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Barriers to non-small cell lung cancer trial eligibility

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ABSTRACT

Introduction: Cancer clinical trial (CCT) enrollment is low potentially threatening the generalizability of trial results and expedited regulatory approvals. We assessed whether type of initial patient appointment for non-small cell lung cancer (NSCLC) is associated with CCT eligibility.

Methods: Using a patient-to-accrual framework, we conducted a quasi-retrospective cohort pilot study at Sidney Kimmel Comprehensive Cancer Center (SKCCC), Baltimore, Maryland. 153 NSCLC patients new to SKCCC were categorized based on type of initial appointment: patients diagnosed or treated and patients seen for a consultation. CCT eligibility was determined by comparing eligibility criteria for each open trial to the electronic medical record (EMR) of each patient at every office visit occurring within 6-months of initial visit.

Results: We found no association between type of initial appointment and CCT eligibility (OR, 1.15; 95% CI, 0.49–2.73). Analyses did suggest current smokers were less likely to be eligible for trials compared to never smokers (OR, 0.15; 95% CI, 0.03–0.64), and stage 4 patients with second line therapy or greater were more likely to be eligible than stage 1 or 2 patients (OR, 5.18; 95% CI, 1.08–24.75). Additional analyses suggested most current smokers and stage 1 or 2 patients had trials available but were still ineligible.

Conclusions: SKCCC has a diverse portfolio of trials available for NSCLC patients and should consider research strategies to re-examine eligibility criteria for future trials to ensure increased enrollment of current smokers and stage 1 or 2 patients. We could not confirm whether type of initial visit was related to eligibility.

1. Introduction

Cancer clinical trial (CCT) enrollment has been low for decades and is a central issue in oncology because the profile of trial participants does not match the diversity found in treatment populations. CCTs differentially exclude minorities, female, and older patients threatening the generalizability of trial results and expedited regulatory approvals [1,2].

Patient-, physician-, and protocol-centered factors are known to affect CCT enrollment [3]. A patient's willingness to enroll may depend on travel distance, treatment options, internet access, income, trust, and patient preferences [4–10]. Known physician-centered factors include incompatibility of protocols with normal practice, lack of compliance with protocols, consent procedures, discussion of trials, timing of trial information presentation, and time constraints [9,11,12]. Protocol-centered factors include limited trial availability and potentially overly restrictive eligibility criteria (e.g., prior cancer in early-stage or stage 4 lung cancer patients) [2,3,13–15].

Previous interventions to remove barriers to CCT enrollment have focused on physician- and patient-centered factors, like trial education and navigation systems [16–18]. In practice, intervention benefits have been limited suggesting protocol-centered or more comprehensive interventions should be considered [16–21]. For example, Ohio State University Comprehensive Cancer Center (OSUCCC) increased CCT enrollment 40% within two years by increasing oversight of the CCT process; educating stakeholders (e.g., patients, physicians, staff, leadership, etc.); ensuring CCTs are available irrespective of cancer type and stage of disease; and improving trial enrollment operations and infrastructure [20].

Building on the OSUCCC campaign, patient-to-accrual frameworks that address patient-, physician-, and protocol-centered factors have the potential to identify barriers and increase enrollment through subsequent interventions [20,22]. According to one established framework, there are seven steps to enrollment [1]: trials must be available for a patient's cancer type, stage, and line of therapy [2], patient must be eligible for the trial(s) [3], physician must not triage the patient [4], physician must discuss the trial with the patient [5], patient must be interested [6], patient must sign a consent form, and [7] patient must

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pass the final screen and enroll in the trial. Each step is conditional on the previous step [22]. Therefore trial availability and eligibility are upstream steps and potential barriers to enrollment that would require institution- or protocol-specific interventions.

Lung cancer is the number one cause of cancer-related death in the U.S. making it a research priority across the country, and, like other CCTs, enrollment is low [1,23]. Given that National Cancer Institute (NCI) sponsored CCTs are listed online to help cancer patients determine their eligibility prior to seeking care, our primary goal was to assess whether type of initial appointment was related to CCT eligibility among a sample of non-small cell lung cancer (NSCLC) patients seen at Sidney Kimmel Comprehensive Cancer Center (SKCCC) [24,25]. We hypothesized consult patients would have higher odds of eligibility compared to patients seen for a diagnosis or treatment because savvy patients may self-navigate to trials they believe they are eligible for [26]. Secondary goals included assessing whether type of initial appointment or other factors were related to trial availability or eligibility conditional upon an available trial.

