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# Factors associated with early mortality in non-small cell lung cancer patients following systemic anti-cancer therapy: A 10 year population-based study

Amanda J.W. Gibson[a], Haocheng Li[a], Adrijana D'Silva[a], Anifat A. Elegbede[a], Roxana A. Tudor[a], Shannon Otsuka[a], D. Gwyn Bebb[a], Winson Y. Cheung[a,b,*]

[a] Department of Oncology, Cumming School of Medicine, University of Calgary, 3300 Hospital Drive NW, Calgary, AB, T2N 4N1, Canada
[b] Tom Baker Cancer Centre, Alberta Health Services, 1331 29th Street, NW, Calgary, AB, T2N 4N2, Canada

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ABSTRACT

*Objectives:* To investigate how clinical, demographic and treatment-related factors in non-small cell lung cancer (NSCLC) patients impact the risk of mortality in the 30 days following receipt of systemic anti-cancer therapies (SACT), and undertake a comprehensive review of the treatment decisions and experiences of a real-world population.

*Materials and methods:* We reviewed NSCLC patients receiving SACT from 2005 to 2014, and captured in the Glans-Look Lung Cancer Database, which contains demographic, clinical, pathological, treatment and outcome data. The 30-day post-SACT mortality rate was calculated, and regimen changes in the last 14 days of life were identified. Univariate analysis and multivariate logistic regression were used to identify demographic, tumor and treatment-related factors that correlated with mortality risk.

*Results:* 1044 patients receiving ≥ 1 cycle of SACT in 2005–2014 were identified. 233 (22.3%) deaths occurred ≤ 30 days following SACT receipt; 32 (13.7%) of which had new SACT regimens ≤ 14 days prior to death. Risk of 30-day mortality and regimen changes at the end of life increased in association with being male [OR: 1.48 (1.12–1.95), p = 0.005], advanced disease at diagnosis [OR: 1.85 (1.19–2.88), p = 0.006], palliative-intent treatment [OR: 6.75 (3.88–11.77), p < 0.001], and use of EGFR-targeting agents [OR: 4.5 (3.27–6.18) p < 0.001]. Risk of early mortality decreased for never-smokers [OR: 0.62 (0.41–0.95), p = 0.028], and those receiving SACT in more recent years (2010–2014) [OR: 0.65 (0.49–0.86), p = 0.002].

*Conclusion:* Our findings identified several factors that affected the risk of early mortality in NSCLC patients following SACT. These results from a representative population provide insights regarding the benefits and risks of SACT and can serve to inform clinical and palliative best practices.

## 1. Introduction

Systemic anti-cancer therapy (SACT) is widely used in the treatment of lung cancer for both curative-intent settings where treatment is given to reduce the risk of recurrence, and in palliative-intent settings where treatment is given to prolong survival and mitigate symptoms [1,2]. While SACT is a powerful tool for managing lung cancer, it is not without serious side-effects. In order for SACT to be effective, patients must be able to withstand not only the immediate side-effects but to survive long enough for the benefits of SACT to be realized. Patients dying within 30-days of receipt of SACT are therefore unlikely to benefit. Consequently, delivery of SACT to these patients may actually pose harm, as end-of-life SACT is frequently associated with aggressive or intensive end-of-life care, which may be at odds with patient preferences and optimal quality of life [3,4].

Intervention-based audits that examine peri-operative mortality have become mandatory reporting features and are used as key indicators of safety for patients undergoing surgery [5,6]. Interest in measuring quality of care has also broadened to include other treatment modalities, such as SACT, where cessation of SACT in the last two weeks of life has been established as a clinical practice improvement benchmark by the Quality Oncology Practice Initiative for the American Society of Clinical Oncology and endorsed by the National Quality Forum. Likewise, 30-day mortality was proposed as part of United

* Corresponding author at: Tom Baker Cancer Centre, 1331 29th Street NW, Calgary, AB, T2N 4N2, Canada.
*E-mail addresses:* ajwgibso@ucalgary.ca (A.J.W. Gibson), haocheng.li@ucalgary.ca (H. Li), asevo@ucalgary.ca (A. D'Silva), haocheng.li@ucalgary.ca (A.A. Elegbede), Roxana.tudor@ucalgary.ca (R.A. Tudor), smotsuka@ucalgary.ca (S. Otsuka), gwyn.bebb@ahs.ca (D.G. Bebb), winson.cheung@ahs.ca (W.Y. Cheung).

