

Are clinical trial eligibility criteria an accurate reflection of a real-world population of advanced non-small-cell lung cancer patients?

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ABSTRACT

Background Advanced non-small-cell lung cancer (NSCLC) represents a major health issue globally. Systemic treatment decisions are informed by clinical trials, which, over years, have improved the survival of patients with advanced NSCLC. The applicability of clinical trial results to the broad lung cancer population is unclear because strict eligibility criteria in trials generally select for optimal patients.

Methods We performed a retrospective chart review of all consecutive patients with advanced NSCLC seen in outpatient consultation at our academic institution between September 2009 and September 2012, collecting data about patient demographics and cancer characteristics, treatment, and survival from hospital and pharmacy records. Two sets of arbitrary trial eligibility criteria were applied to the cohort. Scenario A stipulated Eastern Cooperative Oncology Group performance status (ECOG PS) 0–1, no brain metastasis, creatinine less than 120 µmol/L, and no second malignancy. Less-strict scenario B stipulated ECOG PS 0–2 and creatinine less than 120 µmol/L. We then used the two scenarios to analyze treatment and survival of patients by trial eligibility status.

Results The 528 included patients had a median age of 67 years, with 55% being men and 58% having adenocarcinoma. Of those 528 patients, 291 received at least 1 line of palliative systemic therapy. Using the scenario A eligibility criteria, 73% were trial-ineligible. However, 46% of “ineligible” patients actually received therapy and experienced survival similar to that of the “eligible” treated patients (10.2 months vs. 11.6 months, $p = 0.10$). Using the scenario B criteria, only 35% were ineligible, but again, the survival of treated patients was similar in the ineligible and eligible groups (10.1 months vs. 10.9 months, $p = 0.57$).

Conclusions Current trial eligibility criteria are often strict and limit the enrolment of patients in clinical trials. Our results suggest that, depending on the chosen drug, its toxicities and tolerability, eligibility criteria could be carefully reviewed and relaxed.

Key Words Non-small-cell lung cancer, NSCLC, clinical trial eligibility

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INTRODUCTION

Lung cancer is the most common cancer in the world and the leading cause of cancer death worldwide^{1,2}. Although 5-year survival in lung cancer has slowly improved to approximately 18% in 2011 from 12% in the 1970s¹, the disease remains lethal for most^{1,3}.

Clinical trials have undoubtedly improved the outcomes of NSCLC treatment in both early- and late-stage

disease^{4–11}. However, fewer than 5% of all cancer patients participate in clinical trials^{5,12–14}. Lung cancer patients represent only about 12.5% of all cancer clinical trial participants¹⁴, being 3rd in participation after breast and colorectal cancer patients, which demonstrates a true underrepresentation of lung cancer despite its remarkable epidemiology and lethality^{15,16}.

One important obstacle to participation is the high selectivity of lung cancer clinical trials, which often have

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very restrictive eligibility criteria^{17–19}. In fact, studies show that eligibility for a trial might require meeting as many as 44 criteria^{19–21}. Restrictive eligibility not only constitutes a barrier to clinical trial enrolment, but also creates other problems, including difficulty in generalizing results to the broader patient population^{22–28}.

In the present study, we took an existing dataset of patients with advanced NSCLC that had previously been reported²⁹. We then used hypothetical clinical trial eligibility criteria to explore how many patients might be trial-eligible. We further assessed how outcomes varied between patient groups based on their trial eligibility and treatments actually received.

METHODS

Patient Data

After ethics approval, we performed a chart review of all patients with *de novo* advanced NSCLC (stage IIIB palliative and all stage IV) seen in the outpatient department at The Ottawa Hospital Cancer Centre between September 2009 and September 2012. The Ottawa Hospital Cancer Centre is an academic centre that is the sole provider of medical and radiation oncology services to a population of approximately 1.5 million in Eastern Ontario.

Data collected from hospital and pharmacy records included patient demographics, cancer characteristics, treatment details, and survival information. The primary analysis has previously been reported²⁹.

Clinical Trial Criteria

We designed two clinical trial eligibility scenarios and then assessed how many patients in the cohort would have been “trial eligible” based on the inclusion criteria in each scenario. Subsequently, for each scenario, we compared the trial-eligible and -ineligible patients, the proportion of each group that received systemic therapy, and survival in the two groups.

