

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Ngo, P;Goldsbury, DE;Karikios, D;Yap, S;Yap, ML;Egger, S;O'Connell, DL;Ball, D;Fong, KM;Pavlakis, N;Rankin, NM;Vinod, S;Canfell, K;Weber, MF

Title:

Lung cancer treatment patterns and factors relating to systemic therapy use in Australia

Date:

2022-10-01

Citation:

Ngo, P., Goldsbury, D. E., Karikios, D., Yap, S., Yap, M. L., Egger, S., O'Connell, D. L., Ball, D., Fong, K. M., Pavlakis, N., Rankin, N. M., Vinod, S., Canfell, K. & Weber, M. F. (2022). Lung cancer treatment patterns and factors relating to systemic therapy use in Australia. ASIA-PACIFIC JOURNAL OF CLINICAL ONCOLOGY, 18 (5), pp.E235-E246. <https://doi.org/10.1111/ajco.13637>.

Persistent Link:

<https://hdl.handle.net/11343/298738>

TITLE

Lung Cancer Treatment Patterns and Factors Relating to Systemic Therapy Use in Australia**AUTHORS**

Preston Ngo^{a,b,*}, David E. Goldsbury^a, Deme Karikios^{c,d}, Sarsha Yap^a, Mei Ling Yap^{a,b,e,f,g}, Sam Egger^a, Dianne L. O'Connell^{a,b,h}, David Ball^{i,k}, Kwun M. Fong^{l,m}, Nick Pavlakis^{n,o}, Nicole M. Rankin^{b,p}, Shalini Vinod^q, Karen Canfell^{a,b,i}, and Marianne F. Weber^{a,b}

^a The Daffodil Centre, The University of Sydney, a joint venture with Cancer Council NSW, NSW 2011, Australia

^b Sydney School of Public Health, The University of Sydney, NSW 2050, Australia

^c Nepean Cancer Care Centre, Nepean Hospital, NSW 2747, Australia

^d Nepean Clinical School, the University of Sydney, NSW 2747, Australia

^e Collaboration for Cancer Outcomes Research and Evaluation (CCORE), Ingham Institute, the University of New South Wales, NSW 2170, Australia

^f Liverpool Cancer Therapy Centre, Liverpool Hospital, NSW 2170, Australia

^g Macarthur Cancer Therapy Centre, Campbelltown Hospital, NSW 2560, Australia

^h School of Medicine and Public Health, University of Newcastle, NSW 2308, Australia

ⁱ University of New South Wales, NSW 2052, Australia

^j Sir Peter MacCallum Department of Oncology, The University of Melbourne, VIC 3010, Australia

^k Department of Radiation Oncology Peter MacCallum Cancer Centre, VIC 3000, Australia

^l UQ Thoracic Research Centre, The Prince Charles Hospital, University of Queensland, QLD 4032, Australia

^m Department of Thoracic Medicine, The Prince Charles Hospital, QLD 4032, Australia

ⁿ Northern Clinical School, University of Sydney, NSW 2065, Australia

^o Department of Medical Oncology, Royal North Shore Hospital, NSW 2065, Australia

^p Sydney Health Partners, University of Sydney, NSW 2006, Australia

^q South Western Sydney Clinical School, University of NSW, NSW 2170, Australia

*** Corresponding author**

Preston Ngo

Email: preston.ngo@nswcc.org.au

153 Dowling St, Woolloomooloo NSW 2011, Australia

RUNNING TITLE**Lung cancer systemic therapy patterns****DATA AVAILABILITY STATEMENT**

The data used in this study cannot be made available by the authors as this may compromise participants' confidentiality and privacy. The data are available from the data custodians (Sax Institute, Services Australia, NSW Ministry of Health) for approved research projects. Enquiries can be made to the Sax Institute (see <https://www.saxinstitute.org.au/our-work/45-up-study/governance/>).

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/ajco.13637](https://doi.org/10.1111/ajco.13637).

This article is protected by copyright. All rights reserved.

FUNDING STATEMENT

This research was supported by an Australian Government Research Training Program (RTP) Scholarship.

ETHICS APPROVAL

Ethics approval for the 45 and Up Study provided by The University of NSW Human Research Ethics Committee and for this analysis by the NSW Population and Health Services Research Ethics Committee.

ABSTRACT:

Aim: Systemic therapies for lung cancer are rapidly evolving. This study aimed to describe lung cancer treatment patterns in New South Wales, Australia, prior to the introduction of immunotherapy and latest-generation targeted therapies.

Methods: Systemic therapy utilization and treatment-related factors were examined for participants in the New South Wales 45 and Up Study with incident lung cancer ascertained by record linkage to the New South Wales Cancer Registry (2006-2013). Systemic therapy receipt to June 2016 was determined using medical and pharmaceutical claims data from Services Australia, and in-patient hospital records. Factors related to treatment were identified using competing risks regressions.

Results: 1,116 lung cancer cases were identified with a mean age at diagnosis of 72 years and median survival of 10.6 months. Systemic therapy was received by 45% of cases. Among 400 cases with metastatic non-small-cell lung cancer, 51% and 28% received first- and second-line systemic therapy, respectively. Among 112 diagnosed with small-cell lung cancer, 79% and 29% received first- and second-line systemic therapy. The incidence of systemic therapy was lower for participants with indicators of poor performance status, lower educational attainment, and those who lived in areas

of socioeconomic disadvantage; and was higher for participants with small-cell lung cancer histology or higher body mass index.

Conclusion: This population-based Australian study identified patterns of systemic therapy use for lung cancer, particularly small-cell lung cancer. Despite a universal healthcare system, the analysis revealed socioeconomic disparities in health service utilization and relatively low utilization of systemic therapy overall.

KEYWORDS

chemotherapy, lung cancer, systemic therapy, targeted therapy treatment patterns

INTRODUCTION

Lung cancer is the leading cause of cancer death worldwide. Survival for lung cancer is poor, predominantly due to the high proportion of patients diagnosed with metastatic disease¹. For most metastatic patients, curative options are not available and treatment is limited to palliative radiation, supportive care, and systemic therapy².

In recent years, the treatment landscape for lung cancer has been transformed with the arrival of novel systemic therapies, many of which are subsidized by the Australian government as part of the universal healthcare system. These include latest-generation tyrosine kinase inhibitors (TKI) for EGFR-, ALK-, and ROS1-positive non-small cell lung cancer (NSCLC); and immune checkpoint inhibitors for both advanced NSCLC and small cell lung cancer (SCLC)³.