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Kingdom's Department of Health National Cancer Strategy (2011) as a clinical indicator of 'avoidable harm', and aligns with Scotland's National Quality Performance Indicator Program [7–10]. Outside of clinical trials, SACT-associated mortality rates are not well documented, particularly in the more heterogeneous spectrum of lung cancer patients presenting at regional cancer care centres in North America. Likewise, mortality rates have not been well explored in this population since the introduction and use of new, oral anticancer treatments [11–13].

The decisions to offer or continue SACT treatment are complex. Ascertaining futility of treatment requires balancing patient and family preferences and the potential to modify survival/prognosis. [14,15] Currently, the limited data on post-SACT mortality suggest that this is an unappreciated area of concern even though such data can provide practicing oncologists relevant information to guide decisions regarding SACT usage, particularly in terminally ill patients. Therefore, identifying 30-day mortality rates and adopting a policy of regular review of SACT-associated mortality can inform potential service improvements and ensure highest standards of patient care [13,16]. In response, this population-based study aims to investigate how clinical, demographic, and treatment-related factors impact the risk of early mortality following SACT. By emulating the approach of Wallington el al. (2016) [4] who investigated 30-day mortality rates following SACT among NSCLC patients in England in 2014, and by adopting a retrospective, population-based approach of selecting all patients undergoing SACT, this allows for a more comprehensive review of the treatment decisions and experiences of a heterogeneous population of NSCLC patients.

## 2. Methods and materials

### 2.1. Patient population and covariates

A review of patients with a diagnosis of NSCLC in the Glans-Look Database (GLD) was conducted. The GLD is an institutional database which captures the demographic, clinical, pathological, treatment and outcome data of individuals, over the age of 18 years, identified by the Alberta Cancer Registry (ACR), who presented to the Tom Baker Cancer Centre (TBCC) in Calgary, Canada for the management of their disease. Patients undergoing SACT at the TBCC (defined as receipt of any systemic therapy for cancer, including cytotoxic chemotherapy, targeted biological therapy, or immunotherapy, administered as part of standard of care or a clinical trial protocol) between 2005 and 2014 were included in the analysis, irrespective of the number of lines of therapy received. We excluded patients who were affected with other primary malignancies, lost to follow-up, or had incomplete SACT documentation. Patients receiving multiple cycles of SACT within the 2005–2014 time period were included in the dataset only once, using details from their last SACT treatment. Additional variables extracted from the GLD that were incorporated in the analyses included age at diagnosis, sex, histology, smoking history, stage at diagnosis, disease duration, treatment-intent categorized as palliative or curative as denoted in physician-generated consultation and progress notes, SACT regimen and history, and year of SACT receipt (categorized into two eras: 2005–2009 and 2010–2014) to investigate changes in SACT mortality over time. Since 2010, routine testing for molecular markers, specifically EGFR mutation status, was integrated as part of standard of care. [17] This testing in conjunction with more tolerable, oral anticancer therapies which specifically target driver-mutations such as EGFR have changed the treatment paradigm for NSCLC and could have impacted SACT use at the end-of-life as well as 30-day mortality rates.

### 2.2. Outcome measures

The outcome of interest was post-SACT survival and end-of-life (EOL) regimen change. Post-SACT survival was calculated as the time interval (in days) between the last recorded SACT treatment date and the date of death from any cause, as recorded in the GLD. Post-SACT survival was subsequently used to identify patients experiencing early mortality following SACT, where early mortality was defined as $\leq$ 30 days. Additionally, in order to provide a more comprehensive view of SACT usage at EOL, we also calculated 14 and 60-day mortality rates and identified patients with EOL regimen changes, defined as new or changed SACT regimens within 14 days prior to death.

### 2.3. Statistical analysis

Patients were subdivided into those experiencing early mortality (death $\leq$ 30 days following SACT) and those who survived > 30 days post SACT treatment. Baseline demographic, clinical and treatment details were summarized with descriptive statistics. Chi-square and Fisher Exact tests were used to compare non-parametric categorical factors, among patients in each survival group.

