Review

The role of smoking cessation in lung cancer patients

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Key words:
- Lung cancer
- Smoking cessation

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ABSTRACT

Lung cancer is the leading cause of death from cancer. The association of the disease with smoking is undeniable, and in the majority of cases the patients are active or former smokers. The continuation of smoking in patients with lung cancer reduces the survival and increases the risk of disease recurrence and second primary tumor incidence. Furthermore, it reduces the response to chemotherapy and or radiotherapy, delays the healing time of surgical wounds, increases the risk of postoperative complications and finally causes exacerbation of chronic diseases from which the patient may be suffering. As has been documented that smoking cessation has multiple and significant benefits for patients with lung cancer, the success of this goal in this specific patient population is a challenge. It seems that the diagnosis is a powerful incentive for patients to stop smoking, but many will require organized and systematic help. Health professionals should have an active role and education on smoking cessation methods. The opportunity to participate in smoking cessation programs should be offered to all patients and their relatives who wish to stop smoking. The treatment for smoking cessation including counseling, behavioral therapy, medication and regular monitoring, should be an integral part of treating patients with lung cancer.

Pneumon 2015, 28(4):333-339.

INTRODUCTION

Every year the new cases of lung cancer rises up to 1,800,000 and the deaths from the disease worldwide are 1,180,000. More than 210,000 new cases diagnosed in 2012 and 157,000 patients died in the US, while in Europe more than 400,000 new cases diagnosed. Lung cancer is now the leading cause of death by neoplasia since it is responsible for 20% of mortality among all cancers[1-5].

Cigarette smoking is responsible for 90% of lung cancer cases[6]. It is estimated that at the time of diagnosis, the prevalence of smoking is 24-60%,

and up to 83% of all smokers seem to continue smoking after diagnosis of lung cancer[7-13]. Although most patients want to quit, many of them cannot succeed[14-16].

IS THERE A BENEFIT OF SMOKING CESSATION IN PATIENTS WITH LUNG CANCER;

A large number of studies suggest that smokers have a 20 times higher relative risk of suffering from lung cancer than non-smokers. It seems that this risk is mainly associated with the duration of exposure to tobacco products and daily cigarette consumption[17]. Cigarette smoke is irritating the pulmonary tissue and has been shown to influence lung function, as assessed by spirometry. Cigarette smoke contains almost 5000 chemicals, fifty of which are known carcinogens. The most important are polycyclic aromatic hydrocarbons and nitrosamines. These substances can bind to the DNA, thereby predisposing to the occurrence of mutations. Also according to recent data, nicotine is involved in development processes of cancer both by promoting angiogenesis and through direct effects on the control mechanisms of cell death and apoptosis[18-23]. Quitting smoking has short and long term benefits for the smoker. The short term benefits include better control of blood pressure, improving oxygen transport, improve cardiorespiratory function and immune response as well as the restoration of smell and taste senses[24]. Stop smoking is also associated with improved cognition, mental wellbeing and self-esteem that lead to an overall improved quality of life[25]. Patients with lung cancer have the same benefits as other smokers from quitting so they can observe a decrease of fatigue and shortness of breath, increase physical activity and improve appetite, sleep, mood and their performance status[26,27]. A reduction in mortality associated with other diseases related to smoking such as coronary heart disease, stroke and chronic obstructive pulmonary disease has also been observed[28,29].

Smoking cessation is associated with increased survival of patients with non-small cell lung cancer (NSCLC) at early stages. The results depend on the duration of cessation before the diagnosis[30]. A recent study which examined the effect of smoking in the quality of life of patients with small cell lung cancer (SCLC) which survived at least 6 months after diagnosis confirmed the negative effect of smoking in the quality of life of these patients. Furthermore it was observed that smoking cessation even in time near the diagnosis can improve the quality of life and symptoms of patients[31].

