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ORIGINAL SCIENTIFIC REPORT

Impact of Timeliness of Surgical Treatment on the Outcomes of Patients with Non-metastatic Non-small Cell Lung Cancer: Findings From the PLCO Trial

Omar Abdel-Rahman[1,2]

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Abstract

Background This study aimed to assess the impact of timeliness of surgical resection among patients with non-metastatic non-small cell lung cancer (NSCLC) treated with upfront surgery.

Methods Cases with confirmed non-metastatic NSCLC diagnosis treated with upfront surgery within the cohort of participants in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial were included in the current study. Multivariate logistic regression analysis was used to assess factors predicting time from diagnosis to surgical resection. Multivariate Cox regression analysis was used to assess factors affecting lung cancer-specific survival.

Results A total of 1022 patients were included in the current analysis. A total of 873 patients underwent surgical resection within 30 days of diagnosis, while a total of 149 patients underwent surgical resection after 30 days from diagnosis. Through multivariate logistic regression analysis, the following factors were predictive for longer time to surgical resection: older age (odds ratio 1.077; 1.043–1.112; $P < 0.001$) and advanced stage at presentation (odds ratio 1.923; 1.056–3.502; $P = 0.033$). Through multivariate Cox regression analysis, time to surgical resection ($\leq$30 days vs. >30 days) did not affect lung cancer-specific survival (hazard ratio 0.999; 0.739–1.350; $P = 0.994$). When the same multivariate analysis was repeated using time to surgical resection as a continuous variable, there was no impact on lung cancer-specific survival (hazard ratio 1.002; 0.997–1.007; $P = 0.383$).

Conclusions Time to surgical resection did not affect survival outcomes of non-metastatic NSCLC patients. Current therapy timeline targets need to be reviewed in our healthcare systems in order to redirect and prioritize the existing resources.

Introduction

Timeliness of cancer care is considered one of the important benchmarks of cancer care quality as well as patient satisfaction [1]. Numerous healthcare organizations have published target timeliness for both referral of suspicious cases to diagnosis and diagnosis to treatment [2]. It is not clear, however, whether deviation from these recommended timelines would affect oncological outcomes of cancer patients.

Numerous studies have previously examined the impact of timeliness of care on survival outcomes of non-metastatic NSCLC patients. However, the results of many of these studies were conflicting [3–5]. Moreover, most of these studies relied on retrospectively collected institutional databases, a fact which poses questions about the accuracy of timeline reporting in these studies.

Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial is a randomized screening trial that

✉ Omar Abdel-Rahman
omar.abdelsalam@ahs.ca

[1] Department of Oncology, Cross Cancer Institute, University of Alberta, Edmonton Alberta T6G 1Z2, Canada

[2] Clinical Oncology Department, Faculty of Medicine, Ain Shams University, Cairo Egypt

recruited participants between 1993 and 2001. It recruited more than 150,000 participants, and the primary aim of this trial was investigating the impact of cancer screening on cancer-specific mortality of each of the four solid tumors (prostate, lung, colorectal, and ovarian cancers) [6]. This trial was designed and sponsored by the National Cancer Institute (NCI). ClinicalTrials.gov numbers for PLCO trial are NCT01696968, NCT00002540, NCT01696994, and NCT01696981. Primary results of PLCO trial were published elsewhere [7].

The NCI recently launched an initiative to allow interested investigators to access de-identified individual patients' data from this trial. This provided a good opportunity to study the impact of timeliness of care in the context of prospectively collected datasets, thus overcoming potential drawbacks of previously published studies.

The current study could provide important guidance to strained public healthcare systems which struggle to provide good service of the patients in a timely manner. It could as well help prioritize our healthcare resources in a more evidence-based fashion.

Objective

The main objective was to assess the impact of timeliness of surgical resection among patients with non-metastatic NSCLC treated with upfront surgery.