These innovations have generated considerable optimism but the overall impact on patients' outcomes will depend on the uptake of new treatments, highlighting the importance of healthcare utilization data. Prior studies estimated systemic therapy use by Australian lung cancer patients at 33-54% for metastatic NSCLC and 62-82% for all SCLCs⁴⁻⁹. However, knowledge gaps remain. Only one study has reported NSCLC treatment patterns beyond the first-line setting for Australian

patients¹⁰ and, to our knowledge, no such data have been reported for SCLC. Furthermore, no Australian studies have investigated the factors related to systemic therapy receipt.

In this study, we characterized treatment patterns between 2006 and 2016 for Australians diagnosed with lung cancer in *The 45 and Up Study*, providing estimates for systemic therapy delivery prior to the widespread adoption of novel targeted and immunotherapeutic agents. We expanded on a prior analysis of NSCLC cases in this cohort¹¹ to include all histological subtypes of lung cancer and more recent diagnoses, with a focus on systemic therapy.

MATERIALS AND METHODS

The 45 and Up Study

The study sample was selected from the Sax Institute's 45 and Up Study, a longitudinal cohort study of 267,153 adults from New South Wales (NSW), Australia, aged 45 and above^{12,13}. Participants were randomly sampled from the Services Australia Medicare enrolment database. Individuals aged over 80 years and residents of regional and remote areas were highlighted as groups of interest. To obtain sufficient numbers, these populations were oversampled by a factor of two. Participants joined the study by completing a baseline postal questionnaire (distributed 2006-2009) and gave consent for linkage of their records to population health databases. Information relating to health, lifestyle, socio-demographic characteristics were self-reported at baseline.

Ethics approval for the 45 and Up Study as a whole was provided by The University of NSW Human Research Ethics Committee and for this analysis by the NSW Population and Health Services Research Ethics Committee.

Data sources and record linkage

Questionnaire data were linked probabilistically to a number of population-wide health databases: (1) the NSW Admitted Patient Data Collection (APDC; Jul 2001-Jun 2016), a census of all public and

private hospital admissions in NSW; (2) the NSW Cancer Registry (NSWCR; Jan 1994–Dec 2013), contains all notifications of primary cancer diagnoses (except keratinocyte cancers) for NSW residents; (3) the NSW Emergency Department Data Collection (EDDC; Jan 2005–June 2016), captures the majority of Emergency Department (ED) presentations to NSW public hospitals; and (4) the Register of Births, Deaths, and Marriages (RBDM; Jan 2006–Jun 2016), contains death notifications. Datasets were linked by the Centre for Health Record Linkage using a best practice approach in privacy-preserving record linkage and the open-source probabilistic record linkage software ChoiceMaker¹⁴. A more detailed description of the linkage process has been provided previously¹⁵. Medication use and subsidized outpatient medical services from Jun 2004–Jun 2016 were available for all study participants from the Pharmaceutical Benefits Scheme (PBS; a database of government subsidized prescription pharmaceuticals) and the Medicare Benefits Schedule (MBS; a database of the Medicare services subsidized by the Australian government and available to all Australian residents), which are administered by Services Australia (formerly the Department of Human Services). MBS and PBS records were supplied to the Sax Institute, with linkage using a unique identifier that was provided to Services Australia.

Study sample

The sample contained participants whose first primary cancer diagnosis in the NSWCR was a malignant neoplasm of the bronchus or lung (ICD-10-AM code C34) that occurred between completion of the baseline questionnaire and 31 December 2013.

Participants were excluded if they:

- Had evidence of a false linkage, were aged <45 years at recruitment, participated in a pilot study, or were diagnosed at death.
- Were a client of the Department of Veterans' Affairs (DVA); PBS and MBS records for DVA clients were incomplete.

- Had a PBS record of an antineoplastic agent (ATC code beginning with 'L01') more than 90 days prior to their lung cancer diagnosis. Cases who received rituximab were retained due to its use for non-cancer indications.

Participants' characteristics

Lung cancer characteristics obtained from the NSWCR included the degree of spread at diagnosis (localized, regional, distant metastases, and unknown), age at diagnosis, and histology (non-squamous cell carcinoma [non-SCC], squamous cell carcinoma [SCC], small-cell lung cancer [SCLC], and other-specified or not-otherwise-specified histology [Other/NOS]). Localized and regional spread describes cancers that are limited to the tissue of origin or neighboring organs, tissues, and/or lymph nodes, respectively. Distant metastasis describes cancers that have spread to distant parts of the body and, throughout the text, is referred to as metastatic disease. Non-SCC included adenocarcinoma and large-cell carcinoma. Where mentioned, NSCLC comprised both non-SCC and SCC.

Demographic and health-related factors obtained at recruitment included self-reported body mass index (BMI), smoking status, disability, married / partnered, highest qualification, private health insurance status, area-level socioeconomic status quintile (SES; measured with Socio-Economic Indexes for Areas), Accessibility and Remoteness Index of Australia for place of residence (ARIA). Disability was a binary flag indicating that the participant reported requiring help with daily tasks or was unable to work due to illness or disability. The Charlson comorbidity index was calculated from in-patient records from the APDC for the 5-years prior to lung cancer diagnosis^{16–18}. Emergency department (ED) presentations were identified from the EDDC for the 12 months prior to diagnosis.

Outcomes

Systemic therapy was identified from PBS claims (ATC codes beginning with 'L01'), hospital records with procedure codes indicating chemotherapy administration, and MBS claims for chemotherapy

administration. This approach captures fact of treatment in 96% of lung cancer patients who receive systemic therapy¹⁹. Rituximab was not considered anti-cancer treatment for this population.

Immune checkpoint inhibitors for lung cancer were first listed on the PBS in 2017 and, therefore, were not captured in the data for this analysis.

To identify lines of therapy received, an algorithm based on other published work^{20–26} was developed and used to interpret PBS claims for participants diagnosed with metastatic NSCLC and all SCLCs.

Briefly, the algorithm organized PBS claims into distinct regimens based on the following rules:

- First-line therapy began with the first supply of an anti-cancer drug.
- Regimens ended when a 90 day gap occurred in which no claims for anti-cancer drugs were made.
- The line of therapy was advanced (e.g., from first-line to second-line) if a new drug was claimed and prescribed more than 28 days after the initiation of the previous regimen.
- If a new drug was claimed and was prescribed within 28 days of or before the first claim of the regimen, the regimen was classified as combination therapy.
- Cisplatin and carboplatin were interchangeable.

Claims for molecular diagnostics were also identified, including fluorescence in situ hybridization (FISH) tests for ALK rearrangement (available from July 2015) and EGFR mutation tests (available from May 2012). Codes used in this study are available in the supporting information (Table S1).

