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Variable impact of prior cancer history on the survival of lung cancer patients

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ABSTRACT

Introduction: Non-Small Cell Lung Cancer (NSCLC) is commonly diagnosed in patients who have survived a prior malignancy. However, it is currently unclear whether NSCLC patient survival is impacted by the potential for previously-treated malignancies to recur. Understanding the impact of a prior cancer history on NSCLC survival could not only enhance decision making but could affect eligibility for NSCLC studies.

Methods: The National Cancer Database (NCDB) was queried for NSCLC patients (stage I–IV) diagnosed between 2004–2014. Kaplan-Meier survival curves and multivariable Cox proportional hazards regression models were estimated to analyze overall survival across a variety of treatment approaches and stages in the presence and absence of a prior cancer history.

Results: A total of 821,323 patients with a newly diagnosed NSCLC were identified including 179,512 (21.9%) with a prior history of cancer. The unadjusted 5-year overall survival of patients with a prior cancer history (9.8%) was slightly better to those without a cancer history (9.5%, 95% CI 11.76–11.84, $P < 0.0001$). However, adjusted analyses revealed the impact of prior cancer history was extremely heterogenous across stage and treatment approach. Ultimately, 51.4% of patients fell into a subgroup in which prior cancer history appeared to compromise survival, 16.3% in which the difference was not significant, and 32.3% in which prior cancer was associated with increased survival. Patients with earlier-staged tumors were the most negatively NSCLC impacted by prior cancer history.

Conclusions: The association between prior cancer history and survival of newly diagnosed NSCLC patients is highly variable and to some degree reflects a patient's potential for cure.

1. Introduction

Non-Small Cell Lung Cancer (NSCLC), currently the leading cause of cancer-related mortality, frequently affects patients who have survived a prior malignancy [1]. Recent estimates indicate that 1 out of every 5 newly diagnosed lung cancer patients have a prior cancer history [2–4]. Estimating the prognosis within the prior cancer history subset is complex, because previously treated malignancies may recur and pose additional risk to survival. Previous attempts to clarify the impact of prior malignancy on cancer outcomes have generated mixed results [5–9]. More recently, several studies using Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data have suggested that prior cancer history does not impact survival for early stage NSCLC and may even be associated with improved survival for later stages [3,10–12]. However, the studies using SEER-Medicare data were limited to elderly patients and several potentially important variables (including treatment) were not fully explored. Therefore, additional refinement of prognostic estimates for the subset of NSCLC patients with a prior cancer history is indicated and may enhance informed decision making for patients and physicians.

Prior cancer history may also complicate efforts to delineate the optimal treatment of NSCLC. More specifically, patients who have been previously treated for a separate malignancy are frequently excluded from prospective [13] and retrospective studies [14] due to concerns that previously treated cancers could recur and pose a competing risk to survival. While rational, the exclusion of the prior cancer subset may also be problematic. Clinical trial accrual can be challenging, and many studies struggle to enroll sufficient numbers of patients to address their