Multivariate logistic regression models were constructed to detect factors which predispose patients to early death and those at risk for futile treatment modifications at EOL, while controlling for multiple confounders, including age, gender, smoking status, histology, stage at diagnosis, year of SACT treatment, and SACT treatment details. A p-value of $< 0.05$ was considered *a priori* to be statistically significant. All analyses were conducted using the R statistical package v3.3.0 [18].

## 3. Results

### 3.1. Baseline demographics, clinical characteristics & mortality rates

In total, 1974 lines of SACT were identified, representing 1089 NSCLC patients receiving at least one cycle of SACT in 2005–2014. 23 (2%) were excluded due to lost to follow-up, and a further 22 (2%) were excluded due to incomplete SACT documentation, leaving 1044 patients for analysis. Among these 1044 patients, 51% were female, 62% were adenocarcinoma, 79% were current/former smokers, 83% were advanced stage at diagnosis, and 77% received palliative-intent treatment. Of the 46 patients on a trial protocol, 70% participated in a trial using cytotoxic chemotherapy agents, 22% in a trial with targeted agents, and the remaining 8% received a combination of SACT modalities. Table 1 outlines the characteristics of patients in each of the post-SACT survival groups. Patients experiencing early post-SACT mortality showed no significant differences in terms of age at diagnosis or histology than those surviving > 30 days post-SACT, but patients experiencing early mortality were significantly more likely to be male (56% vs. 47%, $p = 0.008$), report a former smoking history (62% vs. 52%, $p = 0.025$), receive SACT in 2005–2009 (53% vs. 44%), $p = 0.021$), have a disease duration less than 12 months (59% vs. 28%, $p < 0.001$), have more advanced disease (Stage III or IV) at diagnosis (91% vs. 81%, $p < 0.001$), receive palliative-intent treatment (95% vs. 72%, $p < 0.001$), have had prior SACT treatment (59% vs 37%, $p < 0.001$) and be on a TKI regimen (54% vs. 17%, $p < 0.001$) than those who survived more than 30 days post-SACT. The most common SACT modality used at the EOL were TKIs, with 54% (129/233) of patients using such drugs in their last month of life.

Cumulative 14, 30 and 60-day post-SACT mortality were 129 (12.4%), 233 (22.3%) and 370 (35%), respectively. Of the 233 patients dying within 30 days, 32 (14%) also experienced a new or changed SACT regimen within 14 days of death. (Fig. 1).

Fig. 2 describes the deaths within, or prior to, each post-SACT time interval, grouped by year of SACT receipt, and demonstrates that incident deaths in each interval, as well as cumulative mortality rates, decreased in 2010–2014, when compared to 2005–2009. Specifically, 30-day mortality rates dropped from 26% in 2005–2009 to 19% in 2010–2014.