Surgery and radiotherapy were identified through MBS claims data and ICD-10-AM procedure codes from in-patient hospital records (Table S1). Fact and date of death were obtained from the RBDM.

Statistical analysis

We calculated the proportion of participants receiving treatment to 30 June 2016. Second- and third-line systemic therapy use was estimated for participants diagnosed with all SCLCs or metastatic non-SCC, SCC, and Other/NOS disease. The algorithm for identifying lines of therapy relied on PBS

claims which may not capture all treatment (e.g. a small number of participants may have only received systemic therapy as an inpatient in a public hospital and were therefore captured in the hospital billing system). To estimate the proportion of cases missed, we calculated the percentage of cases with records of systemic therapy identified through the MBS or APDC with no records of systemic therapy in the PBS.

Survival probabilities by stage and histology were estimated using the Kaplan-Meier method.

Multivariable regressions identified factors related to systemic therapy use among those diagnosed with metastatic disease. As early death precludes treatment, we applied a competing risks approach. Cause-specific hazard (CSH) regressions were used for death and systemic therapy separately and provided hazard ratios (HR) for each factor among those who were alive and untreated, respectively. Subdistribution hazards (SH) regressions²⁷ were performed to estimate subdistribution hazard ratios (SHR) which summarize the effects of factors on the cumulative incidence of treatment.

Schoenfeld residuals were plotted and a test of correlation was used to identify violations to the proportional hazards assumption. Where non-proportional hazards were present, time interaction terms were used. These terms were retained if they led to a material difference in the estimates of effect for the other covariates in the model.

Fully-adjusted and minimally-adjusted regressions were used for each analysis. All factors were included in the fully-adjusted regressions. The minimally-adjusted regressions included age, sex, and smoking status. Individuals in categories with low counts were removed.

All statistical analyses were performed in SAS v9.4 (SAS Institute Inc, Cary, NC) and R v3.6.1²⁸.

RESULTS

Study sample

The study sample comprised 1,116 eligible participants with lung cancer (Figure 1). At 30 June 2016, 903 (81%) participants in the sample had died. Among those who were alive, median follow-up was 3.9 years with a minimum of 2.5 years.

Participants' characteristics

Of the 1,116 cases identified, 632 (57%) were diagnosed with non-SCC, 183 (16%) with SCC, 112 (10%) with SCLC, and 189 (17%) with Other/NOS histology (Table 1). Metastatic disease was present at diagnosis for 49% of participants overall. A higher proportion of metastatic cases were observed for participants with SCLC (59%) and non-SCC (54%) compared to those with SCC (31%).

Overall, 57% of cases were men (Table 1). Mean age at diagnosis was higher than in the NSW lung cancer population in 2007 (72 versus 70 years)¹. Age at diagnosis by histology in our sample was highest for participants with Other/NOS histology and lowest for those with SCLC (74 years and 70 years). SCLC and SCC cases were predominantly former or current smokers at baseline (>95% and 91%), more so than those with non-SCC and Other/NOS histology (80% and 79%).

In this sample, 13% had a university degree and 58% did not have private health insurance (Table 1). The distribution of participants by area-level SES was skewed with 31% in the most disadvantaged quintile compared to 12% in the least disadvantaged quintile.

Survival

Median survival was 10.6 months (95% CI:9.4-11.8) and was higher for participants diagnosed with localized/regional disease (36.5 months, 95% CI:28.5-44.9) compared to those with metastatic disease (4.8 months, 95% CI:4.3-5.7). Median survival was 5.1 months (95% CI:4.4-5.8) for metastatic

NSCLC, 2.7 months (95% CI:1.9-4.5) for metastatic Other/NOS disease, and 7.9 months (95% CI:3.8-9.7) for metastatic SCLC.

Molecular testing

Biomarker testing was predominantly received by participants with non-SCC histology. EGFR mutation tests were received by 33% of metastatic non-SCC cases diagnosed between May 2012 (when the test was first subsidized through the MBS) and December 2013 (the end of NSWCR coverage). FISH tests for ALK rearrangement were too infrequent to report.

Systemic therapy and other treatments

Overall, 317 (28%) participants received no active anti-cancer treatment and 505 (45%) received radiotherapy. Among participants with NSCLC, 158 (19%) received surgery (Table 2). Systemic therapy was received by 506 (45%) participants, including 183 (53%) metastatic non-SCC cases, 20 (35%) metastatic SCC cases, 25 (31%) metastatic Other/NOS cases, and 88 (79%) all-stage SCLC cases (Table 2).

PBS claims data captured systemic therapy treatments for 93% of participants, for which second-line systemic therapy was identified for 105 (31%) participants with metastatic non-SCC, 7 (12%) with metastatic SCC, 8 (10%) with metastatic Other/NOS disease, and 32 (29%) with any SCLC (Table 2). Third-line systemic therapy was identified for 45 (13%) metastatic non-SCC cases and 8 (7%) all-stage SCLC cases. Third-line systemic therapy rates for metastatic SCC and Other/NOS cases were too low to report. SCLC cases with localized/regional disease and metastatic disease had similar systemic therapy rates so their outcomes were combined.

For metastatic NSCLC cases, 145 first-line regimens (75%) consisted of platinum-based chemotherapy, which decreased to 13 in the second-line setting (12%). For all SCLC cases, 78 first-line regimens (96%) and 10 second-line regimens (31%) contained a platinum compound, mostly in combination with etoposide. Regimens containing cyclophosphamide, doxorubicin, and vincristine

were absent in first-line therapy but made up 18 (56%) second-line regimens for SCLC cases. EGFR TKIs were primarily used by participants with metastatic non-SCC. For these individuals, 13 (8%) first-line regimens and 25 (24%) second-line regimens contained an EGFR TKI. These predominantly contained erlotinib.

Factors associated with systemic therapy

Of the 546 participants diagnosed with metastatic disease, 544 were included in the multivariable analyses. Of these, 279 (51%) received systemic therapy. Results from the minimally-adjusted regressions are available in Table S2.

The fully-adjusted regressions suggested no statistically significant variation in death or systemic therapy use by sex, smoking status, married/partnered status, or private health insurance status (Table 3). Older participants had both a significantly lower probability of when observations were censored at death (HR/year-increase:0.96, 95% CI:0.95-0.97) and a higher risk of death when observations were censored at treatment (HR/year-increase:1.04, 95% CI:1.02-1.06). The incidence of systemic therapy decreased overall with older age (SHR/year-increase:0.96, 95% CI:0.94-0.97). A time-dependent effect was identified for age in both the SH regressions and the CSH regressions. However, time interactions did not result in a material difference in the HRs and SHRs for other factors in the models and were, therefore, not retained.

