Review Article

Disparities in the surgical management of early stage non-small cell lung cancer: how far have we come?

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Abstract: It is currently estimated that nearly one-third of patients with newly diagnosed non-small cell lung cancer (NSCLC) have stage I–II disease on clinical evaluation. Curative-intent surgical resection has been a cornerstone of the therapeutic management of such patients, offering the best clinical and oncologic outcomes in the long-term. In 1999, Peter Bach and colleagues brought attention to racial disparities in the receipt of curative-intent surgery in the NSCLC population. In the time since this seminal study, there is accumulating evidence to suggest that disparities in the receipt of definitive surgery continue to persist for patients with early stage NSCLC. In this review, we sought to provide an up-to-date assessment of 20 years of surgical disparities literature in the NSCLC population. We summarized common and unrecognized disparities in the receipt of surgical resection for early stage NSCLC and demonstrated that demographic and socioeconomic factors such as race/ethnicity, special patient groups, income and insurance continue to impact the receipt of definitive resection. Additionally, we found that discrepancies in patient and provider perceptions of and attitudes toward surgery, access to invasive staging, distance to treatment centers and negative stigmas about lung cancer that patients experience may act to perpetuate disparities in surgical treatment of early stage lung cancer.

Keywords: Surgical disparities; treatment inequity; early stage non-small cell lung cancer (NSCLC); lung cancer

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Introduction

Lung cancer is the leading cause of cancer associated mortality in the United States (1). Of the 180,000 patients diagnosed with NSCLC each year, approximately one-third are found to have early stage (I–II) disease on clinical evaluation and are potential candidates for curative-intent surgical resection (2-4). The role of surgery as the principle treatment for localized NSCLC is well established, with prior research consistently demonstrating superior long-term overall survival following surgery as compared to treatment with radiation therapy alone or no therapy. For these reasons, guidelines put forth by the American College of Chest Physicians and the National Comprehensive Cancer Network recommend surgical resection for all medically operable patients with stage I–II NSCLC (5,6). However, despite the rigorous clinical and oncologic basis for these guidelines, disparities in the receipt of surgery for the treatment of early stage NSCLC exist.

Perhaps the seminal study on this topic was published by Peter Bach and colleagues in *The New England Journal of Medicine* in 1999 (7). Using the Surveillance, Epidemiology, and End Results (SEER) program

database, the authors found that black patients with stage I–II NSCLC experienced significantly lower overall 5-year survival rates as compared to white patients with similarly staged disease. Importantly, this survival discrepancy was not observed when comparing black and white patients that underwent resection, which suggests that the observed difference in overall survival was a consequence of unequal rates of surgery between these two groups. Among the many important implications of this work was that it not only highlighted the existence of racial disparities in survival within a nationally representative cohort of lung cancer patients, but it also reaffirmed the importance of delivering appropriate therapies as an actionable approach to mitigating these survival differences in practice.

Since Bach's publication, the literature on disparities in the surgical management of lung cancer has grown substantially. To date, several studies have characterized treatment and outcome inequities in different racial, socioeconomic status, and other disadvantaged groups. Therefore, the central goal of this narrative review is to provide a contemporary examination of nearly 20 years of surgical disparities literature in the lung cancer population. Specifically, this study aims to summarize common and unrecognized disparities in the receipt of surgical resection for early stage NSCLC and the potential mechanisms that may perpetuate these disparities in clinical practice.

Methods

Data source

The MEDLINE (PubMed) database was queried to identify articles describing surgical disparities in the surgical management of early stage NSCLC published between January 1999 and October 2018. The following terms were used to guide this search strategy: "surgical disparities", "treatment disparities", or "disparities" combined with "early stage non-small cell lung cancer" or "lung cancer". Manuscript abstracts were reviewed to determine inclusion eligibility as primary source references. We focused on reports that specifically evaluated disparities in the receipt of surgery or in the patient, physician, or health system factors potentially associated with the decision to pursue surgery for localized NSCLC. In addition to the articles identified using this methodology, we included other studies as necessary to provide sufficient background and to contextualize the summarized findings.

Results

Since 1999, there has been a proliferation of studies on disparities in the receipt of surgery for localized NSCLC. While the majority of these studies have been performed in United States lung cancer patient cohorts, assessments of treatment and outcome disparities in the NSCLC population have also been reported in other regions such as Asia, Western Europe, and the United Kingdom (8-12). Despite more homogeneous racial/ethnic patient cohorts, these studies have found patient and neighborhood socioeconomic status to be associated with surgical disparities in NSCLC patients. Together these reports demonstrate that similar trends in the unequal access to surgical care observed in the United States are also observed in the international NSCLC population. Below we summarize common and less recognized disparities in the surgical management of NSCLC, focusing on race/ethnicity, socioeconomic and insurance payer status, area of residence, and selective patient cohorts.

Common and unrecognized disparities in the receipt of surgery for early stage NSCLC

Race and ethnicity

Bach and colleagues published one of the first major studies on racial disparities in the surgical management of early stage NSCLC in 1999 (7). Using the SEER program database, these authors observed that black patients were 12.7% less likely to undergo surgical resection for stage I–II NSCLC and experienced a significantly lower overall 5-year survival rate as compared to white patients with comparably staged disease (26.4% *vs.* 34.1%, P<0.001) (7). To emphasize the central findings of their work, the authors applied these results to a hypothetical cohort of 1,000 black and 1,000 white patients and demonstrated that up to 44 of the 77 additional deaths among black patients could be prevented with the appropriate delivery of surgical therapies. In the time since this publication, multiple groups have described similar observations in the black NSCLC population (13-16). Together, the cumulative data presented in these various institutional, regional, and national analyses suggest that black patients persistently experience inequity in the surgical management of NSCLC (*Table 1*).