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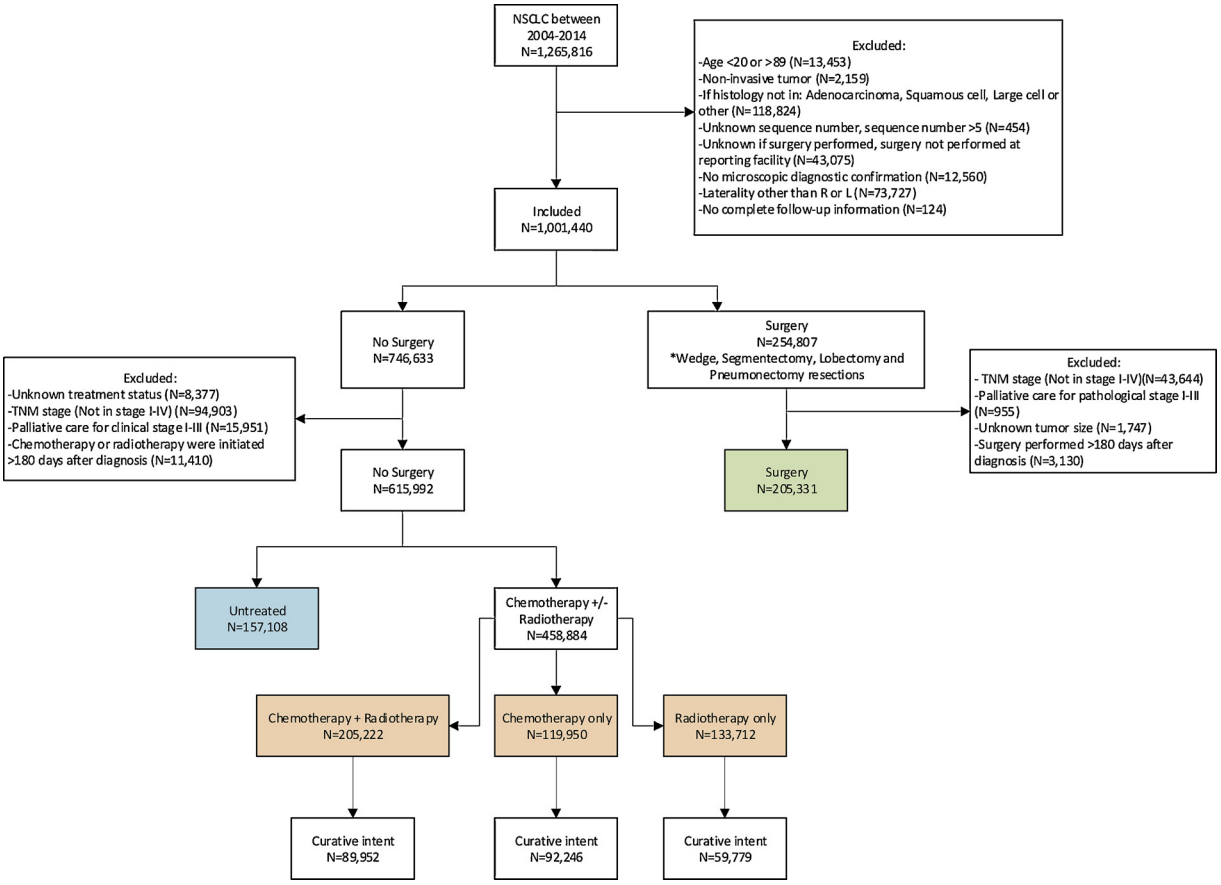

Fig. 1. Consort diagram of patient selection.

research questions. A large proportion of trials take far longer than anticipated to reach accrual targets and it has been estimated that 28% of adult cancer trials close prematurely because of the inability to accrue sufficient patients [15–17]. Restricting prior cancer patients (representing 20–25% of newly diagnosed patients) from trial eligibility no doubt contributes to the accrual challenge [18]. In addition, it is unclear whether the results of studies that exclude the prior cancer history cohort are equally applicable to patients who have survived a prior malignancy [10]. More specifically, there may be biologic, immunologic, or physiologic nuances shared by survivors of prior cancers that have implications for cancer treatment. Therefore, the ability to clarify the impact of prior cancer history on the prognosis of patients newly diagnosed with NSCLC is of significant importance to both patients and the oncology community. In an effort to further characterize the relationship between prior cancer history and prognosis, the adjusted mortality risk associated with a prior cancer history was evaluated in a cohort of NSCLC patients in the National Cancer Database (NCDB).

2. Patients and methods

2.1. Data source

The NCDB is cosponsored by the American College of Surgeons and the American Cancer Society and captures the care of patients treated by hospitals accredited by the Commission on Cancer. The NCDB is one of the largest and most comprehensive clinical oncology hospital-based registries in the world, currently capturing around 70% of all newly diagnosed NSCLC in the United States [14]. The data used in this analysis is derived from the linked 2004–2015 (2015 version) of the deidentified site-specific NCDB participant user file [19]. Institutional Review Board of Yale University School of Medicine has approved this study with consent waived. The NCDB is not responsible for the conclusions drawn from the analytic or statistical methodology used in these analyses [20].

2.2. Study population

The NCDB was queried for adult patients between 20 and 89 years diagnosed with stage I—IV invasive NSCLC from 2004 to 2014. The NCDB sequence number variable was used to separate patients into two cohorts based on prior cancer history: 1) the “prior cancer history cohort” – included patients who had a cancer diagnosis that preceded the NSCLC diagnosis, and 2) the “first primary cohort” – included patients in which the newly diagnosed NSCLC represented their first and only malignancy. To minimize the impact of outliers, patients with incomplete survival information and follow-up were excluded. Only microscopically confirmed NSCLC with squamous cell, adenocarcinoma, large cell and other (undifferentiated carcinoma (squamous or glandular component), non-small cell carcinoma, papillary carcinoma, verrucous carcinoma, papillary squamous/epidermoid carcinoma, mucoepidermoid carcinoma and signet ring cell carcinoma) histologic subtypes were included. Patients with missing stage were excluded due to the potential for misclassification bias in our stratification and adjustment strategies. The study period was affected by a transition from the 6th edition to the 7th edition of the American Joint Committee on Cancer (AJCC) lung cancer staging system, reflected in the NCDB starting in 2010. A homogenous study group was created by converting patients with 7th AJCC edition to the corresponding 6th edition stage. Clinical stage I-III patients treated palliatively were excluded, because patients with locoregionally- confined disease who are treated with palliative intent are likely different than those treated with curative

Table 1
Patient Characteristics.