Scenario A had more-strict eligibility criteria. Patients had to have an Eastern Cooperative Oncology Group performance status (PS) of 0 or 1, absence of brain metastasis, creatinine less than 120 µmol/L (approximately 1.5 times the upper limit normal), and absence of a second malignancy.

Scenario B had less-strict eligibility criteria: Eastern Cooperative Oncology Group PS 0–2 and creatinine less than 120 µmol/L. If data relating to the eligibility criteria were missing, the patient was excluded from the analysis. Eastern Cooperative Oncology Group PS was missing for 8% of patients, and baseline creatinine, for 2%.

Statistical Methods

For this retrospective analysis, the chi-square test was applied. The survival analysis used the Kaplan–Meier method. All analyses were conducted using the SAS software application (version 9.3: SAS Institute, Cary, NC, U.S.A.).

RESULTS

The full descriptive analysis for this cohort of patients was reported in a previous publication²⁹. In brief, 528 patients were included in the study (Table 1). Median age in the

cohort was 67.5 years; 55% of all patients were men; 43% were current smokers.

Of all NSCLCs, 58% were adenocarcinomas; only 22% were squamous cell carcinomas. Patients with stage IV disease represented 93% of the population; the remaining

TABLE 1 Demographic data for the study cohort

Variable	Value
Patients (n)	528
Age at diagnosis (years)	
Median	67.5
Range	34.9–89.7
Sex [n (%)]	
Men	292 (55)
Women	236 (45)
ECOG PS [n (%)]	
0	46 (9)
1	220 (42)
2	111 (21)
3	92 (17)
4	19 (4)
Unknown	40 (8)
Smoking status [n (%)]	
Current smoker	228 (43)
Ex-smoker	257 (49)
Never-smoker	37 (7)
Unknown	6 (1)
Weight loss [n (%)]	
<5%	235 (45)
>5%	255 (48)
Unknown	38 (7)
Histologic subtype [n (%)]	
Adenocarcinoma	308 (58)
Large-cell	27 (5)
Mixed	1 (0.2)
Other NSCLC	29 (6)
Squamous cell	118 (22)
Unknown	45 (9)
Stage [n (%)]	
IIIB	35 (7)
IV	493 (93)
Reason for no CTx (if stated) [n (%)]	
Poor performance status	158 (67)
Age	3 (1)
Comorbidities	5 (2)
Patient choice	49 (23)
Others	22 (9)

ECOG PS = Eastern Cooperative Oncology Group performance status; NSCLC = non-small-cell lung cancer; CTx = chemotherapy.

7% had stage IIIb disease and were treated with palliative intent. Half the patients had a PS of 0 or 1.

Nearly half the patients ($n = 237$, 45%) did not receive any systemic therapy. Treated patients were younger (median age: 64.8 years vs. 71 years for untreated patients, $p < 0.0001$). A platinum doublet was the most common first-line therapy (88%); pemetrexed–docetaxel was the most common therapy in the second-line setting.

Only 5% of the patients participated in a clinical trial for any given line of therapy. In 89 patients (17%), a second malignancy had been diagnosed. In about 40 patients, creatinine was elevated above 120 $\mu\text{mol/L}$, and 16 of them were still treated with chemotherapy.

Survival Analysis

Scenario A

Table II presents the patient demographic data for scenario A by trial eligibility. Using scenario A (strict criteria), only 27% of the patients ($n = 144$) would have been trial-eligible. Of those 144 patients, 113 (78%) were treated with at least 1 line of systemic therapy. Of the 384 patients

(73%) who were not eligible, 178 (46%) were still treated with systemic therapy (Table III).

The patients who were treated experienced similar median overall survival (OS) regardless of whether they were trial-eligible or -ineligible (11.6 months vs. 10.2 months, $p = 0.1$). However, compared with ineligible untreated patients, the eligible untreated patients experienced significantly superior survival (8.1 vs. 3.8 months, $p = 0.003$, Table IV, Figure 1).

Scenario B

Table V presents the patient demographic data for scenario B by trial eligibility. Using scenario B (relaxed criteria), more than half the patients (65%, $n = 343$) would have been trial-eligible. Of those 343 patients, 240 (70%) were treated (Table III). Of the 185 patients (35%) who were not eligible, only 51 (28%) were still treated (Table III).