Treatment disparities have also been described in other minority groups. In 2005, Wisnivesky *et al.* used the SEER database to study this question in the Hispanic population with stage I NSCLC (13). These authors found

Table 1 Retrospective, observational studies investigating disparities based on race/ethnicity.

Source	Data source	# of lung cancer patients	Years studied	Research question	Finding
Bach *et al.* (7)	Surveillance, Epidemiology, and End Results Program	10,984	1985–1993	Do surgical disparities exist between white and black NSCLC patients and does this impact overall survival?	Black patients have worse survival and are less likely to undergo curative resection than whites
Esnaola *et al.* (14)	South Carolina Central Cancer Registry	3,056	1996–2002	Does race impact the receipt of surgical resection for localized NSCLC?	Black patients were less likely to undergo surgery than whites
Hamid *et al.* (17)	Surveillance, Epidemiology, and End Results Program	190,046	2004–2010	Do API experience disparities in clinicopathologic features or survival for NSCLC?	API experience improved survival for early stage NSCLC
Hardy *et al.* (15)	Surveillance, Epidemiology, and End Results Program	83,101	1991–2002	Do black and white NSCLC patients differ in survival outcomes and do racial disparities persist after adjusting for established risk factors and years of diagnosis?	A greater proportion of black NSCLC patients did not undergo surgery. Racial disparities in overall survival do not persist after adjusting for treatments and other confounders
Saeed *et al.* (18)	Surveillance, Epidemiology, and End Results Program	172,398	1988–2007	Impact of Hispanic ethnicity on survival for NSCLC	Hispanics have a reduced risk of mortality compared to NH-whites and blacks with NSCLC
Soneji *et al.* (16)	Surveillance, Epidemiology, and End Results Program	105,121	2004–2013	Do Hispanics, non-Hispanic whites, non-Hispanic blacks, and non-Hispanic Asians differ in overall survival and treatment for early stage NSCLC?	NH-black patients are less likely to undergo surgery. Among those undergoing surgery, NH-blacks have worse survival. NH-Asians and Hispanics have a lower risk of death
Wisnivesky *et al.* (13)	Surveillance, Epidemiology, and End Results Program	16,036	1991–2000	Do surgical disparities exist between Hispanic and NH-white NSCLC patients and does this impact overall survival?	Hispanics were less likely to undergo resection and had higher lung cancer specific survival

NSCLC, non-small cell lung cancer; API, Asian/Pacific Islanders.

that Hispanic patients experienced lower rates of lung cancer-specific survival and surgical resection as compared to white patients (survival =54.2% *vs.* 64.2%, P=0.008; rate of resection =83% *vs.* 86%, P=0.03). Similar to the trends observed in the black population, after accounting for treatment received and stage at diagnosis, the racial differences in lung cancer-specific survival between Hispanic and white patients were no longer observed.

In 2017, Soneji *et al.* compared the use of surgery across four racial/ethnic groups (non-Hispanic whites, non-Hispanic blacks, Hispanics, and non-Hispanic Asians) with stage I–II NSCLC in the SEER database (16). After adjusting for other demographic and clinical factors, these authors found that non-Hispanic black patients experienced significantly worse overall survival as compared to non-Hispanic whites [adjusted hazard ratio (HR) =1.05; 95% CI: 1.02–1.08]. Among those who underwent surgery, the relative risk of death from lung cancer was similar between non-Hispanic black patients and whites. However, non-Hispanic blacks who received surgery did experience a higher relative risk of death from other causes as compared to white patients (adjusted RR =1.07; 95% CI: 1.02–1.12) (16). Notably, differences in the receipt of surgery were not observed in Hispanics or non-Hispanic Asians. After accounting for the treatment received, these groups experienced a lower risk of mortality as compared to white patients. While the exact reasons for the survival advantage among Hispanic and non-Hispanic Asian patients in this study were unclear, improved lung cancer survival

among Asian patients has been reported in other studies as well (17,18).

American Indians and Alaskan Natives (AI/AN) together comprise a less commonly recognized racial minority group with disparate outcomes in the cancer literature. Smith *et al*. found that AI/AN SEER-Medicare lung cancer patients had more advanced disease at diagnosis and lower rates of lung cancer specific survival at 5-years (47%; 95% CI: 43.5–50.5%) as compared to non-Hispanic whites (56%; 95% CI: 55.7–56.3%), blacks (51%; 95% CI: 50.0–51.4%), Hispanic (55%; 95% CI: 53.8–56.2%), and other races/ethnicities (59%; 95% CI: 57.8–59.6%) (19). These authors determined that AI/AN patients were at increased risk of lung cancer associated morality as compared to white patients (HR =1.36; 95% CI: 1.15–1.62). As with previous minority groups, this difference was no longer observed after controlling for the stage at diagnosis and the use of surgery and/or radiation therapy (HR =1.17; 95% CI: 0.98–1.39), suggesting that underlying disparities in access to appropriate care may serve as the driving force behind the survival inequity among AI/AN patients. To this end, while Adams *et al.* reported that AI/AN SEER-Medicare patients do not experience significant delays in the receipt of lung cancer treatment, Javid *et al.* showed that AI/AN patients were less likely than whites to receive guideline-directed surgical and non-surgical care for the treatment of breast, colon, prostate, and lung cancer (20,21). Taken together, these data suggest that survival discrepancies in the AI/AN population are at least in part due to the failure to receive appropriate stage-specific therapies.

Socioeconomic and insurance payer status

While no consensus exists regarding a single metric to quantify socioeconomic status (SES), observational studies have frequently represented SES using variables such as median household income or occupational status. Given the relationship between these variables and health insurance, we examined SES in conjunction with insurance payer status (*Table 2*).

