Resilience in Advanced Lung Cancer

Abstract

Background: Advanced non-small cell lung cancer (NSCLC) patients are the most distressed of all cancer patients. While new therapies are improving survival, it is unknown if receiving immunotherapy or targeted therapy during the coronavirus (COVID) pandemic increases patients’ psychological vulnerability. To meet clinical needs, knowledge of patients’ COVID perceptions and safety behaviors is essential. Thus, we 1) compare patients’ psychological responses at diagnosis and during COVID, and 2) compare patients to similar individuals without cancer during the same period.

Patients and Methods: Patients with advanced NSCLC enrolled at diagnosis for cohort study participated (NCT03199651). Those with follow-ups from 4/28/20-7/14/20 (n=76) were assessed again including COVID measures. Simultaneously, community Controls with similar sociodemographics and smoking histories were solicited (n=67). Measures were COVID perceptions (Brief Illness Perceptions Questionnaire), social distancing, and depressive (Patient Health Questionnaire-9) and anxiety (Generalized Anxiety Disorder-7) symptoms. First, analyses evaluated differences in NSCLC patients’ psychological responses at diagnosis and during COVID. Second, patients and Controls were contrasted on COVID perceptions, social distancing, and psychological symptoms.

Results: NSCLC patients’ depressive and anxious symptoms were greater at diagnosis (ps<.02) than during COVID, ~1 year later. NSCLC and Controls did not differ on sociodemographics except patients were more racially diverse, older, with greater smoking history (ps<.05). Groups did not differ on concern, understanding, or perceived control over COVID (ps>.406). Notably, Controls viewed COVID as lasting longer, practiced more social distancing, were more concerned about family (ps<.05), and reported worse psychological symptoms (ps<.023).
Discussion: With less depression and anxiety, NSCLC patients viewed COVID as a shorter-term threat and had fewer COVID-related worries than Controls. For Controls, COVID was more salient, heightening worries and psychological symptoms.  

Conclusions: Despite multiple health stressors, NSCLC patients demonstrated resilience when receiving cancer treatment during COVID. Nonetheless, this population remains psychologically vulnerable, requiring support at diagnosis and thereafter.  

Keywords: stress, anxiety, depression, resilience, lung cancer, non-small cell lung cancer, NSCLC, COVID-19
Cancer Treatment During COVID-19: Resilience of Individuals with Advanced Non-Small Cell Lung Cancer versus Community Controls

1.0 Background

Cancer patients are more vulnerable to the novel coronavirus (COVID) than otherwise healthy individuals. Lung cancer (LC) patients are uniquely vulnerable to coronaviral pneumonias (SARS-CoV-2), along with acute respiratory distress syndrome (ARDS), and if infected, they have a greater likelihood of dying. COVID notwithstanding, the scope of the LC problem is without parallel. In the United States (US), LC accounts for 25% more cancer deaths than deaths from prostate, breast, and colon cancer combined, accounted for, in part, by 84% of LC patients being diagnosed at advanced stage. Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers and is the fifth-costliest tumor to treat, with estimated national expenditures of $14.7 billion for 2020.

As the pandemic continues, LC patients are, unfortunately, vulnerable for other reasons: they are the most emotionally distressed of all cancer groups, having the greatest prevalence of mood and anxiety disorders. At diagnosis, many patients with advanced (stage IV) NSCLC perceive cancer as consequential and uncontrollable, even in the context of new immunotherapy and targeted treatments. Roughly 40% report moderate to severe depressive symptoms, anxiety, and trauma levels of cancer-specific stress, and cross-sectional studies post-diagnosis show heightened symptom levels. Many might assume that COVID adds further stress to NSCLC patients, although the extent to which this occurs is unknown. It is possible, however, that this population actually exhibits a positive adaptation known as resilience, the ability to maintain or regain mental health despite experiencing adversity. Without information, providers may be ill-
prepared to meet patients’ needs during this difficult time and may not know the extent to which COVID exacerbates patients’ stress, particularly as they try to continue therapy during the pandemic. Such issues are time-sensitive, considering the devastation attributable to mental health consequences of the pandemic,\textsuperscript{14} the multiple waves of COVID cases in the US, and the “stalling” of vaccine uptake.\textsuperscript{15}

