IASLC Position Statement on the Documentation of Tobacco Use in Cancer Clinical Trials

In recent years, there has been growing awareness of the negative impact of tobacco use on clinical outcomes for cancer patients. The 2014 US Surgeon General's report compiled compelling evidence that cigarette smoking by cancer patients and survivors causes adverse outcomes, including increased all-cause mortality, cancer-specific mortality and increased risk of a second primary cancer (1). The report further demonstrated that continued smoking was strongly associated with a greater risk of cancer treatment toxicity and poor quality-of-life. There is now evidence that smoking cessation after a cancer diagnosis is associated with improved survival (2,3).

Tobacco use has effects that are both prognostic (directly harming patients) and predictive (interfering with cancer therapies). Among lung cancer patients undergoing surgery, there is evidence of more frequent postoperative complications and increased perioperative mortality (4,5). For those patients receiving radiotherapy, there is a greater risk of treatment-related toxicity (6), and less therapeutic efficacy as a result of lower tissue oxygen levels (7). For those receiving systemic therapy with either chemotherapy or molecular targeted agents, there is evidence of less myelosuppression (8) and/or decreased tumour response (9) suggesting that the induction of hepatic enzymes by polycyclic aromatic hydrocarbons in tobacco smoke can increase the rate of clearance of these agents making them less effective (10,11). On the other hand, it appears that patients with a smoking history may have a greater benefit with immune checkpoint inhibitor treatment compared with never smokers (12). Studies of the impact of tobacco on clinical outcomes do not comprehensively address the large number of systemic therapy agents in current use today (13). Nonetheless, the available evidence indicates that smoking can be an important predictive factor that should be accounted for when testing the efficacy of novel cancer therapies. Further research is needed to address the impact of continued smoking after a diagnosis of cancer, to provide guidance on how best to manage treatment for those cancer patients who continue to smoke cigarettes, and to determine the magnitude of clinical benefit that is achieved with smoking cessation (14).

Newer, alternative tobacco products, including electronic cigarettes (e-cigarettes) and heated tobacco products purportedly lower health risks relative to smoking combustible tobacco cigarettes. However, data on their long-term health effects, including the risk of lung cancer, and their impact on treatment outcomes are unavailable. To characterize the potential association between the use of alternative tobacco products on cancer risk and their impact on

cancer treatment outcomes, there is a need to collect data on their use in cancer treatment trials (15).

Large reviews of cooperative group clinical trials have shown that smoking status is documented in only approximately 20% of trials at patient registration and very few trials capture information on smoking status over the course of the trial (16,17). Furthermore, definitions of smoking status (current, former, never smoking) are inconsistent and information on the intensity of smoking is rarely captured (18). Even when smoking status has been determined, few trials report analyses of the prognostic and predictive impact on clinical outcomes (19). Smoking clearly affects survival, as well as the toxicity of cancer treatments, and these endpoints serve as the primary or secondary objectives of virtually all clinical trials. As a result, it is critical that smoking information be collected and available for analysis to accurately assess the benefits and harms of cancer treatment in clinical trials (20).

To advance knowledge on the impacts of tobacco smoke in the context of cancer clinical trials, the IASLC recommends the following:

1. Documentation of tobacco use status at cancer diagnosis and at clinical trial registration using standardized definitions from the validated Cancer Patient Tobacco Use Questionnaire (C–TUQ) (21)
2. Document the use of tobacco products (including electronic cigarettes and heated tobacco products) at regular intervals over the course of the clinical trial for those individuals who have ever used tobacco products.
3. Document any methods of smoking cessation used by patients over the course of the clinical trial and their effectiveness.
4. Verify smoking status using biochemical measures, whenever possible.
5. Analyze the effect of tobacco use on clinical trial outcomes including response rate, progression free and overall survival, treatment-related toxicity, adverse events, compliance with trial procedures, and quality-of-life.

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