Methods

About the PLCO trial

PLCO trial accepted men and women aged between 55 and 74 years without known cancers of prostate, colon, rectum, lung or ovary and without surgical removal of any of these organs. Participants were equally randomized to a control arm or an intervention arm. Those in the control arm received usual care, while those in the intervention arm received screening exams for prostate, lung, colorectal, and ovarian cancers. Screening for lung cancer was done through annual chest radiograph for 4 years.

Selection criteria of the current study cohort

Within the PLCO trial dataset, all patients with the following criteria were selected for inclusion into the current study: (1) patients with histologically confirmed diagnosis of NSCLC; (2) no evidence of distant metastases; (3) patients were treated with upfront surgical resection without neoadjuvant treatment.

Data extraction

The following data were extracted from each patient's record (where available): age at lung cancer diagnosis, body mass index, sex, PLCO study arm, race, cigarette smoking history, comorbidities (including: diabetes mellitus, hypertension, heart attack, stroke and emphysema), social characteristics (including educational level, marital status and occupation), clinical stage of lung cancer, histological subtype, time from diagnosis to surgical resection, and type of surgical resection. Time from pathological diagnosis to surgical resection was reported both as a continuous variable and as a categorical variable ($\leq$30 days vs. >30 days). The cutoff of 30 days was chosen because it is commonly used by some healthcare organizations in the Western world [8]. The primary endpoint of the current study is lung cancer-specific survival. It has to be noted that the available PLCO datasets from the NCI platform contain follow-up data collected up to December 2009. Details about clinical staging (including type of imaging, preoperative biopsy as well as indications for invasive mediastinal staging) were not available in the study dataset. Pathological staging was missing for some patients; thus, it was not included into the statistical analyses.

Statistical analysis

Chi-squared testing was used to compare categorical variables between patients who underwent surgery before and after 30 days of diagnosis. Independent t test was used to compare the means of continuous variables between both groups.

A multivariate logistic regression model was used to examine the factors predicting earlier versus delayed surgical resection. This model was adjusted for age at lung cancer diagnosis, race, PLCO study arm, sex, and clinical stage. Multivariate Cox regression analysis was then used to evaluate factors affecting lung cancer-specific survival. This multivariate analysis included: age at lung cancer diagnosis, race, PLCO study arm, sex, cigarette smoking history, clinical stage and time from diagnosis till surgery. Variables were selected for inclusion in both models based on the presence of clinical rationale for impacting either time from diagnosis to surgery or lung cancer-specific survival. Adjuvant therapy was not included in the multivariate Cox regression model because technical details about the adjuvant treatments (e.g., agents/number of cycles) were not available in the study datasets. SPSS statistics (version 20; IBM, NY) was used to perform the above statistical analyses.

Results

Patients' characteristics

A total of 1022 patients with confirmed NSCLC diagnosis and upfront resection were included in the current analysis. Mean time from diagnosis to surgery is 12.03 days (standard deviation: 21.13). A total of 873 patients underwent surgical resection within 30 days, while a total of 149 patients underwent surgical resection after 30 days. Mean time from diagnosis to surgery in the group having surgical resection within 30 days was 4.95 (SD: 8.93), while median time from diagnosis to surgery in the group having surgical resection after 30 days was 53.46 (SD: 24.24). Compared to patients who underwent surgical resection after 30 days of diagnosis, patients who underwent surgical resection within 30 days were more likely to be diagnosed through screening ($P = 0.002$) and have younger age ($P < 0.001$), less hypertension ($P = 0.023$), and less advanced clinical stage ($P = 0.002$). There was no difference between both groups with regard to body mass index ($P = 0.681$), sex ($P = 0.144$), race ($P = 0.224$), PLCO study arm ($P = 0.209$), cigarette smoking ($P = 0.078$), diabetes ($P = 0.862$), heart attack ($P = 0.098$), stroke ($P = 0.110$), emphysema ($P = 0.605$), education ($P = 0.882$), marital status ($P = 0.210$), occupation ($P = 0.151$), type of surgery ($P = 0.243$), adjuvant chemotherapy ($P = 0.439$), or adjuvant radiotherapy ($P = 0.959$) (Table 1).