NSCLC patients, enrolled at diagnosis and followed for cohort study (ClinicalTrials.gov identifier: NCT0319965), enabled analysis of two important issues. First, patients’ psychological responses at diagnosis (pre-COVID) were compared to those during COVID. Prior to COVID, many cancer groups have shown a declining trajectory of stress or depression from diagnosis across time.\textsuperscript{16-18} We were uncertain if that trend would still be evidenced with patients in treatment amidst the pandemic. Secondly, NSCLC patients’ responses during COVID were compared with a time-equivalent “normative” sample, i.e., similar individuals from the community also coping with COVID, but cancer-free. Having health risk from multiple sources, would NSCLC patients show greater negative affect, such as pessimism or worry, or difficulties with social distancing, than others trying to cope while free of the added cancer burden? Relevant to clinical care, would the picture for LC patients be one of unique, added burden or one, possibly, of resilience?

The study was done in Ohio as infections were beginning to climb in April 2020. At that time, 750 new cases were occurring per day (21,000 total), a rate that remained stable until early June. Thereafter, cases accelerated at more than double the daily rate (1,630) and approached a total nearly four times higher (78,000) by the end of data collection (July 2020). NSCLC patients still enrolled and alive completed a COVID-specific assessment during the study window; archival psychological data from the patients at diagnosis were also used. As COVID risk varies
across time and US states, data from comparison individuals (Controls) residing in Ohio were obtained during the same window.

2.0 Methods

2.1 Procedures

The Institutional Review Board of XXXXXX approved the study and all procedures in accordance with the Declaration of Helsinki. All participants completed written informed consent. A group comparison design was used.

An NCI-designated Comprehensive Cancer Center enrolled stage IV NSCLC patients at diagnosis into an observational cohort (Beating Lung Cancer in Ohio [BLCIO]; ClinicalTrials.gov identifier: NCT03199651) beginning in 2017. Electronic Supplementary Table 1 provides inclusion/exclusion criteria. Patient-reported outcomes (PROs) for anxiety and depressive symptoms were completed by telephone at diagnosis with the aid of a survey research firm. In the same manner, patient follow-ups scheduled from April 28th 2020 to July 14th 2020 were done, with COVID-specific items additionally completed. Of the 99 patients to be assessed in the time window, 76 were completed (76.8%). Reasons for the 23 missing responses are: 4 too ill to complete assessment, 9 contacted but not completed before assessment window (30 days) closed, 10 not contacted within assessment window. Overall, BLCIO has a mean completion rate of 80% of available N across follow-ups from diagnosis to 24 months.

Published data from the cohort at diagnosis (N=186 through April 2019) showed a mean age of 62.5 years, 91.4% with a smoking history, low education and income levels, with all residing in Ohio. These characteristics guided the solicitation of Controls. As difficulty with matching was anticipated, two web-based platforms (ResearchMatch, CloudResearch) were used with the following participation criteria: no prior or current cancer diagnosis, age 45-90 years,
Resilience in Advanced Lung Cancer

≤high school education, ≤$75,000 annual income, current or former smoker, Ohio residence, and ability to complete online assessments in English. From May 8th to June 19th 2020, n=67 Control individuals enrolled and completed measures on Qualtrics.

2.2 Measures

2.2.1 Psychological symptoms. American Society of Clinical Oncology (ASCO) recommended measures were used. Symptoms of major depressive disorder were assessed with the Patient Health Questionnaire-9 (PHQ-9) measure. The PHQ-9 total score can range from 0 to 27, with each of nine items measured on a Likert scale from 0 (not at all) to 3 (nearly every day). Symptoms of generalized anxiety disorder were assessed with the Generalized Anxiety Disorder-7 (GAD-7) measure. The GAD-7 total score can range from 0 to 21, with each of seven items measured on the same Likert scale as the PHQ-9. Cutoffs suggestive of at least moderate symptom levels are >9 for both measures.

2.2.2 General health concern. NSCLC patients rated the following item: “Has the COVID-19 pandemic worsened your concern about your lung cancer?” and Controls rated “Has the COVID-19 pandemic worsened your concern about your health?” The scale for each ranged from 0 (not at all concerned) to 10 (extremely concerned).