A 10 studies review with meta-analysis by Parsons et al found that the continuation of smoking in patients with early-stage NSCLC was associated with a significantly increased risk of disease recurrence and increased all-cause mortality, while in patients with SCLC with limited disease, the risk of disease relapse, the risk of second primary tumor growth and mortality were also increased in patients who continued smoking after diagnosis. Thus, patients who continued to smoke have twice the risk of death compared to those who stopped smoking. That fact was attributed mainly to the delay of the progression of cancer than to the prevention of cardiopulmonary diseases achieved with smoking cessation[32].

SMOKING EFFECT IN POSTOPERATIVE COURSE OF PATIENTS WITH LUNG CANCER

Approximately 20% of patients who are about to undergo surgery for lung cancer continue to smoke in the immediate preoperative period and 30%-60% continue to smoke postoperatively[33]. Smoking can adversely affect the postoperative course of patients undergoing lung cancer surgery, because of the increased risk of developing postoperative respiratory and cardiovascular complications compared to non and former smokers[34]. Furthermore the healing of surgical wounds is delayed in smokers because both nicotine and carbon monoxide cause vasoconstriction, cell hypoxia and inhibition of tissue regeneration. It also increases the risk of infections and bronchopleural fistula, as well as the morbidity and mortality[35,36]. Smoking was an independent predictor of morbidity in the first 30 postoperative days in patients who undergo pneumonectomy[37]. In another study, smoking was found to be a predictor of prolonged hospitalization (>14 days) in patients who underwent lobectomy. Prolonged treatment was associated with more complications such as bronchoconstriction, need for re-intubation and aspiration in these patients compared to non-smokers[38,39].

A prospective study of Barrera et al with 300 patients who had undergone lung cancer surgery for primary or metastatic lung cancer, showed that non-smokers had significantly higher values of FEV1 and DLCO compared to smokers. The overall rate of postoperative complications, including pneumonia, was statistically significantly lower for non-smokers. They finally found that smoking history of more than 60 pack-years is an independent risk factor for respiratory complications after thoracotomy[40].

In another study the relationship between the period of preoperative abstinence and the occurrence of complications after surgery was investigated in 288 patients who underwent surgery for lung cancer. It was observed that the risk of respiratory complications decreased in patients who stopped smoking at least 4 weeks before surgery, while those who had quitted for more than 10 weeks, had the same risk with non smokers. Smoking cessation was associated with fewer complications in patients who did not smoke for at least one month before surgery[41,42].

Gajdos et al retrospectively studied the effect of smoking on the occurrence of postoperative complications and mortality in patients undergoing surgery for cancer and the differences depended on the location of the primary cancer. It was observed that smokers had a higher incidence of pneumonia, difficulty in weaning from the ventilator, higher re-intubation rate compared to non-smokers, and higher mortality at first year. By directly comparing smokers and former smokers in the same patient group the existence of higher risk for postoperative complications and death in the first year was discovered for the smokers. Thus, the authors conclude that intervention for smoking cessation should be imposed before any surgery for cancer in order to reduce the risk of postoperative complications, prolonged hospitalization and risk of death[43].

Patients with lung cancer by stopping smoking early before surgery may have better postoperative course, so patients should be encouraged and assisted to stop smoking. The time that must elapse from smoking cessation to surgery to achieve the best results is not fully clarified. However, the surgery would be done promptly, even if the period of interruption is less than one month, since there is a risk of cancer progression[44,45].

Ebbert et al studied 4577 patients with SCLC and NSCLC, of which 11% were smokers, 58% were former smokers (had stopped smoking at least 6 months before diagnosis) and 31% were smokers (smoked every day or had stopped smoking for at less than six months at the diagnosis). The median survival for NSCLC patients was 1.4 years for non-smokers, 1.3 years for former smokers and 1.1 years for smokers ($p < 0,01$). In women patients who did not smoke greater improvement in survival was observed compared to men. In contrast, there were no differences in the survival of patients with SCLC[46].