Prior Cancer History Vs First Primary Malignancy (NSCLC)				
Characteristics	Full cohort	Prior Cancer History	First primary Cohort	P-value
Prior Cancer History				
Yes	179,512 (21.9)[a]	NA	NA	< .0001
No	641,811 (78.1)	NA	NA	
Facility type				
Non-Academic program[b]	565,912 (68.9)	122,639 (68.3)	443,273 (69.1)	< .0001
Academic/Research program	255,411 (31.1)	56,873 (31.7)	198,538 (31.9)	
Sex				
Male	444,724 (54.2)	96,987 (54)	347,737 (54.2)	0.25
Female	376,599 (45.9)	82,525 (46)	294,074 (45.8)	
Race				
White	702,346 (85.5)	159,709 (89)	542,637 (85.5)	< .0001
Non-white	118,977 (14.5)	19,803 (11)	99,174 (15.5)	
Age				
20-44	13, 428 (1.6)	970 (0.5)	12,458 (1.9)	< .0001
45-64	268,658 (32.7)	37,121 (20.7)	231,537 (36.1)	
65-89	539,237 (65.7)	141,421 (78.8)	397,816 (62)	
Insurance Status				
Not insured	27,008 (3.3)	2229 (1.2)	24,779 (3.9)	< .0001
Private Insurance	218,245 (26.6)	36,415 (20.3)	181,830 (28.3)	
Government programs	561,542 (68.4)	138,146 (77)	423,396 (66)	
Unknown	14,528 (1.8)	2722 (1.5)	11,806 (1.8)	
Charlson-Deyo Score				
0	477,534 (58.1)	104,715 (58.3)	372,819 (58.1)	0.001
1	236,871 (28.9)	51,737 (28.8)	185,134 (28.9)	
2	79,198 (9.6)	17,250 (9.6)	61,948 (9.7)	
≥ 3	27,720 (3.4)	5810 (3.2)	21,910 (3.4)	
Year of diagnosis				
2004	61,232 (7.5)	11,768 (19.2)	49,464 (80.8)	< .0001
2005	63,297 (7.7)	12,597 (19.9)	50,700 (80.1)	
2006	63,326 (7.7)	12,916 (20.4)	50,410 (79.6)	
2007	64,190 (7.8)	13,425 (20.9)	50,765 (79.1)	
2008	71,405 (8.7)	15,069 (21.1)	56,336 (78.9)	
2009	74,637 (9.1)	16,264 (21.8)	58,373 (78.2)	
2010	80,455 (9.8)	17,841 (22.2)	62,614 (77.8)	
2011	81,671 (9.9)	18,532 (22.7)	63,139 (77.3)	
2012	84,382 (10.3)	19,556 (23.2)	64,826 (76.8)	
2013	87,311 (10.6)	20,561 (23.6)	66,750 (76.5)	
2014	89,417 (10.9)	20,983 (23.5)	68,434 (76.5)	
Primary site				
Upper lobe	464,089 (56.5)	99,900 (55.7)	364,189 (56.7)	< .0001
Middle lobe	35,453 (4.3)	8271 (4.6)	27,182 (4.2)	
Lower lobe	227,348 (27.7)	53,529 (29.8)	173,819 (27.1)	
Overlapping lesion of lung	12,831 (1.6)	2231 (1.2)	10,600 (1.7)	
Lung, NOS	81,602 (9.9)	15,581 (8.6)	66,021 (10.3)	
Tumor size				
0-2 cm	153,023 (18.6)	47,269 (26.3)	105,754 (16.5)	< .0001
2-3 cm	143,090 (17.4)	35,487 (19.8)	107,603 (16.8)	
3-5 cm	203,992 (24.9)	42,386 (23.6)	161,606 (25.2)	
5-7 cm	108,752 (13.2)	19,291 (10.8)	89,461 (13.9)	
> 7 cm	211,587 (25.8)	34,910 (19.5)	176,677 (27.5)	
Unknown	879 (0.1)	169 (0.09)	710 (0.1)	
Tumor histological type				
Adenocarcinoma	412,110 (50.2)	91,285 (50.9)	320,825 (50)	< .0001
Squamous cell carcinoma	247,794 (30.2)	58,333 (32.5)	189,461 (29.5)	
Large cell carcinoma	26,303 (3.2)	4831 (2.7)	21,472 (3.4)	
Other[c]	135,116 (16.4)	25,063 (14)	110,053 (17.2)	
Grade				
1	37,436 (4.6)	10,750 (6)	26,686 (4.2)	< .0001
2	169,303 (20.6)	42,579 (23.7)	126,724 (19.7)	
3	258,135 (31.4)	53,466 (29.8)	204,669 (31.9)	
4	12,674 (1.5)	2418 (1.4)	10,256 (1.6)	
Not determined	343,775 (41.9)	70,299 (39.2)	273,476 (42.6)	
Stage				