Shi *et al.* studied the effect of insurance payer status on survival for early stage NSCLC patients diagnosed between 1998 and 2011 in the National Cancer Database (NCDB) (26). When accounting for demographic, tumor, and clinical characteristics, Medicaid (HR =1.36; 95% CI: 1.31–1.42; P<0.0001), Medicare (HR =1.17; 95% CI: 1.15–1.20; P<0.0001), and uninsured patients (HR =1.21; 95% CI: 1.14–1.28; P<0.0001) had a greater hazard of death compared to those with private insurance. In addition to insurance type, Shi *et al.* observed that median household income was also significantly associated with survival. They reported an increased risk of mortality with each stepwise reduction in median household income (<$30,000: HR =1.16, 95% CI: 1.13–1.20, P<0.0001; $30,000–34,000: HR =1.09, 95% CI: 1.06–1.12, P<0.0001; $35,000–$45,000: HR =1.07, 95% CI: 1.05–1.09, P<0.0001), but did not include survival curves segregated according to these income strata. This work supports the hypothesis that socioeconomic and insurance payer status impacts survival in the NSCLC population, however, the authors did not evaluate whether these same factors were associated with the receipt of surgery, as has been reported in other state and institutional series.

In a study using stage I–II patients enrolled in the South Carolina state registry, Esnaola *et al.* showed that patients living in poverty had significantly lower odds of undergoing resection compared to those with higher incomes (OR =0.84; 95% CI: 0.72–0.99; P=0.038) (14). Insurance status was also found to be a significant covariate in their model, as patients with self-pay (OR =0.32; 95% CI: 0.21–0.48; P<0.0001), Medicaid (OR =0.27; 95% CI: 0.17–0.43; P<0.0001), Medicare (OR =0.31; 95% CI: 0.24–0.38; P<0.0001), or HMO insurance types (OR =0.50; 95% CI: 0.29–0.85; P=0.011) had increased odds of not receiving surgery as compared to those with private insurance.

Johnson *et al.* investigated the impact of residential and neighborhood characteristics on lung cancer treatment and outcomes using the Georgia Comprehensive Cancer Registry (24). To more comprehensively represent socioeconomic status, the authors constructed an "economic deprivation" variable. This composite metric was calculated based on the percentage of households that were: (I) below the poverty line, (II) had a female head of house and children, (III) on public assistance, and (IV) had non-married owners. The authors classified economic deprivation by quartile intervals for their analysis, and found that as economic deprivation increased, the receipt of surgery declined. These trends were independently observed in both black and white patients.

The impact of insurance status on treatment has also been demonstrated in institutional studies. In a cohort of 247 patients with resectable stage I–II NSCLC treated at an academic center in Texas, Yorio *et al.* found that patients with Medicaid or public county insurance (OR =0.13; 95% CI: 0.04–0.43) were significantly less likely to undergo resection than those with private insurance (28). When controlling for treatments rendered, this group did not

Table 2 Retrospective, observational studies investigating disparities based on insurance and area of residence

Source	Data source	# of lung cancer patients	Years studied	Research question	Finding
Atkins *et al.* (22)	Surveillance, Epidemiology, and End Results Program	348,002	2000–2006	Do rates of lung cancer incidence and mortality vary according to urban-rural areas of residence?	Patients with early-stage NSCLC living in rural areas show lower rates of resection and have shorter survival
Crowell *et al.* (23)	Surveillance, Epidemiology, and End Results Program	21,144	1988–1997	Do treatment and outcome disparities exist for NSCLC patients living in New Mexico compared to other states?	New Mexico patients had lower rates of resection and higher rates of mortality compared
Johnson *et al.* (24)	Georgia Comprehensive Cancer Registry	8,322	2000–2009	What is the impact of residential and neighborhood characteristics on lung cancer treatment and outcomes?	Those living in segregated and economically deprived neighborhoods were less likely to undergo surgery
Osuoha *et al.* (25)	Nevada Central Cancer Registry	12,964	2003–2010	Are there variations in lung cancer treatment and survival within the state of Nevada?	Those living in rural areas of Nevada are less likely to undergo surgery and exhibit poorer survival rates
Shi *et al.* (26)	National Cancer Database	299,914	1998–2011	What is the effect of insurance status on overall survival of early stage NSCLC?	Compared with private insurance, those with no insurance, Medicaid, and Medicare were at increased risk of death
Sineshaw *et al.* (27)	North American Association of Central Cancer Registries	110,711	2007–2011	Is there state-level variation in the receipt of curative-intent surgery across the United States?	Receipt of curative-intent surgery varies across states in the United States. Receipt of surgery was statistically significantly lower for blacks compared to whites in Texas and Florida
Yorio *et al.* (28)	Institutional	450	2000–2005	Are treatment disparities for lung cancer due to individual or institutional characteristics?	Treatment disparities persist at the institutional level, as patients with non-private insurance are less likely to undergo resection

NSCLC, non-small cell lung cancer.

demonstrate increased risk of mortality.

Area of residence (urban-rural status and geography)

In addition to disparities based on patient demographics, inequity due to residential and geographic region has been reported (*Table 2*). Atkins *et al.* published a comprehensive study on the impact of urban-rural area of residence on disease incidence, treatment, and outcomes in the SEER population (22). These investigators stratified patients according to nine rural-urban continuum (RUCA) codes abstracted from county-level population estimates ranging from less than 2,500 (most rural) to over 1 million (most urban). They found that increased rurality positively correlated with annual lung cancer incidence and associated mortality. For patients with stage I NSCLC, those living in the most rural areas experienced significantly lower median overall survival rates and were less likely to undergo surgical resection as compared to patients residing in the most urban regions (survival 38.5 *vs.* 52 months, P=0.0006; rate of surgery 69% *vs.* 75%). While there was no reported difference in the receipt of radiation therapy, rural patients were more likely to undergo no treatment compared to urban patients (17.6% *vs.* 13.2%; OR =1.40; P=0.007).