**Table 1**
Patient, Tumor and SACT characteristics for patients undergoing SACT 2005–2014.

| | All Patients n = 1044 (%) | Post-SACT Survival | | | | p-value |
|---|---|---|---|---|---|---|
| | | ≤ 14 days n = 129 | 15-30 days n = 104 | 31-60 days n = 137 | > 61 days n = 674 | |
| **Age** (years), median (IQR) | 63.0 (55-70) | 62.0 (52-72) | 64.0 (56.8-70) | 63.0 (54-69) | 63.0 (55-70) | |
| ≤ 65 years | 579 (55%) | 71 (55%) | 56 (54%) | 79 (58%) | 373 (55%) | 0.942 |
| > 65 years | 465 (45%) | 58 (45%) | 48 (46%) | 58 (42%) | 301 (45%) | |
| **Gender** | | | | | | |
| Female | 536 (51%) | 59 (46%) | 44 (42%) | 68 (50%) | 365 (54%) | 0.063 |
| Male | 508 (49%) | 70 (54%) | 60 (58%) | 69 (50%) | 309 (46%) | |
| **Histology** | | | | | | |
| Adenocarcinoma | 644 (62%) | 75 (58%) | 68 (65%) | 88 (64%) | 413 (61%) | 0.237 |
| Not Otherwise Specified | 109 (10%) | 20 (16%) | 12 (12%) | 18 (13%) | 59 (9%) | |
| Other | 79 (8%) | 7 (5%) | 6 (6%) | 7 (5%) | 59 (9%) | |
| Squamous Cell | 212 (20%) | 27 (21%) | 18 (17%) | 24 (18%) | 143 (21%) | |
| **Smoking History** | | | | | | |
| Current | 259 (25%) | 27 (21%) | 20 (19%) | 38 (28%) | 174 (26%) | 0.234 |
| Former | 563 (54%) | 78 (60%) | 66 (64%) | 67 (49%) | 352 (52%) | |
| Never | 222 (21%) | 24 (19%) | 18 (17%) | 32 (23%) | 148 (22%) | |
| **Year of SACT Receipt** | | | | | | |
| 2005-2009 | 484 (46%) | 69 (53%) | 55 (53%) | 64 (47%) | 296 (44%) | 0.11 |
| 2010-2014 | 560 (54%) | 60 (47%) | 49 (47%) | 73 (53%) | 378 (56%) | |
| **Disease Duration** | | | | | | |
| ≤ 12 months | 365 (35%) | 77 (60%) | 60 (58%) | 72 (53%) | 156 (23%) | < 0.001[b] |
| > 12 months | 679 (65%) | 52 (40%) | 44 (42%) | 65 (47%) | 518 (77%) | |
| **Stage at Diagnosis**[a] | | | | | | |
| Stage I and II | 175 (17%) | 11 (9%) | 10 (10%) | 14 (10%) | 140 (21%) | < 0.001 |
| Stage III and IV | 869 (83%) | 118 (91%) | 94 (90%) | 123 (90%) | 534 (79%) | [b] |
| **Treatment Intent** | | | | | | |
| Curative | 240 (23%) | 9 (7%) | 2 (2%) | 6 (4%) | 223 (33%) | < 0.001 [b] |
| Palliative | 804 (77%) | 120 (93%) | 102 (98%) | 131 (86%) | 451 (67%) | |
| **SACT History** | | | | | | |
| Treatment Naive | 610 (58%) | 53 (51%) | 43 (41%) | 64 (47%) | 450 (67%) | < 0.001 [b] |
| Previous SACT Treatment | 434 (42%) | 76 (49%) | 61 (59%) | 73 (53%) | 224 (33%) | |
| **SACT Regimen** | | | | | | |
| Cytotoxic chemotherapy | 737 (71%) | 48 (38%) | 51 (49%) | 86 (62%) | 551 (81%) | < 0.001 [b] |
| Tyrosine Kinase Inhibitor | 261 (25%) | 76 (59%) | 50 (48%) | 42 (31%) | 93 (14%) | |
| Trial Protocol | 46 (4%) | 4 (3%) | 3 (3%) | 9 (6%) | 30 (5%) | |

IQR – interquartile range; NOS – not otherwise specified; SACT - systemic anti-cancer therapy; TKI – tyrosine kinase inhibitor.
[a] AJCC 7th edition clinical stage.
[b] denotes significant result.

### 3.2. Multivariable analysis of prognostic factors

Fig. 3a and 3b present the results of multivariable analysis for models constructed to assess the patient level factors associated with early mortality, and EOL SACT regimen changes. The models identified factors associated with a significantly increased risk of early mortality and EOL SACT regimen changes: males (OR: 1.48; p = 0.006 and OR: 1.84, p = 0.01), advanced disease at diagnosis [Stage III or IV disease (AJCC 7th edition; any T, N2, N3, M; any T, any N, M1a or M1b, respectively] (OR: 1.85; p = 0.006 and OR: 3.4, p = 0.021), palliative-intent SACT (OR: 6.75; p < 0.001 and OR: 4.43, p = 0.003), and use of EGFR-targeting agents (OR: 4.5; p < 0.001 and OR: 1.81, p = 0.02). Two factors were identified as being associated with a significantly decreased risk of early mortality following SACT: never smokers (OR: 0.62, p = 0.028) and individuals receiving SACT in the 2010–2014 (OR: 0.65, p = 0.002).