(*continued on next page*)

Table 1 (*continued*)

Prior Cancer History Vs First Primary Malignancy (NSCLC)				
Characteristics	Full cohort	Prior Cancer History	First primary Cohort	P-value
I	218,034 (26.6)	66,992 (37.3)	151,042 (23.5)	< .0001
II	54,261 (6.6)	12,526 (7)	41,735 (6.5)	
III	190,225 (23.2)	38,065 (21.2)	152,160 (23.7)	
IV	358,803 (43.7)	61,929 (34.5)	296,874 (46.3)	
Surgical treatment (N = 205,331)				
Surgical procedures				
Wedge and Segmental resection	34,216 (16.7)	12,857 (7.2)	21,359 (3.3)	< .0001
Lobectomy	159,867 (77.9)	39,500 (22)	120,367 (18.8)	
Pneumonectomy	11,248 (5.5)	2057 (1.2)	9191 (1.4)	
Neoadjuvant therapy				
Neoadjuvant chemotherapy and radiotherapy	4,298 (2.1)	564 (0.27)	3734 (1.8)	< .0001
Neoadjuvant chemotherapy	4,806 (2.34)	1037 (0.5)	3769 (1.8)	
Neoadjuvant radiotherapy	208 (0.1)	50 (0.11)	158 (0.08)	
Medical treatment (N = 615,992)				
Chemotherapy plus radiotherapy	205,222 (33.3)[d]	34,073 (16.6)	171,149 (83.5)	< .0001
Chemotherapy	119,950 (19.5)	24,492 (20.4)	95,458 (79.6)	0.29
Radiotherapy	133,712 (21.7)	34,060 (25.5)	99,652 (74.5)	< .0001
No treatment	157,108 (25.5)	32,473 (20.7)	124,635 (79.3)	< .0001
Guideline compliance non-surgical treatment				
Chemotherapy plus Radiotherapy	67,031 (10.9)[d]	12,182 (9.7)	54,849 (11.2)	< .0001
Chemotherapy	92,246 (15)	18,118 (14.5)	74,128 (15.1)	
Radiotherapy	28,534 (4.6)	8938 (1.5)	19,596 (3.2)	

NOS = Not otherwise specified.

Note – percentages might not add up to 100% due to rounding.

[a] Percentage of population listed in column header.

[b] Includes Community Cancer Program, Comprehensive Community Cancer Program, Integrated Network Cancer Program and other specified types of cancer programs.

[c] Non-small cell not further defined: undifferentiated carcinoma (squamous or glandular component), non-small cell carcinoma, papillary carcinoma, verrucous carcinoma, papillary squamous/epidermoid carcinoma, mucoepidermoid carcinoma and signet ring cell carcinoma.

[d] Percentage of patients managed without surgery.

intent (in ways that affect prognosis). On the other hand, stage IV patients treated with palliative intent were included, as this is applicable to vast majority of stage IV patients. Patients who initiated treatment more than 180 days after diagnosis were excluded, timing was considered outside the standard of care (cohort selection – Fig. 1).

2.3. Adjusted analyses – stratified across treatment and stage

The effect of prior cancer on survival was evaluated by stratifying patients across stage and treatment modality. A "surgical cohort" included patients who underwent wedge resection, segmentectomy, lobectomy or pneumonectomy. Of note, a proportion of the "surgical cohort" also received perioperative chemotherapy and radiation, which was accounted for in the adjusted Cox regression models described below. The "nonsurgical cohort" included patients treated primarily with chemotherapy, radiotherapy, or both (but not surgery). "Untreated patients" did not receive treatment during their initial course (typically considered within the first year following diagnosis).

2.4. Data elements

Detailed definitions of NCDB variables are available online [21]. Independent covariates evaluated in the current study included age, sex, race, Charlson-Deyo comorbidity index score (modified by NCDB to three groups = 0, 1, 2, ≥3), income (median income of patient's zip code area), education (percentage of adults with no high school diploma), insurance status, area of residence, facility type and location, year of diagnosis, chemotherapy (single or multi-agent), neoadjuvant therapy, histological subtype, grade, tumor size, anatomic site of origin for the cancer, and laterality. Specific information regarding the prior malignancy (i.e. time interval between NSCLC diagnosis and prior malignancy diagnosis, histologic type, site of origin, stage, treatment and disease status) were not available in the NCDB. For reference, the distribution of prior tumor attributes determined from the SEER registries database (which is nationally representative for patients > 65) is provided in Supplemental Table 1.

