

SMOKING CESSATION WITH LUNG CANCER: NOT TOO LITTLE, NEVER TOO LATE!

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ABSTRACT

Smoking is the leading cause of lung cancer (LC) worldwide, however any continuing effects of smoking or cessation following a diagnosis are less well known. With around 40% of patients with LC smoking at the time of diagnosis and the majority presenting with an incurable/progressive disease, should clinicians be strongly recommending smoking cessation programmes? The evidence proposes that they should be. Current literature suggests that stopping smoking following a diagnosis of LC can lead to better treatment responses, fewer treatment complications, and less recurrence or new tumours. These benefits translate into reduced mortality and importantly, better quality of life. This review will look at the growing body of evidence that suggests smoking cessation should be prioritised in patients who have been diagnosed with LC.

Keywords: Lung cancer (LC), smoking cessation, mortality, treatment complications, quality of life.

INTRODUCTION

Lung cancer (LC) has the highest mortality rate of any cancer,¹ with >1.6 million new cases and 1.4 million deaths per year worldwide.² The current 1, 5, and 10-year survival rates of patients with LC remain poor despite advances in treatment and diagnostic techniques.^{3,4} Worldwide, smoking prevalence is increasing.⁵ Smoking causes around 85% of LC and the impact of LC and other smoking-related diseases, especially on low and middle-income countries, is rising.

Aside from the rate of LC caused by smoking (80–85%),^{6,7} less is known about the effect of continuing to smoke versus cessation on prognosis and survival in patients already diagnosed with LC. This review examines the current evidence for the effects of continued smoking and smoking cessation on clinical outcomes following LC diagnosis, providing some recommendations for a tailored smoking cessation service specifically for this vulnerable group.

Most studies report that ~40% of patients are smoking at the time of their LC diagnosis;⁸⁻¹⁰ this represents a considerable number of people, e.g. at least 18,000 in the UK alone¹¹ and 164,000 individuals across Europe per annum.¹² Moreover, some ex-smokers may restart under the stress of diagnosis or treatments. Therefore, even small clinical effects may have public health implications. Continued smoking is likely to adversely affect outcomes in several ways.

IMPACT OF TOBACCO SMOKE ON TUMOUR CELLS

It is biologically plausible that continuing to smoke affects cancer cells. The 2014 Surgeon General Report stated that 69 carcinogens in tobacco smoke (TS) had been identified;¹³ these include polycyclic aromatic hydrocarbons and nicotine-specific nitrosamines, and continued exposure to TS has been shown to increase the rate of tumour growth by further increasing cellular damage, mainly by causing more genetic mutations and by

suppressing the body's defenses.¹⁴ TS affects the integrity of DNA by alkylation, which can facilitate the development of existing and new cancer. In addition, *in vitro* studies have shown that smoking was significantly related to more chemo-resistant tumours.^{15,16} Continuing to smoke following a diagnosis of LC can lead to an increased risk of recurrence or subsequent primary malignancies.¹⁷⁻¹⁹

Nicotine itself may also directly accelerate the development of the tumour by increasing capillary and collateral growth. Enhanced tissue perfusion has been observed in mouse models of LC,²⁰ but this has not been confirmed in human studies, and the benefits of nicotine replacement therapy in helping people quit and reduce TS exposure far outweigh any direct potential carcinogenic effects of the compound itself.

IMPACT OF SMOKING ON IMMUNE-SURVEILLANCE

Within humans, TS can affect the immune system and response, leading to reduced defences such as natural killer cells and, subsequently, further cancer.¹⁴ Application of TS to lung tumours has certainly caused faster growth in animal studies.¹⁷ It also depresses the immune system's response to malignant growths and increases the risk of metastatic development.²¹

IMPACT OF TOBACCO SMOKE ON TREATMENT FOR LUNG CANCER

Surgery

A systemic review highlighted the association between smoking at the time of any surgery and increased surgical and especially respiratory complications in smokers compared with non-smokers, producing an odds ratio (OR) of 5.5 (95% confidence interval [CI]: 1.9-16.2).²²

More interestingly, quitting smoking even for short periods prior to any type of surgery is associated with reduced postoperative risks, including pulmonary and respiratory complications,^{23,24} as well as better wound healing,²⁵ shortened bone fusion time,²⁶ and decreased time in hospital following the procedure.²⁷ However, the evidence suggests that longer periods of abstinence have greater effectiveness at reducing surgical complications.²³

Between 14% and 40% of patients who undergo surgery for lung or colorectal cancer smoke;^{28,29}

observational studies again suggest that cancer patients in general who smoke are also independently at higher risk of surgical complications and mortality.³⁰

In particular, patients with LC were significantly more likely to develop complications such as pneumonia after surgery if they were currently smoking (OR: 1.62, 95% CI: 1.25-2.11).³⁰ A retrospective cohort study comparing smokers with those who had abstained or had never smoked showed a decrease in survival at 120 weeks following surgical resection, from 60-70% to 25%.³¹ This difference in fatality could be due to the increased risk of postoperative complications, increased recurrence, or presence of new malignancies in smokers.³² Even following potentially curative resection for head and neck cancers, smokers are also at a higher risk of recurrence or secondary cancers.^{33,34} Smokers are also more likely to have or develop comorbid conditions, such as chronic obstructive pulmonary disease (COPD) or chronic heart disease, which may also contribute to this mortality rate.

