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A landscape of treatment options and survivorship for non-small cell lung cancer by Stage and Age.

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Northwest A&F University

2017

Thesis Committee Chair: Yuan Liu, Ph.D.

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Abstract

A landscape of treatment options and survivorship for non-small cell lung cancer by Stage and Age.

By Mengyu Di

Objectives: To examine the utilization and the effect of surgery (SG), systemic therapy (ST) and radiation (RT) in patients with non-small-cell lung cancer (NSCLC) using a large national tumor registry database.

Methods: Patients diagnosed with NSCLC were identified using the National Cancer Data Base (NCDB). They were classified into 12 strata based on their age groups (<60, 60-75, >75) and AJCC stage (I, II, III, IV). The treatment utilization pattern was assessed in each stratum. The impact of the treatment on overall survival (OS) was explored through multivariable (MVA) Cox proportional hazards model by controlling for baseline demographics and disease characteristics.

Results: Results: A total of 1,393,073 patients were diagnosed with NSCLC from 2004 to 2015. After applying inclusion and exclusion criteria, a total of 759,155 patients were included. From the distribution of utilization in each stratum, surgery was the most frequently used treatment modality in early stage (stage I and II), including surgery only and treatments containing surgery. With stage and age increasing, the utilization rate of surgery obviously decreased. The Cox model confirmed that surgery was associated with longer survival time after adjusted for other covariates. Radiation and systemic therapy were used more for older NSCLC patients. The result of survival analysis showed that if stage of cancer and other covariates were controlled, radiation related treatments tended to have better survival with age increasing. Another finding is that systemic therapy could bring benefits to NSCLC patients except patients in stage I.

Conclusions: Surgery is still the mainstay of therapy for patients with resectable and operable early stage NSCLC. Radiation therapy offers significant long-term survival advantage in elderly patients with NSCLC. The systemic therapy can provide benefits to patients when it was combined with other treatments. Patients who are candidates to no treatment should be carefully defined.

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1. Introduction

Lung cancer is the leading cause of cancer deaths (18.4% of the total cancer deaths) and the second most common cancer among both men and women [1, 2]. Overall, the chance that a man will develop lung cancer in his lifetime is about 1 in 15; for a woman, the risk is about 1 in 17. More people die of lung cancer than colon, prostate, ovarian and breast cancers combined [3]. There are two main types of lung cancer, non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). NSCLC accounts for about 85% of all cases of lung cancer cases in the United States [4]. The reason why lung cancer is an aggressive malignant disease is that more than 60% of the patients are diagnosed at advanced and usually incurable stage IIIB or IV [5]. Long-term survival for patients with advanced/metastatic disease is typically less than one year [6]. This study was limited to patients with NSCLC, as the natural history and prognosis of small cell lung cancer is drastically different from the non-small cell population.

The management of NSCLC requires a multidisciplinary approach. Patients will generally require a combination of surgery, radiation and/or systemic therapy, based mainly on the stage of the cancer. Other factors, such as a person's overall health and lung function, as well as certain traits of the cancer itself, are also important [7]. Surgery to remove the cancer may be the most consistent and successful option when feasible [4]. However, about 70% of lung cancer patients are with locally advanced or metastatic disease at the time of diagnosis. These patients are candidates for nonsurgical treatment. Chemotherapy is beneficial for

patients with metastatic disease, and the administration of concurrent chemotherapy and radiation is indicated for stage III lung cancer. Female patients with NSCLC taking hormone therapy were found to live longer than those who did not [8]. Systemic therapies are drugs that spread throughout the body to treat cancer cells wherever they may be, which include chemotherapy, hormonal therapy, and immunotherapy [9]. It's quite a complex process to choose the treatment that is right for patients with NSCLC, which can be confounded by the existing comorbidities, as a tremendous physiologic demand on the cardiovascular and respiratory system is required to place surgery.

However, there is a shortage of studies comparing the associated effects of different treatment modalities for NSCLC on overall survival. In this paper, we provided a birdview of distribution of treatment options among NSCLC patients stratified by their age and stage of cancer. We explored the survival pattern by treatments through detecting the survival differences between different treatment modalities as the main independent variable. The analysis was adjusted for patients' demographics and tumor characteristics such as site laterality, comorbidity score, TNM stages, histology of tumor at the time of diagnosis.

2. Materials and methods

2.1 Data source and patient selection

The National Cancer Database (NCDB) is jointly sponsored by the American College of Surgeons and the American Cancer Society. It is a clinical oncology database sourced from hospital registry data collected by more than 1500

Commission on Cancer (CoC)-accredited facilities tracking treatment and outcomes of patients [10]. This database includes patient demographics, socioeconomic factors, disease characteristics, treatment details and survival outcomes.

Cases were identified using the NSCLC Participant User File (PUF). A total of 1,393,073 adult patients (aged 18 years) were identified who were diagnosed with NSCLC between 2004 and 2015. This dataset then was limited to patients with invasive behavior from stage I to stage IV. Among patients who received treatment, the exclusion criteria include: those whose treatment started 180 days after diagnosis, patients who had previous or concurrent malignancy or with unknown treatment status, patients who received radiation with total radiation dose less than 40 GY, and patients with palliative care. A patient's cancer stage was determined by his pathologic stage group. The eligible patients were then stratified into 12 groups based on their age and stage: 1) patients in stage I and their age less than 60; 2) patients in stage I and their age between 60 to 75; 3) patients in stage I and their age greater than 75; 4) patients in stage II and their age less than 60; 5) patients in stage II and their age between 60 to 75; 6) patients in stage II and their age greater than 75; 7) patients in stage III and their age less than 60; 8) patients in stage III and their age between 60 to 75; 9) patients in stage III and their age greater than 75; 10) patients in stage IV and their age less than 60; 11) patients in stage IV and their age between 60 to 75; 12) patients in stage IV and their age greater than 75 (Table 1).

2.2 Definition of treatment cohorts, covariates and outcome

Pertinent patient demographics and treatment characteristics were available in NCDB. The patient's treatment facility type, age, gender, race-ethnicity group, site laterality, histology, comorbidity condition, size and/or extension of the primary tumor (T stage) and absence or presence of regional lymph node metastasis (N stage) were used in this analysis. Note that facility type was determined by the Commission on Cancer based on services provided and total annual case number. Comprehensive community cancer programs treat ≥ 500 cancer patients/year and participate in research. Academic programs, including those with NCI designation, treat >500 cancer patients, participate in research, and also provide postgraduate medical education. Patient's race-ethnicity non-Hispanic white, non-Hispanic black, Hispanic and Asian. Location of tumor was classified as right lower lobe (RLL), right middle lobe (RML), right upper lobe (RUL), left lower lobe (LLL) left upper lobe (LUL) and other. Histology was classified as adenocarcinomas, squamous cell carcinomas and other/unknown. Patient comorbidities were assessed using the Charlson-Deyo comorbidity score. The American Joint Committee on Cancer (AJCC) staging system was used to determine the T stage and N stage.

In each stratum, the patients were stratified into 8 groups based on their treatment status. Treatment modalities were classified as: 1) no-treatment for patients who received no treatment, or we could not find any record of treatment, 2) surgery only (SG) for patients that received only surgery, 3) systemic therapy only (ST) for patients who received only systemic therapy, 4) radiation only (RT) for patients

that received only radiation therapy, 5) surgery and systemic therapy (SG+ST) for patients who received both surgery and systemic therapy but no radiation, 6) surgery and radiation (SG+RT) for patients who received both surgery and radiation but no systemic therapy, 7) systemic therapy and radiation (ST+RT) for patients who received systemic therapy and radiation but no surgery, 8) surgery, systemic therapy and radiation (SG+ST+RT) for patients who received surgery, systemic therapy and radiation. No-treatment was the reference group.

