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RESEARCH ARTICLE

Smoking Cessation Management for Lung Cancer Smokers: An Essential Component of Treatment

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ABSTRACT

In 2020 lung cancer has been the leading cause of cancer death, with an estimated 1.8 million deaths; in other words of 18% of cancer deaths. Tobacco smoking is cause of 90% of lung cancers. Despite advances in lung cancer treatment, tobacco control is the most effective measure for curbing the lung cancer epidemic. Smoking cessation, at all stages of the cancer process, is associated with benefits in terms of cure, increased life expectancy and quality of life for patients, reduced medical and surgical complications, as well as it reduces risks of recurrence or of a second primary cancer. Smoking cessation medications combined with psychological support facilitate to quit smoking. Smoking cessation management is an essential component of lung cancer treatment. Researches into the best modalities to manage smoking cessation in lung cancer patients must be conducted. Nevertheless, healthcare professionals involved in the care of cancer patients must be trained to provide personalized assistance to help smokers stopping smoking.

Keywords: Lung cancer, Cancer treatment, Cigarette smoking, Smoking cessation management.

I - Introduction.

In 2020, the International Agency for Research on Cancer (IARC) recorded 19.3 million new cases of cancer and 10 million deaths. Lung cancer (11.4% of new cancer cases) is the leading cause of cancer deaths (18%).¹ Despite advances in treatment, five-year survival for all stages combined is just 17%. Incidence continues to rise worldwide. It is highest in the developed countries of North America, Europe and Asia, rising significantly in women, who have mainly started smoking over the past five decades. It is a major public health issue, lung cancer incidence set to rise by 47% from 2020 to 2040; this trend would particularly affect emerging countries, whose populations are now affected by the smoking epidemic and more exposed to all lung cancer risk factors.¹ The paradox of this cancer lies in the fact that smoking, the main cause, is preventable.^{2,3} A global tobacco control policy is more essential than ever.⁴ Smoking cessation at the time of lung cancer diagnosis is associated with a multitude of benefits. Therefore, smoking cessation management of smokers with lung cancer smoker is an essential component of cancer treatment and must involve all health workers.^{5,6}

II - Smoking and lung cancer risk.

MULTIPLE RISK FACTORS FOR LUNG CANCER.

Occupational exposure to carcinogens is thought to account for 5-10% of lung cancers.⁷ Asbestos is the most frequently implicated carcinogen.⁸ The International Agency for Research on Cancer (IARC)⁹ has identified "human carcinogens", chemicals agents (arsenic, cadmium, beryllium, chromium, diesel fumes) or radioactive agents (uranium) implicated in the onset of cancer. Outdoor air pollution, including particulate pollution (PM_{2.5}; PM₁₀) and nitrogen dioxide (NO₂)¹⁰, exposure to coal combustion and heating or cooking fuels may be the cause as well as exposure to radon gas.⁷ Other risk factors are suspected: estrogens, chronic respiratory pathologies, pulmonary infections and infections with Human papillomavirus (HPV) or Human immunodeficiency virus (HIV).⁷ Together, these could be implicated in the occurrence of lung cancer in non-smokers.¹¹ Whatever the mechanisms of carcinogenesis involving these agents, the association of smoking has a significant potentiating effect on the risk of lung cancer.^{2,7,8}

- CIGARETTE SMOKING: THE LEADING RISK FACTOR FOR LUNG CANCER.

Cigarette smoke contains thousands of compounds, including over 60 carcinogens: polycyclic aromatic

hydrocarbons (PAHs), N-nitrosamines, aromatic amines, aldehydes, volatile organic hydrocarbons and metals.^{2,7} Metabolites of these substances are more concentrated in urine of smokers than in non-smokers. Most of the carcinogens present in cigarette smoke, including PAHs, require a process of metabolic activation, generally catalyzed by cytochrome P-450 enzymes to form DNA adducts, essential to the process of carcinogenesis. Levels of DNA adducts in the lungs are higher in smokers than in non-smokers with a link between the importance of their levels and the probability of developing cancer. If cellular repair systems eliminating DNA adducts or controlling cell growth are overwhelmed, the likelihood of developing somatic mutations and lung cancer increases. Polymorphisms in CYP1A1 and deletion of the glutathione-s-transferase (GSTM1) gene are associated with high levels of DNA adducts, suggesting that variations in metabolic pathways condition the individual response to carcinogens.^{1,2} A specific relationship between DNA adducts caused by carcinogens and the types of somatic mutations is observed; the KRAS oncogene reflect DNA damage caused by activated PAHs. Microsomal epoxide hydrolase (MEH) can act as activator or detoxifier of carcinogens. As an activator, MEH is involved in the metabolism of PAH epoxides and may be associated with lung cancer risk; a low activity in detoxifying environmental pollutants may be implicated in cancer in non-smokers. N-nitrosamines and aldehydes are implicated in carcinogenesis, cocarcinogens or tumor promoters increase carcinogenicity; cigarette smoke, which activates EGFR, is involved in cell proliferation.²