Slatore et al.³⁵ estimated that providing smoking cessation prior to surgery for LC could result in a monetary saving by reducing postoperative complications and recovery times. This value should however be regarded with speculation, as quitting smoking may be a marker of other positive health behaviours that may contribute to recovery time.

Chemo-Radiotherapy

In addition to surgery, there is also a notable effect of smoking status on those receiving chemotherapy and radiotherapy. Smoking induces the hepatic cytochrome P450 system, potentially reducing blood/tissue levels of chemotherapeutic agents.³⁶ Preclinical studies show that smoking increases carboxyhaemoglobin levels, which impairs tumour oxygenation and in turn reduces the effectiveness of radiotherapy,^{37,38} increasing treatment complications.³⁹ Following radiation therapy, those with LC who did not smoke had a median survival of 27.9 months, compared with 13.7 months in those who smoked ($p=0.01$).⁴⁰

Smoking tobacco directly affects drug metabolism, which can impact responses to targeted therapy and chemotherapy. TS can also impact responses to targeted therapy directed at the estimated glomerular filtration rate. An early phase intervention study found that doubling the dosage in those who smoked only led to a similar incidence

of diarrhoea and skin toxicity, compared with non-smokers taking the standard dose.⁴¹ This indicates that smokers clear their therapeutic agents more quickly, and so are less likely to respond.

A retrospective study of 285 patients found that non-responders (n=191) had smoked significantly more than responders (67.8±35.1 versus 38.7±27.1 pack-years; p<0.001). Multivariate analysis confirmed that heavy tobacco consumption (≥40 pack-years) was the most important independent negative predictor of response (adjusted OR: 10.4; 95% CI: 5.1-21.3).⁴² This may be because those who smoke may have a faster systemic clearance, meaning that to be effective they would require a larger dose of treatment or because the tumours are more resistant to treatment due to their previous exposure to carcinogenics from tobacco. In addition, among patients with LC, retrospective studies suggest that continuing to smoke⁸ independently increases treatment-related complications such as radiation pneumonitis and neutropenic sepsis.²⁸ Further research is needed in this area to look at the effects of increasing chemotherapy dose in patients who continue to smoke but current evidence suggests these higher doses of chemotherapy and radiotherapy are very likely to lead to additional complications and greater side effects in this population.

Despite this evidence, many trials of new therapeutic agents neglect to even record smoking status or assess any impact of smoking on outcome.⁴³ Those that do record smoking usually rely on self-reported measures and therefore lack validation. The benefits of smoking cessation for patients receiving chemotherapy are equally biologically plausible, but any survival advantage will in part be mitigated by the poorer overall survival of people with more advanced cancers selected for these treatments.

IMPACT OF TOBACCO SMOKE ON COMORBIDITIES IN PEOPLE WITH LUNG CANCER

Smoking can adversely affect outcome by causing and accelerating other illnesses in people with LC. Smokers are more likely to be diagnosed with COPD, heart disease, cerebrovascular disease, high blood pressure, diabetes, thrombosis, and many other conditions.⁴⁴ Continued smoking worsens any comorbid condition, which can lead to an

increased risk of infections and result in delays or interruptions to LC treatment.

For those with head and neck cancer, patients who stopped smoking following diagnosis had double the survival rate than those who continued to smoke, whilst those who continued to smoke had a 4-times higher chance of recurrence.⁴⁵ In patients with breast cancer, recurrence in smokers increased by 15% (p=0.039) compared with those who quit.⁴⁶ This finding has been replicated in patients with prostate cancer.⁴⁷

OVERALL IMPACT OF TOBACCO SMOKING ON MORTALITY IN PEOPLE WITH LUNG CANCER

Smoking and Early Stage Lung Cancer

In a study comparing 215 patients with limited disease small-cell lung cancer (SCLC) treated with radio-chemotherapy, 5-year survival was improved in those who quit smoking prior to treatment commencing. Patients who abstained from smoking had a median survival time of 18.0 versus 13.6 months compared with those who continued to smoke. This indicates that smoking cessation is an important factor when advising on long-term survival and day-to-day treatment.⁴⁸ This is further supported by a meta-analysis of 10 randomised controlled trials and longitudinal studies that examined the effect of quitting smoking after a diagnosis of LC on outcomes. Continued smoking was associated with a significantly increased risk of all-cause mortality (hazard ratio [HR]: 2.94, 95% CI: 1.15-7.54) and recurrence (HR: 1.86; 95% CI: 1.01-3.41) in early stage non-SCLC (NSCLC) and of all-cause mortality (HR: 1.86, 95% CI: 1.33-2.59), development of a second primary tumour (HR: 4.31, 95% CI: 1.09-16.98), and recurrence (HR: 1.26, 95% CI: 1.06-1.50) in limited stage SCLC. In limited stage SCLC, an estimated 29% of continuing smokers survive for 5 years versus 63% of quitters.⁴⁹

A recent meta-analysis by Parsons et al.⁴⁹ highlighted the effect on survival in patients with early stage LC who quit smoking after diagnosis. This review found that the 5-year survival in continued smokers was 33%, compared with 70% survival in LC patients who quit.