Indicators of poor performance status (PS) – namely ED visits pre-diagnosis, comorbidities, and disability – were associated with a lower incidence of systemic therapy (Table 3). The CSH analyses showed that for individuals with ED presentations or comorbidities, the lower utilization was largely driven by higher mortality. On the other hand, participants with self-reported disability had a lower probability of systemic therapy when observations were censored at death (HR:0.66, 95% CI:0.44-0.97), but did not have an elevated risk of death when observations were censored at treatment (HR:1.06, 95% CI:0.75-1.50).

Other clinical factors were associated with systemic therapy receipt. The incidence of systemic therapy was higher for SCLC cases compared to non-SCC cases (SHR:2.48, 95% CI:1.77-3.48; Table 3).

Further, systemic therapy incidence was higher for individuals with higher BMI (SHR:1.53, 95% CI:1.09-2.16 for 30+ kg/m² versus <25 kg/m²).

Socio-demographic factors were also associated with treatment utilization. Participants who lived in less disadvantage areas had a higher incidence of systemic therapy (SHR:2.52, 95% CI:1.64-3.86 for least versus most disadvantaged quintiles), where 73% of individuals in the least disadvantaged quintile received systemic therapy compared to 39% in the most disadvantaged quintile (Table 3). Compared to participants who lived in major cities, those in regional and remote areas were more likely to receive treatment when observations were censored at death (HR:1.50, 95% CI:1.15-1.97) but also had a higher risk of death when observations were censored at treatment (HR:1.53, 95% CI:1.16-2.02; Table 3). As both effects were in the same direction, the incidence of treatment did not differ by remoteness of residence (SHR:1.21, 95% CI:0.93-1.58). Further, systemic therapy incidence was higher for those with a school certificate compared to those with no qualifications (SHR:1.58, 95% CI:1.07-2.31).

DISCUSSION

This is one of few Australian studies to characterize systemic therapy patterns for lung cancer patients, and the first to describe treatment after first-line therapy for SCLC. We found that half of all cases received systemic therapy, and a quarter of metastatic cases received second-line therapy. Systemic therapy use was higher for participants living in less disadvantaged areas, and those with higher BMI, or diagnosed with SCLC; and lower for those with older age, ED presentations prior to diagnosis, comorbidities, or disability.

Our results are consistent with prior Australian studies (Table S3) which report systemic therapy rates of 33-54% for metastatic NSCLC and 62-82% for all SCLCs⁴⁻⁹. Second- and third-line therapy

rates were also comparable to those observed in the PivOTAL study, which documented treatment patterns for 208 Australian patients with metastatic NSCLC diagnosed between 2011 and 2013. The PivOTAL study found that 60% of Australian patients who received first-line therapy went on to receive second-line therapy, of whom 39% received third-line therapy¹⁰. In our cohort, the corresponding proportions for metastatic NSCLC cases were 58% and 40%.

Treatment patterns reflected the coverage of subsidized medicines during the study period (2006-2016). EGFR TKIs were only available as first-line therapy in Australia from 2014³, resulting in the small proportion receiving them as first-line therapy in our study. Moreover, prescribers were not required to confirm EGFR mutation for erlotinib therapy prior to 2014, potentially creating less incentive for EGFR mutation tests during the study period. This may explain the low testing rates observed in our sample. Crizotinib and FISH tests for ALK rearrangement were subsidized late in the study period (July 2015) and therefore saw little use in this study³.

As expected, the incidence of systemic therapy was lower for cases with indicators of poor PS – namely older age, ED presentations, comorbidities, and disability. Similar results have been found in studies in Japan²⁶, Canada^{29–31}, and the United States^{21,32–34}. In addition, the association between systemic therapy receipt and BMI has previously been reported²⁶, and may reflect the role of weight loss as a prognostic factor²⁹. Our observation that systemic therapy use was lower for participants living in areas of socioeconomic disadvantage is also consistent with international evidence that socioeconomic disparities exist in chemotherapy delivery, even in universal healthcare settings³⁵. Unlike in prior analyses, we used competing risks regression to show that, in our cohort, these disparities were not explained by differences in survival alone. Further research is needed to determine the extent to which differences in healthcare access, patients' preferences, or factors that are as yet undescribed contribute to the disparities observed.

Systemic therapy rates observed here fell short of published benchmarks. In 2010, it was estimated that 73% of SCLC and NSCLC patients would receive systemic therapy under perfect adherence to

guidelines³⁶. In contrast, only 49% of SCLC and NSCLC cases in this sample received systemic therapy. Observed utilization fell short of these targets for both metastatic NSCLC (51% observed use versus 79% optimal use) and all SCLCs (79% observed use versus 93% optimal use). It is possible that fewer individuals were eligible for systemic therapy in our cohort than the “optimal” rates suggest due to the oversampling of elderly participants. Nevertheless, the gaps between “optimal” and observed utilization were large and unlikely to be accounted for by the older case-mix alone, suggesting that treatment was underutilized. Moreover, the association between socio-demographic factors and systemic therapy receipt after controlling for age, comorbidity, ED presentations, and disability suggests that treatment was underutilized by those living in the most disadvantaged areas.

To our knowledge, this is the first Australian study to implement a claims-based algorithm to identify second- and third-line systemic therapy. The algorithm was based on methods described in other published work and shares similar limitations^{20–26}. For example, it may have misclassified planned changes in anti-cancer drugs as the initiation of a new line of therapy. This was mitigated somewhat in our analysis because the delayed introduction of a drug did not count as a new line of therapy if it was prescribed in advance. Further, the algorithm did not capture unsubsidized treatment such as treatment that is funded out-of-pocket or provided as part of a clinical trial or medicines access program. We note that 5% of patients with a respiratory or thoracic cancer in the Western Sydney area participated in a clinical trial during this time period³⁷. Therefore, the second- and third-line therapy rates reported here may be underestimates. Despite these limitations, the algorithm provided a plausible picture of lung cancer treatment that is consistent with published data¹⁰.

PS at diagnosis was not available in this study, however, age at diagnosis, ED presentations, and the presence of comorbidities are demonstrated predictors of PS³⁸. Additionally, self-reported disability, indicating that a person had limited ability for self-care, roughly corresponds to an ECOG scale PS of 3 or 4 where systemic therapy is not recommended^{2,39}. Indeed, systemic therapy use was lower for those with disability in this study compared to those without. Combined, these variables likely

provide a reliable proxy for PS. However, we expect that some of the variation in treatment was due to uncaptured differences in PS.