The primary outcome measure was overall survival, which was defined as time from diagnosis to time of death or last follow-up.

2.3 Statistical methods

Statistical analysis was conducted using SAS Version 9.4, and SAS macros developed by the Biostatistics and Bioinformatics Shared Resource at Winship Cancer Institute [11]. Apache ECharts was used to visualize data [12].

First, a table of descriptive statistics of all patients was generated, where continuous variables were expressed as mean ± standard error of the mean. Second, in each stratum, frequencies of all different treatment utilizations were calculated and displayed in bubble charts. Third, a multivariable (MVA) logistic regression was carried out for predicting utilization of no treatment group vs. all other treated groups in stage I and II patients. Fourth, Kaplan-Meier (KM) plots were calculated for every stratum to compare the survival curves by treatment cohorts. The five-, and ten-year survival rates were estimated for patients diagnosed with NSCLC from 2004 and 2014 with follow-up until the end of 2015. Then, a MVA Cox

proportional hazard model for OS was fitted to detect the survival differences between different treatment modalities. Treatment modalities, facility type, age, gender, race-ethnicity group, site laterality, histology, Charlson-Deyo score, T stage and N stage were included in the MVA model.

3. Results

3.1 Patient characteristics

After applying inclusion and exclusion criteria, a total of 759,155 patients with NSCLC were analyzed (Figure 1). Of all patients, the treatment modalities were as follows: no treatment, 102,526 (13.5%); SG, 142,005 (18.7%); ST, 179,985 (23.7%); RT, 50,385 (6.6%); SG+ST, 89,230 (11.8%); SG+RT, 4,196 (0.6%); ST+RT, 166,932 (22.0%); SG+ST+RT, 23,896 (3.1%). There were 396,892 (52.3%) male and 362,263 (47.7%) female patients, and their average age at diagnosis was 67.73 (SD=10.91) years. About 77.5% (N=588,150) of patients were non-Hispanic White, and 69,272 (9.1%) patients were Hispanic. There were 237,555 (31.5%) cases reported to the NCDB by academic/research program and 355,157 (47.1%) cases reported by comprehensive community cancer program. The distribution of location of tumor was showed as follows: RLL, 112,181 (14.8%); RML, 32,753 (4.3%); RUL, 226,629 (29.9%); LLL, 88,811 (11.7%); LUL, 175,545 (23.1%). Adenocarcinoma was the most common subtype of NSCLC, accounting for 48.8% of cases. About 42.4% (N=321,942) of patients had Charlson-Deyo score not less than 1. Detailed patient treatment and characteristics are provided in Table 1.

Patients were then stratified into 12 subgroups as mentioned before: 1) stage I, age < 60 (N=42061, 5.54%); 2) stage I, age 60-75 (N=123247, 16.23%); 3) stage I, age > 75 (N=64116, 8.45%); 4) stage II, age < 60 (N=16762, 2.21%); 5) stage II, age 60-75 (N=40859, 5.38%); 6) stage II, age > 75 (N=19672, 2.59%); 7) stage III, age < 60 (N=49611, 6.54%); 8) stage III, age 60-75 (N=102055, 13.44%); 9) stage III, age > 75 (N=47823, 6.3%); 10) stage IV, age < 60 (N=64815, 8.54%); 11) stage IV, age 60-75 (N=123278, 16.24%); 12) stage IV, age > 75 (N=64856, 8.54%).

3.2 Nature distribution of treatment options by stage and age groups

A bubble chart (Figure 2) was used to display the distribution of treatment modalities by stage and age groups. In stage I, surgery was the most popular among patients whose condition permitted. The proportion of patients who received surgery only was 58.09%, 54.12% and 42.49% for age groups <60, 60-75 and >75 years, respectively. The combination of surgery and systemic therapy was applied to 24.27%, 19.21% and 10.76% of patients with age <60, 60-75 and >75 years, respectively. In stage II, the combination of surgery and systemic therapy became the most common treatment, 45.31% (age<60), 38.85% (age 60-75) and 20.96% (age>75) of patients got this therapy. The proportion of patients who received surgery had significant reduction compared with stage I, but it still was the second most common treatment, with 15.77%, 18.44% and 20.31% utilization rate in age group <60, 60-75 and >75 years, respectively. The combination of systemic therapy and radiation was provided to 13.16%, 17.72% and 20.19% of patients with age <60, 60-75 and >75 years, respectively. In stage III, the combination of systemic therapy and radiation was used the most frequently, 52.27% (age<60),

48.00% (age 60-75) and 33.53% (age>75) of patients received this therapy. The utilization of systemic therapy only also deserved mention. The proportion of patients who got this therapy was 16.47%, 19.22% and 26.23% for age groups <60, 60-75 and >75 years, respectively. In stage IV, the systemic therapy had overwhelming advantage with 46.47% (age<60), 50.47% (age 60-75) and 49.44% (age>75) of patients received it. The combination of systemic therapy and radiation was provided to 27.87%, 19.36% and 9.62% of patients with age < 60, 60-75 and >75, respectively. The utilization rate of no treatment was 16.46%, 21.48% and 33.35% for age groups <60, 60-75 and >75 years. Based on the bubble chart (Figure 2) and the data above, we could find that the utilization rates of no treatment, radiation and systemic therapy increased with age raising. When age increased, the growth rate of no treatment became greater, while those of radiation and systemic therapy were smaller. Detailed utilization rates of treatments by stage and age group are provided in Table 2.

3.3 Variables associated with receipt of no treatment

Table 3 illustrates the demographics and disease characteristics variables related to the receipt of no treatment in stage I and II patients, with associated odds ratios (OR) and 95% confidence intervals (CI). MVA logistic regression model demonstrated multiple factors associated with increased likelihood of no treatment: treatment at other facility [OR 1.46, CI [1.40– 1.52], p < 0.001], male patients [OR 1.08, [CI 1.05-1.12], p < 0.001], non-Hispanic Black patients [OR 1.68, CI [1.60-1.76], p < 0.001], other or unknown site laterality [OR 1.93, CI [1.82-2.04], p < 0.001], other or unknown histology [OR 1.55, CI [1.50-1.62], p < 0.001], no

comorbid conditions recorded [OR 1.09, CI [1.06-1.12], p < 0.001], unknown N stage [OR 11.60, CI [8.92-15.10], p < 0.001], and greater age [OR 1.04, CI [1.03–1.04], p < 0.001].

3.4 Association with overall survival

3.4.1 Overall five-year and 10-year survival rate by stage and age group

The model-based average five-year and ten-year survival rates by stage and age are shown in table 4. In early stage (stage I and stage II), except for no treatment group, the lowest survival rates were observed for the systemic therapy group, which were significantly lower than other treatment modalities. The combination of surgery and radiation was the best choice for early stage patients who were greater than 75 years old but still had the energy and vitality to undergo a surgery. In stage I, treatments included surgery had better survival, especially in patients under 75 years old. In stage II, the combination of surgery and radiation had the highest ten-year survival rate, above 90% in age group <=75 and above 85% in age group >75. In stage III and IV, the combination of surgery, systemic therapy and radiation and the combination of surgery and systemic therapy were good choices for available patients.

3.4.2 MVA survival analysis by stage and age group

Based on the results of MVA Cox proportional hazard model in each stratum (Figure 3), the academic/research program and Asians were associated with significantly better survival. In early stage, the top 2 most frequently used treatments, surgery only and the combination of surgery and systemic therapy had

significantly better survival than others. But in stage III and IV, having more treatments didn't indicate more effective. When adjusted for other covariates, the results of survival rates were confirmed with multivariable analysis. The combination of surgery and systemic therapy and the treatment included surgery, systemic therapy and radiation were the most powerful treatment in stage III and IV. When stage of cancer was adjusted, radiation related treatments tended to have better survival with age increasing.