2. Materials and methods

2.1. Study design

A quasi-retrospective cohort design was used to investigate whether the type of initial appointment was related to trial eligibility at SKCCC. We examined each patient's electronic medical record (EMR) longitudinally for six months to determine trial availability and eligibility for each trial at every appointment. The date that eligibility screenings occurred in clinic was not recorded due to an assumption that each appointment was an opportunity to screen patients for eligibility.

The Johns Hopkins School of Medicine Institutional Review Board approved this study.

2.2. Study population

NSCLC patients seen for their first appointment at a Baltimore-area NCI comprehensive cancer center from July 2012 through January 2013 were identified in the EMR as new patients (n = 153). Each patient was followed in the EMR until they became eligible for a trial or they were administratively censored 6 months after their initial visit.

2.3. Independent variables

The independent variable was type of initial appointment, which was dichotomized: those seeking diagnosis or treatment at the initial appointment and those seeking a consult but no diagnosis or treatment at the initial appointment. The Johns Hopkins Hospital cancer registry categorized each study patient.

Administrative staff at SKCCC recorded patients' smoking status (never, former, or current) and demographic data before the patients' initial visit. Patient demographics included: age at time of initial visit, sex (male or female), and race (white, black, or other races). It is presumed the patients self-reported their race. Each variable was abstracted from the EMR by one of the investigators (JH).

2.4. Outcomes

The primary outcome was clinical trial eligibility. Eligibility was determined by comparing eligibility criteria for each open trial with the EMR of each patient at each appointment until they were eligible for a trial or 6 months from their initial visit had passed.

Secondary outcomes were trial availability and trial eligibility conditional on trial availability. Both were ascertained using the seven-step framework for CCT enrollment [7]. More specifically, trial availability was determined by crosschecking each patient's NSCLC stage-and-line of therapy with a list of available trials at each appointment.

Table 1
Baseline characteristics of NSCLC patients new to SKCCC.

Characteristic	Diagnosis or treatment (n = 67)	Consult only (n = 86)	Total (n = 153)	P value
Age, y	26 (38.8)	30 (34.9)	56 (36.6)	0.48
< 60	21 (31.3)	35 (40.7)	56 (36.6)	
60–69	20 (29.9)	21 (24.4)	41 (26.8)	
> = 70				
Sex, %	32 (47.8)	44 (51.2)	76 (49.7)	0.68
Male	35 (52.2)	42 (48.9)	77 (50.3)	
Female				
Race	46 (68.7)	63 (73.3)	109 (71.2)	0.13
White	16 (23.9)	11 (12.8)	27 (17.6)	
Black	5 (7.5)	12 (14.0)	17 (11.1)	
Other				
Smoking status	16 (23.9)	24 (27.9)	40 (26.1)	0.05
Never	33 (49.3)	52 (60.5)	85 (55.6)	
Former	18 (26.9)	10 (11.6)	28 (18.3)	
Current				
Stage and line of	11 (16.4)	4 (4.7)	15 (9.8)	< 0.001
treatment	16 (23.9)	11 (12.8)	27 (17.6)	
Stage 1 or 2	30 (44.8)	25 (29.1)	55 (35.9)	
Stage 3	10 (14.9)	46 (53.5)	56 (36.6)	
Stage 4: first line therapy				
Stage 4: second line therapy or greater				
Eligibility	41 (61.2)	36 (41.9)	77 (50.3)	0.18
Ineligible	26 (38.8)	50 (58.1)	76 (49.7)	
Eligible				

Lists of available trials were provided for two time points (June 2012 and June 2013). Only patients with available trials were examined further for trial eligibility per the same abstraction protocol as the primary outcome.

2.5. Statistical analysis

One NSCLC patient new to SKCCC had missing demographic values and was dropped from the data set after substantial efforts to locate the missing values were unsuccessful. Dropping one patient was not expected to influence the results. One hundred fifty-three NSCLC patients were included in the analyses.

Before testing our primary hypothesis, we identified covariates and potential confounders. The literature suggested age, sex, and race were related to enrollment but was less conclusive regarding smoking status and cancer stage-and-line of therapy [1]. Thus smoking status and stage-and-line of therapy were considered two potential confounders. Chi-square analyses were conducted to help identify relationships between these variables and our main exposure, appointment type, and our primary outcome, eligibility (Tables 1 and 2, respectively).