In another multicenter study with 169 patients who underwent lung surgery for NSCLC the five-year survival was reduced in smokers than non- and former smokers. The difference in survival was statistically significant only among smokers and non-smokers ($P = 0,02$), suggesting that the period of smoking cessation does not affect the long-term survival[47].

EFFECT OF SMOKING TO CHEMOTHERAPY AND RADIOTHERAPY RESPONSE, IN PATIENTS WITH LUNG CANCER

It has been shown that prolonged administration of nicotine in SCLC cell cultures, causes increased resistance to antineoplastic agents such as etoposide, cisplatin, mitomycin, and taxanes[48]. Nicotine increases the metabolism of many drugs through induction of hepatic enzymes[49]. Smoking affects the pharmacokinetics of erlotinib increasing clearance and decreasing plasma levels. Erlotinib, used in the treatment of NSCLC, is an inhibitor of tyrosine kinase epidermal growth factor receptor (EGFR) and it is metabolized by the liver. It has been hypothesized that induction of cytochrome P450 in the liver of smokers is responsible for increased drug clearance[50,51]. Shepherd et al. found that twice the normal amount of erlotinib needs to be administered to smokers compared to non-smokers, to achieve the necessary level of plasma drug[52].

Systemic therapy for lung cancer has a narrow therapeutic index such that small changes in plasma concentrations or exposure in smokers may result in suboptimal therapy and poor outcomes. However, prospective trials should take into consideration the effects of smoking history on drug pharmacokinetics and efficacy. The metabolizing enzyme phenotype in smokers may require individualized dose algorithms for specific agents[53].

Elevated levels of carbon monoxide (CO) found in smokers were associated with relative tissue hypoxia due to easier binding of CO to hemoglobin and leftward shift of the release curve of oxyhemoglobin. Tissue hypoxia in turn seems to cause decreased response to chemotherapy and radiotherapy[54].

It has further been found that smoking is a major risk factor for the development of radiation pneumonitis in patients with lung cancer who have been treated with radiotherapy[55]. A higher rate of respiratory tract infections has also been observed in smokers undergoing radiotherapy for lung cancer, which was combined with reduced survival[56].

A study showed that among patients with early stage NSCLC, smokers had worse survival prognosis after radiotherapy. It has also been found that patients with small cell lung cancer who quit smoking before chemotherapy or radiotherapy, have higher response rates and longer

survival compared to those who have not ceased[57,58].

Despite the growing evidence that the existence of smoking cessation after diagnosis of lung cancer is associated with better treatment outcomes and better prognosis, the perception that smoking cessation in these patients does not offer substantial benefits remains[59]. Survival rates in lung cancer are poor, about 7% for the five-year survival, while some patients are candidates for palliative treatment only. However, about 20% of patients are diagnosed early enough and could be cured. These patients have a relatively good prognosis with a five-year survival rate of 60%-75% and 36%-50% for NSCLC stages I and II respectively[60,61]. When the prognosis of the primary tumor is favorable, then there is strong evidence that continued smoking increases the risk of a second primary tumor. Data indicate that cigarette smoking before first cancer diagnosis increases second cancer risk among cancer survivors, and elevated cancer risk in these survivors is likely due to increased smoking prevalence[62]. More specifically, in a study of patients with SCLC lung the risk of a second neoplasm, particularly NSCLC, was 3.5 to 4.4 times greater than in the general population. In those who continued smoking the risk was significantly higher, especially in those who had undergone radiotherapy and those who had received chemotherapy with alkylating agents while second primary lung cancer are rare in never-smokers[63]. Additionally it was found that for patients who stopped smoking at the time of diagnosis the risk was greater than for those who had stopped 6 months before diagnosis[64]. Smoking increases not only the first cancer but also a second or subsequent primary cancer. Moreover, the results from recent quitters versus current smokers suggest that smoking cessation may decrease the risk for subsequent primary cancer, especially for smoking-related subsequent primary cancers in cancer survivors[65].

