to stop smoking and even a single session with a smoking cessation specialist seems effective with 22% abstinent at 6 months compared to 14% among a general population of smokers offered the same support [29]. Given the high prevalence of smoking in a common cancer with poor low survival rates, any advantage associated with quitting smoking has big implications. We must now consider the feasibility and cost-effectiveness of specialised tailored smoking cessation services for people with LC.

We also need to consider why clinicians do not refer patients with cancer for smoking cessation treatments. It is likely that doctors find it difficult to discuss smoking at the time of diagnosis. Many will consider the balance between potentially increased survival, better quality of life and reduced treatment complications versus the additional burden of more appointments, difficulties of nicotine withdrawal and possible feeling of failure if they cannot stop smoking. We are undertaking qualitative research into the facilitators and barriers to uptake to smoking cessation service. We are continuing recruitment and recording longer-term survival, quality of life, impacts of co-morbidities, histological subtype, outcomes in those receiving radical and palliative treatments, frequency, duration and severity of treatment complications, and dose reductions in chemoradiotherapy. We are also collecting data on cause of death.

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Bronglais Hospital; Broomfield Hospital; Queens Hospital; Cheltenham General Hospital; Countess of Chester Hospital; Croydon University Hospital; Darlington Memorial Hospital; George Eliot Hospital; Ysbyty Glan Clwyd; Alexandra Hospital; Huddersfield Royal Infirmary; Kings Mill Hospital; Royal Lancaster Hospital; Leeds Teaching Hospital; Luton & Dunstable Hospital; Macclesfield Hospital; Milton Keynes Hospital; Mount Vernon Cancer Centre; Neville Hall Hospital; North Tyneside General Hospital; Prince Philip Hospital; Princess of Wales Hospital; Royal Preston Hospital; Prince Charles Hospital; Royal Gwent Hospital; Shrewsbury Hospital; Stafford Hospital; Musgrove Park Hospital; University Hospitals Coventry & Warwickshire; Walsall Manor Hospital; Worthing Hospital; Withybush Hospital; New Cross Hospital; Worcester Royal Hospital; Wrexham Maelor Hospital; Ysbyty Gwynedd.

Transparency

The manuscript's authors (REG, RG, GC, DP, IC, GD, KD and KEL) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing

Requests for available data can be made by contacting the corresponding author.

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Conflict of interest statement

None Declared.

Competing interest statement

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work [or describe if any]; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence.

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