To test our primary hypothesis we created a multiple logistic regression model using the backwards selection method. Three separate models derived from the backwards selection were also compared using Akaike information criterion (AIC). The final model included the independent variable and all covariates and confounders: type of initial appointment, age, sex, race, smoking status, and cancer stage-and-line of therapy. A scatterplot of residuals versus fitted values was used to check model fit. Given that SKCCC has a smaller catchment area for African Americans, we also evaluated whether race modified the association between appointment type and eligibility using a likelihood ratio test [4].

To further examine the upstream steps or barriers to enrollment, we tested the relationships between type of initial appointment and trial availability and eligibility conditional on trial availability using chi-square analyses. Associations between significant confounders and secondary outcomes were also analyzed by chi-square analyses.

Table 2
Baseline characteristics of NSCLC patients new to SKCCC.

Characteristic	Ineligible for trials (n = 77)	Eligible for trials (n = 76)	Total (n = 153)	P value
Age, y	25 (32.5)	31 (40.8)	56 (36.6)	0.40
< 60	28 (36.4)	28 (36.8)	56 (36.6)	
60–69	24 (31.2)	17 (22.4)	41 (26.8)	
> = 70				
Sex, %	43 (55.8)	33 (43.4)	76 (49.7)	0.12
Male	34 (44.2)	43 (56.6)	77 (50.3)	
Female				
Race	50 (64.9)	59 (77.6)	109 (71.2)	0.15
White	18 (23.4)	9 (11.8)	27 (17.6)	
Black	9 (11.7)	8 (10.5)	17 (11.1)	
Other				
Smoking status	17 (22.1)	23 (30.3)	40 (26.1)	< 0.0001
Never	36 (46.8)	49 (64.5)	85 (55.6)	
Former	24 (31.2)	4 (5.3)	28 (18.3)	
Current				
Stage and line of treatment	12 (15.6)	3 (4.0)	15 (9.8)	< 0.0001
Stage 1 or 2	24 (31.2)	3 (4.0)	27 (17.6)	
Stage 3	23 (29.9)	32 (42.1)	55 (35.9)	
Stage 4: first line therapy	18 (23.4)	38 (50.0)	56 (36.6)	
Stage 4: second line therapy or greater				
Type of initial appointment	41 (53.3)	26 (34.2)	67 (43.8)	0.02
Diagnosis or treatment	36 (46.8)	50 (65.8)	86 (56.2)	
Consult only				

Stata software, version 13 (http://www.stata.com) was used for all statistical analyses.

3. Results

3.1. Study participants and baseline characteristics

There were 834 oncology patients screened for inclusion into our study. 681 of which were excluded because they did not have NSCLC, had an appointment prior to our study start date, or were missing demographic data. The primary analysis was conducted on 153 NSCLC patients new to the SKCCC with an average age of 64.0 years (SD, 10.3 years).

Of the 153 patients, 67 (43.8%) were diagnosed or scheduled for treatment at their first visit and 86 (56.2%) were not diagnosed or scheduled for treatment at their first visit because they were at the clinic for a consult only. Patients categorized by type of initial appointment differed significantly by smoking status and cancer stage-and-line of therapy ($p = 0.05$ and $p < 0.001$, respectively) (Table 1).

3.2. Covariates and potential confounders

Previous studies have found that age, sex, and race are related to patient comorbidities and clinical trial enrollment [9]. Therefore we adjusted for these covariates in our examination of the hypothesis. According to the chi-square analyses, smoking status and stage-and-line of therapy were related to the independent variable and the primary outcome supporting the notion they confound the relationship between initial appointment type and eligibility (Tables 1 and 2). Further investigation of these relationships were carried out in the model-building portion of our analysis.

3.3. Logistic regression

Multiple logistic regression was used to assess the relationship between type of initial appointment and eligibility, and the final model was built using the backwards selection method. The final logistic regression model examined eligibility as function of type of initial appointment, age, sex, race, smoking status, and stage-and-line of therapy and suggested both smoking status and stage-and-line of therapy were confounders.

Three models were derived from the backwards selection. The full model contained six variables; another contained all variables except for smoking status; and the last model contained all variables except for stage-and-line of therapy. The AIC results confirmed that the full model contained the least variation attributed to error and was the best overall fit.