As the survival of patients with lung cancer prolongs, the quality of life of these patients is becoming more important and a series of studies show that smoking cessation improves the quality of life. Therefore smoking cessation should be an integral part of treatment of these patients[66-68].

THE DIAGNOSIS OF LUNG CANCER AS MOTIVATION FOR SMOKING CESSATION

Continued smoking after diagnosis of lung cancer reduces survival, increases the risk of relapse and the risk of a second primary tumor, reduces the therapeutic effects and increases the complications of the disease and of the antineoplastic treatment[69-73]. However, a proportion of 13%-20% of patients with lung cancer continues to smoke after diagnosis[74,75].

In a study of patients with lung and head and neck cancer, the causes for which many patients avoid joining in smoking cessation programs were investigated. Those who did not participate were mainly the patients with head and neck cancer, those who had fewer respiratory symptoms, who smoked fewer cigarettes and felt less ready to quit smoking. A similar study showed that among smokers, the younger ones, those with early stage disease and those with a smoker partner were more interested to participate in smoking cessation programs. However finally, only 50% of smokers participated, although the majority of the patients were informed about such programs. We wish to emphasize the need for interventions in order to inform and motivate patients to increase their participation in smoking cessation programs[76,77]. Although the diagnosis of lung cancer is a strong motivating factor for patients to quit smoking, it is not sufficient on its own and many patients will need additional support. Many are those who resumed smoking after tumor resection, usually in the first two months after surgery. Most susceptible are those who stop smoking for a shorter period before the surgery, and those who feel greater desire to smoke. Intervention for maintaining abstinence should begin immediately after surgery[78].

The combination of medication and behavioral therapy increases the success rates of smoking cessation[79]. Strong prognostic value for the likelihood of recurrence of the smoker is living with smokers. Patients with lung cancer often live with a smoker and it is appropriate to extend the process of smoking cessation in/being partner and close family environment to achieve better results[80].

Physicians who care for lung cancer patients recognize the importance of tobacco cessation as a necessary part of clinical care, but many still do not provide assistance to their patients as a routine part of cancer care[81].

Regarding the use of e-cigarettes for smoking cessation, the International Association for the Study of Lung Cancer (IASLC) advices against recommending their use at this time. There is absence of sufficient evidence that e-cigarettes are effective and safe for treating nicotine dependence in cancer patients. The IASLC does recommend that research be done to evaluate the safety and efficacy of e- cigarettes as a cessation treatment in cancer patients[82].

CONCLUSIONS

A large number of patients with lung cancer are former smokers. Many of those who were diagnosed with lung cancer were current smokers and some of them continue to smoke after diagnosis, while others after a period of abstinence relapse and continue smoking.

Several investigators have ruled that smoking should be discontinued preoperatively in patients able to undergo lung surgery, as well as prior to chemotherapy or radiotherapy. There are several indications that continuing smoking after diagnosis of cancer reduces the survival period, increases the risk of recurrence and second primary tumor incidence, reduces the therapeutic effect, delays the time to healing of surgical wounds. Furthermore, patients who quit smoking have better quality of life.

Smoking cessation in these patients is a challenge. It has been observed that the diagnosis is a strong incentive to disrupt the patient from smoking, but not enough for everyone. The right time for intervention, the appropriate approach to achieve the best results is the subject of studies. Maybe early intervention, with active involvement and training of health professionals who cure these patients, would motivate them to participate massively in smoking cessation programs. The patients could play an active role to motivate their familiars to stop smoking but it remains to identify the most effective course of action. Information, encouragement and participation in such programs should be offered to all patients, but also to their relatives who want to stop smoking. The weaning from tobacco should be pursued in patients with lung cancer at all stages of the disease: diagnosis, treatment and monitoring.

The smoking cessation therapy including counseling, behavioral therapy, medication and regular monitoring should be an integral part of treating patients with lung cancer.

FUNDING

No financial conflicts of interest.

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