As in scenario A, survival for the patients who received systemic therapy was similar whether they were trial-eligible or -ineligible (10.9 months vs. 10.1 months, $p = 0.57$). However, compared with ineligible untreated patients, the eligible untreated patients experienced significantly better

TABLE II Demographic data, scenario A

Variable	Patient group			
	Trial eligible		Trial ineligible	
	Treated	Untreated	Treated	Untreated
Patients (n)	113	31	178	206
Age (years)				
Mean	64.6 \pm 9.7	71.2 \pm 11.3	64.4 \pm 8.5	70.8 \pm 9.8
Median	64.8	71.1	64.7	70.9
Range	34.9–83.8	43.6–87.5	43.0–86.7	46.2–89.7
Sex [n (%)]				
Men	61 (54)	19 (61)	99 (55.62)	113 (54.85)
Women	52 (46)	12 (39)	79 (44.38)	93 (45.15)
Weight loss >5% [n (%)]	45 (40.9)	16 (53.33)	75 (46.01)	119 (63.64)
Histology [n (%)]				
Adenocarcinoma	77 (71.96)	18 (58.06)	106 (66.25)	107 (57.84)
Squamous cell	20 (18.69)	12 (38.71)	35 (21.88)	51 (27.57)
Large-cell	6 (5.61)	0	11 (6.88)	10 (5.41)
Other NSCLC	4 (3.74)	1 (3.23)	8 (5.0)	16 (8.64)
Mixed	0	0	0	1 (0.54)
ECOG PS [n (%)]				
0	18	5	18 (11.54)	5 (2.66)
1	95	26	70 (44.87)	29 (15.43)
2	0	0	54 (34.62)	57 (30.32)
3	0	0	13 (8.33)	79 (42.02)
4	0	0	1 (0.64)	18 (9.57)
Stage [n (%)]				
IIIB	10 (8.85)	5 (16.13)	3 (1.69)	17 (8.25)
IV	103 (91.15)	26 (83.87)	175 (98.31)	189 (91.75)

NSCLC = non-small-cell lung cancer; ECOG PS = Eastern Cooperative Oncology Group performance status.

survival (4.9 months vs. 3.5 months, $p < 0.001$); however, the difference was less dramatic than in scenario A (Table IV, Figure 2).

Importantly, despite using the relaxed criteria in scenario B, median os was superior in the eligible treated patients compared with the eligible untreated patients (10.9 months vs. 4.9 months, $p < 0.0001$).

Scenario B included patients with brain metastasis ($n = 96$), 60 of whom were treated with systemic therapy, and 36 of whom were not. The survival analysis showed superior os in treated compared with untreated patients with brain metastasis (10.0 months vs. 5.0 months, $p = 0.001$).

Scenario Comparison

Statistically, the median os for ineligible patients treated in scenarios A and B did not differ (10.2 months vs. 10.1 months respectively, $p = 0.83$). A detailed multivariate analysis of the overall cohort was previously published²⁹. That analysis indicated that omission of chemotherapy, poor performance status, and weight loss greater than 5% are associated with poor os.

DISCUSSION

Patients with NSCLC represent about 87% of all patients diagnosed with lung cancer³⁰, and about 40% of that group present with stage IV disease³¹. Our results demonstrate that, whether trial-eligible or not, if patients are considered by their treating physicians to be fit for systemic therapy, they experience similar os. That finding has not been well described before. Using a simple yet logical concept, we were able to identify important clinical findings. Our study shows clearly that even trial-ineligible patients derive clinical benefit from chemotherapy. That observation highlights questions about the usefulness of strict eligibility criteria in clinical trials. Given similar survival in treated patients, whether trial-eligible or not, it could be argued that the physician’s judgment is as effective as

trial eligibility criteria for anticipating benefit from therapy, and therefore trial eligibility criteria could be relaxed.

The stricter of our trial eligibility scenarios (scenario A) had only 4 criteria, but they were enough to exclude 73% of patients. We were limited by the data points collected, but presumably, if more extensive criteria had been applied to the dataset, more and more patients would have been excluded. That 73% is close to what has been reported previously^{32,33}. In fact, a study showed that the average number of trial eligibility criteria was about 23¹⁹, making it even more difficult to find eligible participants to enrol in clinical trials. Surprisingly, two studies showed that half of all exclusion criteria in clinical trials might not be backed by strong clinical evidence^{19,34,35}.