CONCLUSION

In summary, this study establishes a baseline for lung cancer treatment patterns in Australia prior to the arrival of immunotherapies and novel targeted therapies. Our findings suggest that systemic therapy was underutilized and highlight a gap in care that was pronounced for cases living in areas of socioeconomic disadvantage. As treatment continues to innovate, disparities in care will likely translate to disparities in survival, emphasizing the need for improved implementation in underserved populations.

ACKNOWLEDGEMENTS

This research was completed using data collected through the 45 and Up Study (www.saxinstitute.org.au). The 45 and Up Study is managed by the Sax Institute in collaboration with major partner Cancer Council NSW; and partners: the National Heart Foundation of Australia (NSW Division); NSW Ministry of Health; NSW Government Family & Community Services – Ageing, Carers and the Disability Council NSW; and the Australian Red Cross Blood Service. We thank the many thousands of people participating in the 45 and Up Study, the Centre for Health Record Linkage, Services Australia, NSW Ministry of Health, and the Cancer Institute NSW for use of their data.

This research was supported by an Australian Government Research Training Program (RTP) Scholarship.

CONFLICT OF INTEREST STATEMENT

DK reports personal fees from Merck Sharp & Dohme outside the submitted work. KC is co-principal investigator of an unrelated investigator-initiated trial of cervical screening in Australia (Compass; ACTRN12613001207707 and NCT02328872), which is conducted and funded by the VCS Foundation

(VCS), a government-funded health promotion charity. The VCS Foundation received equipment and a funding contribution from Roche Molecular Systems USA. However, neither KC nor her institution on her behalf (Cancer Council NSW) receives direct funding from industry. DB reports personal fees from AstraZeneca outside the submitted work. KMF reports grants from various funding bodies; travel support for talks at industry-sponsored scientific meetings pro bono, non-financial support from Mevis and Olympus, and personal fees from various universities, international funding bodies, UpToDate, and Cochrane Clinical Answers, outside the submitted work. NP reports grants from Bayer, Roche, and Pfizer; personal fees from Roche, Pfizer, Bristol Myers Squibb, Merck Sharp & Dohme, Merck KgA, Ipsen, Amgen, Novartis, Takeda, and Boehringer Ingelheim, outside the submitted work. SV reports personal fees from AstraZeneca outside the submitted work. All other authors declare no competing interests.

REFERENCES

1. Australian Institute of Health and Welfare. Lung cancer in Australia. Canberra; 2011.
2. Cancer Council Australia Lung Cancer Guidelines Working Party. Clinical practice guidelines for the treatment of lung cancer. [Internet]. Vol. 2020; Sydney: Cancer Council Australia; [cited 2020 Sep 16]. Available from: <https://wiki.cancer.org.au/australiawiki/index.php?oldid=192285>
3. Department of Health. Schedule of Pharmaceutical Benefits. [Internet]. Vol. 2020; Canberra. ; 2020. Available from: <http://www.pbs.gov.au/browse/publications>
4. Bishnoi S, Pittman K, Colbeck M, Townsend A, Hardingham J, Sukumaran S, et al. Small Cell Lung Cancer: Patterns of care and their influence on survival - 25 years experience of a single Australian oncology unit. *Asia Pac J Clin Oncol*. 2011 Sep;7(3):252–7.
5. Duggan KJ, Wiltshire J, Strutt R, Boxer MM, Berthelsen A, Descallar J, et al. Palliative care and psychosocial care in metastatic non-small cell lung cancer: factors affecting utilisation of services and impact on patient survival. *Support care cancer Off J Multinatl Assoc Support Care Cancer*. 2019 Mar;27(3):911–9.
6. Jiwa M, Maujean E, Spilsbury K, Threlfal T. The trajectory of lung cancer patients in Western Australia—A data linkage study: Still a grim tale. *Lung Cancer*. 2010 Oct;70(1):22–7.
7. Mitchell PL, Thursfield VJ, Ball DL, Richardson GE, Irving LB, Torn-Broers Y, et al. Lung cancer in Victoria: are we making progress? *Med J Aust*. 2013/11/19. 2013;199(10):674–9.
8. Richardson GE, Thursfield VJ, Giles GG. Reported management of lung cancer in Victoria in 1993: comparison with best practice. *Anti-Cancer Council of Victoria Lung Cancer Study Group. Med J Aust*. 2000/06/09. 2000;172(7):321–4.

9. Vinod SK, O'Connell DL, Simonella L, Delaney GP, Boyer M, Peters M, et al. Gaps in optimal care for lung cancer. *J Thorac Oncol*. 2008/08/02. 2008 Aug;3(8):871–9.
10. de Castro J, Tagliaferri P, de Lima VCCCC, Ng S, Thomas M, Arunachalam A, et al. Systemic therapy treatment patterns in patients with advanced non-small cell lung cancer (NSCLC): PivOTAL study. *Eur J Cancer Care (Engl)*. 2017/07/28. 2017 Nov;26(6):e12734.
11. Yap S, Goldsbury D, Yap ML, Yuill S, Rankin N, Weber M, et al. Patterns of care and emergency presentations for people with non-small cell lung cancer in New South Wales, Australia: A population-based study. *Lung Cancer*. 2018/07/24. 2018;122:171–9.
12. Banks E, Redman S, Jorm L, Armstrong B, Bauman A, Beard J, et al. Cohort profile: the 45 and up study. *Int J Epidemiol*. 2007/09/21. 2008;37(5):941–7.
13. Mealing NM, Banks E, Jorm LR, Steel DG, Clements MS, Rogers KD. Investigation of relative risk estimates from studies of the same population with contrasting response rates and designs. *BMC Med Res Methodol*. 2010/04/02. 2010;10:26.
14. Centre for Health Record Linkage (CHeReL). Centre for Health Record Linkage [Internet]. 2020 [cited 2020 Sep 16]. Available from: <https://www.cherel.org.au/>
15. Bentley JP, Ford JB, Taylor LK, Irvine KA, Roberts CL. Investigating linkage rates among probabilistically linked birth and hospitalization records. *BMC Med Res Methodol*. 2012;12(1):149.
16. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373–83.
17. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011 Mar;173(6):676–82.
18. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. *J Clin Epidemiol*. 2004 Dec;57(12):1288–94.
19. Tervonen H, Creighton N, Zhao G, Ng M, Currow D. Capture of systemic anticancer therapy use by routinely collected health datasets. *Public Heal Res Pract*. 2020;
20. Abernethy AP, Arunachalam A, Burke T, McKay C, Cao X, Sorg R, et al. Real-world first-line treatment and overall survival in non-small cell lung cancer without known EGFR mutations or ALK rearrangements in US community oncology setting. *PLoS One*. 2017;12(6):e0178420.
21. Davidoff AJ, Tang M, Seal B, Edelman MJ. Chemotherapy and survival benefit in elderly patients with advanced non-small-cell lung cancer. *J Clin Oncol*. 2010/03/31. 2010;28(13):2191–7.
22. Karve SJ, Price GL, Davis KL, Pohl GM, Smyth EN, Bowman L. Comparison of demographics, treatment patterns, health care utilization, and costs among elderly patients with extensive-stage small cell and metastatic non-small cell lung cancers. *BMC Heal Serv Res*. 2014/11/14. 2014;14:555.
23. McKay C, Burke T, Cao X, Abernethy AP, Carbone DP. Treatment Patterns for Advanced Non-Small-cell Lung Cancer After Platinum-containing Therapy in U.S. Community Oncology

Clinical Practice. Clin Lung Cancer. 2016/05/10. 2016;17(5):449-460.e7.