Rural disparities have also been observed at the regional and state levels. In 2007, Crowell *et al.* published a study comparing treatment and outcome patterns for urban and rural patients from New Mexico to those from eight other SEER state registries, including California, Connecticut, Detroit, Hawaii, Iowa, Washington, Utah, and Atlanta (23). Independent of racial and ethnic differences, patients with localized NSCLC in New Mexico had a greater risk of adjusted mortality (adjusted HR =1.22; 95% CI: 1.12–1.32)

and lower rates of surgery compared to patients in other states (adjusted OR =0.46; 95% CI: 0.39–0.54; P<0.0001).

Osuoha *et al.* compared rates of resection and survival for lung cancer patients within the state of Nevada (25). These authors demonstrated that patients with localized NSCLC from rural and Southern Nevada were significantly more likely to not undergo surgery than patients from Northwestern Nevada with similarly staged disease (rural: OR =1.65, 95% CI: 1.07–2.53; southern region: OR =1.67, 95% CI: 1.20–2.13). After adjusting for sex, age, race, marital status, insurance, and income, such patients were also at increased risk of morality.

Sineshaw *et al.* evaluated state-level variation in the receipt of curative-intent surgery for stage I–II NSCLC using data sourced from over 110,000 patients across 38 different states in the North America Association of Central Cancer Registry (27). The authors showed that rates of resection varied considerably across the states examined, ranging from 52.2% in Wyoming to 77.2% in Utah. Additionally, after controlling for demographic, tumor-related factors, and the year of diagnosis, patients in 28 states were significantly less likely to undergo curative resection than patients in Massachusetts (selected as the reference because it had the lowest rate of uninsured residents among the states included in the study). Since their models also accounted for insurance type, area-level poverty, and urban-rural status, their work suggests that additional factors within the state of residence influence the surgical management of lung cancer.

Special patient cohorts

Traditionally, much of the literature on lung cancer disparities has used data sourced from state or national registries. One challenge in characterizing treatment disparities in these large, heterogeneous datasets is the potentially confounding effect of uncontrolled variables that may influence access to healthcare services. To limit some of these residual confounders, some investigators have studied treatment and survival disparities in special patient cohorts with more predictive patterns of care and/or balanced demographic characteristics (*Table 3*). Here we focus on US Veterans, clinical trial participants, young and elderly patients, and members of sexual minority populations.

Ganti *et al.* evaluated the impact of race on surgical treatment in United States veterans with localized NSCLC from 1995–2009 (33). Despite having equal access to care through the Veterans Affairs (VA) Healthcare System, a significantly lower proportion of black patients than white patients underwent surgery for stage I disease (41% *vs.* 48%, P<0.001) and palliative chemotherapy for stage IV disease. Interestingly, even with lower rates of surgery, black patients did not demonstrate lower overall survival for stage I or II disease in this analysis.

Williams *et al.* published a follow up study on racial disparities in the VA population (35). Unlike the prior work by Ganti *et al.*, Williams and colleagues provided data on the annual rates of resection and highlighted significantly different trends between black and white patients. Whereas the proportion of white patients undergoing resection did not vary from 2001 to 2010, the rate of resection among black patients increased by 7% during this period (49% in 2001 to 56% in 2010). When analyzing the entire study cohort, these authors found that black patients experienced lower rates of resection and higher rates of non-surgical or no treatment as compared to white patients, corroborating Ganti's prior findings.

Balekian *et al.* assessed whether surgical disparities were present among stage I NSCLC patients previously enrolled in the National Lung Screening Trial (NLST) (31). In accordance with the NLST study criteria, patients were randomized to undergo routine lung cancer screening with low-dose CT or chest radiography. Given that the study cohort was enrolled in this clinical trial, the authors presumed that such patients would be surgically fit and therefore hypothesized that surgical disparities, if present, would be observed in older patients with greater comorbidities. While older age was found to be significantly associated with a reduced likelihood of undergoing surgery, the authors also observed racial disparities in the receipt of surgery between black and white men (65% black men *vs.* 93% white men). This trend persisted in the adjusted analysis with a random effects model to control for enrollment center variation (OR =0.15, 95% CI: 0.05–0.43; RR =0.72, 95% CI: 0.50–0.99). Racial disparities were not observed among women, as 90% of black women and 93% of white women underwent surgery.

Age-related disparities have previously been described in the lung cancer literature. While age is frequently included as a covariate in treatment prediction models, for the purpose of this review, we chose to focus on studies that specifically looked at treatment and outcome patterns for NSCLC patients at relative extremes of age.

Nadpara *et al.* described the treatment patterns and factors associated with the receipt of guideline concordant care in elderly SEER-Medicare patients with resectable NSCLC (34). Notably, the authors found that only 44.3%

Table 3 Retrospective, observational studies investigating disparities in special populations