3.4. Types of initial appointment and eligibility

After adjusting for the covariates and confounders, there was no statistically significant relationship between type of initial appointment and trial eligibility (Odds Ratio [OR], 1.32; 95% Confidence Interval [CI], 0.57–3.07) (Table 3).

While race may be an important modifier of the association between appointment type and eligibility, the likelihood ratio test comparing the null versus extended model did not suggest it influenced the relationship ($p = 0.63$).

3.5. Other variables and eligibility

Despite failing to reject the null hypothesis, we discovered other potentially important associations that merit attention. Current smokers, for instance, appear to be far less likely to be eligible for trials than never smokers after adjustment (OR, 0.15; 95% CI, 0.03–0.64) (Table 3). Stage 4 NSCLC patients receiving 1st line therapy appear 4.43 times more likely than stage 1 or 2 patients to be eligible for trials (OR, 4.43; 95% CI, 0.99 to 19.94). Stage 4 patients receiving 2nd line therapy or greater were 5.18 times more likely than stage 1 or 2 patients to be eligible for trials (OR, 5.18; 95% CI, 1.08 to 24.75).

Table 3
Results of multiple logistic regression analyses: Eligibility for NSCLC clinical trials.

Covariates	OR (95% CI)	P value
Age, y	ref	ref
< 60	0.66 (0.26–1.63)	0.36
60–69	0.56 (0.20–1.51)	0.25
> = 70		
Sex, %	ref	ref
Male	1.44 (0.63–3.32)	0.39
Female		
Race	ref	ref
White	0.67 (0.22–2.06)	0.49
Black	0.48 (0.13–1.79)	0.27
Other		
Smoking status	ref	ref
Never	0.85 (0.29–2.48)	0.77
Former	0.15 (0.03–0.64)	0.01
Current		
Stage and line of treatment	ref	ref
Stage 1 or 2	0.36 (0.06–2.30)	0.28
Stage 3	4.43 (0.99–19.94)	0.05
Stage 4: first line therapy	5.18 (1.08–24.75)	0.04
Stage 4: second line therapy or greater		
Type of initial appointment	ref	ref
Diagnosis or treatment	1.32 (0.57–3.07)	0.51
Consult only		

Wald Test: Age ($p = 0.47$), Race ($p = 0.44$), Smoking status ($p = 0.02$), and Stage-and-line of treatment ($p < 0.0001$).

Table 4
Additional analyses of NSCLC patients using patient-to-Accrual framework.

Characteristic	Not available (n = 13)	Available (n = 140)	P value	Available but not eligible (n = 64)	Available and eligible (n = 76)	P value
Smoking status	0 (0.0)	40 (28.6)	0.08	17 (26.6)	23 (30.3)	< 0.0001
Never	10 (76.9)	75 (53.6)		26 (40.6)	49 (64.5)	
Former	3 (23.1)	25 (17.9)		21 (32.8)	4 (5.3)	
Current						
Stage and line of treatment	0 (0.0)	15 (10.7)	< 0.0001	12 (18.8)	3 (4.0)	< 0.0001
Stage 1 or 2	12 (92.3)	15 (10.7)		12 (18.8)	3 (4.0)	
Stage 3	1 (7.7)	54 (38.6)		22 (34.4)	32 (42.1)	
Stage 4: First line therapy	0 (0.0)	56 (40.0)		18 (28.1)	38 (50.0)	
Stage 4: Second line therapy or greater						
Type of initial appointment	10 (76.9)	57 (40.7)	0.012	31 (48.4)	26 (34.2)	0.09
Diagnosis or treatment	3 (23.1)	83 (59.3)		33 (51.6)	50 (65.8)	
Consult only						

3.6. Upstream associations examined further

To this point, we have focused on trial eligibility. In the following analyses, we examined the relationship between our independent variables and trial availability and the relationship between independent variables and trial eligibility conditional on trial availability [7]. Relationships between the variables, smoking status and stage-and-line of therapy, and the secondary outcomes were also assessed. The main purpose for conducting these analyses was to better understand the upstream effects preventing certain patients from moving past the eligibility phase of the enrollment process.

Our study population contained 28 current smokers. Of these, 25 (89%) had an available trial. Only 4 (16%) with an available trial were eligible for a CCT (Table 4). Out of the 15 stage 1 or 2 patients, 15 (100%) had an available trial, but only 3 (20%) with an available trial were eligible for a trial.