24. Ramsey S, Henk HJ, Smith GL, Sollano J, Chen C. First-, second- and third-line lung cancer treatment patterns and associated costs in a US healthcare claims database. Lung Cancer Manag. 2015 Dec 17;4:131+.
25. Ramsey SD, Martins RG, Blough DK, Tock LS, Lubeck D, Reyes CM. Second-line and third-line chemotherapy for lung cancer: use and cost. Am J Manag Care. 2008/05/13. 2008;14(5):297–306.
26. Wang F, Mishina S, Takai S, Le TK, Ochi K, Funato K, et al. Systemic Treatment Patterns With Advanced or Recurrent Non-small Cell Lung Cancer in Japan: A Retrospective Hospital Administrative Database Study. Clin Ther. 2017/05/22. 2017;39(6):1146–60.
27. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. J Am Stat Assoc. 1999;94(446):496–509.
28. R Foundation for Statistical Computing. R: A Language and Environment for Statistical Computing [Internet]. Vienna, Austria; 2020. Available from: <https://www.r-project.org/>
29. Brule SY, Al-Baimani K, Jonker H, Zhang T, Nicholas G, Goss G, et al. Palliative systemic therapy for advanced non-small cell lung cancer: Investigating disparities between patients who are treated versus those who are not. Lung Cancer. 2016/05/31. 2016;97:15–21.
30. Doherty J, Dawe DE, Pond GR, Ellis PM. The effect of age on referral to an oncologist and receipt of chemotherapy among small cell lung cancer patients in Ontario, Canada. J Geriatr Oncol. 2018/10/16. 2019;10(3):449–58.
31. Sachter AG, Le LW, Lau A, Earle CC, Leighl NB. Real-world chemotherapy treatment patterns in metastatic non-small cell lung cancer: Are patients undertreated? Cancer. 2015/04/22. 2015;121(15):2562–9.
32. Behera M, Ragin C, Kim S, Pillai RN, Chen Z, Steuer CE, et al. Trends, predictors, and impact of systemic chemotherapy in small cell lung cancer patients between 1985 and 2005. Cancer. 2015/10/07. 2016;122(1):50–60.
33. Davis KL, Goyal RK, Able SL, Brown J, Li L, Kaye JA. Real-world treatment patterns and costs in a US Medicare population with metastatic squamous non-small cell lung cancer. Lung Cancer. 2014/12/24. 2015;87(2):176–85.
34. Parsons HM, Harlan LC, Stevens JL, Ullmann CD. Treatment of small cell lung cancer in academic and community settings: factors associated with receiving standard therapy and survival. Cancer J. 2014/03/29. 2014;20(2):97–104.
35. Forrest LF, Adams J, Wareham H, Rubin G, White M. Socioeconomic inequalities in lung cancer treatment: systematic review and meta-analysis. PLoS Med. 2013/02/09. 2013;10(2):e1001376.
36. Jacob S, Hovey E, Ng W, Vinod S, Delaney GP, Barton MB. Estimation of an optimal chemotherapy utilisation rate for lung cancer: an evidence-based benchmark for cancer care. Lung Cancer. 2010 Sep;69(3):307–14.
37. Smith A ‘Ben,’ Agar M, Delaney G, Descallar J, Dobell-Brown K, Grand M, et al. Lower trial participation by culturally and linguistically diverse (CALD) cancer patients is largely due to language barriers. Asia Pac J Clin Oncol. 2018 Feb;14(1):52–60.

38. Salloum RG, Smith TJ, Jensen GA, Lafata JE. Using claims-based measures to predict performance status score in patients with lung cancer. *Cancer*. 2010/10/20. 2011;117(5):1038–48.
39. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649–56.

Table 1. Characteristics of participants in the 45 and Up Study (2006-2009) with an incident lung cancer diagnosed to December 2013 by histological subtype.

Patient characteristics	Non-SCC (N [%])	SCC (N [%])	SCLC (N [%])	Other/NOS (N [%])
All cases	632 (100)	183 (100)	112 (100)	189 (100)
Sex				
Male	328 (52)	134 (73)	73 (65)	103 (55)
Female	304 (48)	49 (27)	39 (35)	86 (46)
Age at diagnosis				
<60	85 (13)	9 (5)	19 (17)	19 (10)
60-69	191 (30)	58 (32)	40 (36)	45 (24)
70-79	220 (35)	70 (38)	37 (33)	62 (33)
80+	136 (22)	46 (25)	16 (14)	63 (33)
Stage at diagnosis				
Localized / Regional	233 (37)	105 (57)	38 (34)	77 (41)
Distant Metastases	343 (54)	57 (31)	66 (59)	80 (42)
Unknown	56 (9)	21 (12)	8 (7)	32 (17)
Emergency department visits 12 months pre-diagnosis				
No	374 (59)	113 (62)	72 (64)	108 (57)
Yes	258 (41)	70 (38)	40 (36)	81 (43)
Charlson comorbidity index				
0 at diagnosis	497 (79)	132 (72)	82 (73)	125 (66)
1+ at diagnosis	135 (21)	51 (28)	30 (27)	64 (34)
Disability at baseline				
No	550 (87)	151 (83)	86 (77)	162 (86)
Yes	82 (13)	32 (18)	26 (23)	27 (14)
Body mass index at baseline†				
< 25	265 (42)	69 (38)	31 (28)	81 (43)
25 to 30	201 (32)	74 (40)	31 (28)	55 (29)
30+	121 (19)	25 (14)	42 (38)	31 (16)
Smoking status at baseline†				
Never-smoker	122 (19)	16 (9)	+	38 (20)
Former smoker	361 (57)	114 (62)	+	97 (51)
Current smoker	147 (23)	53 (29)	+	52 (28)
Remoteness of residence (ARIA)				
Major cities	325 (51)	95 (52)	60 (54)	100 (53)
Regional / Remote	307 (49)	88 (48)	52 (46)	89 (47)
SES Quintile				
1 (Most disadvantaged)	185 (29)	66 (36)	29 (26)	61 (32)