2.5. Statistical analysis

Categorical patient characteristics were compared using the Chi-square test. Unadjusted Kaplan-Meier survival curves with 95% confidence intervals were generated to compare the prior cancer history cohort and the first primary cohort, overall and stratified by stage, using the log-rank test. NCDB calculates patient vital status based on the date of last contact or death, and therefore five-year survival was estimated as months from diagnosis to death or end of available follow-up (December 31, 2014). Cox proportional hazards regression models were adjusted for patient, tumor, and treatment characteristics. Violations of the proportional hazards assumption were evaluated visually based on Schoenfeld residuals [22]. No violations were identified. Two-tailed P-values of < 0.05 were considered statistically significant for all analyses. Statistical analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, North Carolina).

2.6. Sensitivity analyses

Recognizing that the efficacy of chemotherapy and radiation therapy could be impacted by variable dosimetry and the selection of regimens, a sensitivity analysis was performed on the subset of non-surgically managed patients whose treatment was more in accordance with NSCLC guidelines (referred to as "guideline consistent"). For patients receiving chemotherapy, "guideline consistent" treatment included "multi-agent" chemotherapy (as opposed to "single agent"). Specific agents and number of cycles are not captured by the NCDB. For

patients treated with radiation therapy, "guideline consistent" treatment was defined as greater or equal to 60 Gy [23,24]. Results for this guideline-compliant subset were similar to those of the full study population (Supplemental Table 2). The effect of prior cancer on survival across stage and treatment modality, further stratified by age < 65 vs. age ≥65 years (Supplemental Fig. 1).

3. Results

3.1. Patient characteristics

A total of 821,323 NSCLC patients were identified, including 179,512 (21.9%) in the "prior cancer history" cohort. The prevalence of patients with prior cancer history increased from 19.1% in 2004 to 23.5% in 2014. In general, the prior cancer history cohort contained more elderly patients, had smaller tumors, and more early-staged tumors compared to the "first primary" cohort (Table 1).

3.2. Unadjusted survival comparisons

A Kaplan-Meier survival analysis was performed with a median follow up of 38.4 months (range, 0–157 months) for surviving patients. The "prior cancer history" cohort experienced slightly better 5-year overall survival (9.8%, 95% CI 15.67–15.93, P < 0.0001) compared to the "first primary" cohort (9.5%, 95% CI 11.76–11.84, P < 0.0001) (Fig. 2A). Stage-stratified Kaplan-Meier analysis suggested the impact of prior cancer was to some degree stage dependent. Patients with a prior cancer history exhibited worse survival for stages I–II but did not appear to have a meaningfully different survival than the first primary cohort for patients with stage III-IV disease (Fig. 2B–E). When all stages were combined (Fig. 2A) patients with prior cancer history showed better survival, this observation is counterintuitive as it mirrors the unequal distribution of patients within each stage; with a larger proportion of early-stage patients with prior cancer history compared to the smaller proportion of patients with a history of cancer in stage IV.

3.3. Adjusted survival comparisons – stratified by stage and treatment approach

Cox proportional hazard models were adjusted for patient characteristics and stratified by tumor stage and treatment (Fig. 3). The impact of a prior cancer history on mortality risk was heterogenous across stage and treatment strata. More specifically, prior cancer history was associated with worse survival for 51.4% of patients, prior cancer history was associated with improved survival for 32.3% of patients, and the impact of prior cancer history was not statistically significant for a total of 16.3% of patients. In general, among patients with stage I NSCLC, prior cancer history was associated with worse survival compared to the first primary cohort across all treatment modalities, with the strongest association among surgically managed patients (HR: 1.28, 95% CI 1.25–1.30, P < 0.0001). In contrast, the impact of prior cancer history was favorable (i.e. better survival than first primary cohort) among the majority of patients with stage IV NSCLC. For the minority of stage IV patients who were treated with surgery or with chemotherapy and radiation, the impact of prior cancer history was not significant.

3.4. Impact of prior cancer, stratified by age

There are potentially age-related nuances to this study (e.g. the types of cancers that patients were previously diagnosed with, the prevalence of health-related factors that may compete with NSCLC survival, etc.). A sensitivity analysis was performed stratifying patients into two age-related cohorts (< 65 and ≥65 years of age), demonstrating further heterogeneity (Supplemental Fig. 1). For example, in stage I-III patients treated with chemotherapy that were older than 65, prior cancer history did not impact survival. However, in patients younger than 65 prior cancer appeared to have an adverse impact on overall survival.