Predictors of delayed surgical resection

Through multivariate logistic regression analysis, the following factors were predictive for longer time to surgical resection: older age (odds ratio 1.077; 1.043–1.112; $P < 0.001$) and advanced stage at presentation (odds ratio 1.923; 1.056–3.502; $P = 0.033$) (Table 2).

Survival outcomes according to time from diagnosis until surgical resection

Through multivariate Cox regression analysis, time to surgical resection (≤30 days vs. >30 days) did not affect lung cancer-specific survival (hazard ratio 0.999; 0.739–1.350; $P = 0.994$) (Table 3). When the same multivariate analysis was repeated using time to surgical resection as a continuous variable, there was no impact on lung cancer-specific survival (hazard ratio 1.002; 0.997–1.007; $P = 0.383$).

Impact of time to surgical resection was further analyzed separately among patients with clinical stage I, II, or III. This was done through multivariate analysis adjusted for age at lung cancer diagnosis, race, PLCO study arm, sex, and cigarette smoking history. Within each of the three clinical stages of lung cancer, time to surgical resection did not seem to affect lung cancer-specific survival (stage I: $P = 0.804$; stage II: $P = 0.655$; stage III: $P = 0.608$) (Table 4).

Impact of time to surgical resection was also analyzed separately among patients with squamous versus non-squamous histology. This was done through univariate Cox regression analysis. Within both histological categories, time to surgical resection did not predict overall survival (hazard ratio for death for time ≤30 days versus time >30 days for squamous histology 0.988; 95% CI: 0.575–1.697; $P = 0.965$; and for non-squamous histology 1.045; 95% CI: 0.701–1.570; $P = 0.828$).

Discussion

The current study evaluates the impact of timeliness of surgical resection on the outcomes of non-metastatic NSCLC. It shows that time to surgical resection did not affect survival outcomes of non-metastatic NSCLC patients. It suggests that current therapy timeline targets need to be reviewed in our healthcare systems in order to make the best use of our existing resources.

Interpretation

The current study is in line with a number of previously published studies which failed to show an impact of the diagnosis to treatment time on the outcomes of NSCLC patients [9, 10]. However, the current study is characterized by its high-quality data sources (i.e., prospectively collected clinical trial dataset).

The current study did not evaluate the timeliness among patients undergoing non-surgical treatment (i.e., radiotherapy or chemoradiotherapy). This is because the available PLCO datasets did not report enough technical details about the aim, site, and schedule of radiation therapy. Thus, it was not clear whether all patients received a radical dose of radiation therapy. The absence of such information might have confounded any analysis of the impact of timeliness on survival. The current study also could not evaluate the impact of time from referral to diagnosis as this information was not available in the PLCO datasets. It has to be remembered also that PLCO trial included only participants aged 55–74 years. Thus, it is not possible to generalize these data to patients diagnosed younger than 55 years of age.

The current study has suggested that older age is associated with a longer time to resection. This finding might reflect a greater need for preoperative optimization, a