Eligibility criteria are commonly used to achieve more homogenous populations and to minimize the chance that confounding factors will affect trial results. However, some of the exclusions are seemingly unwarranted, and variety in the enrolled patients might not significantly affect results. There is increasing evidence that patients with a ps of 2, although having a poorer prognosis than those with a ps of 0–1, can still derive a significant survival advantage from systemic therapy^{36–38}. In addition, diagnosis of a prior malignancy in advanced lung cancer patients might not be relevant, with one manuscript failing to report worse survival for such patients compared with their counterparts not having a prior diagnosis²². Furthermore, the presence of brain metastasis remains an exclusion criterion in many

TABLE III Proportion of treated ineligible patients in scenarios A and B

Trial eligibility	Scenario A patients [n (%)]		Scenario B patients [n (%)]	
	Total	Treated	Total	Treated
Eligible	144 (27)	113 (78.5)	343 (65)	240 (70)
Ineligible	384 (73)	178 (46)	185 (35)	51 (28)

TABLE IV Overall survival in scenarios A and B, in months

Trial eligibility	Scenario A				Scenario B			
	Treated		Untreated		Treated		Untreated	
	Median	95% CI	Median	95% CI	Median	95% CI	Median	95% CI
Eligible	11.6	10.1 to 15.9	8.1	3.4 to 12.9	10.9	9.9 to 11.8	4.9	3.6 to 6.5
Ineligible	10.2	8.7 to 11.5	3.8	3.2 to 4.2	10.1	6.3 to 13.4	3.5	3.1 to 4.0
	$p = 0.1$		$p = 0.003$		$p = 0.57$		$p < 0.001$	

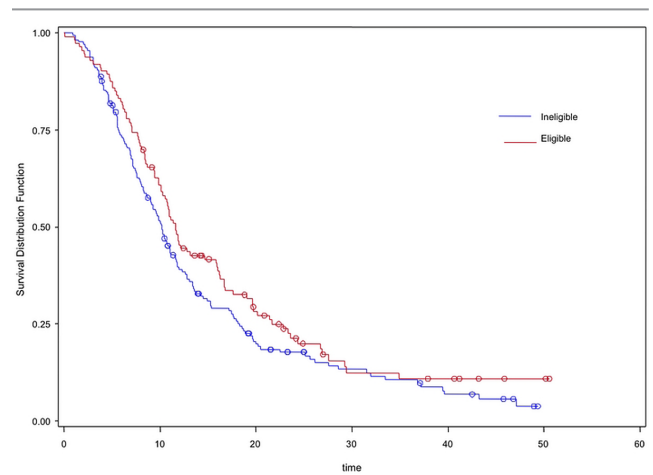


FIGURE 1 Kaplan–Meier survival curves for trial eligibility scenario A, reflecting treated eligible (red) and treated ineligible (blue) patients.

TABLE V Demographic data, scenario B

Variable	Patient group			
	Trial eligible		Trial ineligible	
	Treated	Untreated	Treated	Untreated
Patients (<i>n</i>)	240	103	51	134
Age (years)				
Mean	64.7±8.9	70.4±11.1	63.2±9.1	71.2±9.1
Median	65.0	70.2	62.5	71.8
Range	34.9–86.7	43.6–88.9	45.4–83.5	49.1–89.7
Sex [<i>n</i> (%)]				
Men	129 (53.75)	57 (55.34)	31 (60.78)	75 (55.79)
Women	111 (46.25)	46 (44.66)	20 (39.22)	59 (44.03)
Weight loss >5% [<i>n</i> (%)]	99 (43.23)	52 (53.61)	21 (47.73)	83 (69.17)
Histology [<i>n</i> (%)]				
Adenocarcinoma	152 (69.09)	55 (58.51)	31 (65.96)	70 (57.38)
Squamous cell	46 (20.91)	29 (30.85)	9 (19.15)	34 (27.87)
Large-cell	13 (5.91)	4 (4.26)	4 (8.51)	6 (4.92)
Other NSCLC	9 (4.09)	6 (6.38)	3 (6.38)	11 (9.02)
Mixed	0	0	0	1 (0.82)
ECOG PS [<i>n</i> (%)]				
0	35 (14.58)	9 (8.74)	1 (3.45)	1 (0.86)
1	155 (64.58)	46 (44.66)	10 (34.48)	9 (7.76)
2	50 (20.83)	48 (46.6)	4 (13.79)	9 (7.76)
3	0	0	13 (44.83)	79 (68.1)
4	0	0	1 (3.45)	18 (15.52)
Stage [<i>n</i> (%)]				
IIIB	13 (5.42)	9 (8.74)	0	13 (9.7)
IV	227 (94.58)	94 (91.26)	51 (100)	121 (90.3)

NSCLC = non-small-cell lung cancer; ECOG PS = Eastern Cooperative Oncology Group performance status.