Source	Data source	# of lung cancer patients	Years studied	Research question	Finding
Adams *et al.* (20)	Surveillance, Epidemiology, and End Results Program	241,672	2001–2007	Do American Indian/Alaskan Natives experience significant delays in the treatment of breast, colorectal, lung or prostate cancer?	AI/AN experienced treatment delays driven by prostate cancer, but not lung cancer
Arnold *et al.* (29)	National Cancer Database	173,856	2003–2009	What are current treatment patterns and outcomes of young patients (<47 years) with NSCLC?	Younger patients are more likely than older patients to undergo surgery. Younger patients have improved overall survival at all stages
Arnold *et al.* (30)	National Cancer Database	616	2004–2012	What are the treatment outcomes for nonagenarians with NSCLC?	One third of nonagenarians underwent surgery or SBRT for the treatment of their cancer, these patients experienced improved survival compared to those treated with other or no therapy
Balekian *et al.* (31)	National Lung Screening Trial	723	2002–2004	Do racial disparities exist among National Lung Screening Trial participants?	Black men were less likely to undergo surgery than white males. This racial disparity was not observed in women
Boehmer *et al.* (32)	Surveillance, Epidemiology, and End Results Program	158,185	1996–2004	Is there an association between geographical areas with greater sexual minority density and incidence and mortality rates for lung cancer?	Significant positive association exists between both incidence and mortality rates for lung cancer and areas with a higher density of sexual minority men. The opposite trend was found in areas with a higher density of sexual minority women.
Ganti *et al.* (33)	Veterans Affairs Central Cancer Registry	82,414	1995–2009	Do racial disparities in lung cancer treatment and outcomes exist among United States veterans?	Black VA patients were less likely than whites to receive surgery for early stage and chemotherapy for advanced disease
Javid *et al.* (21)	Surveillance, Epidemiology, and End Results Program	6,451	1996–2005	Are American Indian/Alaskan Native patients less likely to receive guideline concordant surgical treatment for cancers of the breast, colon, lung, or prostate cancer?	AI/AN patients were less likely to undergo surgery for all cancers (including lung)
Nadpara *et al.* (34)	Surveillance, Epidemiology, and End Results Program	42,323	2002–2007	Is there variation in the receipt of guideline concordant care for the treatment of lung cancer in the elderly (>65 years)?	Less than half of older patients receive guideline recommended therapies
Smith *et al.* (19)	Surveillance, Epidemiology, and End Results Program	69,138	1988–2006	Do treatment and survival disparities exist in American Indian/ Alaskan Natives (AI/AN)?	AI/AN were less likely to undergo resection and had lower rates of overall survival as compared to whites
Williams *et al.* (35)	VA Central Cancer Registry	18,466	2001–2010	Do racial disparities in the receipt of treatment exist in the VA population?	Black VA patients experienced lower rates of resection and higher rates of non-surgical or no treatment compared to whites

AI/AN, American Indians and Alaskan Natives; NSCLC, non-small cell lung cancer; SBRT, stereotactic body radiation therapy; VA, Veterans Affairs.

of the study cohort received stage-specific guideline recommended therapies. They found that the odds of receiving guideline concordant care were inversely correlated with age, as patients aged 66–69 were more than twice as likely to receive appropriate treatment than those ≥80 years (OR =2.66; 95% CI: 2.44–2.89) (34). Though this model controlled for patient comorbidity using modified Charlson comorbidity scores, other relevant factors such as pulmonary function, physiologic tolerance, and patient preference for surgery were not included.

Arnold *et al.* evaluated the effectiveness of local therapy for the treatment of stage I NSCLC in nonagenarians in the NCDB (30). These authors defined local therapy as the receipt of surgery or stereotactic body radiation therapy (SBRT). Among those who received local therapy, 37% underwent resection and 63% underwent SBRT. Patients that underwent local therapy had significantly improved overall 5-year survival compared to those with other therapy or no treatment (23% local *vs.* 13% other *vs.* 8% no therapy, P<0.0001) (30). The therapeutic benefit conferred by local surgical or SBRT therapy in this study suggests that old age alone should not be viewed as a contraindication to the use of such therapies.

On the other end of the spectrum, patients under the age of 55 currently represent approximately 8.6% of incident lung cancer cases in the country (36). In contrast to the average lung cancer patient, this younger cohort tends to be female, non-white, with fewer comorbidities and more advanced disease at the time of diagnosis (29,37-40). Studies in both SEER and the NCDB have independently shown that young lung cancer patients demonstrate significantly better stage-specific survival as compared to older patient cohorts (29,38-40). In one example, Arnold *et al.* evaluated stage-specific treatment patterns in the NCDB and found that a greater proportion of patients aged 20–46 with stage I–II NSCLC received surgery (± adjuvant chemotherapy) than older patients with equivalently staged disease (29). Moreover, after controlling for other clinical and tumor related variables, including comorbidity status, the authors found that older stage II patients remained more likely to receive radiation therapy only, which was associated with an increased risk of mortality in their model (HR =2.32, P<0.0001) (29). While this analysis demonstrated that young lung cancer patients are more likely than older patients to receive appropriate treatment for early and advanced NSCLC, it did not investigate the factors associated with treatment or survival within the younger cohort.

Sexual minority populations (lesbian, gay, and bisexual), reflect an emerging patient cohort in which disproportionate rates of cancer incidence and mortality have been reported (41-43). In a SEER analysis using same-sex patient households as a surrogate for sexual minority status, Boehmer *et al.* observed a significant association between sexual minority density and lung cancer incidence and mortality (32). After correcting for race, education, and poverty, the authors found lung cancer incidence and mortality to be positively correlated with male sexual minority density [incidence rate ratio (IRR) =1.05, 95% CI: 1.04–1.07, P<0.0001; mortality rate ratio (MRR) =1.03, 95% CI: 1.01–1.05, P=0.0083] (32). The impact of sexual minority status on the receipt of lung cancer surgery has not been investigated, but these studies suggest that additional focus on surgical treatments and outcome patterns in sexual minority populations with lung cancer is warranted.

Potential mechanisms that perpetuate underlying surgical disparities for the treatment of early stage NSCLC

Though significant progress has been made in the identification of NSCLC patient groups at risk of not receiving guideline-recommended surgery, the causal determinants of these discrepancies remain unclear. Studies in the literature have shown that differences in patient, physician, and health system factors may, at least in part, perpetuate the ongoing trends in surgical disparities reported in lung cancer patients.