Nicotine is not a carcinogen, but it increases the risk of cancer in smokers, by inducing dependence and prolonging smoking. The presence of nicotinic acetylcholine receptors (nAChR) on the cell membranes of lung cancer cell lines has been identified and nicotine can promote angiogenesis.^{2,3} Mutations in the q24-25 region of chromosome 15 (SNP rs16969968) containing the *CHRNA5-CHRNA3-CHRNA4* gene cluster encoding $\alpha 5$, $\alpha 3$, $\beta 4$ nAChRs, increase nicotine dependence and vulnerability to lung cancer.¹²

The smoker's entourage is exposed to the second-hand smoke. A 2006 Report by the US Surgeon General¹³ on the health consequences of involuntary exposure to tobacco smoke revealed a causal relationship between such exposure and lung cancer in non-smokers, with an estimated 25% increase in risk. Cannabis, the most frequently inhaled drug after tobacco, whether used

exclusively or combined with tobacco, delivers the same carcinogenic agents as tobacco smoke, increasing the risk of lung cancer.¹⁴

All these facts explain why almost 90% of lung cancers are linked to smoking. Active smokers have an eleven-fold higher risk of lung cancer: RR=10.92(95% CI:8.28-14.40) and the duration of exposure to tobacco smoke is a greater determinant of cancer risk than the total number of cigarettes smoked.¹⁵ Despite advances in lung cancer treatment made possible by immunotherapy and targeted therapies.¹⁶ Nevertheless, the best way to avoid lung cancer is to never start smoking, or to quit as soon as possible.

III - Smoking cessation in lung cancer patients.

BENEFITS OF SMOKING CESSATION.

Smoking cessation is accompanied by short-term benefits: improving cognitive performance, tissue oxygenation, increasing activity level, mood and appetite, reducing fatigue, breathlessness and normalizing cardiovascular parameters.⁵ In the longer term, continued smoking in the early stages of non-small-cell lung cancer (NSCLC), is associated with increased risks of all-cause mortality (HR= 2.94; 95% CI: 1.15-7.54), recurrence (HR=1.86; 95% CI: 1.01-3.41) and in cases of limited-stage SCLC to increased all-cause mortality (HR= 1.86; 95% CI 1.33-2.59), recurrence (HR 1.26; 95% CI: 1.06-1.50), development of a second primary cancer (HR= 4.31, 95% CI: 1.09-16.98).¹⁷ On the other hand, smoking cessation at the time of diagnosis of early-stage lung cancer, improves prognosis: in the case of NSCLC, 5-year survival is 33% for patients who continued to smoke versus 70% for those who quit smoking; in the case of non-disseminated SCLC, 29% of smokers survive versus 63% of abstainers.¹⁷ A prospective study¹⁸ has recruited 517 current smokers with NSCLC (IA-III A) and demonstrated a reduced risk of all-cause mortality (HR= 0.67; 95% CI: 0.53 - 0.85) and disease progression (HR = 0.70; 95% CI: 0.56 - 0.89), with 5-year overall survival (60.6% vs. 48.6%; P = 0.001) and progression-free survival (54.4% vs. 43.8%; P = 0.004) higher in patients who have given up smoking than in those who continued to smoke.

Smoking cessation enhances chemotherapy efficacy. In smokers, interferences of pharmacodynamic or pharmacokinetic nature may induce accelerated metabolism of irinotecan or erlotinid and increase in adverse events with cisplatin-based chemotherapy; stopping smoking corrects these disorders.^{3,5,19}

Perioperative (respiratory, cardiac, critical care) complications, are more frequent (OR= 1.62; CI 95%: 1.25-2.11), one-year mortality is higher (OR= 1.50; CI 95%: 1.17-1.92) length of hospital stay longer (9.0% p<0.001) in smokers compared with nonsmokers.²⁰ Smoking cessation as soon as possible, at best 4 weeks before surgery, reduces these risks (19% less per week).^{3,19} Smokers have a poorer response to radiotherapy, with a higher risk of radiation pneumonia, lung infection and shorter life expectancy.^{3,5} Finally, smoking cessation improves patients' quality of life (QOL), irrespective of the lung cancer treatment and the QOL assessment method.^{3,5,21}

SMOKING CESSATION MANAGEMENT.