2	160 (25)	43 (24)	31 (28)	50 (27)
3	123 (20)	25 (14)	17 (15)	28 (15)
4	82 (13)	35 (19)	23 (21)	25 (13)
5 (Least disadvantaged)	82 (13)	14 (8)	12 (11)	25 (13)
Private health insurance				
Yes	290 (46)	69 (38)	33 (30)	72 (38)
No	342 (54)	114 (62)	79 (71)	117 (62)
Highest Qualification‡				
No school certificate or other qualification	111 (18)	40 (22)	30 (27)	33 (18)
School certificate	181 (29)	44 (24)	29 (26)	53 (28)
High school / Trade / Diploma	234 (37)	72 (39)	43 (38)	68 (36)
University degree or higher	91 (14)	20 (11)	7 (6)	25 (13)

Note: Percentages may not add up to 100 due to rounding and missing data.

† Small numbers suppressed; >95% of SCLC cases were former or current smokers at baseline.

‡ Missing data not shown.

Abbreviations: Non-SCC, non-squamous cell carcinoma; SCC, squamous cell carcinoma; SCLC, small-cell lung cancer; Other/NOS, other-specified or not-otherwise-specified carcinoma; ARIA, Accessibility and Remoteness Index of Australia; SES, socioeconomic status.

Table 2. Systemic therapy utilization to June 2016 among incident lung cancer patients in the 45 and Up Study (2006-2009), diagnosed to December 2013.

	Non-SCC (N [%])	SCC (N [%])	Other/NOS (N [%])
All cases	632	183	189
No treatment	176 (28)	39 (21)	84 (44)
Surgery	113 (18)	45 (25)	31 (16)
Radiotherapy	276 (44)	96 (53)	69 (37)
Systemic therapy	290 (46)	75 (41)	53 (28)
Localized/Regional	233	105	77
No treatment	44 (19)	12 (11)	27 (35)
Surgery	100 (43)	41 (39)	28 (36)
Radiotherapy	103 (44)	55 (52)	24 (31)
Systemic therapy	86 (37)	49 (47)	21 (27)
Distant Metastases	343	57	80
No treatment	104 (30)	18 (32)	41 (51)
Surgery	12 (4)	†	†
Radiotherapy	157 (46)	31 (54)	32 (40)
Systemic therapy	183 (53)	20 (35)	25 (31)
First-line (PBS only†)	174 (51)	19 (33)	22 (28)
Second-line (PBS only‡)	105 (31)	7 (12)	8 (10)
Third-line (PBS only‡)	45 (13)	†	†
Unknown stage	56	21	32
No treatment	28 (50)	9 (43)	16 (50)
Surgery	†	†	†
Radiotherapy	16 (29)	10 (48)	13 (41)
Systemic therapy	21 (38)	6 (29)	7 (22)
SCLC (N [%])			
All cases	112		
No treatment	18 (16)		

Surgery	†
Radiotherapy	64 (57)
Systemic therapy	88 (79)
First-line (PBS only‡)	81 (72)
Second-line (PBS only‡)	32 (29)
Third-line (PBS only‡)	8 (7)

Note: Stage-specific outcomes for SCLC cases not presented due to small numbers.

† Small numbers suppressed.

‡ Lines of therapy identified in Pharmaceutical Benefits Scheme claims dataset alone (accounts for 93% of utilization), systemic therapy identified in hospital records from the Admitted Patient Data Collection and Medicare Benefits Schedule claims excluded.

Abbreviations: Non-SCC, non-squamous cell carcinoma; SCC, squamous cell carcinoma; SCLC, small-cell lung cancer; Other/NOS, other-specified or not-otherwise-specified carcinoma; PBS, Pharmaceutical Benefits Scheme.

Table 3. Multivariable analyses of factors associated with systemic therapy receipt among 544 metastatic lung cancer cases in the 45 and Up Study (2006-2009), diagnosed to December 2013.

	Received ST (N [%])	Subdistribution hazard analysis SHR for ST (95% CI)	Cause-specific hazard analysis HR for ST (95% CI)	HR for ST (95% CI)
Age at diagnosis (years)		0.96 (0.94-0.97)‡	0.96 (0.95-0.97)‡	
< 60	54 (76)			
60-69	109 (65)			
70-79	91 (50)			
80+	25 (20)			
p-value		<.001	<.001	
Sex				
Male	151 (48)	1.00	1.00	
Female	128 (56)	1.02 (0.79-1.32)	1.02 (0.79-1.33)	
p-value		.87	.87	
Smoking status at baseline				
Current smoker	84 (54)	1.00	1.00	
Ex-smoker	149 (48)	1.05 (0.78-1.41)	1.04 (0.77-1.41)	
Never-smoker	46 (57)	1.28 (0.86-1.91)	1.13 (0.75-1.70)	
p-value		.46	.84	
Histology				
Non-SCC	183 (53)	1.00	1.00	
SCC	20 (35)	0.82 (0.51-1.32)	0.81 (0.50-1.31)	
SCLC	51 (77)	2.48 (1.77-3.48)	2.72 (1.92-3.87)	
Other/NOS	25 (32)	0.65 (0.42-0.99)	0.75 (0.49-1.16)	
p-value		<.001	<.001	
Private health insurance				
No	149 (45)	1.00	1.00	
Yes	130 (60)	1.23 (0.94-1.62)	1.25 (0.95-1.65)	
p-value		.14	.11	
SES Quintile				
1 (most disadvantaged)	66 (39)	1.00	1.00	
2	67 (48)	1.49 (1.05-2.12)	1.34 (0.94-1.92)	
3	53 (58)	1.72 (1.18-2.50)	1.65 (1.12-2.42)	
4	48 (59)	1.85 (1.25-2.73)	1.82 (1.22-2.71)	
5 (least disadvantaged)	45 (73)	2.52 (1.64-3.86)	2.52 (1.63-3.89)	
p-value		<.001	<.001	
Remoteness of residence				
Major cities	147 (52)	1.00	1.00	
Regional or remote	132 (51)	1.21 (0.93-1.58)	1.50 (1.15-1.97)	
p-value		.16	.003	