4. Discussion

In this large retrospective population-based study, we found that the treatment modalities for NSCLC patients are mainly based on the stage of the cancer, but other factors, such as a patient's demographics and overall health are also important.

Results of this study confirm that surgery is the mainstay of treatment for NSCLC and offers the best chance of cure or longer survival [7]. However, according to the guideline of NSCLC, it may not be the best choice for patients who are older or with advanced cancer, because most of them have high rates of comorbidity and don't have adequate organ function to tolerate surgery resection [13]. Fortunately, technical improvements have led to the development of lung resection with video-assisted thoracoscopic surgery (VATS lung resection). Of the 21 comparative studies (two of which were randomized), a systematic review concluded that there were lower systemic recurrences and improved 5-year survival with VATS. [14] This approach is also better tolerated in older populations [15]. The United Nations

has agreed that 65+ years may be usually denoted as old age. This definition is dated, and while it remains accurate, in this day and age there are many 65-year-olds who are running marathons, working full time, and enjoying life to the fullest. And this trend is expected to continue as people continue to live longer. Nowadays, 70 is the new 50. The improvement of technology and individual's health condition may explain why all significantly effective treatments for elder patients include surgery resection. And a previous study also suggests that surgical treatment can extend the survival in stage IV NSCLC patients if the patients can tolerate surgery [16]. So, patients shouldn't decline surgery if they have the energy and vitality to undergo it. Even though novel therapies have quick development, surgery resection still plays the most important role in NSCLC treatment.

In the treatment of stage I and stage II NSCLC, radiation therapy alone is considered only when surgical resection is not possible because of limited pulmonary reserve or the presence of comorbidities [17]. Radiation is a reasonable option for lung cancer treatment in patients who are not candidates for surgery [18]. So elderly patients with NSCLC are more likely to be offered radiation only, despite existing evidence regarding the safety of surgery in selected elderly patients [19-21]. In our study, the uptrend with increasing age does apply to radiation alone, but the increasing rates slow down as cancer becoming more advanced. In patients with advanced or metastatic disease, radiation therapy can help achieve palliation and symptom control. Our results show that the proportion of combination of systemic therapy and radiation in stage III and IV is higher than that in early stage, and this combination can provide better survival than systemic therapy only. As

for the combination of surgery and radiation, it can't be proven that adding radiation has better effect than surgery only.

As the drugs of systemic therapy can be taken by mouth or injected into a vein, muscle, or another part of the body [22], it's more accessible for patients who are not surgery candidates. So, with age increasing and stage becoming more advanced, the proportion of patients receiving systemic therapy is growing. Chemotherapy for early stage NSCLC has a modest improvement in survival but it is often associated with serious adverse effects [23]. It can be confirmed by the results of Cox model in stage I. Systemic therapy only associates with shorter survival time. But the side effects of chemotherapy can be minimized with the latest supportive treatments [24]. From our results, when combined with other therapy, there is a beneficial effect instead. So, in early stage, more patients received a combination treatment.

With age raising and stage becoming advanced, more and more patients are without treatments. However, McGarry proves that patients with untreated early stages NSCLC have a very poor prognosis [24]. Our research shows that early stage patients are more treatable and most of treatment modalities provide benefits to patients compared to no treatment. So, patients who are not candidates to anticancer therapies should be carefully defined in early stage. Based on the MVA logistic regression model, there is a racial disparity indicating the odds for non-Hispanic black people receiving no treatment is 68% higher than that for non-Hispanic white patients. And patients are more likely to receive nothing if they are in better condition, such as without comorbidity, in N0 and N1 stage. Based on our

findings, better health means good time to undergo surgery instead of no treatment needed.

This study does have limitations. First, the data set lacks information about survival outcomes of patients diagnosed NSCLC in 2015, which limited our ability to analyze the entire cohort between 2004 and 2014. Second, various other factors could be involved in cox model besides what have been included, such as patients' smoking status, geographic location, income class, education level and preference. This study is additionally limited by the inherent limitations of an analysis of a national database, including the possibility of misclassification or errors in coding.

The strengths of this study include the use of a national level database with large sample size and long follow-up over an extended period. The ability to report five- and ten-year survival rates provides more insight into the mortality and survival of NSCLC patients.

5. Conclusion

In summary, the treatment modalities for NSCLC patients are mainly based on the stage of the cancer, but other factors, such as a patient's demographics and overall health are also important. With the quick development of new treatments for NSCLC, surgery still plays an important role in stage I to stage IV. If patients are suitable to receive surgery, it would be the most supportive treatment. Radiation therapy offers significant long-term survival advantage in elderly patients with NSCLC. This study also indicates that the systemic therapy can provide benefits to

patients when it was combined with other treatment and patients who are candidates to no treatment should be carefully defined.

Reference

[1] Cruz, C. S. D., Tanoue, L. T., & Matthay, R. A. (2011). Lung cancer: epidemiology, etiology, and prevention. Clinics in chest medicine, 32(4), 605-644.

[2] Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians, 68(6), 394-424.

[3] American Cancer Society. Facts & Figures 2019. American Cancer Society. 2019.

[4] Molina, J. R., Yang, P., Cassivi, S. D., Schild, S. E., & Adjei, A. A. (2008, May). Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. In Mayo Clinic Proceedings (Vol. 83, No. 5, pp. 584-594). Elsevier.

[5] Katzel, J. A., Fanucchi, M. P., & Li, Z. (2009). Recent advances of novel targeted therapy in non-small cell lung cancer. Journal of hematology & oncology, 2(1), 2.

[6] Paccagnella, A., Oniga, F., Bearz, A., Favaretto, A., Clerici, M., Barbieri, F., ... & Tumolo, S. (2006). Adding gemcitabine to paclitaxel/carboplatin combination increases survival in advanced non–small-cell lung cancer: Results of a phase II-III study. Journal of clinical oncology, 24(4), 681-687.

[7] Ettinger, D. S., Bepler, G., Bueno, R., Chang, A., Chang, J. Y., Chirieac, L. R., ... & Jahan, T. (2006). Non-small cell lung cancer: Clinical Practice Guidelines in Oncology™. JNCCN Journal of the National Comprehensive Cancer Network, 4(6), 548-582.

[8] Katcoff, H., Wenzlaff, A. S., & Schwartz, A. G. (2014). Survival in women with NSCLC: the role of reproductive history and hormone use. Journal of Thoracic Oncology, 9(3), 355-361.

[9] Canadian Cancer Society. Survival statistics for non–small cell lung cancer: Canadian Cancer Society; 2018.

[10] Bott, M. J., Patel, A. P., Crabtree, T. D., Morgensztern, D., Robinson, C. G., Colditz, G. A., ... & Broderick, S. (2015). role for surgical resection in the multidisciplinary treatment of stage IIIB non–small cell lung cancer. The Annals of thoracic surgery, 99(6), 1921-1928.

[11] Liu, Y., Nickleach, D. C., Zhang, C., Switchenko, J. M., & Kowalski, J. (2018). Carrying out streamlined routine data analyses with reports for observational studies: introduction to a series of generic SAS® macros. F1000Research, 7.

[12] Li, D., Mei, H., Shen, Y., Su, S., Zhang, W., Wang, J., ... & Chen, W. (2018). ECharts: A declarative framework for rapid construction of web-based visualization. Visual Informatics, 2(2), 136-146.