2.2.3 COVID measures.

2.2.3.1 Illness perceptions. The Brief Illness Perceptions Questionnaire (BIPQ) assessed patients’ and Controls’ perceptions of COVID (its consequences, timeline, personal control, concern, understanding). For example, the timeline item asks, “How long do you think the COVID-19 pandemic will continue?” The concern item asks, “How concerned are you about getting COVID-19?” Each item was rated from zero to ten. Omitted were two items not relevant
Resilience in Advanced Lung Cancer

to COVID (treatment control, identity/symptoms). See Electronic Supplementary Table 2 for complete description.

2.2.3.2. Exposure, social distancing, and stress/worry. Infection Tally. Items from Wang et al. were used.23 Three items assessed knowledge (number) of persons with COVID in the family, friends, and acquaintances (e.g., “How many family members have been diagnosed with COVID-19?”). Social Distancing. One item was used: “Have you been able to ‘socially distance’ yourself from household members?” rated from 0 (not at all) to 6 (all the time). Stress and Worry. Three items were used. a) “How would you rate your stress during isolation or social distancing?” and b) “Has isolation or social distancing created tension in your household?” were both rated on a 0-6-point scale, with higher scores indicating more stress/tension. c) “How worried are you that any of your close family members will contract COVID-19?” was rated from 0 (not worried at all) to 10 (extremely worried). See Electronic Supplementary Table 2 for complete description.

2.2.4 Descriptive. Sociodemographic items were included. For NSCLC patients, data were obtained from the electronic medical record and verified by two raters. NSCLC disease and treatment characteristics were obtained as well as the Charlson Comorbidity Index (CCI) quantitatively summarizing the presence and severity of 17 common medical conditions. CCI scores range from 0 to 37; NSCLC scores were a minimum of 6 for “metastatic solid tumor.” Controls self-rated all CCI items.

2.3 Statistical Analysis

One-way analysis of variances (ANOVAs) and \( \chi^2 \) tests examined group differences in demographics. A Fisher’s exact test was run for race, due to small cell size (n=3 for non-White
participants in the Control group). Variables significantly different between groups were used as controls.

For the first analyses, paired sample t-tests were used to test change in NSCLC patients’ depressive and anxiety symptoms from diagnosis (pre-COVID) to follow-up during COVID. Secondly, multivariate linear regressions tested for group differences in outcomes, controlling for variables significantly different by group. A p-value < .05 was considered statistically significant. A sensitivity analysis using the g-power program\textsuperscript{25} was performed to confirm a sufficient sample size. Sensitivity analysis indicated a small-medium effect size of group differences in outcomes ($f^2 = .106$).

3.0 Results

3.1 Description

3.1.1 NSCLC patients. Table 1 provides summary statistics. Comparing the sample to that of the Surveillance, Epidemiology, and End Results (SEER) Program,\textsuperscript{26} the NSCLC group was younger ($M = 65.8$ years; range = 29-80), roughly equivalent in terms of sex (female $n=31$; 40.8%), married/partnered (58%), and less ethnically/racially diverse (80.3% Caucasian). The sample was equivalent in the large majority of the tumors (79%) being adenocarcinoma. Other sample characteristics included education level: less than high school for 6.6% ($n=5$), high school for 35.5% ($n=27$), more than high school for 57.9% ($n=44$); and income, with 22.6% ($n=16$) below the Ohio poverty line for a family of four ($25,000). At follow-up, all patients, excepting 5, were in treatment with novel immunotherapies or targeted therapies.

3.1.2 Controls; Comparison of groups on sociodemographics. Table 1 provides summary statistics. Similarity of samples was approximated. NSCLC and Control groups did not differ on sex, education, income, marital status, or residence (Ohio). The Control group was less
diverse (5% vs. 20% non-White; OR=5.246, 95% CI 1.447, 19.024, \( p=.006 \)), younger (57 vs. 63 years; Cohen’s \( d=.392, \ p=.023 \)), and had somewhat fewer current/former smokers (75% vs. 89%; OR=2.890, 95% CI 1.156, 7.225, \( p=.036 \)). Thus, the latter variables were entered as controls in the multivariate linear regression analyses.