Highest qualification			
No school certificate or other qualification	42 (40)	1.00	1.00
School certificate	80 (56)	1.58 (1.07-2.31)	1.47 (0.99-2.16)
High school / Trade / Diploma	115 (55)	1.35 (0.94-1.94)	1.11 (0.77-1.60)
University degree or higher	40 (56)	1.25 (0.79-1.97)	1.00 (0.63-1.60)
Missing	†	0.36 (0.09-1.50)	0.31 (0.07-1.28)
p-value		.03	.03
Married or partnered			
No	116 (50)	1.00	1.00
Yes	163 (52)	0.99 (0.77-1.29)	1.04 (0.80-1.35)
p-value		.96	.75
ED visits pre-diagnosis			
No	180 (59)	1.00	1.00
Yes	99 (41)	0.76 (0.59-0.98)	0.85 (0.65-1.10)
p-value		.03	.21
Charlson comorbidity index			
0	240 (58)	1.00	1.00
1+	39 (30)	0.63 (0.43-0.91)	0.77 (0.53-1.12)
p-value		.01	.17
Disability at baseline			
No	248 (54)	1.00	1.00
Yes	31 (38)	0.62 (0.42-0.92)	0.66 (0.44-0.97)
p-value		.01	.03
BMI at baseline (kg/m ²)			
< 25	98 (45)	1.00	1.00
25-30	102 (56)	1.37 (1.03-1.84)	1.25 (0.93-1.68)
30+	61 (61)	1.53 (1.09-2.16)	1.44 (1.02-2.03)
Invalid / Missing	18 (40)	1.52 (0.91-2.56)	1.37 (0.81-2.32)
p-value		.045	.17

Note: Estimates adjusted for all variables included in the table.

† Small numbers suppressed.

‡ Estimate of effect of one additional year of age at diagnosis.

Abbreviations: ST, systemic therapy; SHR, subdistribution hazard ratio; HR, hazard ratio; CI, confidence interval; Non-SCC, non-squamous cell carcinoma; SCC, squamous cell carcinoma; SCLC, small-cell lung cancer; Other/NOS, other-specified or not-otherwise-specified carcinoma; ED, emergency department; SES, socioeconomic status; BMI, body mass index

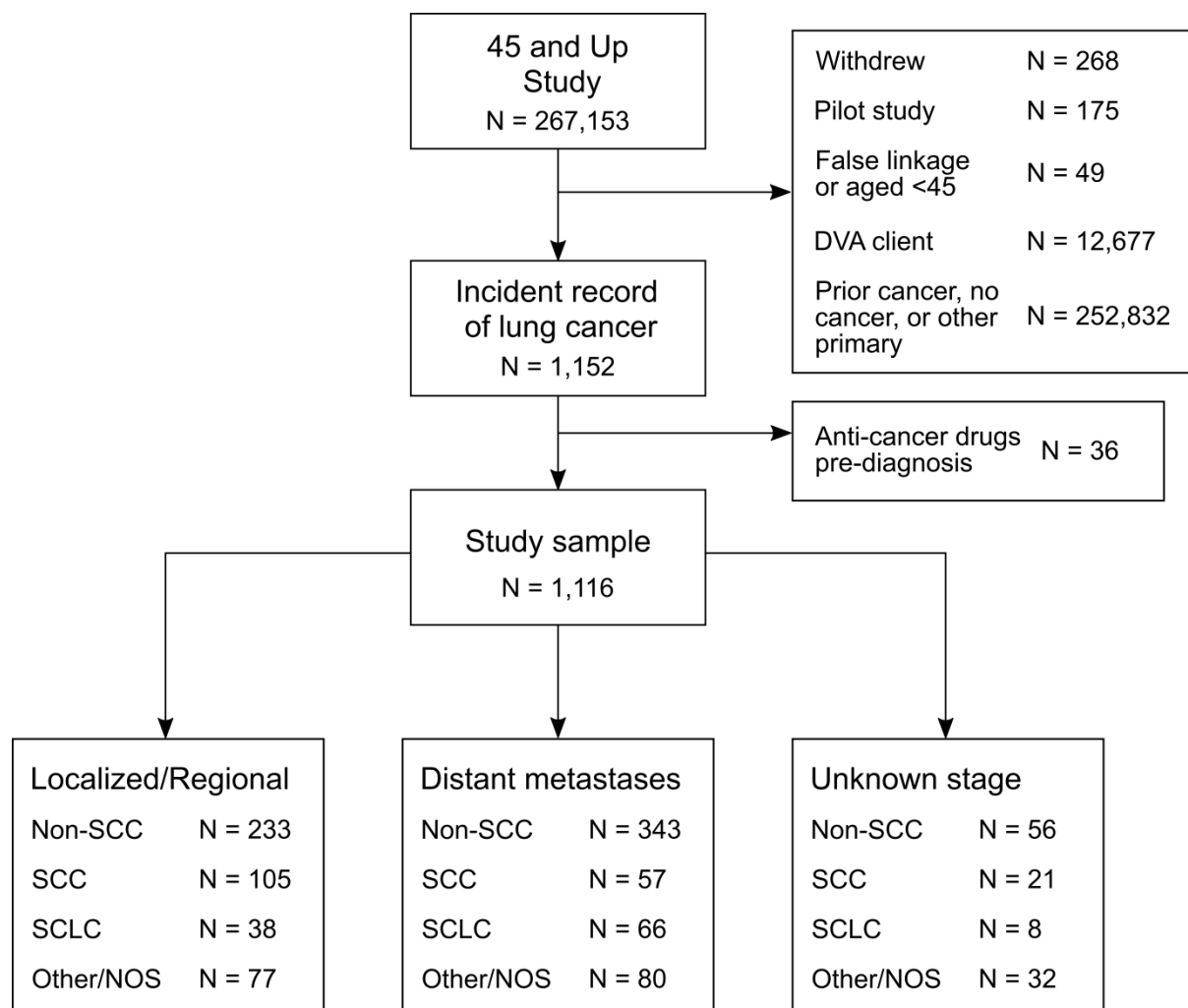


Figure 1. Study sample selection process.

Abbreviations: DVA, Department of Veterans' Affairs; Non-SCC, non-squamous cell carcinoma; SCC, squamous cell carcinoma; SCLC, small-cell lung cancer; Other/NOS, other-specified or not-otherwise-specified carcinoma.

Abstract

Systemic therapy for lung cancer participants in the 45 and Up Study (2006-2009; Australia) was relatively low, received by 45% of those with NSCLC and 79% with SCLC. Multivariable regressions found that treatment was more likely for participants who were healthy, had high SES, high BMI, and had SCLC. Competing risks regressions found that SES disparities in care were not explained by differences in mortality.

How many lung cancer patients receive systemic therapy?



Factors predicting treatment

- Socio-economic advantage
- High BMI
- Younger age at diagnosis
- No disability / ED visits / comorbidities

Auth