Table 1 Baseline characteristics of patients included in the current study

Parameter	All patients (1022 patients)	Surgical resection ≤30 days (873 patients)	Surgical resection >30 days (149 patients)	*P* value
Age at lung cancer diagnosis (mean; SD)	69.66; 6.006	69.30; 5.93	71.77; 5.99	< 0.001
Body mass index (mean; SD)	25.15; 7.02	25.18; 6.96	24.93; 7.38	0.681
Sex				0.144
Male	568 (55.6%)	477 (54.6%)	91 (61.1%)	
Female	454 (44.4%)	396 (54.4%)	58 (38.9%)	
Race				0.224
White	894 (87.5%)	772 (88.4%)	122 (81.9%)	
Black	59 (5.8%)	48 (5.5%)	11 (7.4%)	
Hispanic	10 (1%)	8 (0.9%)	2 (1.3%)	
Asian	28 (2.7%)	21 (2.4%)	7 (4.7%)	
Unknown	31 (3%)	24 (2.7%)	7 (4.7%)	
Study arm				0.209
Intervention arm	556 (54.4%)	482 (55.2%)	74 (49.7%)	
Control arm	466 (45.6%)	391 (44.8%)	75 (50.3%)	
Lung cancer detection				0.002
Control arm	466 (45.6%)	391 (44.8%)	75 (50.3%)	
Never screened	46 (4.5%)	34 (3.9%)	12 (8.1%)	
Post-screening	273 (26.7%)	229 (26.2%)	44 (29.5%)	
Interval	51 (5%)	45 (5.2%)	6 (4%)	
Screen diagnosis	186 (18.2%)	174 (19.9%)	12 (8.1%)	
Cigarette smoking status				0.078
Never smoker	121 (11.8%)	96 (11%)	25 (16.8%)	
Current smoker	380 (37.2%)	333 (38.1%)	47 (31.5%)	
Former smoker	521 (51%)	444 (50.9%)	77 (51.7%)	
Comorbidities				
Diabetes	72 (7%)	61 (7%)	11 (7.4%)	0.862
Hypertension	342 (33.5%)	280 (32.1%)	62 (41.6%)	0.023
Heart attack	117 (11.4%)	94 (10.8%)	23 (15.4%)	0.098
Stroke	33 (3.2%)	25 (2.9%)	8 (5.4%)	0.110
Emphysema	111 (10.9%)	93 (10.7%)	18 (11.1%)	0.605
Social factors				
Education: Postgraduate	109 (10.7%)	94 (10.8%)	15 (10.1%)	0.882
Marital status: Married	716 (70.1%)	615 (70.4%)	101 (67.8%)	0.210
Occupation: Working	319 (31.2%)	284 (32.5%)	35 (23.5%)	0.151
Lung cancer clinical stage (at presentation)				0.002
I	727 (71.1%)	628 (71.9%)	99 (66.4%)	
II	70 (6.9%)	59 (6.8%)	11 (7.5%)	
III	73 (7.1%)	56 (6.4%)	17 (11.4%)	
Unclear	152 (14.9%)	130 (14.9%)	22 (14.7%)	
Histology				0.028
Squamous	296 (29%)	245 (28.1%)	51 (34.2%)	
Non-squamous	629 (61.5%)	537 (61.5%)	92 (61.7%)	
NSCLC, NOS	97 (9.5%)	91 (10.4%)	6 (4%)	
Type of surgery				0.243
Pneumonectomy/bilobectomy	97 (9.5%)	79 (9%)	18 (12.1%)	
Lobectomy/sublobar resection	925 (90.5%)	794 (91%)	131 (87.9%)	

Table 1 continued

Parameter	All patients (1022 patients)	Surgical resection ≤30 days (873 patients)	Surgical resection >30 days (149 patients)	*P* value
Adjuvant chemotherapy				0.439
Yes	195 (19.1%)	170 (19.5%)	25 (16.8%)	
No	827 (80.9%)	703 (80.5%)	124 (83.2%)	
Adjuvant radiotherapy				0.959
Yes	129 (12.6%)	110 (12.6%)	19 (12.8%)	
No	893 (87.4%)	763 (87.4%)	130 (87.2%)	

Table 2 Multivariate logistic regression analysis for factors predicting time from diagnosis to surgery

Parameter	Odds ratio (95% CI)	*P* value
Age at diagnosis of lung cancer (continuous)	1.077 (1.043–1.112)	<0.001
Race		
White	Reference	
Black	1.631 (0.803–3.311)	0.176
Hispanic	1.701 (0.344–8.425)	0.515
Asian	1.626 (0.654–4.041)	0.296
Study arm		
Control arm	Reference	
Intervention arm	0.860 (0.601–1.231)	0.410
Sex		
Female	Reference	
Male	1.319 (0.915–1.904)	0.138
Clinical stage		
I	Reference	
II	1.126 (0.563–2.252)	0.737
III	1.923 (1.056–3.502)	0.033

greater need for cardiac clearance or stoppage of anti-platelet medications (or other medications which might interfere with surgical resection).