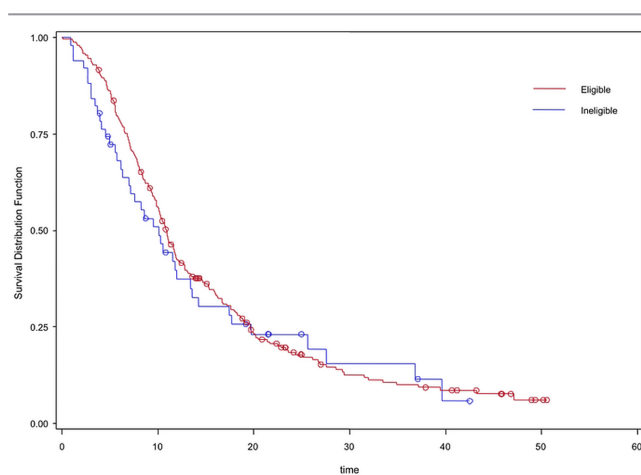


FIGURE 2 Kaplan–Meier survival curves for trial eligibility scenario B, reflecting treated eligible (red) and treated ineligible (blue) patients.

ongoing clinical trials—or in others, at least requires that central nervous system–directed therapy be given³⁹. That

criterion has clinical implications when patients present with asymptomatic millimetric central nervous system disease that might have little immediate clinical relevance, but that would require time-consuming brain radiotherapy (with its associated risks and short-term toxicities)—and a mandated radiation washout period—before the patient could subsequently enrol in a trial.

Although the present manuscript concentrates on the effect of inclusion and exclusion criteria, there are, of course, other major factors that limit clinical trial enrolment. Those factors include patient participation factors (for example, worry about uncertainty), physician participation factors (for example, problems complying with the protocol), and other factors such as the cost of clinical trials, legislation, and public health policies⁴⁰. A comprehensive effort to increase trial enrolment would address all those factors.

The limitations of our study include its single-centre nature and its retrospective design, which meant that the data available for collection were limited to what had been recorded in the patient chart during management. The limited data led to the small number of eligibility criteria

used for the study scenarios, unlike the case of a real clinical trial. Given its retrospective nature, our study could not provide prospective data about quality of life and treatment-related toxicity; however, for this same cohort of patients, we were able to show that scores from the Edmonton Symptom Assessment System were able to predict survival, as published in a separate paper⁴¹. Furthermore, our cohort did not include hospitalized patients, and it largely included patients managed before reflexive molecular profiling for *EGFR* mutations and *ALK* translocations became a standard of care.

In the last century, strong initiatives set out to have what is called “proportionality” in clinical trials. “Proportionality” meant enrolling participants of different races and ages to mirror the general distribution of the cancer patient population^{42,43}. We would argue that ongoing initiatives are needed to further that process by reviewing trial eligibility criteria. Seeking to include patients with poorer performance status, brain metastasis, prior malignancy, or significant organ impairment should help not only to increase trial accrual, but also to make results more applicable to a general lung cancer population. The U.S. Food and Drug Administration, the American Society of Clinical Oncology, and the Friends of Cancer Research have launched an initiative to modernize clinical trial eligibility. The initiative is “designed to identify opportunities where eligibility criteria could be broadened, and ultimately influence investigators and sponsors to adjust these criteria where clinically appropriate”^{44,45}.

CONCLUSIONS

The generalizability of clinical trial results can be questioned because of the high selectivity that results from restrictive eligibility criteria. Our research raises questions about whether simple clinical judgment and limited criteria could be as effective, but lead to improvements in clinical trial access and broad application of the results. We advocate a consideration of relaxed eligibility criteria to better represent the wider lung cancer patient community. Another option is to use the concept of “large simple trials.”

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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