The announcement of a lung cancer diagnosis is a « teachable moment » for proposing quit smoking.³ Smokers with lung cancer have a higher level of motivation to quit than other patients (p<0.003), abstinence rate at 6 months is higher (22% vs. 14 %; p<0.024). However, 10% to 30% were still smoking 6 months after diagnosis. Factors predictive of continued smoking have been identified: highly dependent smokers, existence of depressive disorders, exposure to smoking of the spouse (ORa= 9,57; CI 95 %:2,50-36,44).³

Motivation to quit smoking can be reinforced by counselling marked by empathy, avoiding smoker stigmatization, specifying the benefits of quitting and taking care to reinforce the patient's self-efficacy sense. The five steps of the « 5 A's » strategy can help counselling: *Ask* (Identify tobacco use), *Advise* (urge smoker to quit), *Assess* (appreciate if smoker is ready to make a quit attempt), *Assist* (help smoker willing to quit to performe quit attempt), *Arrange* (schedule follow up after the quit date); as well as the « 5 R's » method using open-ended questions can help patients implement smoking cessation: *Relevance* (encouraging smokers to give their reasons for quitting), *Risks* (helping them to identify the negative effects of smoking), *Rewards* (asking them about benefits of quitting), *Roadblocks* (making them specify the obstacles to quitting), *Repetitions* (repeating this motivational interview at each consultation).^{3,5,22} Simple reduction in consumption does not reduce the risk of all-cause mortality but aided by pharmacotherapies can prepare complete cessation.^{3,5,22}

Combining behavioral and cognitive therapies (CBT) with smoking cessation pharmacothérapies give the best results to quit smoking.^{3,5}

The use of CBT at each step of follow-up, increase the efficacy of médicaments, reinforces the patient's

sense of self-efficacy, therapeutic compliance, enables better control of craving, facilitating abstinence.^{3,5,22} Long-distance support (telephone counselling) help patients to maintain abstinence and a smoke-free home.^{5,22,23}

The combination of short-acting nicotine replacement therapy (NRT) (gum, lozenge, spray) and long-acting NRT (patch) with a duration of 12 to 24 weeks, increases the odds of success nearly 3-fold compared with placebo (OR= 2.73; CI 95%: 2.07-3.65). No carcinogenic effects of NRT have been reported.^{5,22} Varenicline, an $\alpha 4\beta 2$ -nAChR partial agonist, is the most effective treatment with the odds of smoking cessation by almost 3-fold compared with placebo (OR= 2.88; CI 95%: 2.40-3.47) with a duration of 12 to 24 weeks. Some side effects (nausea, vomiting, insomnia, vivid dream) can be troublesome for patients undergoing chemotherapy and require dosage adjustment.^{5,22} Bupropion is a dopamine and norepinephrine reuptake inhibitor, effective in smoking cessation (OR= 2.07; CI 95%: 1.75-2.45). It may require dose adjustments in patients with hepatic or renal insufficiency. It can reduce the convulsive threshold, making it contraindicated in patients with epilepsy or brain metastases.^{5,22} Combination of pharmacotherapies (NRT and bupropion, varenicline and NRT or bupropion) can ameliorate nicotine withdrawal symptoms in high dependent smokers.^{3,5,22}

Taking into account specific features that increase the risk of cessation difficulties (economic insecurity, lifestyle: lesbian, gay, bisexual, transgender individuals, use of other drugs, COPD, mental disorders, HIV infection) gives rise to specific interventions.^{7,24,25}

Electronic-cigarette is safer than combustible cigarette, but long-term toxicity is likely. In lung cancer patients who continue to smoke; it could be, in exclusive use, a temporary alternative way to quit smoking.²⁶

LUNG CANCER SCREENING AND SMOKING CESSATION?

Lung cancer screening using low-dose CT scans, aimed at patients aged between 50 and 80 who have smoked at least 20 pack-years, can reduce lung cancer mortality. It helps to raise smokers' awareness of the need to stop smoking and to implement smoking cessation in a cost-effective manner; studies are underway to determine the best strategies of smoking-cessation interventions during the screening program.^{27,28}

IMPROVING SMOKING CESSATION MANAGEMENT IN CANCER CENTERS?

A cross-sectional study, conducted by the Cancer Center Cessation Initiative, to clarify factors that improve smoking cessation has involved 28 centers and 692,662 patients.²⁹ Median smoking prevalence was 7.4%, evidence-based smoking cessation assistance was provided in 15.4%, and median 7-day abstinence at month 6 was 18.4%. The best results were achieved by centers with a smoking treatment protocol and the best resources including expert professionals to support smokers.²⁹ The organization of care for smokers and the training of healthcare professionals must be improved.³⁰

IV - Conclusion.

Smoking is the leading cause of lung cancer. Smoking cessation has many advantages for patients. Smoking cessation is an essential part of cancer treatment. The management of smoking cessation in the treatment of lung cancer patients needs to be improved. Nevertheless, healthcare professionals caring for lung cancer patients need to get trained and involved in smoking cessation support.

Conflict of Interest:

The authors have no conflict of interest to declare.

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