4. Discussion

The current study findings suggest that a prior cancer history has an important but heterogenous effect on the survival of NSCLC patients, and varies across tumor stage and treatment. To some degree, the unadjusted analyses best illustrate the complexity of this relationship and the need to consider other tumor and treatment variables. For example, when all patients are evaluated (all stages, all treatments), the prior cancer cohort has a slightly better survival (Fig. 2A). Yet when all the stages are examined individually (Fig. 2B–E), prior cancer patients never have a better survival. This pattern is counterintuitive, but simply reflects heterogeneity in the stage distribution (fewer stage IV patients in the prior cancer cohort). Overall, the observed heterogeneous relationship between prior cancer history and NSCLC patient survival contrasts a

number of studies that found a *singular* effect of prior cancer history in lung cancer [3,10–12,25]. Our results extend the thoughtful work of the team led by Gerber et al, studying the impact of prior cancer history in elderly lung cancer patients [10–13]. More specifically, the studies led by Gerber et al found that prior cancer history was not associated with inferior clinical outcomes and suggested the prior cancer history subset could be considered for inclusion in prospective clinical trials. This team actually went further to examine the stage of the prior cancer and found non-metastatic stage cancers (defined in study as in situ, localized and regional) were particularly unlikely to impact survival in early-stage lung cancer [12] Perhaps as a result of these studies and others, some NSCLC trials are loosening eligibility, allowing patients with early stage prior cancers to be included in the trial (e.g. Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial – "ALCHEMIST") authorized the inclusion for early-stage prior cancer patients [26]. Although portions of our study are consistent with the results of the Gerber research team, we extend these findings by including a more complete range of adult patient ages (as opposed to only elderly), and further stratifying by stage and treatment. As a result, we identified far greater heterogeneity in the relationship between prior cancer history and survival, ultimately leading us to draw different conclusions. We would caution against including NSCLC patients with a prior cancer history in prospective clinical trials without a defined strategy to account for the potential heterogenous impact that prior cancer history may have on survival.

The extent of heterogeneity in the association between prior cancer history and survival is intriguing. It most likely reflects an interplay between: 1) the lethality of the newly diagnosed lung cancer, 2) the risk of prior cancer recurring, and 3) the patient's engagement with the health care system. Early stage lung cancer is likely to be cured, therefore the additional risk of the previously treated cancer worsens the overall survival of the cohort. Late-stage lung cancer patients are most likely to die from lung cancer progression; therefore, the risk of their prior cancer recurring is not likely to be relevant. However, cancer survivors may be more engaged with the health care system, which could represent a survival advantage in some cancer scenarios. Prior cancer history patients may be more vigilant in reporting symptoms, or more compliant with screening programs, potentially leading to diagnosis at an earlier point in their course (i.e. still stage IV, but with a lower volume of disease). This could also have implications for overall patient health [27], as prior cancer patients that are more engaged with health systems may be more likely to be treated for comorbid conditions and more likely to abstain from detrimental habits (e.g. smoking). While the observed difference in mortality risk between patients with and without a prior cancer history would be considered relevant for many of the studied scenarios (10–30%), it is important to note that not every prognostic factor is considered in trial eligibility or randomization. For example, smoking status is not uniformly included in NSCLC