Patient-mediated mechanisms

One potential mechanism underlying differences in the receipt of surgery is patient preference for surgery and treatment in general (*Table 4*). Multiple studies have reported a disproportionate rate of refusal to undergo surgery among black patients with early stage NSCLC. In an institutional series of 281 patients, McCann *et al.* described a significantly lower rate of surgery among black patients despite no significant differences in the recommendation to undergo surgery (black 70% *vs.* white 79%, P=0.11) (46). On further evaluation, it was found that black patients were disproportionately more likely to decline surgery than white patients (18% *vs.* 5%, P=0.002) (46). Higher rates of refusal of surgery have also been reported in the SEER population. In a cohort of stage I–II NSCLC patients over the age of 50, Mehta *et al.* found that after adjusting for age, sex, and marital status, black patients and patients of other race were at increased odds of refusing surgical treatment as compared to white patients (black:

Table 4 Observational studies investigating patient mediated mechanisms that perpetuate surgical disparities

Source	Data source	# of lung cancer patients	Years studied	Research question	Finding
Cykert *et al.* (44)	Community practice	437	2005–2008	Are there potentially modifiable factors associated with the decision to undergo lung cancer surgery and do these factors contribute to racial disparities in the receipt of surgery?	Negative patient perceptions toward surgery are associated with the decision to decline surgical treatment. These perceptions were not found to be race-specific
Farjah *et al.* (45)	Surveillance, Epidemiology, and End Results Program	17,739	1992–2005	Are there racial differences in the refusal of surgical treatment among patients over the age of 66 who were recommended surgery?	Older black patients were more likely than white patients to refuse recommended surgery
McCann *et al.* (46)	Institutional	281	1995–1998	What are the specific factors that might account for the difference in surgical rates of stages I and II NSCLC between blacks and whites?	Black patients had lower rates of surgery despite being recommended surgery as often as whites. Blacks were found to decline surgery more often than whites
Mehta *et al.* (47)	Surveillance, Epidemiology, and End Results Program	62,514	1988–2002	What is the impact of race and health disparities on the refusal of recommended surgery for lung cancer?	Black patients were more likely than whites to refuse recommended surgical treatment
Williams *et al.* (48)	VA Central Cancer Registry	1,314	2006–2007	Is comorbidity burden associated with racial differences in receipt of surgery among lung cancer patients?	Black patients had a greater prevalence of non-pulmonary comorbidities. Black patients were less likely than whites to undergo surgery and more likely to refuse surgery independent of comorbidity burden

NSCLC, non-small cell lung cancer.

OR =1.88, 95% CI: 1.50–2.36, P<0.001; other: OR =1.95, 95% CI: 1.50–2.52, P<0.001) (47). An earlier study by Farjah *et al.* investigated whether racial differences exist among SEER-Medicare patients over the age of 66 who were recommended surgery for stage I–II disease (45). They reported a 14% difference in the proportion of black and white patients that underwent resection (black 69% *vs.* white 83%). Though this study did not specifically mention why patients did not undergo resection, variation in patient preference cannot be ruled out.

Williams *et al.* investigated racial differences in attitudes toward surgery in a cohort of VA patients (48). After stratifying patients by comorbidity burden, they showed that a greater proportion of black patients did not receive surgery in each comorbidity category (mild, moderate, severe) as compared to white patients. In addition, black patients were also more likely than whites to refuse surgery in each severity category. Like Farjah *et al.*, these authors did not include data on the reasons for patient refusal of surgery (45).

Cykert *et al.* examined the factors associated with the decision to undergo surgery among patients with newly diagnosed stage I–II NSCLC in North and South Carolina (44). Similar to Williams *et al.*, they described lower rates of surgery among black patients with high morbidity burden (OR =0.04; 95% CI: 0.01–0.25) not observed in highly comorbid white patients (OR =0.45; 95% CI: 0.10–2.0) (48). Additionally, the authors identified multiple potentially modifiable factors associated with the decision to not undergo surgery, including the patient's belief that the lung cancer diagnosis was less than 90% certain (OR =0.37; 95% CI: 0.14–0.93), negative perceptions of patient-physician communication (OR =0.42; 95% CI: 0.32–0.74) and negative perceptions of prognosis 1 year following surgery (OR =0.27; 95% CI: 0.14–0.50) (44). Though these beliefs were not found to be race-specific, other reports have described racial differences in perceptions toward surgery and physician communication (49,50).

Table 5 Observational studies investigating staging inequity as a mechanism perpetuating surgical disparities

Source	Data source	# of lung cancer patients	Years studied	Research question	Finding
Farjah *et al.* (56)	Surveillance, Epidemiology, and End Results Program	43,912	1998–2002	What are the trends and factors associated with single *vs.* multi-modality staging?	Patients of black race, low income, low education, and living in rural areas were less likely to receive multi-modality staging
Gould *et al.* (57)	Cancer Care Outcomes Research and Surveillance Consortium	3,638	2003–2005	Are demographic and tumor related factors associated with PET imaging for lung cancer?	Hispanics and those of non-white race were less likely to undergo PET staging, even after controlling for income, education, or insurance payer status
Lathan *et al.* (58)	Surveillance, Epidemiology, and End Results Program	14,224	1991–1999	What is the impact of race on patterns of invasive staging and treatment for lung cancer?	Black patients were less likely to undergo invasive staging than white patients. Staged black patients remained less likely to undergo surgery than whites due to lower recommendations for surgery and higher rates of refusal
Suga *et al.* (59)	California Cancer Registry	12,395	1994–2004	Do racial disparities exist in the receipt of noninvasive and invasive staging modalities?	There were no racial differences in the receipt of non-invasive or invasive staging techniques. However, rural patients were less likely to undergo staging

PET, positron emission tomography.

Disparities in staging evaluation

NCCN guidelines recommend timely and appropriate staging and surgical evaluation following the diagnosis of lung cancer (5). In keeping with these recommendations, the use of positron emission tomography (PET) imaging and other mediastinal staging modalities have been shown to improve staging accuracy and prevent unnecessary surgery in NSCLC patients (51-55). However, significant underutilization and variability in the use of these advanced staging techniques has been reported (*Table 5*) (56-58,60-62).