3.2 NSCLC patients’ psychological responses at diagnosis versus during COVID

Table 2 provides summary statistics. NSCLC patients reported significantly more depressive (\( \Delta M=1.737, 95\% \ CI .493, 2.98, p=.007 \)) and anxiety symptoms (\( \Delta M=1.592, 95\% \ CI .264, 2.920, p=.019 \)) at diagnosis (pre-COVID) than during COVID. Percentages of NSCLC patients above cutoff values at diagnosis and at COVID follow-up were, respectively, 17.1\% (\( n=13 \)) versus 11.8\% (\( n=9 \)) on the PHQ-9 and 15.8\% (\( n=12 \)) versus 13.2\% (\( n=10 \)) on the GAD-7.

3.3 Multivariate linear regressions comparing NSCLC patients and Controls during COVID

3.3.1 Psychological symptoms. Table 2 provides summary statistics. Notably, NSCLC patients reported significantly fewer depressive (\( \beta=-.206, 95\% \ CI -4.142, -.355, p=.020 \)) and anxiety symptoms (\( \beta=-.196, 95\% \ CI -4.037, -.308, p=.023 \)) than Controls, with racial group, age, and smoking status controlled. Percentages of individuals above cutoff values in the NSCLC and Control groups were, respectively, 11.8\% versus 28.1\% on the PHQ-9 and 13.2\% versus 30.3\% on the GAD-7.

3.3.2 Health concern. COVID worsened Controls’ moderate concern about their health (\( M=5.45 \)) and interestingly, this was similar (\( p=.943 \)) to NSCLC patients’ moderately worsening concern about their lung cancer (\( M=5.91 \)). See Table 2.

3.3.3 COVID analyses
3.3.3.1. **Illness perceptions.** Controlling for racial group, age, and smoking status, NSCLC patients and Controls perceived COVID similarly. Patients and Controls perceived they had high knowledge about COVID, felt they had similar (moderate) control over their own COVID risk, and had similar levels of concern about contracting COVID. However, unlike NSCLC patients, Controls anticipated the COVID threat would last significantly longer (β = -0.278, 95% CI -0.925, -0.180, p = 0.004).

3.3.3.2 **Exposure, social distancing, and stress/worry.** Controlling for relevant variables, groups did not differ on knowledge of persons with COVID. However, NSCLC patients reported being significantly more successful with social distancing (β = 0.300, 95% CI 0.217, 0.797, p = 0.002), less stressed about COVID (β = -0.177, 95% CI -0.701, -0.002, p = 0.049), and less worried about family contracting COVID (β = -0.192, 95% CI -0.734, -0.028, p = 0.035) than did Controls.

4.0 **Discussion**

To our knowledge, this is the first empirical, controlled comparison study of the psychological and behavioral impacts of COVID-19 among US cancer patients. The data are novel, as thus far, studies come from Europe and Asia only.27,28 LC patients are an important group, representing nearly 13% of all new cancer cases in the US annually. Survival for those with advanced NSCLC is changing dramatically as new immunotherapies and targeted therapies become available and treatment guidelines shift regularly. Thus, it is important to understand and appreciate how NSCLC patients with the most severe disease burden and symptom severity—one uniquely susceptible to COVID infection and death—are emotionally and behaviorally able to travel to the hospital and receive treatment, monthly if not weekly. Results are discussed
in terms of NSCLC patients’ resilience and the differential salience\textsuperscript{29} of COVID for the Controls. Implications for clinical practice are provided.

As noted\textsuperscript{7}, LC patients are regularly identified with the highest levels of stress or depression, and depression at diagnosis predicts premature death for them (e.g., HR 1.39, 95% CI 1.24-1.56).\textsuperscript{30} Pre-COVID, a downward trajectory of psychological symptom severity from diagnosis onward has been found for cancer patients.\textsuperscript{16-18} Some might view the significant declines in NSCLC patients’ psychological symptoms from diagnosis to follow-up as a “response shift.”\textsuperscript{31} In response shift, patients “recalibrate” the meaning of questionnaire items, particularly if items are general, e.g., “rate your quality of life.” Response shift is unlikely for the PHQ/GAD items, as they are the DSM-IV criteria for major depressive disorder and generalized anxiety disorder, and thus by design are not open to interpretation. The items have rigorous reliability and validity support. Therefore, we view the NSCLC patients’ lower levels of depressive and anxiety symptoms during COVID as accurately reflecting their self-reported psychological status.

