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Tobacco Assessment in Completed Lung Cancer Treatment Trials

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Smoking is well documented to be responsible for 87% of all lung cancer-related deaths in the US (1). The 2014 Report of the Surgeon General concluded, for the first time, that a causal relationship links cigarette smoking and adverse cancer-related outcomes, including all-cause and cancer-specific mortality, and risk for second primary cancers known to be caused by cigarette smoking (1). The Report, basing its conclusion on studies of various cancer types, treatments, follow-up timeframes, and outcomes, noted that the general consistency across studies with varying methodologies strengthens the inference that cigarette smoking is causally associated with myriad adverse health outcomes and not just one or a few endpoints (1). Although the Report based its conclusion on a preponderance of available evidence, methodological limitations of the review included retrospective, relatively crude, and inconsistent assessment of cigarette smoking (1,2,3). These methodological differences have limited the ability to adequately characterize the relationship between smoking and lung cancer treatment outcomes.

Observational studies suggest that smoking cessation – even after cancer diagnosis – can improve cancer treatment outcomes (4–8). Clinical trials of cancer treatment that incorporate tobacco use assessment offer important information that can confirm or disconfirm observational data; analysis of secondary data from completed clinical trials is a promising

strategy. The National Cancer Institute (NCI) Cooperative Group clinical trials, characterized by rigorous and centralized, standardized scientific designs, offer potential secondary data sources for analysis of the relationship of smoking and cancer treatment outcomes. Furthermore, because of their similar design elements, NCI Cooperative Group clinical trials are well-suited for analysis that pools secondary data across studies, thereby providing large sample sizes and good statistical power.

In 2013, a pooling project of secondary data from completed cancer clinical trials of one NCI Cooperative Group, the Alliance for Clinical Trials in Oncology (Alliance), was developed. The aim of the project was to address two issues of clinical significance among lung cancer patients: (1) the association of changes in smoking from treatment entry through follow-up (i.e., quitting or reducing smoking after treatment entry, resuming smoking during follow-up) with cancer treatment outcomes; and (2) variation in the association of cigarette smoking with cancer treatment outcomes according to patient characteristics and cancer treatment modality. Approval from the Alliance to conduct the pooling project and IRB exemption from human subjects review were obtained. To reduce methodological and population heterogeneity in the analysis, *a priori* criteria were that studies had to: (1) be closed to recruitment of new participants; (2) be of lung cancer treatment; and (3) have assessment of cigarette smoking at least at treatment entry.

The Alliance had records of 32 completed studies of lung cancer treatment trials. A keyword search (e.g., “cigarette”; “smoking”; “tobacco”) of the protocols and forms of these 32 studies showed that ten had collected smoking data and, thus, were feasible for inclusion. Based on target accrual of the protocols, the projected pooled sample size across the ten studies was 5,004. Of the ten trials proposed for inclusion, four did not have usable data: one did not have electronic data, and three studies were ongoing (i.e., actively recruiting participants or had not published data from primary outcomes). This left six studies with usable, accessible data. In these remaining six studies, there was no explicit, consistent definition of tobacco use. Although all 6 of the studies had a variable for smoking status (i.e., never vs. former vs. current smoker), only one explicitly defined a former smoker as someone who had smoked at least 100 cigarettes in his lifetime and quit smoking over 1 year ago; in the other studies, there was no definition of a former smoker based on lifetime smoking quantity or duration of smoking cessation. In two studies, there was a variable for smoking pack-years, and in one study there was a variable for number of years smoking; in three studies, there was no variable for smoking quantity. There were no other smoking-related variables in the six studies with usable data. One study - the only one of these remaining six studies to have assessed smoking at any point after treatment entry - had been terminated after accruing 34 of 1620 targeted participants. The total sample size across the six studies with usable data ($N=623$) was far less than the projected total sample size for the original ten studies ($N=5004$), raising concerns about methodological and participant heterogeneity. A keyword search of other cooperative group protocols failed to yield a sufficient number of studies that met *a priori* criteria for study inclusion. Due to a lack of usable data, the planned pooling project was terminated in 2016.

Although it has been recognized that smoking may decisively affect the outcome of cancer treatment, an effort over 3 years to conduct a data pooling project on the association of

smoking and lung cancer treatment outcomes showed that, of several completed lung cancer treatment trials, most have no usable data on smoking. The lack of smoking-related information among NCI Cooperative Group clinical trials that have completed accrual is consistent with results previously reported from NCI Cooperative Group clinical trials that are actively accruing patients (2). Because smoking is so clearly a factor in lung and in head and neck cancer (3), the fact that only a minority of completed lung cancer treatment trials in this one Cooperative Group had any usable data on smoking was surprising. The paucity of data related to smoking profoundly limits the ability to evaluate the complete effect of smoking – and of smoking cessation – on cancer treatment outcomes. It is possible that the impact of smoking and smoking cessation on cancer treatment outcomes is modest, but cancer clinical trials must evaluate smoking as rigorously as possible to clarify the magnitude of the relationship.

The NCI-AACR Cancer Patient Tobacco Use Assessment Task Force recently put forth recommendations for “Core” and “Extension” assessment items for smoking at initial and follow-up time points (9). Core items provide information about status as an ever/never-smoker, and the duration, intensity, and recency of smoking. Extension items capture smoking during time frames relative to diagnosis and treatment; current smoking; age at smoking initiation; use of alternative tobacco products; longest cessation interval after diagnosis; cessation attempts; and use of cessation products or assistance (9). These recommendations were issued after the initiation of most of the studies proposed for this pooling project, partially explaining why the smoking-related variables available for our pooling project did not align with these recommendations. In the future, data collected from these recommended assessment items – at treatment entry and at follow-up – are absolutely needed for accurate identification of the impact of smoking on cancer treatment outcomes.

Several barriers may help explain the lack of smoking-related data: the perception that smoking, relative to other factors (e.g., cancer stage), has little impact on outcome; time and resource demands; and the perception that cessation is not a viable option (10). Some oncologists may assume that the effect of smoking may already be known. To promote the implementation of smoking assessment in cancer research and facilitate future pooling projects on the association of smoking and cancer treatment outcomes, empirical information on smoking and cessation at treatment entry and at follow-up is badly needed. This information could be used to motivate smoking cessation among cancer patients, many of whom may believe that quitting smoking after cancer diagnosis will not affect their survival (10). Clinicians need to know how much difference smoking cessation might make.

There is now a recognized need to address tobacco use as a standard of care in cancer treatment (11–15). More complete characterization of the relationship between smoking and treatment outcomes would quantify the extent to which smoking is not just a prognostic but a modifiable factor in cancer patient survival. Clinical trials research is an important but yet untapped resource for informing cancer patients and their doctors about the impact of smoking on the course of their disease.

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