Gould *et al.* conducted a prospective cohort analysis of disparities in PET staging for 3,638 patients with newly diagnosed stage I–II NSCLC from 2003 to 2005 enrolled in the Cancer Care Outcomes Research and Surveillance Consortium (57). This consortium includes patients from four different geographical regions, representing approximately 10% of the United States population. The authors found PET use to be significantly lower among patients who were older than 69 years of age (RR =0.91; 95% CI: 0.81–1.00), of non-white race (RR =0.87; 95% CI: 0.77–0.97), had Medicare insurance (RR =0.87; 95% CI: 0.76–0.99), or had less than 9 years of formal schooling (RR =0.76; 95% CI: 0.57–0.98) (57).

Lathan *et al.* examined the impact of race on patterns of invasive staging and treatment in SEER-Medicare patients (58). These authors found black race to be independently associated with reduced odds of undergoing invasive staging (OR =0.75; 95% CI: 0.67–0.83) and surgery (OR =0.55; 95% CI: 0.47–0.64) (58). When evaluating the potential reasons for this discrepancy, they found that black patients were recommended surgery less often (67% *vs.* 71.4%, P<0.05) and had higher rates of refusal for surgery (3.4% *vs.* 2.0%, P<0.05) than white patients (58).

Farjah *et al.* assessed the patterns and factors associated with the use of single (CT), bi- (CT + PET or CT + invasive staging), and tri-modality (CT + PET + invasive staging) staging in SEER-Medicare beneficiaries with NSCLC from 1998 to 2005 (56). These authors found that between 1998 and 2002, there was a statistically significant decrease the use of single modality staging (90% to 67%, P<0.001) and a reciprocal increase in the use of multi-modality staging techniques (bi-modality 10% to 30%; tri-modality 0.4% to 5%) (56). The increase in multi-modal staging appeared to be driven primarily by increases in PET (2% to 31%, P<0.001) as compared to invasive techniques, which decreased over the study period (9% to 8%, P=0.005) (56). The authors identified several demographic and socioeconomic status factors associated with lower odds of undergoing multi-modal staging by multivariable regression, including increased age (OR =0.97; 95% CI:

Table 6 Retrospective, observational studies investigating geographic/travel distance as a mechanism perpetuating surgical disparities

Source	Data source	# of lung cancer patients	Years studied	Research question	Finding
Lieberman-Cribbin *et al.* (63)	New York Statewide Planning and Research Cooperative System	31,931	1995–2012	Are there racial disparities in hospital utilization and outcomes in New York?	Patients living at greater distances from high volume hospitals were less likely to undergo surgery at such centers. These differences existed in both black and white patients
Liu *et al.* (64)	New York Statewide Planning and Research Cooperative System	9,099	1995–2012	What factors influence the receipt of lobectomy for the treatment of lung cancer in New York?	Patients of black race and Hispanic ethnicity were more likely to undergo lobectomy at distant low volume centers. Treatment at low volume centers was associated with increased postoperative complications

0.96–0.97), black race (OR =0.63; 95% CI: 0.55–0.72), low income (OR =0.84; 95% CI: 0.77–0.93), low education (OR =0.89; 95% CI: 0.81–0.97), living in the Mid-West (OR 0.68, 95% CI: 0.62–0.74), and rural area of residence (OR =0.80; 95% CI: 0.71–0.91) (56). In contrast, Suga *et al.* reported no association between race and non-invasive or invasive staging in a cohort of patients from the California Cancer Registry (59). Instead, these authors found that patients residing in rural areas were less likely to undergo non-invasive staging (PET, MRI, and CT) as well as invasive staging modalities (bronchoscopy, mediastinoscopy, and thoracoscopy) (59). These data suggest that the factors underlying staging discrepancies may differ according to region.

Collectively, these studies outline significant disparities in the receipt of staging. Given the importance of timely and accurate staging in the evaluation of surgical candidacy, staging disparities may subsequently perpetuate treatment disparities.

Geographic/travel distance

The literature concerning the impact of travel distance on resource utilization and clinical outcomes for cancer surgery has been mixed (*Table 6*). In some studies, increased travel distance has been shown to be associated with later stage at diagnosis, longer time to treatment initiation, and lower rates of surgery (65-69). Conversely, other studies have found that cancer patients who travel greater distances are more likely to receive care at higher volume centers, undergo surgical resection, and experience improved outcomes (70-72). Unfortunately, data specifically evaluating the relationship between travel distance and surgical outcomes in the United States lung cancer population are limited.

In an observational study of lung cancer patients undergoing resection in the state of New York, Lieberman-Cribben *et al.* found that patients living further away from high volume or very high volume centers (top two quintiles of surgical volume) had significantly lower odds of undergoing surgery at such centers (>2.3–6.1 miles: OR =0.51, 95% CI: 0.46–0.56; >6.1 miles: OR =0.27, 95% CI: 0.24–0.30) and were concomitantly more likely to undergo surgery at low volume or very low volume centers (>2.3–6.1 miles: OR =1.44, 95% CI: 1.23–1.67; >6.1 miles: OR =2.70, 95% CI: 2.34–3.13) (63). This trend was maintained in a subgroup analysis comparing white and black patients.

In a second study published by the same group, the authors assessed the factors associated with the receipt of lobectomy (64). In this analysis, non-Hispanic ethnicity (OR =2.25; 95% CI: 1.60–3.16), other race/ethnicity (OR =1.41; 95% CI: 1.16–1.71), greater Elixhauser comorbidity index (OR =1.02; 95% CI: 1.01–1.02), and greater median income (OR =2.88; 95% CI: 2.51–3.32) were each found to be independently associated with a greater likelihood of undergoing lobectomy at a distant high volume hospital (64). In contrast, black race (OR =1.69; 95% CI: 1.26–2.26) and Hispanic ethnicity (OR =2.27; 95% CI: 1.51–3.42) were associated with increased odds of undergoing lobectomy at a distant low volume hospital (64). Importantly, patients treated at distant low volume centers were more likely to experience adverse postoperative events compared to those treated at near high volume centers (OR =1.49; 95% CI: 1.25–1.78). Together these data suggest that racial/ethnic differences in travel patterns may profoundly affect the quality of care received for the treatment of NSCLC, though additional research into the impact of travel distance and the receipt of surgery in nationally representative cohorts is necessary.