[13] Hurria, A., & Kris, M. G. (2003). Management of lung cancer in older adults. CA: a cancer journal for clinicians, 53(6), 325-341.

[14] Yan, T. D., Black, D., Bannon, P. G., & McCaughan, B. C. (2009). Systematic review and meta-analysis of randomized and nonrandomized trials on safety and efficacy of video-assisted thoracic surgery lobectomy for early-stage non-small-cell lung cancer. J Clin Oncol, 27(15), 2553-2562.

[15] Cattaneo, S. M., Park, B. J., Wilton, A. S., Seshan, V. E., Bains, M. S., Downey, R. J., ... & Rusch, V. W. (2008). Use of video-assisted thoracic surgery for lobectomy in the elderly results in fewer complications. The Annals of thoracic surgery, 85(1), 231-236.

[16] Kawano, D., Takeo, S., Katsura, M., Tsukamoto, S., Masuyama, E., & Nakaji, Y. (2011). Surgical treatment of stage IV non-small cell lung cancer. Interactive cardiovascular and thoracic surgery, 14(2), 167-170.

[17] Rowell, N. P., & Williams, C. (2001). Radical radiotherapy for stage I/II non-small cell lung cancer in patients not sufficiently fit for or declining surgery (medically inoperable). Cochrane Database of Systematic Reviews, (1).

[18] Strand, T. E., Brunsvig, P. F., Johannessen, D. C., Sundstrøm, S., Wang, M., Hornslien, K., ... & Norstein, J. (2011). Potentially Curative Radiotherapy for Non–Small-Cell Lung Cancer in Norway: A Population-Based Study of Survival. International Journal of Radiation Oncology* Biology* Physics, 80(1), 133-141.

[19] Senbaklavaci, O. (2014). Lobar lung resection in elderly patients with non-small cell lung carcinoma: impact of chronic obstructive pulmonary disease on surgical outcome. International surgery, 99(4), 319-324.

[20] Senbaklavaci, O., Taspinar, H., Hartert, M., Ergun, S., Keranen, S., & Vahl, C. F. (2012). Lobar lung resection in elderly patients with non-small cell lung carcinoma: impact of cardiac comorbidity on surgical outcome. Swiss medical weekly, 142(5152).

[21] Takamochi, K., Oh, S., Matsuoka, J., & Suzuki, K. (2011). Risk factors for morbidity after pulmonary resection for lung cancer in younger and elderly patients. Interactive cardiovascular and thoracic surgery, 12(5), 739-743.

[22] Systemic Therapy Options for Lung Cancer. (2018, June 04). Retrieved from https://www.foxchase.org/clinical-care/conditions/lung-cancer/treatment-lung-cancer/systemic-therapy

[23] Johnson, D. B., Bordeaux, J., Kim, J. Y., Vaupel, C., Rimm, D. L., Ho, T. H., ... & Dimou, A. (2017). Quantitative spatial profiling of PD-1/PD-L1 interaction and HLA-DR/IDO-1 predicts improved outcomes to anti-PD-1 in metastatic melanoma. Age, 65(16), 66-7.

[24] McGarry, R. C., Song, G., des Rosiers, P., & Timmerman, R. (2002). Observation-only management of early stage, medically inoperable lung cancer: poor outcome. Chest, 121(4), 1155-1158.

Tables and Figures

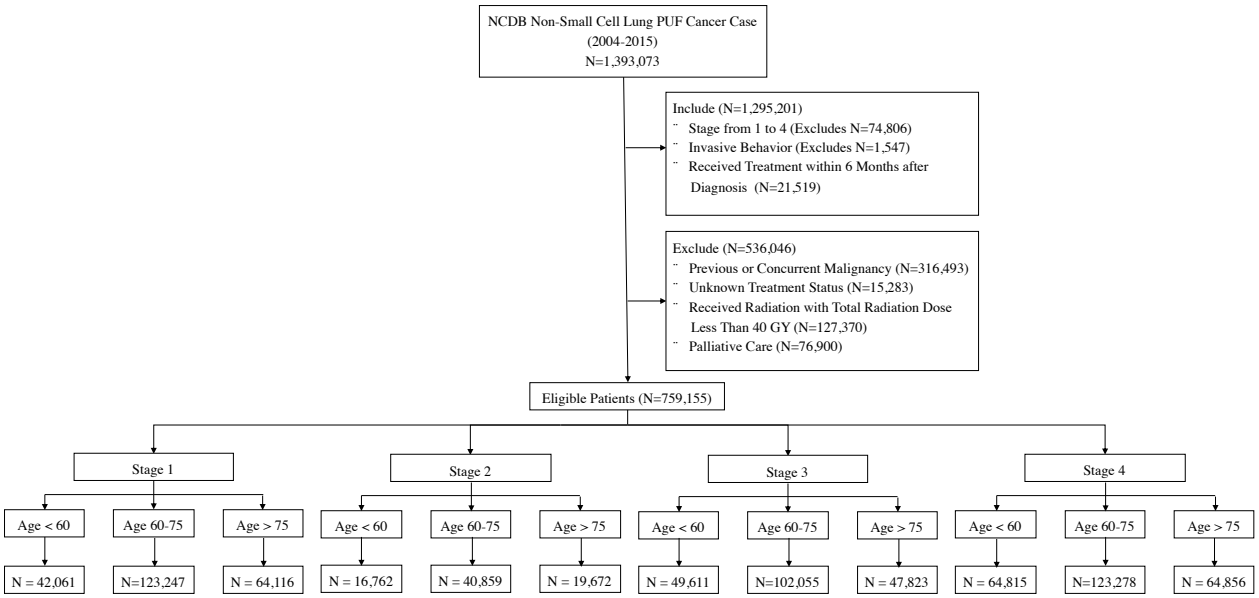


Figure 1 CONSORT diagram for patient selection.

Table 1 Baseline patient demographic, disease, and treatment related characteristics

Variable	Level	N (%) = 759155
Treatment	No treatment	102526 (13.5)
	SG	142005 (18.7)
	ST	179985 (23.7)
	RT	50385 (6.6)
	SG+ST	89230 (11.8)
	SG+RT	4196 (0.6)
	ST+RT	166932 (22.0)
	SG+ST+RT	23896 (3.1)
Facility Type	Academic/Research Program	237555 (31.5)
	Comprehensive Community Cancer Program	355157 (47.1)
	Other	160873 (21.3)
	Missing	5570
Sex	Male	396892 (52.3)
	Female	362263 (47.7)

Race-Ethnic Groups	Non-Hispanic, White	588150 (77.5)
	Non-Hispanic, Black	78268 (10.3)
	Hispanic	69272 (9.1)
	Asian	23465 (3.1)
Site Laterality	RLL	112181 (14.8)
	RML	32753 (4.3)
	RUL	226629 (29.9)
	LLL	88811 (11.7)
	LUL	175545 (23.1)
	Other/Unknown	123236 (16.2)
Histology	Adenocarcinomas	370256 (48.8)
	Squamous cell carcinomas	219451 (28.9)
	Other or Unknown	169448 (22.3)
Charlson-Deyo Score	0	437213 (57.6)
	1+	321942 (42.4)
T Stage	0	2821 (0.4)
	1	140928 (18.6)
	2	136877 (18.0)
	3	51703 (6.8)
	4	54189 (7.1)
	Other	367999 (48.5)
	Unknown	4638 (0.6)
N Stage	0	225364 (29.7)
	1	46569 (6.1)
	2	85238 (11.2)
	3	28119 (3.7)
	Other	369142 (48.6)
	Unknown	4723 (0.6)
Age at Diagnosis	67.73±10.91	

Figure 2 Distribution of treatment modalities by stage and age groups.