Limitations and strengths

The current study has a number of limitations that need to be acknowledged; first, the number of patients in the current study is relatively small. This might have obscured a modest survival impact of care timeliness. Moreover, small sample size might have led to a type II error within the results of some of the analyses in this analysis (particularly in subgroup analyses). Second, PLCO trial datasets do not contain information about performance status at the time of cancer diagnosis. It has to be remembered however that all included patients have undergone lung cancer surgery. This indicates that most (if not all) of them have reasonable performance status and comorbidity burden. Moreover, lung cancer-specific survival was used as the primary endpoint in the current analysis with the hope that it could mitigate the confounding effect of unknown non-cancer mortality. Third, all patients included in the current analysis were diagnosed and treated before December 2009; thus, it can be presumed that not all patients have received current standard of care with regards to postoperative systemic therapies or with regards to systemic therapies at the time of relapse. Fourth, it is possible that low-volume centers/surgeons were more likely to get patients earlier into surgery; however, this might be at the expense of lower oncologic outcomes. It is not possible, however, to determine the volume of the treating center/surgeon from the PLCO dataset.

These limitations need to be weighed against the strengths of the current analysis; most notably and as mentioned above, the reliance on a well-conducted prospective clinical trial dataset increases the veracity of the results of the current study (compared to previous studies which relied on retrospectively collected datasets).

Table 3 Multivariate Cox regression analysis for factors affecting lung cancer-specific survival

Parameter	Hazard ratio (95% CI)	*P* value
Time from diagnosis to surgery	Reference	
>30 days	0.999 (0.739–1.350)	0.994
≤30 days		
Age at lung cancer diagnosis (continuous)	0.978 (0.960–0.997)	0.020
Race		
White	Reference	
Black	1.330 (0.877–2.018)	0.179
Hispanic	0.641 (0.159–2.590)	0.533
Asian	1.284 (0.672–2.451)	0.449
Study arm		
Control arm	Reference	
Intervention arm	0.916 (0.740–1.134)	0.421
Sex		
Female	Reference	
Male	1.492 (1.192–1.868)	<0.001
Clinical stage		
I	Reference	
II	2.049 (1.431–2.936)	<0.001
III	2.472 (1.767–3.459)	<0.001
Cigarette smoking status		
Never smoker	Reference	
Current smoker	1.095 (0.688–1.742)	0.703
Former smoker	1.143 (0.729–1.793)	0.560

Table 4 Impact of time from diagnosis to surgery among patients with different clinical stages

Stage	Time from diagnosis to surgery	Hazard ratio (95% CI)	*P* value
I	>30 days	Reference	0.804
	≤30 days	1.054 (0.697–1.593)	
II	>30 days	Reference	0.655
	≤30 days	1.273 (0.442–3.667)	
III	>30 days	Reference	0.608
	≤30 days	1.209 (0.585–2.500)	

Multivariate Cox regression analysis adjusted for age, race, and study arm

Implications on practice

The current study could be considered hypothesis generating with regard to health policy decisions and benchmarks of lung cancer surgery. Additional population-based studies are needed to better define important timelines (diagnosis to surgery/surgery to adjuvant therapy) with potential impact on the outcomes of lung cancer patients.

Although the current study failed to show unequivocal evidence of survival benefit for earlier surgical resection, other benefits of prompt treatment for cancer patients cannot be excluded. These include patient satisfaction with services which might correlate with health-related quality of life among lung cancer patients [11].