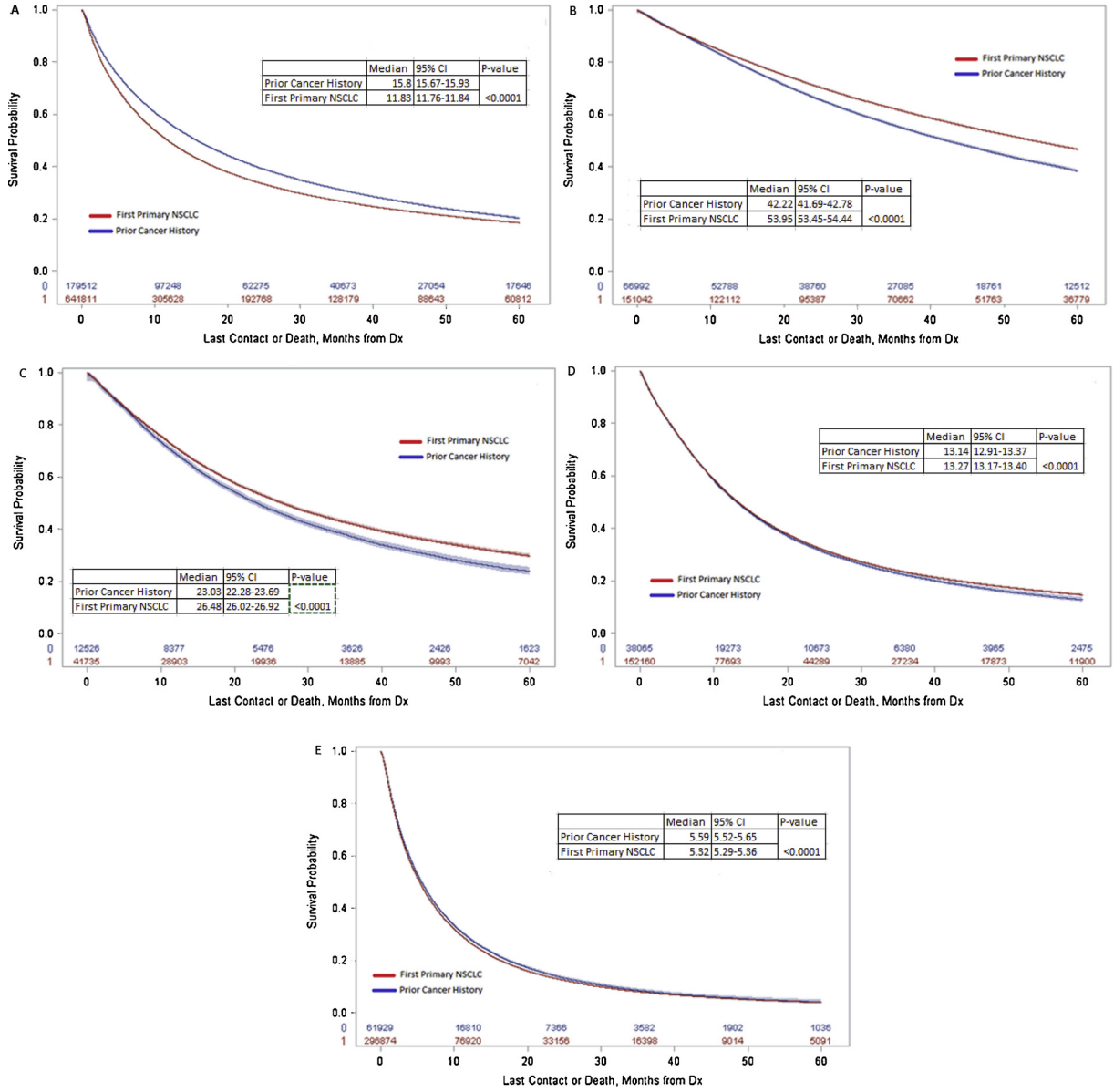

Fig. 2. Kaplan-Meier Survival analysis of prior cancer history impact on overall survival. The unadjusted survival of patients with prior cancer history (blue line) is compared to those in whom the NSCLC represented their first primary (red line) across all patients (Panel A) as well stratified by NSCLC stage (Panel B = Stage I, Panel C = stage II, Panel D = stage III and Panel E = Stage IV) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

trial randomization, but may certainly impact prognosis, as well as several additional prognostic factors [28–33]. That being said, clinical research in NSCLC is evolving and trial design must continue to refine the scope of studied patients to minimize potential bias and maximize the applicability of results [18].

The current findings suggest that the management of the prior cancer history cohort (i.e. inclusion or exclusion) may represent a significant impact in the analysis of *select* retrospective mortality models. More specifically, when the Cox proportional hazard model was estimated within a subset known to be impacted by prior cancer history, the addition of this subgroup demonstrated a significant influence over the magnitude of several independent covariates. Therefore, if there is concern about likely effect of prior cancer history and its distinction from patients without history of cancer, we recommend including the prior cancer history as a covariate in adjusted analysis. Consideration of prior cancer as a stratification variable should be further defined in situations where prior cancer history is known to modify the effect of one or more independent covariates.

The current study contains limitations beyond those traditionally associated with retrospective observational studies. Most importantly, the NCDB does not capture details surrounding prior cancer histories (e.g. tumor type, stage, treatment, date of diagnosis), and therefore we cannot distinguish the index lung cancer from local recurrence. A non-uniform distribution of prior cancer attributes could confound results, as the previously diagnosed cancer could be “likely lethal” (e.g. stage IV pancreatic cancer, diagnosed 6 months earlier) or) or “likely irrelevant” to prognosis (e.g. carcinoma in situ diagnosed 6 years earlier). A dominant mix of either of these two scenarios would likely prevent us from seeing significant patterns. In this regard, the meticulous work by the team led by Gerber et al is revealing. Using SEER-Medicare data, they were able to characterize the distribution of prior cancer attributes in the prior cancer history cohort (Supplemental Table 1). Several key findings include: 1) only 6% of prior malignancies were stage IV, 2) less than 9% of cancers were “in situ”, 3) particularly favorable prognosis