Table 2 Distribution of treatment modalities by stage and age groups.

Stage	Age	No treatment	SG	ST	RT	SG+ST	SG+RT	ST+RT	SG+ST+RT
I	< 60	3.95	58.09	2.62	3.83	24.27	0.71	3.53	3.00
	60 - 75	5.37	54.12	3.37	9.44	19.21	0.95	5.84	1.70
	> 75	10.19	42.49	6.35	19.64	10.76	0.96	8.91	0.69
II	< 60	4.03	15.77	5.05	1.49	45.31	1.16	13.16	14.03
	60 - 75	5.83	18.44	6.83	3.57	38.85	1.12	17.72	7.64
	> 75	12.08	20.31	11.61	10.77	20.96	1.41	20.19	2.67
III	< 60	7.27	2.84	16.47	2.17	9.06	0.34	52.27	9.58
	60 - 75	10.17	3.54	19.22	3.50	8.88	0.34	48.00	6.35
	> 75	19.89	4.06	26.23	8.12	5.56	0.41	33.53	2.20
IV	< 60	16.46	0.79	46.47	4.55	2.22	0.28	27.87	1.36
	60 - 75	21.48	1.07	50.47	4.82	1.96	0.19	19.36	0.65
	> 75	33.35	1.02	49.44	5.09	1.19	0.09	9.62	0.20

Table 3 Multivariable logistic regression for the receipt of no treatment vs. other treatments in stage I and II patients.

Covariate	Level	No Treatment = Yes		
		Odds Ratio	OR P-value	Type3 P-value
Stage Group	**I**	1.02 (0.98-1.06)	0.424	0.424
	II	-	-	
Facility Type	**Comprehensive Community Cancer Program**	1.31 (1.26-1.36)	<.001	**<.001**
	Other	1.46 (1.40-1.52)	<.001	
	Academic/Research Program	-	-	
Sex	**Male**	1.08 (1.05-1.12)	<.001	**<.001**
	Female	-	-	
Race-Ethnic Groups	**Asian**	1.46 (1.33-1.59)	<.001	**<.001**
	Hispanic	1.17 (1.11-1.23)	<.001	
	NH-Black	1.68 (1.60-1.76)	<.001	
	NH-White	-	-	
Site Laterality	**LLL**	1.03 (0.98-1.08)	0.297	**<.001**
	Other/Unknown	1.93 (1.82-2.04)	<.001	
	RLL	1.04 (1.00-1.10)	0.066	
	RML	1.04 (0.96-1.12)	0.341	
	RUL	1.00 (0.96-1.04)	0.94	
	LUL	-	-	
Histology	**Other or Unknown**	1.55 (1.50-1.62)	<.001	**<.001**
	Squamous cell carcinomas	1.14 (1.10-1.18)	<.001	
	Adenocarcinomas	-	-	
Charlson-Deyo Score	**0**	1.09 (1.06-1.12)	<.001	**<.001**
	1+	-	-	
T Stage	**1**	0.04 (0.03-0.06)	<.001	**<.001**
	2	0.04 (0.03-0.06)	<.001	
	3	0.06 (0.04-0.09)	<.001	
	4	0.10 (0.06-0.18)	<.001	
	Other	0.11 (0.08-0.16)	<.001	
	Unknown	0.01 (0.01-0.02)	<.001	
	0	-	-	
N Stage	**1**	0.75 (0.69-0.82)	<.001	**<.001**
	2	2.66 (2.07-3.42)	<.001	
	3	2.67 (1.23-5.79)	0.013	
	Other	2.12 (1.97-2.29)	<.001	
	Unknown	11.60 (8.92-15.10)	<.001	
	0	-	-	
Age at Diagnosis		1.04 (1.03-1.04)	<.001	**<.001**

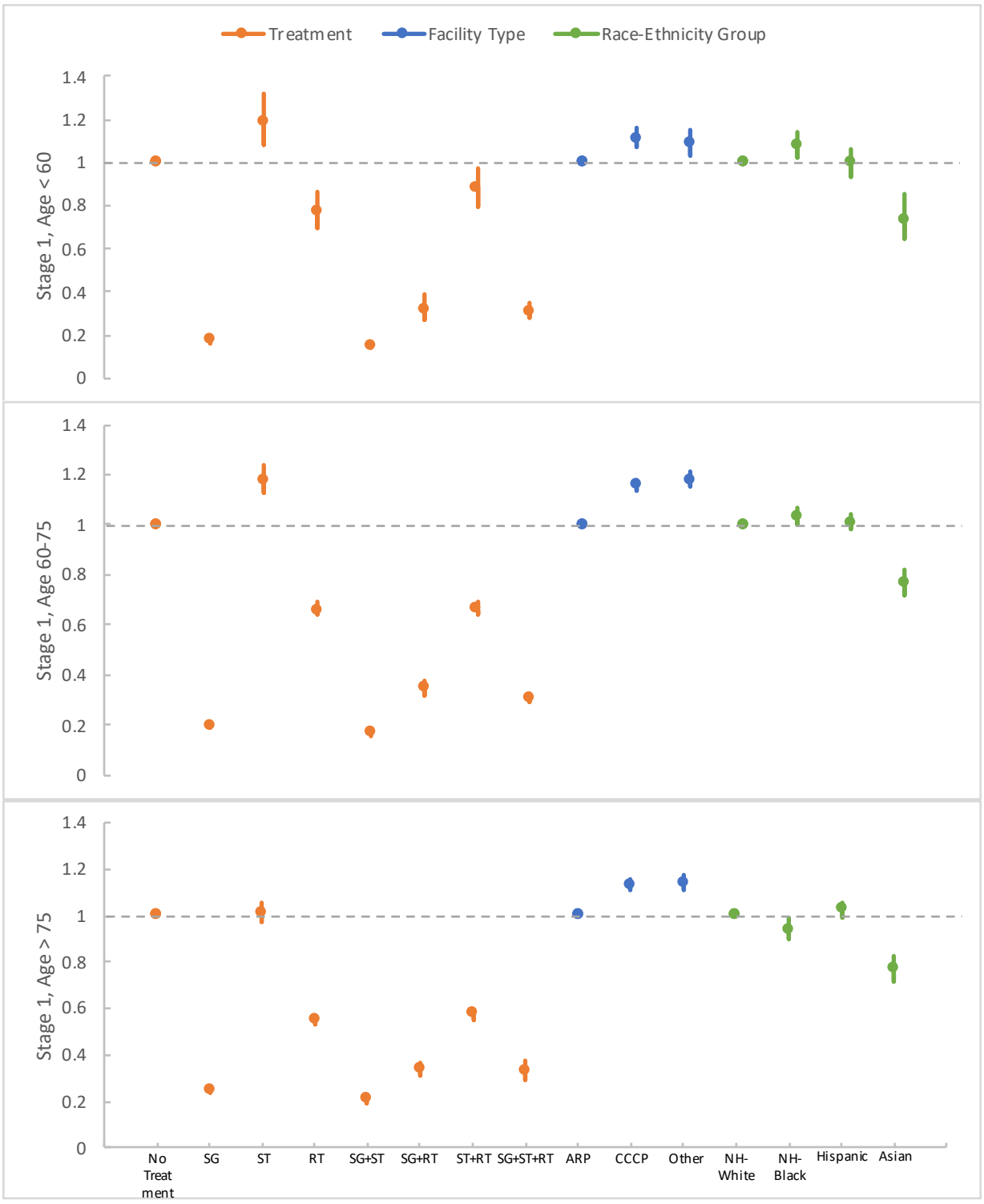
*Number of observations in the original data set=306717. Number of observations used=304511.