## 4. Discussion

In the current, retrospective, population-based study we found an overall 22.3% rate of 30-day post-SACT mortality and an overall 3.1% rate of SACT regimen changes within 14 days of death. Associated with a risk of both 30-day mortality and EOL regimen change were being male, advanced stage disease, palliative-intent treatment and use of EGFR-targeting agents. Never-smokers and those receiving SACT treatment in 2010–2014 showed a reduced risk of early mortality, while no factors were found to be associated with SACT regimen changes near EOL.

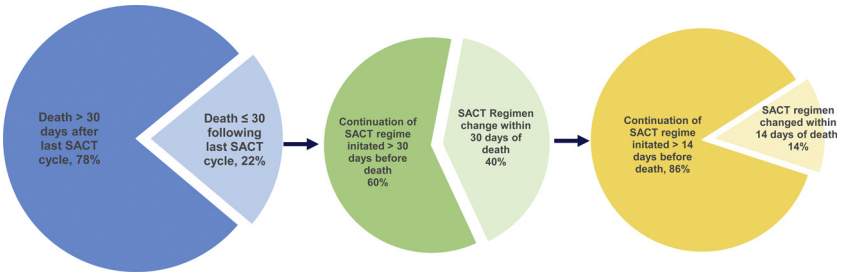


**Fig. 1.** 30-Day Mortality and End-of-Life Regimen Change Among NSCLC Patients Undergoing SACT.2005–2014.

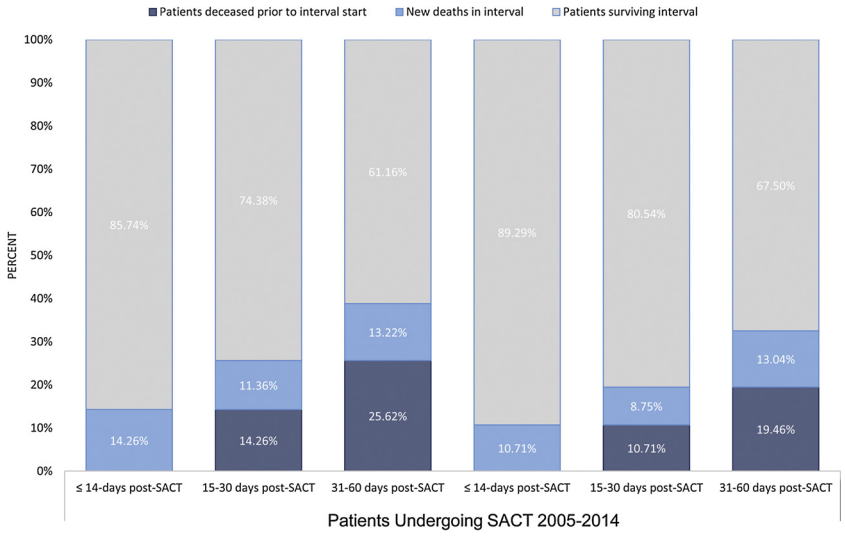


**Fig. 2.** Frequency and Cumulative Mortality in Post-SACT Time Intervals, by Year of SACT Receipt.

Our observed 22.3% rate of early mortality is mid-range of the 3.4–43% 30-day post-SACT mortality rates found in other studies for a variety of solid tumors and patient populations [3,7,11,12,2,13,16,19–25], but exceeds the 8% 30-day mortality rate observed among NSCLC patients receiving SACT in England [4]. One reason for this difference is that our study was population-based and largely included patients who received palliative-intent SACT for either advanced or recurrent disease. If we focused solely on the overall 30-day mortality rate for patients undergoing curative-intent treatment, the rate was 4.6%. In the curative setting, early mortality is less likely to represent futile care, but more likely to serve as a proxy of toxicity.

Our analysis also observed that a new or changed SACT regimen was used within 14-days of death in 3.1% of patients undergoing SACT treatment. This represents 14% of the patients who also experienced early mortality. While this rate itself does not appear to be high, the introduction of a new regimen or a change in regimen near death should be viewed differently than continuing the same regimen at the end of life. The former probably represents a more deliberate attempt from either the clinician or the patient to alter the disease trajectory, which is unlikely to materialize when such efforts are conducted so close to death [9,26], especially where there exist other options, such as best supportive care, to achieve the desired outcomes (symptom mitigation, improved quality of life) [27].