Benefit of Smoking Cessation in all Patients with Lung Cancer

A recent study by Dobson Amato et al.⁵⁰ observed the impact of telephone smoking cessation advice in 250 recently diagnosed patients with LC. Survival data indicated that the 102 patients who had reportedly quit by the time of last contact had a median survival of 29 months compared with 20 months in the 148 continued smokers (HR: 1.79, 95% CI: 1.14–2.82). Continued smoking has also been associated with decreased survival in a variety of cancers, including head and neck cancers⁵¹ and prostate cancer.⁵² With almost half of all LC patients smoking at the time of diagnosis,¹⁰ it is important to look at the continued risk of continuing to smoke following a diagnosis of LC.

Smoking status is likely to affect overall mortality. The Mayo Clinic, Rochester, USA, studied a large cohort of patients (N=5,229) with any stage of either NSCLC or SCLC to prospectively evaluate any potential relationship between duration of smoking abstinence and survival.⁵³ Among NSCLC patients, the median survival was progressively worse among never (1.4 years), former (1.3 years), and current smokers (1.1 years), respectively ($p < 0.01$), whilst no effect of smoking abstinence was observed among SCLC patients. Most recently, in a retrospective analysis of 284 patients with limited SCLC treated in the Mayo Clinic, Chen et al.⁵⁴ found that patients who actually quit at or after diagnosis reduced their risk of death by 45% (HR: 0.55, 95% CI: 0.38–0.79) and patients who quit before LC diagnosis also experienced survival benefit (HR: 0.72, 95% CI: 0.52–1.00). They recommended that “clinicians and all care providers should strongly encourage smoking cessation at diagnosis of limited stage SCLC.”⁵⁴

Benefit of Smoking Cessation in Advanced Lung Cancer

Despite the evidence for smoking cessation following a diagnosis of limited or early stage LC,⁵⁵ the evidence is less clear in patients with advanced LC.⁵⁶ A retrospective analysis of patients with advanced NSCLC showed a 5-month difference in survival between smokers and those who had never smoked, however due to the low number of participants this was not statistically significant.⁵⁷ Tsao et al.⁵⁶ found that continuing smoking during chemotherapy for Stage III and IV LC did not impact prognosis. This could be due to the poor survival following diagnosis in this group which

does not allow for a benefit of cessation to be seen, or because previous exposure to carcinogens has a long-lasting effect.

PROBLEMS WITH CURRENT LITERATURE

Most current research is based on retrospective studies that are open to selection and especially reporting bias. Moreover, in the majority of studies smoking is self-reported and not validated. Smoking status may also be indicative of other prognostic factors. Those who quit smoking are more likely to be of higher socioeconomic status and could have better diet, reduced alcohol consumption, or be more compliant in taking medication and attending appointments. In this context, cessation is merely a marker for other good health behaviours.

The 2011 National Institute for Health Care and Excellence (NICE) guidelines for the treatment of LC highlight the importance of smoking cessation after diagnosis, including the specific recommendation to “advise patients to stop smoking as soon as the diagnosis of LC is suspected.”⁵⁸ NICE calls for more research investigating the benefits of cessation on pulmonary complications, quality of life, and survival.

Based on the current evidence it is clear that quitting smoking is the best thing that any hospitalised patient can do to improve their health⁵⁹ and a combination of pharmacotherapy and counselling should be offered.⁶⁰ There is clear biological plausibility and increasing observational evidence that continued smoking after a diagnosis of LC increases tumour recurrence along with the risk of secondaries and new primaries. Continued smoking also increases resistance to, and complications from, all current modes of treatment. It is probably also a marker for other poor health behaviours. For all these reasons, continued smoking after a diagnosis is associated with or will directly worsen quality of life, and lower survival.

Combining this growing evidence with all the other (non-cancer related) known benefits of smoking cessation, we believe that a randomised, controlled, intervention trial is unethical. However, we believe that adequately powered prospective, observational, cohort studies validating smoking status are important and are relatively easy to do. People with cancer have unique needs and are receiving many treatments. The next practical step

is working with those who have been diagnosed with LC to examine their motivations and barriers to smoking cessation to build a responsive and convenient smoking cessation service. With

integration of this service directly into ongoing treatment plans, perhaps a smoking cessation specialist may even be part of the LC multidisciplinary team in the future.

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