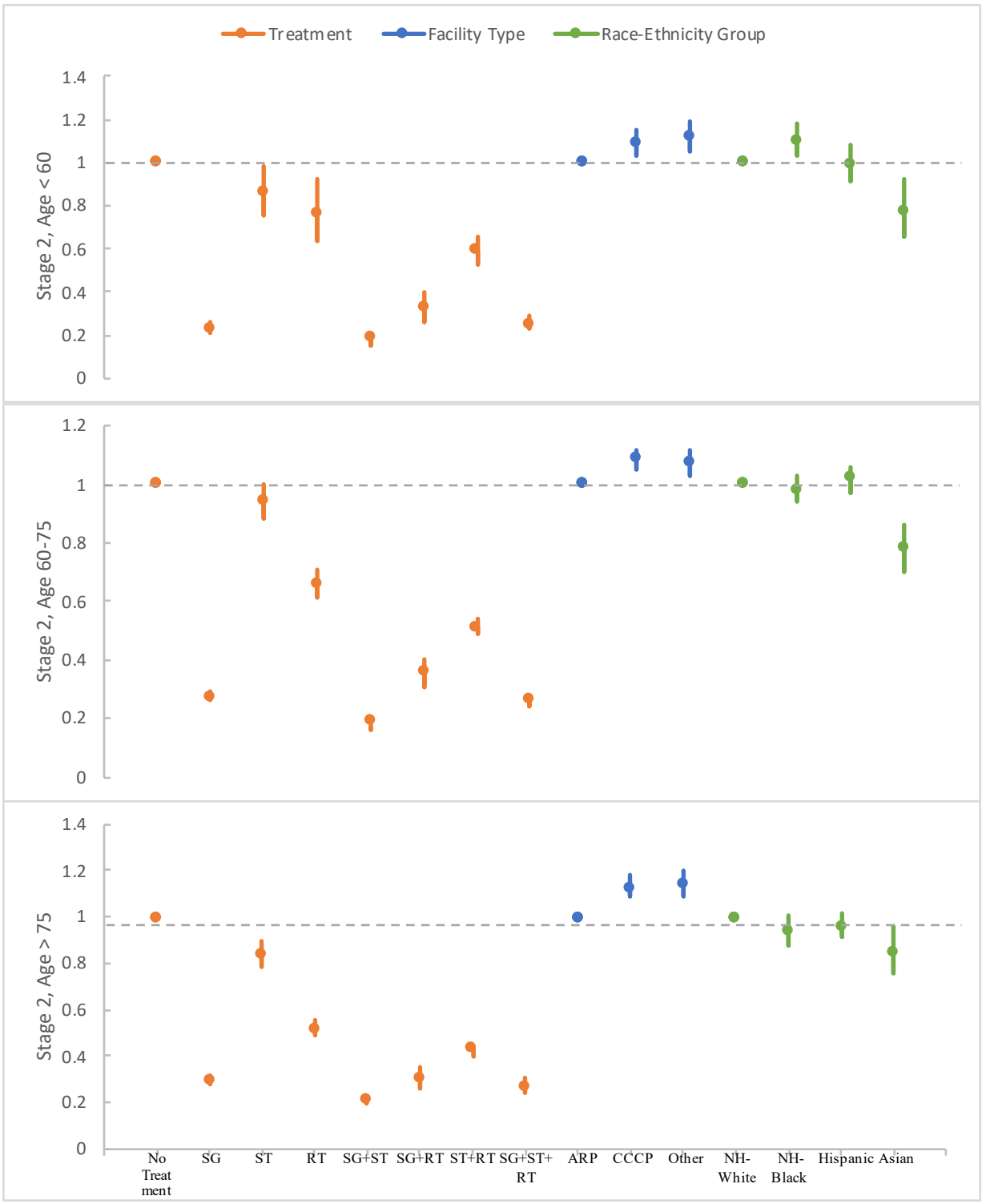
Table 4 5-year and 10-year survival rate of patients with treatment by stage and age