The chi-square analyses suggested unadjusted relationships between the variables, stage-and-line of therapy and type of initial appointment, and trial availability ($p < 0.0001$ and $p = 0.01$, respectively). It also suggested significant unadjusted relationships between the variables, smoking status and stage-and-line of therapy, and eligibility ($p < 0.0001$ and $p < 0.0001$, respectively).

4. Discussion

We found no evidence of an association between type of initial appointment and eligibility for NSCLC clinical trials after adjustment. However we did find the odds of eligibility were 85% lower for current smokers compared to never smokers, and the odds of eligibility were 343% greater for patients with stage 4–1st line therapy and 418% greater for patients with stage 4–2nd line therapy or greater compared to stage 1 or 2 patients.

Upstream steps to trial enrollment, like eligibility, have the potential to limit the overall number of patients and to protect research subjects from unnecessary harm. The key is maintaining an ethical balance that translates to generalizable and safe NSCLC research [2,22]. In addition, Beaver et al., 2017 correctly states, “the Food and Drug Administration (FDA) regulations state that a ‘protocol is required to contain … the criteria for patient selection and for exclusion of patients’ but do not contain detailed language regarding clinical trial eligibility criteria. Regulatory approval, however, must be predicated on data pertinent to the enrolled patients and relevant to the U.S. population and U.S. medical practice.” Ethically conducted interventions based on eligibility criteria have the potential to increase CCT enrollment, address generalizability issues, and safely expedite FDA approval of prescribing information [2]. It is therefore important to carefully describe the ineligible CCT populations; investigate the reason(s) they are not eligible; conduct studies to determine whether the criteria can be eased in future clinical trials without harming participants; and disseminate the results to principal investigators and Institutional Review Boards [2,13,14].

In this particular pilot study, current smokers and stage 1 or 2 patients had trials available but were disproportionately ineligible for trials. Current smokers may have been disproportionately ineligible due to poorer performance status, more severe comorbidities, previous therapies, recent NSCLC diagnosis, or a number of other trial-specific reasons. Stage 1 or 2 patients were likely disproportionately ineligible due to past medical history (i.e., previous case of cancer), previous treatment, or tumor size-based inclusion criteria. A more thorough investigation at SKCCC is needed, but it is possible that criteria, such as prior cases of cancer, may be unnecessarily restricting clinical trial enrollment at SKCCC. For instance, previous studies have found that patients with prior cases of cancer represent a sizeable proportion of cancer patients yet prior cases of cancer do not increase risks for clinical trial participants. Therefore we believe that future studies should aim to: prospectively identify criteria causing current smokers and stage 1 or 2 to be excluded at the eligibility step of enrollment; identify potentially modifiable eligibility criteria; test whether it is safe to modify the criteria; and monitor future enrollment after implementation of the modified criteria [2,13,14].

To our knowledge, this is the only study that has examined the relationship between type of initial appointment and NSCLC-specific trial eligibility. All variables were abstracted twice to verify accuracy. The primary outcome was abstracted by crosschecking all verifiable eligibility criteria for each open trial to each patient's EMR. The outcome abstraction was repeated at every office visit during the study period to more accurately reflect the enrollment process and avoid visit-related biases.

We acknowledge several important limitations. This was a pilot study with a small sample size, which increased the probability of finding significant associations by chance alone. The chart review was conducted at a single comprehensive cancer center limiting the external validity. For practical reasons, the study was retrospective preventing us from controlling the study conditions. The list of available trials may not have been comprehensive because it was not possible to know exactly when new trials were added and old trials removed. Finally, residual confounding cannot be ruled out because variables, such as distance to SKCCC and phase of clinical trials, were not abstracted.

5. Conclusions

The SKCCC has a diverse portfolio of trials available for NSCLC patients but should consider using research strategies to re-examine eligibility criteria for future trials to ensure more inclusive enrollment of current smokers and stage 1 or 2 patients. Future research should prospectively identify criteria causing current smokers and stage 1 or 2

to be excluded at the eligibility step of enrollment; identify potentially modifiable eligibility criteria; test whether it is safe to modify the criteria; and monitor future enrollment after implementation of the modified criteria.

6. Conflicts of interest and source of funding

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Disclaimers

The views expressed in the article are those of the authors only and are not an official position of the institutions or funders.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.conctc.2017.11.010.

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