Previous studies have highlighted a number of successful strategies that might accelerate the referral and treatment process for lung cancer patients. The most notable of which is having a multidisciplinary lung cancer program that works to catch lung cancer cases at its earliest stages as well as to ensure prompt referral to specialist treatments without undue delay [12, 13]. Experiences from other healthcare systems suggest that a rapid investigation clinic for patients with suspected lung cancer might also help to accelerate diagnosis and treatment for patients with lung cancer [14].

Conclusions

In conclusion, time to surgical resection did not affect survival outcomes of non-metastatic NSCLC patients. Current therapy timeline targets need to be reviewed in our healthcare systems in order to redirect and prioritize the existing resources.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This secondary analysis is based on the PLCO trial which has been ethically approved by all participating centers.

Informed consent As this study is based on a publicly available database without identifying patient information, informed consent was not needed.

References

1. Li X, Scarfe A, King K, Fenton D, Butts C, Winget M (2013) Timeliness of cancer care from diagnosis to treatment: a comparison between patients with breast, colon, rectal or lung cancer. Int J Qual Health Care 25(2):197–204
2. https://www.cancerresearchuk.org/sites/default/files/cs_report_cwt.pdf. Last accessed on 17 Mar 2019
3. Gonzalez-Barcala FJ, Garcia-Prim JM, Alvarez-Dobano JM, Moldes-Rodriguez M, Garcia-Sanz MT, Pose-Reino A et al (2010) Effect of delays on survival in patients with lung cancer. Clin Transl Oncol 12(12):836–842
4. Gonzalez-Barcala FJ, Falagan JA, Garcia-Prim JM, Valdes L, Carreira JM, Puga A et al (2014) Timeliness of care and prognosis in patients with lung cancer. Ir J Med Sci 183(3):383–390
5. Olsson JK, Schultz EM, Gould MK (2009) Timeliness of care in patients with lung cancer: a systematic review. Thorax 64(9):749–756
6. https://biometry.nci.nih.gov/cdas/plco/. Last accessed on 17 Mar 2019
7. Oken MM, Hocking WG, Kvale PA, Andriole GL, Buys SS, Church TR et al (2011) Screening by chest radiograph and lung cancer mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) randomized trial. JAMA 306(17):1865–1873
8. https://www.england.nhs.uk/statistics/statistical-work-areas/cancer-waiting-times/. Last accessed 17 Mar 2019
9. Vinod SK, Chandra A, Berthelsen A, Descallar J (2017) Does timeliness of care in non-small cell lung cancer impact on survival? Lung Cancer 112:16–24.
10. Labbé C, Anderson M, Simard S, Tremblay L, Laberge F, Vaillancourt R et al (2017) Wait times for diagnosis and treatment of lung cancer: a single-centre experience. Curr Oncol 24(6):367–373
11. Rankin NM, York S, Stone E, Barnes D, McGregor D, Lai M et al (2017) Pathways to lung cancer diagnosis: a qualitative study of patients and general practitioners about diagnostic and pretreatment intervals. Ann Am Thorac Soc 14(5):742–753
12. Alsamarai S, Yao X, Cain HC, Chang BW, Chao HH, Connery DM et al (2013) The effect of a lung cancer care coordination program on timeliness of care. Clin Lung Cancer 14(5):527–534
13. Ezer N, Navasakulpong A, Schwartzman K, Ofiara L, Gonzalez AV (2017) Impact of rapid investigation clinic on timeliness of lung cancer diagnosis and treatment. BMC Pulm Med 17(1):178
14. Brocken P, Kiers BA, Looijen-Salamon MG, Dekhuijzen PN, Smits-van der Graaf C, Peters-Bax L et al (2012) Timeliness of lung cancer diagnosis and treatment in a rapid outpatient diagnostic program with combined 18FDG-PET and contrast enhanced CT scanning. Lung Cancer 75(3):336–341