In our cohort, 54% of patients used EGFR-targeting drugs in their last month of life. These observations complement the findings of other studies [27,28], and demonstrate that there has been a transition towards preferred use of targeted therapies over conventional cytotoxic chemotherapy in the treatment of NSCLC at the EOL because of their efficacy and better tolerance. It is expected that use of this modality may continue to increase in the future [23,25]. Conversely, this increase in use of EGFR TKIs has translated to them being associated with an increased risk of early mortality following SACT [OR: 4.5, 95% CI: 3.27–6.18, $p < 0.001$]. It is possible that their oral administration, convenience and use beyond progression where alternative treatment options are limited has made it easy to prescribe/administer these drugs at the EOL even though they may not necessarily affect outcomes so close to death.

This study found that gender (biological sex at birth) is a significant modifier of risk for early mortality and EOL regimen changes. Specifically, males were found to have an increased risk for both outcomes [OR: 1.48, 95% CI: 1.12–1.95, $p = 0.006$ and OR: 1.84, 95%CI: 1.16–2.92, $p = 0.010$ respectively]. This is consistent with previous studies which also noted that males with NSCLC have an increased risk of death within 30 days of SACT [4], as well as an increased risk of 30-day post-surgical mortality [29]. Previous data suggested that females have better outcomes by virtue of the fact that they are more likely to be affected by earlier stage disease, more localized cancers, lower smoking rates and fewer comorbidities than males [4,29]. Although these hypotheses have merit, we postulate that further investigation into social and biological differences between males and females are warranted in order to provide further insights into this phenomenon [30]. Furthermore, this study also noted reduced risk of early mortality among never-smokers [OR: 0.62, 95% CI 0.41-0.95, $p = 0.028$], potentially mediated by the fact that NSCLC in never-smokers is considered genetically different than NSCLC in ever-smokers, likely driven by different molecular mechanisms [31]. Specifically, NSCLC in never-smokers is more frequently associated with targetable mutations, higher response to EGFR-targeting agents, and slower time to progression [32,33].

Of note, our analysis revealed that the 2010–2014 era, as compared to the 2005–2009 era, demonstrated lower 30-day mortality rates (19% vs. 26%). The more recent era was also associated with lower risk of early mortality [OR: 0.65, 95% CI: 0.49-0.86, $p = 0.002$]. This improvement coincided with a 26% increase in the number of community palliative and hospice beds in Alberta, as well as the adoption of the use of TKI as standard of care in NSCLC patients possessing a targetable mutation, suggesting that enhanced or more appropriate resources could lead to the uptake of different management options as well as better and more appropriate EOL care [3,34–36]. At our center, there are ongoing initiatives, such as integration of symptom nurses in clinics, to further encourage earlier engagement of palliative care in the disease trajectory so as to reduce futile use of SACT. Finally, our findings complement previous reports that have found an association between early mortality and palliative-intent therapy, and advanced clinical stage [3,12,14,23,25,37].

This study has some limitations. First, it represents a retrospective review of NSCLC cases so there are biases inherent to retrospective studies, namely selection and potential residual confounding secondary to unmeasured factors, such as performance status. However, this is a population-based study from a regional cancer care centre with a catchment of over 1 million residents of southern Alberta, Canada, and where demographics from this region are comparable to the rest of the country. Second, we used 30-day mortality after SACT as a measure of futile or inappropriate care. While this definition has been widely used previously, it is possible that SACT was in fact given appropriately and that the death occurred unexpectedly or unpredictably, and hence may not have been futile in intent per se. In addition, appropriate use of SACT at EOL is a measure that is derived retrospectively; treatment