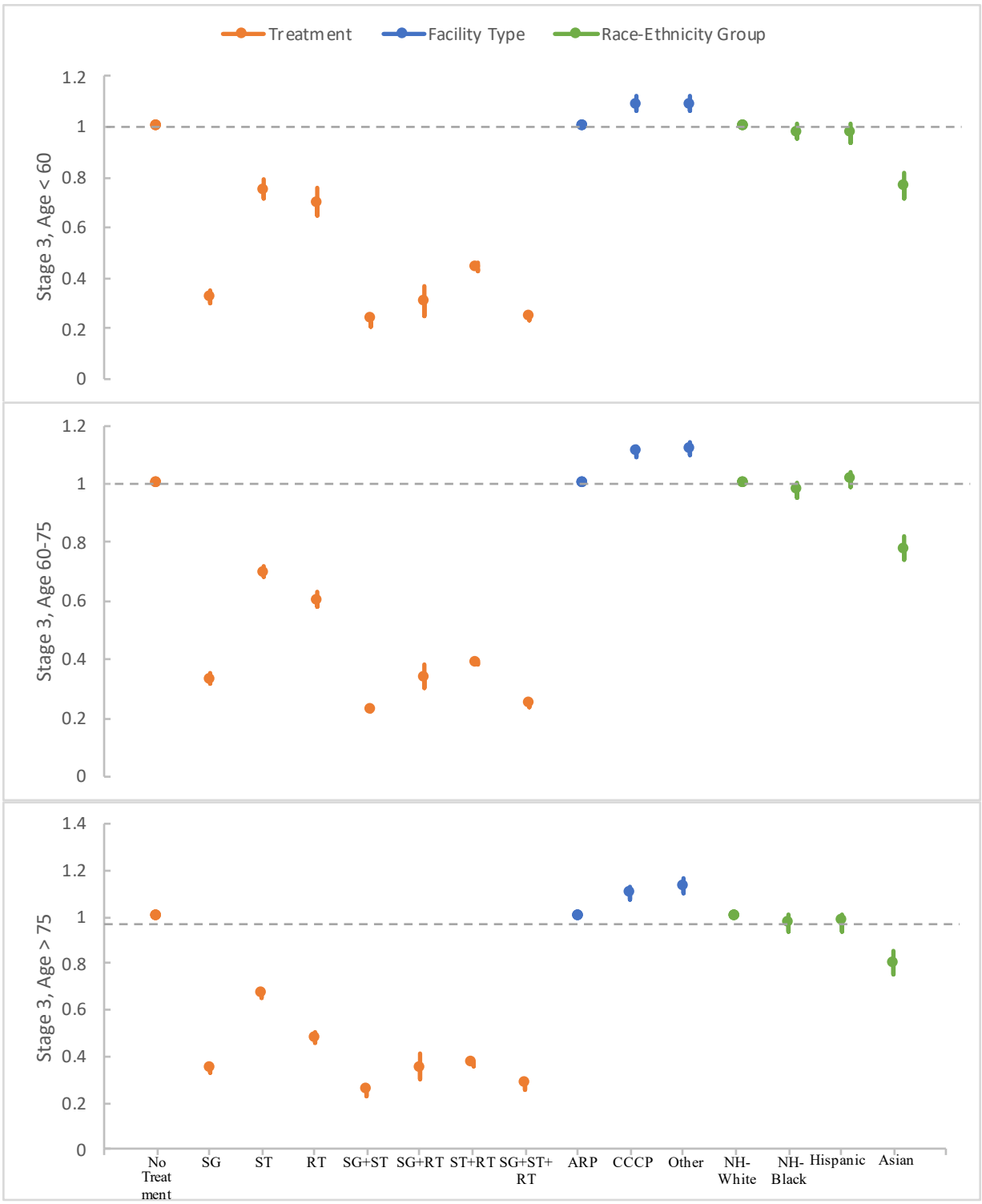
Strata	Treatment	Survival Rate	
		5-year	10-year
stage I, age < 60	**No Treatment**	83.5% (81.5%, 85.4%)	73.3% (70.9%, 75.6%)
	SG	98.2% (98.0%, 98.4%)	96.9% (96.6%, 97.1%)
	ST	83.9% (81.4%, 86.1%)	71.6% (68.6%, 74.3%)
	RT	96.5% (95.4%, 97.3%)	88.4% (86.6%, 90.0%)
	SG+ST	98.9% (98.7%, 99.1%)	97.2% (96.9%, 97.6%)
	SG+RT	98.9% (96.8%, 99.7%)	94.0% (90.5%, 96.2%)
	ST+RT	95.9% (94.7%, 96.8%)	83.3% (81.2%, 85.3%)
	SG+ST+RT	98.9% (98.1%, 99.4%)	94.5% (93.0%, 95.7%)
stage I, age 60-75	**No Treatment**	75.2% (74.1%, 76.3%)	63.3% (62.0%, 64.5%)
	SG	95.9% (95.7%, 96.1%)	93.6% (93.4%, 93.8%)
	ST	77.9% (76.6%, 79.2%)	63.0% (61.4%, 64.6%)
	RT	96.4% (96.1%, 96.8%)	87.8% (87.1%, 88.4%)
	SG+ST	97.6% (97.4%, 97.8%)	95.4% (95.1%, 95.6%)
	SG+RT	97.8% (96.8%, 98.5%)	91.4% (89.6%, 93.0%)
	ST+RT	95.7% (95.2%, 96.2%)	84.7% (83.8%, 85.6%)
	SG+ST+RT	97.6% (96.8%, 98.2%)	90.0% (88.5%, 91.2%)
stage I, age > 75	**No Treatment**	70.5% (69.3%, 71.7%)	57.3% (56.0%, 58.6%)
	SG	92.3% (92.0%, 92.6%)	88.5% (88.1%, 88.9%)
	ST	74.4% (73.0%, 75.8%)	58.7% (57.0%, 60.3%)
	RT	96.0% (95.6%, 96.3%)	85.4% (84.7%, 86.0%)
	SG+ST	94.5% (93.9%, 95.0%)	90.7% (89.9%, 91.4%)
	SG+RT	97.6% (96.1%, 98.6%)	91.1% (88.5%, 93.1%)
	ST+RT	93.8% (93.1%, 94.4%)	81.5% (80.4%, 82.6%)
	SG+ST+RT	93.7% (90.9%, 95.7%)	84.8% (80.9%, 87.9%)
stage II, age < 60	**No Treatment**	69.2% (65.2%, 72.8%)	55.9% (51.7%, 59.9%)
	SG	91.3% (90.1%, 92.3%)	86.4% (85.0%, 87.8%)
	ST	79.8% (76.7%, 82.5%)	63.5% (59.8%, 66.9%)
	RT	92.0% (87.6%, 94.9%)	73.1% (66.8%, 78.5%)
	SG+ST	98.1% (97.8%, 98.4%)	94.4% (93.8%, 94.9%)
	SG+RT	96.3% (92.4%, 98.2%)	89.8% (84.4%, 93.4%)
	ST+RT	94.8% (93.7%, 95.7%)	80.6% (78.8%, 82.3%)
	SG+ST+RT	98.9% (98.3%, 99.2%)	92.9% (91.7%, 93.9%)
stage II, age 60-75	**No Treatment**	59.3% (57.2%, 61.5%)	44.7% (42.5%, 46.9%)
	SG	85.9% (85.1%, 86.7%)	79.0% (78.0%, 79.9%)
	ST	70.0% (68.1%, 71.8%)	52.6% (50.5%, 54.6%)

stage II, age > 75	**RT**	88.0% (86.1%, 89.6%)	71.6% (69.0%, 73.9%)
	SG+ST	96.2% (95.9%, 96.5%)	91.5% (91.0%, 92.0%)
	SG+RT	97.4% (95.4%, 98.6%)	83.2% (79.3%, 86.4%)
	ST+RT	92.9% (92.2%, 93.5%)	77.5% (76.4%, 78.5%)
	SG+ST+RT	97.5% (96.9%, 98.0%)	88.3% (87.1%, 89.4%)
	No Treatment	51.3% (49.1%, 53.4%)	33.4% (31.4%, 35.5%)
	SG	82.4% (81.1%, 83.6%)	73.8% (72.4%, 75.2%)
	ST	61.9% (59.7%, 64.0%)	42.3% (40.1%, 44.5%)
stage III, age < 60	**RT**	87.0% (85.4%, 88.5%)	65.7% (63.5%, 67.8%)
	SG+ST	94.1% (93.3%, 94.8%)	86.5% (85.3%, 87.5%)
	SG+RT	95.9% (92.7%, 97.7%)	80.1% (74.8%, 84.4%)
	ST+RT	90.4% (89.3%, 91.3%)	72.1% (70.6%, 73.6%)
	SG+ST+RT	96.5% (94.4%, 97.8%)	79.0% (75.1%, 82.4%)
	No Treatment	52.6% (50.9%, 54.3%)	38.9% (37.2%, 40.6%)
	SG	81.6% (79.4%, 83.6%)	72.9% (70.4%, 75.2%)
	ST	74.1% (73.1%, 75.1%)	54.5% (53.3%, 55.6%)
stage III, age 60-75	**RT**	77.8% (75.2%, 80.3%)	52.7% (49.6%, 55.7%)
	SG+ST	94.7% (93.9%, 95.3%)	87.8% (86.8%, 88.8%)
	SG+RT	95.0% (90.2%, 97.5%)	87.3% (81.1%, 91.6%)
	ST+RT	92.0% (91.6%, 92.3%)	73.5% (73.0%, 74.1%)
	SG+ST+RT	98.4% (97.9%, 98.7%)	91.2% (90.3%, 92.0%)
	No Treatment	45.2% (44.2%, 46.2%)	31.7% (30.7%, 32.6%)
	SG	76.0% (74.5%, 77.4%)	66.8% (65.1%, 68.3%)
	ST	66.8% (66.1%, 67.5%)	47.2% (46.4%, 47.9%)
stage III, age > 75	**RT**	76.9% (75.4%, 78.3%)	52.4% (50.7%, 54.1%)
	SG+ST	93.3% (92.7%, 93.8%)	85.2% (84.4%, 85.9%)
	SG+RT	90.8% (87.1%, 93.4%)	74.9% (69.9%, 79.2%)
	ST+RT	90.5% (90.2%, 90.8%)	71.2% (70.8%, 71.6%)
	SG+ST+RT	97.5% (97.1%, 97.9%)	86.7% (85.8%, 87.5%)
	No Treatment	36.7% (35.7%, 37.8%)	22.7% (21.8%, 23.6%)
	SG	73.1% (71.0%, 75.1%)	61.8% (59.5%, 64.0%)
	ST	57.1% (56.2%, 58.0%)	38.1% (37.2%, 39.0%)
stage IV, age < 60	**RT**	77.5% (76.1%, 78.8%)	51.5% (49.9%, 53.2%)
	SG+ST	89.7% (88.4%, 90.8%)	78.0% (76.3%, 79.7%)
	SG+RT	90.5% (85.4%, 93.9%)	73.2% (66.3%, 78.9%)
	ST+RT	87.2% (86.6%, 87.7%)	63.7% (62.9%, 64.5%)
	SG+ST+RT	95.2% (93.6%, 96.4%)	80.0% (77.4%, 82.5%)
	No Treatment	30.5% (29.5%, 31.4%)	19.9% (19.1%, 20.7%)
	SG	69.3% (64.9%, 73.2%)	59.0% (54.4%, 63.2%)
	ST	65.2% (64.6%, 65.8%)	45.2% (44.6%, 45.8%)

