

Editorial

Notes on Recurrence and Second Tumors in Lung Cancer[☆]

Apuntes sobre recidivas y segundos tumores en el cáncer de pulmón

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Between 30% and 70% of lung cancer (LC) patients treated with surgery will experience local or distant relapse within the first 5 years, mostly during the first 2 years; recurrence rates after 5 years are between 5% and 15%. Distant recurrences are still the most frequent, and occur in up to 70% of cases.¹ As relapse rates fall with the passing of time, rates of second primary tumors increase. These second primaries occur more often in year 5 post-surgery than in year 2, and the most prevalent are pulmonary strains, with higher relapse rates occurring after small cell carcinomas.² An analysis of recurrence patterns in LC shows that incidence of relapse appears to peak at 3 time points: 9 months, 2 years and 4 years; while the appearance of second primary lung tumors is more linear.³

Investigators Sánchez de Cos Escuín et al. reported that most relapses occur in the first 3 years, and are relatively common up to the 5-year mark, after which recurrence rates fell greatly. In contrast, the appearance of second primary tumors in the lung or in extrapulmonary sites was more common after 5 years. Moreover, the incidence of second primary tumors was higher than the predicted incidence of cancer in general populations of similar age and sex, primary lung cancers being the most common. With regard to histological type, they also found that second primary lung tumors were more common after small cell disease.⁴ These findings, though similar to those reported in previous studies, were observed over a longer follow-up period, irrespective of the treatment initially prescribed.

The reason for recurrence and second tumors is currently a topic of discussion. One of the causes, perhaps the most important, is persistent smoking. This habit plays a significant role in the etiology and pathogenesis of LC and other cancers that subsequently develop as second primary tumors.² Moreover, smoking may be associated with poor response to treatment, since worse outcomes have been observed in patients with a history of smoking

and lung adenocarcinoma treated with tyrosine kinase inhibitors, even in subjects with sensitive EGFR mutation, due to induction of epithelial–mesenchymal transition. Thus, smoking during treatment may induce drug resistance and generate a greater number of recurrences.⁵ Smoking or smoking cessation may also affect the histological type, and the rate of relapse among smokers with lung adenocarcinoma appears to be higher.⁶

One of the most prevalent diseases among smokers is chronic obstructive pulmonary disease (COPD), another cause of LC, and this condition may be associated with recurrence, even in the absence of smoking. Causative factors may include the severity of the disease, the emphysema phenotype, the presence of systemic inflammation and oxidative stress that are often associated with this disease, or possibly even epithelial–mesenchymal transition.⁷

Other possible reasons include the use of radiation therapy,⁸ which may be directly related with the modality and dose administered, although this association has not been clearly characterized, particularly because radiation therapy is very often used concomitantly with chemotherapy. Chemotherapy itself and other immunosuppressive agents used in the treatment of LC may also contribute to the development of relapses or second tumors.

Sánchez de Cos Escuín et al. suggest that relapses and second tumors are caused by smoking, and conclude that in patients with long-term survival after LC, the carcinogenic effects of tobacco persist in the lungs and other organs, increasing the chances of relapse and second tumors. However, they did not find any direct relationship with radiation therapy, and hypothesize that “field cancerization” or “condemned mucosa syndrome” could lie behind the greater incidence of second tumors among patients who did not receive radiation therapy.⁴

A search for other risk factors for local relapse must consider the type of resection, tumor strain, pleural invasion, whether lymphatic or vascular, and incomplete resection, bearing in mind that up to 30% of local relapses can occur in the bronchial stump.⁹ Moreover, epidemiological changes, such as age, environmental exposure, or the increasing prevalence of women with LC, may also play an important role and could be an interesting area for future research into the genesis of relapse or second tumors.

One area under discussion is the potential of molecular parameters for predicting recurrences or second tumors. Although

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scientific evidence is scarce and published results vary widely (studies include different TNM stages), KRAS and Ki67 may be prognostic markers for postoperative recurrence in early stages, and EGFR mutations may predict recurrences in adenocarcinomas resected with curative intent. When using these molecular markers, it is important to bear in mind that some slow-growing recurrent tumors have little clinical impact, and some cases are not recurrences but undetected lesions. Moreover, these mutations may be useful for differentiating between second primary lung cancer and recurrent primary tumors.¹⁰

Another issue currently under debate is the follow-up of LC patients. Two factors in particular are of interest in the early detection of relapses and second tumors: the diagnostic test used and the frequency of follow-up visits. Currently there is no agreement among the international scientific community on the frequency of follow-ups and the diagnostic tools to be used at each visit. What does seem clear is that a multidisciplinary team using well-established protocols is essential for both diagnosis and treatment. We can infer from the results of Sánchez de Cos Escuin et al. that, in the first 3–5 years of follow-up, protocols must focus on detecting relapses and, after 5 years, on determining the appearance of second primary tumors. If these considerations are taken into account, post-surgery protocols in the future will tend to tailor follow-up according to tumor characteristics, smoking habit and treatment received.

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