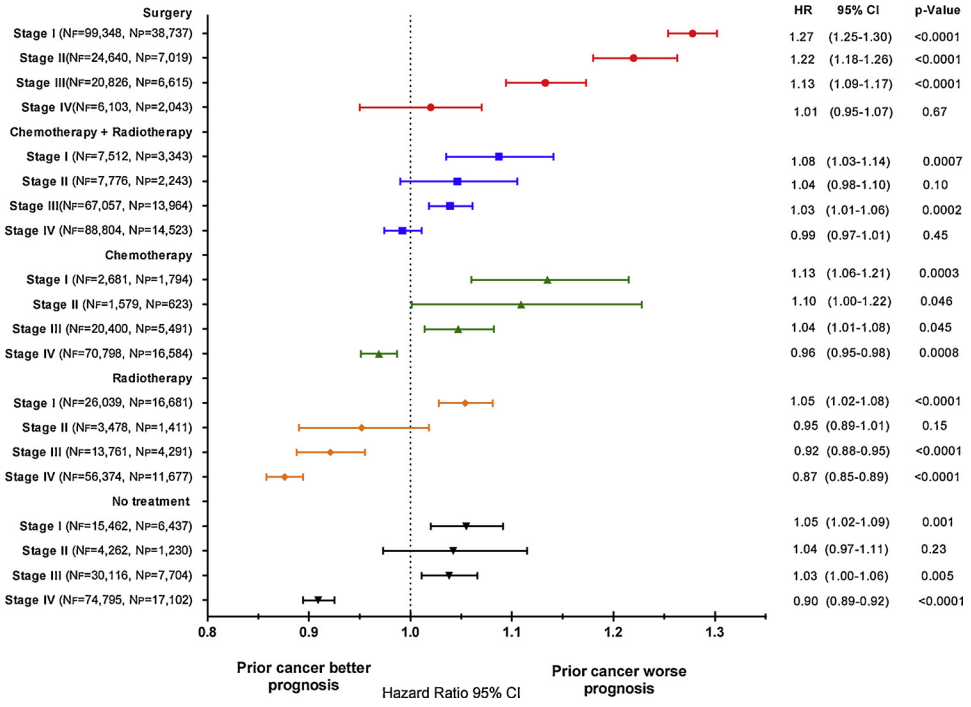

Fig. 3. Forest plot of Cox Proportional Hazard for prior cancer history. Analysis of prior cancer history impact on overall survival by stage and treatment modality. Cohort models adjusted for facility location, facility type, age, gender, race Hispanic ethnicity, income, insurance status, education, area of residence, year of diagnosis, Charlson-Deyo comorbidity score, laterality, primary site, preoperative treatment, histology grade and stage.

tumors (thyroid, captured under "other") were infrequent, and 4) the time interval between the prior malignancy and NSCLC diagnosis was evenly distributed from recent to remote. Therefore, the consistency and significance of our findings across stage and treatment strata likely reflects the relative infrequency of scenarios that are either *"likely lethal" or "likely irrelevant"* to prognosis. The analysis might be subject hidden biases that may explain some of the differences of our study to prior publications. In addition, the NCDB does not capture detailed information ontherapeutic regimens for chemotherapy and radiotherapy or toxicity. Although our sensitivity analysis using a more stringent definition of "guideline compliant" chemotherapy and radiation did not identify differences in our central findings, additional information such as chemotherapy agents, dosimetry, and tolerability could enhance our analysis. The NCDB captures overall survival, but not disease-specific survival or cause of death. As a result, any observed differences in survival between two groups of lung cancer patients may be unrelated to their lung cancer. As NCDB continues to evolve, the addition of cancer-specific outcomes and other relevant clinical trial endpoints could be of considerable benefit.

In conclusion, a prior cancer history appears to have a variable impact on the survival of patients with NSCLC according to disease stage and treatment approach. While a prior history of cancer is generally associated with decreased survival for patients with early stage, surgically treated and "curable" NSCLC, a cancer history exerts a smaller but often favorable impact on those with advanced stage NSCLC. Investigators are cautioned against including the prior cancer history subset in prospective studies without a defined strategy to account for the heterogenous survival effect.

Conflict of interest

Authors declare they have no conflict of interest to disclose.

Acknowledgements

Authors Andres F. Monsalve and Daniel J. Boffa had full access to all data in the study and take responsibility for the accuracy and integrity of the data analysis. NCDB states "The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible or the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator."

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2018.11.040.

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