Table 7 Prospective, observational studies investigating stigma as a mechanism perpetuating surgical disparities

Source	Data source	# of lung cancer patients	Years studied	Research question	Finding
Carter-Harris (73)	Institutional	93	2012–2013	What is the impact of perceived stigma on the timing of medical help-seeking behavior among lung cancer patients?	Self-reported stigma was associated with the desire to delay seeking medical care among lung cancer patients
Criswell *et al.* (74)	Multi-institutional	213	–	To what extent to lung cancer patients feel stigma, regret, and personal responsibility for their disease?	Feelings of personal responsibility were greatest among ever smokers. For never smokers, feelings of regret and stigmatization were associated with greatest adverse psychological outcomes
Ernst *et al.* (75)	German Cancer Registries	125	2016	What is the impact of stigmatization on patient reported quality of life among those with cancers of the breast, colon, lung, and prostate?	Lung cancer patients self-report high levels of perceived isolation and had higher levels of internalized shame compared to patients with other types of cancer. Stigmatization was found to be inversely correlated with quality of life
LoConte *et al.* (76)	Multi-institutional	327	2006	Do levels of guilt, shame, depression, and anxiety differ in patients with lung cancer compared to those with breast or prostate cancer?	Lung cancer patients had greater perceived cancer related stigma. Overall there was no difference in levels of guilt or shame across cancer groups, however, a history of smoking did correlate with generalized guilt and shame
Wassenaar *et al.* (77)	Community practice	672	2005	Do primary care providers differ in treatment and referral patterns for breast cancer patients compared to lung cancer patients?	Primary care physicians were less likely to refer advanced lung cancer patients for additional care than advanced breast cancer patients. Physicians were also less likely to understand the benefits of chemotherapy for advanced lung cancer than advanced breast cancer
Weiss *et al.* (78)	Lung Cancer Alliance	174	2008	What factors are associated with lung cancer patient feelings of stigmatization and self-blame?	Smoking status was associated with feelings of self-blame and stigmatization, as well as perceived differences in treatment by healthcare professionals
Williamson *et al.* (79)	Institutional	101	–	Do feelings of internalized stigma impact physical, emotional, and functional quality of life outcomes in lung cancer patients?	Ever smokers reported higher rates of internalized stigma than never smokers. Higher internalized stigma was associated with poorer emotional, physical, and functional quality of life

Stigma

In recent years, there has been a growing public health awareness and concern surrounding the negative stigma associated with a lung cancer diagnosis and its potential impact on patient care and outcomes. Lung cancer patients have been shown to experience high rates of perceived and internalized negative stigma because of the association with smoking secondary to anti-tobacco advertising campaigns, along with depressive and other psychological symptoms (*Table 7*) (74-76,78,79). Additionally, rates of self-reported negative stigmas and shame were found to be higher among lung cancer patients than patients with breast or prostate cancer (76). Within the lung cancer population, negative self-perception has been shown to differ based on factors such as smoking status, with current/former smokers reporting higher levels of internalized stigma, personal responsibility, and regret as compared to never smokers (74,79).

In addition to its deleterious effects on overall quality of life, patient and physician perceptions of stigma about lung cancer may negatively impact patient care. Wassenaar *et al.* conducted a study in which 672 primary care physicians were

surveyed using clinical scenarios designed to assess treatment and referral patterns for hypothetical breast cancer and lung cancer patients (77). The authors found that primary care physician respondents were less likely to refer advanced lung cancer patients to an oncologist than advanced breast cancer patients, irrespective of performance status. Respondents also believed that chemotherapy was less effective for lung cancer patients than for stage-matched breast cancer patients. Remarkably, these hypothetical survey answers were given despite the two groups of primary care physicians treating similar proportions of breast and lung cancer patients in their actual clinical practice.

As for the implication of perceived stigma on patient attitudes, Carter-Harris *et al.* published a study showing an association between increased patient reported negative stigma and the desire to delay receiving medical care (73). Ultimately, no study to date has reported disparities in the receipt of surgery for NSCLC based solely on perceptions such as stigma and nihilism. However, given the potential additive effect of these perceptions across the patient, physician, and healthcare system levels, an assessment of the potential impact of these factors on the surgical and clinical care of NSCLC patients may be warranted (80).

Discussion

Surgical resection remains a fundamental component of the therapeutic management of NSCLC. For patients with localized disease, curative intent surgery offers the best clinical and oncologic outcomes. While it is currently estimated that 30% of NSCLC patients have resec disease on clinical evaluation, this number is expected to increase with recent national guidelines endorsing annual low-dose computed tomography screening in high risk patients (5,81-83). Conversely, in patients with advanced disease, surgery has conventionally occupied a diagnostic or palliative role. However, recent evidence suggests that multimodal treatment regimens that include surgical resection may confer a therapeutic benefit in select patients with metastatic NSCLC (84). Given the expanding indications and utility for thoracic surgery in the management of NSCLC of all stages, efforts to identify and mitigate disparities in the use of surgery have become exceedingly relevant from a clinical and public health perspective.

In this review, we summarize nearly two decades of surgical disparities literature and highlight common and unrecognized disparities in the receipt of surgery. We demonstrate that inequity persists in the management of lung cancer patients, with racial, socioeconomic, and other special patient groups are at risk of not receiving guideline recommended surgery. While improving effective communication and access to staging and other resources are important areas to target, further study into the mechanisms perpetuating these disparities are warranted.

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Footnote

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