stage IV, age 60-75	**RT**	48.8% (46.9%, 50.6%)	27.3% (25.7%, 29.0%)
	SG+ST	85.4% (83.3%, 87.2%)	72.9% (70.4%, 75.2%)
	SG+RT	73.1% (65.9%, 79.1%)	57.6% (50.0%, 64.6%)
	ST+RT	76.7% (76.0%, 77.3%)	49.5% (48.8%, 50.3%)
	SG+ST+RT	92.9% (91.0%, 94.5%)	76.8% (73.8%, 79.5%)
	No Treatment	25.3% (24.7%, 25.9%)	15.8% (15.3%, 16.3%)
	SG	67.9% (65.2%, 70.4%)	56.4% (53.6%, 59.1%)
	ST	59.6% (59.2%, 60.0%)	40.0% (39.6%, 40.4%)
stage IV, age > 75	**RT**	41.9% (40.7%, 43.2%)	23.5% (22.4%, 24.6%)
	SG+ST	84.8% (83.3%, 86.3%)	71.3% (69.4%, 73.2%)
	SG+RT	72.6% (66.3%, 77.9%)	55.3% (48.6%, 61.5%)
	ST+RT	71.7% (71.1%, 72.3%)	44.2% (43.6%, 44.9%)
	SG+ST+RT	89.9% (87.5%, 91.9%)	72.5% (69.2%, 75.6%)
	No Treatment	22.1% (21.5%, 22.7%)	12.8% (12.4%, 13.3%)
	SG	64.6% (60.7%, 68.2%)	52.9% (48.9%, 56.8%)
	ST	48.4% (47.9%, 49.0%)	30.5% (30.0%, 31.1%)
	RT	46.7% (45.0%, 48.5%)	25.1% (23.6%, 26.6%)
	SG+ST	73.7% (70.3%, 76.8%)	58.0% (54.3%, 61.6%)
	SG+RT	63.0% (48.7%, 74.3%)	35.2% (22.8%, 47.8%)
	ST+RT	65.3% (64.0%, 66.5%)	38.8% (37.6%, 40.1%)
	SG+ST+RT	85.1% (77.4%, 90.4%)	66.9% (57.8%, 74.5%)


Treatment
Facility Type
Race-Ethnicity Group
Stage 1, Age < 60
Stage 1, Age 60-75
Stage 1, Age > 75
1.4
1.2
1
0.8
0.6
0.4
0.2
0
No Treatment
SG
ST
RT
SG+ST
SG+RT
ST+RT
SG+ST+RT
ARP
CCCP
Other
NH-White
NH-Black
Hispanic
Asian


Treatment
Facility Type
Race-Ethnicity Group
Stage 2, Age < 60
Stage 2, Age 60-75
Stage 2, Age > 75
1.4
1.2
1
0.8
0.6
0.4
0.2
0
No Treatment
SG
ST
RT
SG+ST
SG+RT
ST+RT
SG+ST+RT
ARP
CCCP
Other
NH-White
NH-Black
Hispanic
Asian


Treatment
Facility Type
Race-Ethnicity Group
Stage 3, Age < 60
Stage 3, Age 60-75
Stage 3, Age > 75
1.4
1.2
1
0.8
0.6
0.4
0.2
0
No Treatment
SG
ST
RT
SG+ST
SG+RT
ST+RT
SG+ST+RT
ARP
CCCP
Other
NH-White
NH-Black
Hispanic
Asian

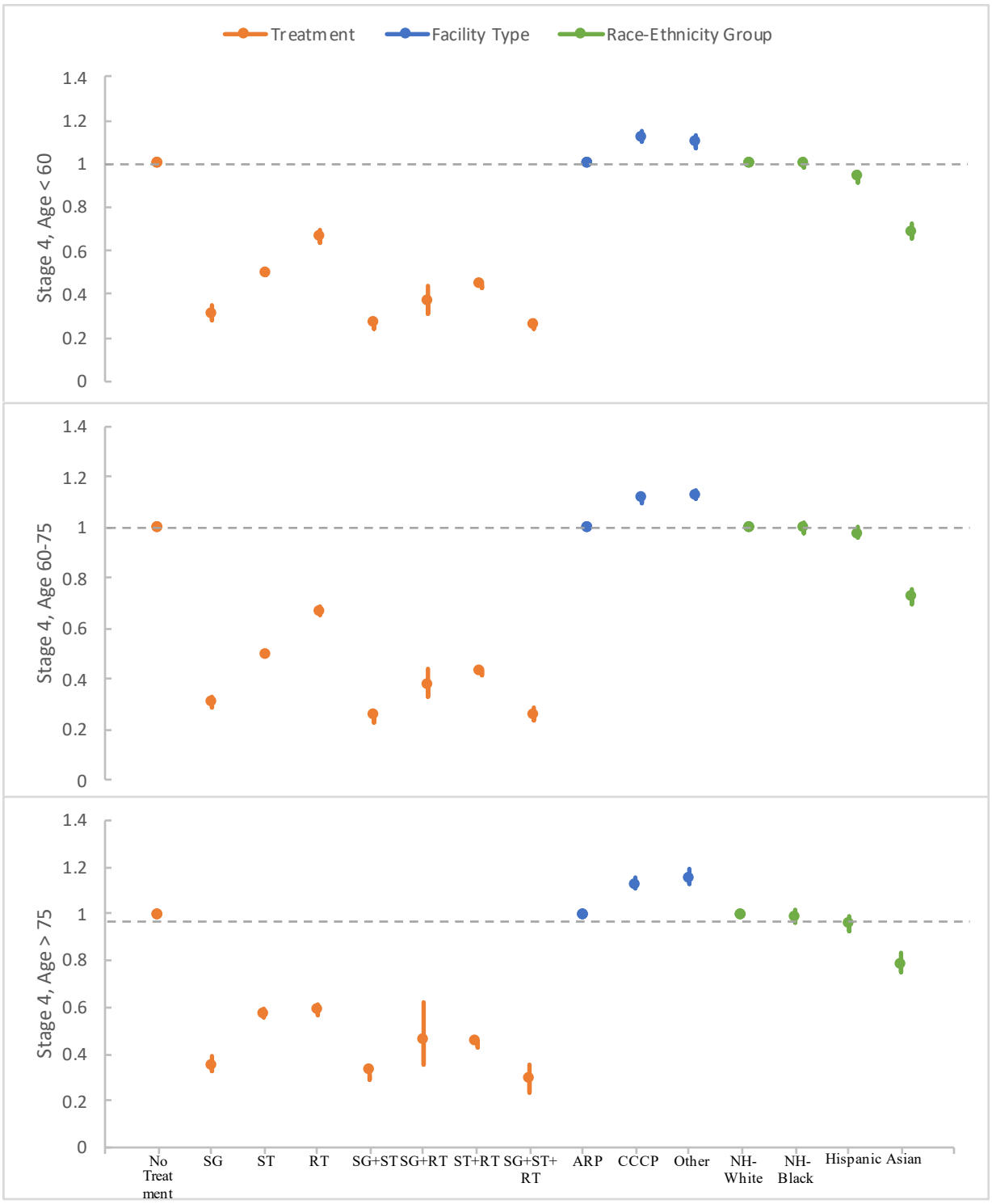


Figure 3 Hazard ratios of treatment, facility type and race-ethnicity group adjusted for other covariates in each stratum.