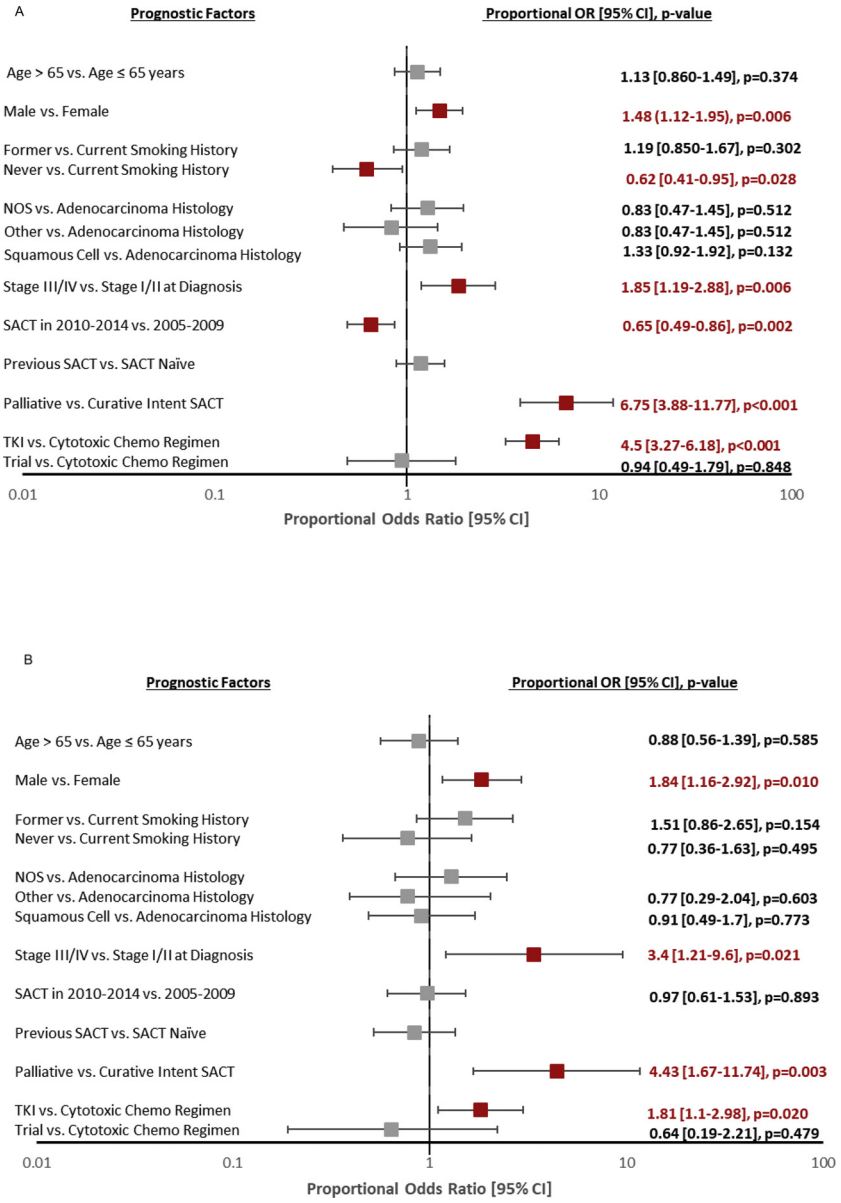


**Fig. 3.** (a) Proportional Odds Ratio of Patient Level Factors and Associated Risk of Early Mortality. (b) Proportional Odds Ratio of Patient Level Factors and Associated Risk of End-of-Life Regimen Change.

decisions are influenced by a variety of other factors (social, psychological, financial, cultural) which may further confound the assessment of EOL SACT [3,38,39]. Therefore, results should be interpreted within the context of these limitations.

This study presents a large scale, multi-year analysis of outcomes for NSCLC patients undergoing SACT, and demonstrates that a number of patients are at risk of early mortality when accessing SACT, particularly those at advanced stages and receiving palliative-intent treatment with EGFR-targeting agents. Importantly, this population-based study offers data that can be used as a reference for similar NSCLC populations, and is timely given the increasing evolution and availability of targeted and immunotherapy SACT agents. Early mortality following SACT likely represents misuse of SACT and underscores the importance of clear communication of the role of SACT and careful consideration of other non-SACT management approaches, such as palliative care. The data from this study provides a basis to inform future conversations between patients and physicians when navigating end-of-life options and late-stage disease management.

Additionally, this study sets a standard for the type of population level data recording, collection, and reporting that should be undertaken by health-care systems to allow for continuous quality improvement. Further efforts to determine the causal factors influencing SACT usage in this population will help to inform practice, mitigate harm, and optimize care for future patients.

## Conflict of interests

HL has received personal fees from Roche, outside the submitted work. All other authors have no relevant disclosures.

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