It is notable how low the patients’ PHQ/GAD scores during the COVID pandemic were. When designing the study, some expected the symptom scores to be elevated. Quite the contrary, the data characterize the patients as \textit{resilient in the face of COVID}. Resiliency is adapting well in the face of adversity, trauma, tragedy, threats, or significant stress (colloquially, “being tough”).\textsuperscript{13,32} As defined, resiliency combines adversity or risk with positive outcomes, with the “positive outcome” often equated to a person “retaining their mental health and not succumbing to a mental illness.”\textsuperscript{33} Evidence for the NSCLC patients’ resilience includes reports of significantly less stress, less worry about their family contracting the virus, greater success with social distancing, and having no/few psychological symptoms at the time. This does not mean
the NSCLC patients were unfazed by the COVID pandemic, as they had moderate concern about their lung cancer. But, the latter was of similar magnitude to the Controls’ concern about their health. These data contextualize the picture of these cancer patients responding during the pandemic. That is, NSCLC patients had cancer plus high COVID risk and comorbidities (e.g., heart disease, COPD), and the stigma of having a cancer others view as self-imposed.\textsuperscript{34}

Group differences may be also understood by differential salience of COVID. US studies have shown heightened COVID anxiety and fear in the general population.\textsuperscript{35,36} For otherwise healthy Controls without chronic conditions (CCI score of 2) and life routines unchanged, COVID was a salient (i.e., novel, unexpected) stressor. Compared to NSCLC patients, Controls reported significantly more stress, worry, and higher psychological symptoms, with more than twice the percentage of individuals scoring above diagnostic cutoffs for anxiety (13\%) and depression (28\%).\textsuperscript{37} Evidence for differential salience is, perhaps, most obvious in that Controls were as concerned about their health as were individuals with advanced NSCLC. By contrast, COVID for NSCLC patients occurred in the midst of ongoing life threat, comorbidities, symptoms, and routines already disrupted by receiving cancer treatment.

Implications for clinical practice are considered (see Table 3). As data show that symptoms of depression and anxiety are higher at NSCLC diagnosis than thereafter, it is suggested that providers continually consider each patient’s timeline, especially during the COVID pandemic. Providers may recognize resilience and also consider that NSCLC patients continue to require supportive care to achieve survival benefits of new therapies. ASCO-recommended measures for depression and anxiety should be used at diagnosis and thereafter, and patients with positive screens would likely benefit from psychological treatment.
Research design and methodological aspects of the study are considered. This study addresses a gap, not only of psychological studies of NSCLC patients receiving new therapies, but also of cancer patients during the COVID pandemic. With any cross-sectional study of cancer patients, it is relevant to appreciate the selection factor, i.e., the NSCLC patients assessed during COVID were those surviving “long enough” to reach an April 2020 follow-up, irrespective of time since diagnosis. However, the median time since diagnosis in this sample (~1 year) highlights the improving prognosis being achieved with new therapies, a sharp contrast to the 4-month median observed for decades.\textsuperscript{38} Equivalence of geographic region and timing are key factors in choosing control conditions for studies of COVID. In general, it is difficult to obtain online research study volunteers for comparison to individuals who are older, with lower education/income, and with negative health behaviors such as smoking. We were fortunate that the strategy for Control accrual resulted in no statistical differences in several social determinants of health, including marital/partner status, education, and income. Notably, the 2019 US Census poverty rate in Ohio was 13.1%, but 18% of individuals in both study groups live below the US-defined poverty line. Still, broad generalization of the Control findings to similar others who are not research platform users is unknown.

In summary, new data provide perspective for appreciating the COVID experience for cancer patients at greatest risk. Cancer patients may be more resilient to COVID stressors than has been assumed or suggested.\textsuperscript{37} While not immune to the stresses of COVID, data show resilience for otherwise heavily burdened NSCLC patients, ones unable to “shelter in place” but leaving home regularly to receive treatment. Whereas recent data from more than 260,000 cancer survivors show LC patients to experience greater distress, disability, and poorer quality of life than those with other common cancers,\textsuperscript{39} the latter studies do not necessarily capture the whole
story. The present data show that, in the face of multiple health stressors and COVID, NSCLC patients demonstrated resilience.
References
