ORIGINAL ARTICLE

The Care and Outcomes of Older Persons with Lung Cancer in England and the United States, 2008–2012

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ABSTRACT

Introduction: Although prior research has demonstrated lower lung cancer survival in England than in the United States, more detailed comparisons are needed. We conducted a population-based analysis to compare diagnostic, treatment, and survival patterns.

Methods: Data from cancer registries and administrative databases were linked for older patients with a diagnosis of NSCLC in England and the United States (2008–2012). We compared patient and clinical characteristics, as well as the distribution of age-standardized receipt of treatment by stage. We compared relative survival overall by stage and treatment. Finally, we assessed the degree to which stage distribution and stage-specific survival contributed to survival differences.

Results: Among patients age 66 years or older with a diagnosis of NSCLC in England (n = 86,978) and the United States (n = 84,415), the rate of pathological confirmation was 63% in England compared with 85% in the United States (a 22.2% difference [99% confidence interval: 22.8%–21.7%]). The rate of receipt of active treatment was lower in England than in the United States (46% versus 60%, for a difference of 14.0% [99% confidence interval: 13.3%–14.7%]). In England, we identified 98 excess deaths per 1000 patients with pathologically confirmed NSCLC; these additional deaths could be partially mitigated by adjusting stage at diagnosis (reduction to 54 excess deaths) or stage-specific survival (reduction to 36 excess deaths).

Conclusions: Compared with patients with NSCLC in the United States, patients with NSCLC in England are less likely to present with early-stage disease and receive treatment and are more likely to die. Future work should explore whether the intensity of resources directed to diagnostic and therapeutic activity may help mitigate disparities in outcomes.

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Introduction

Lung cancer is the leading cause of cancer death in developed countries across the world.[1] Despite the steady decline in lung cancer mortality rates over the past two decades, lung cancer accounts for approximately 21% of all cancer deaths in England and 26% in the United States.[2,3] In addition to comprehensive tobacco control programs[4] that have led to a dramatic decrease in the prevalence of cigarette smoking, the evolving clinical landscape of lung cancer care and outcomes is being shaped by newer approaches to early detection and treatment.[5,6] As these techniques diffuse into clinical practice, understanding how care differs between health systems represents an opportunity for improvement.

In comparisons across developed countries such as England and the United States, substantial variation exists in lung cancer incidence and mortality.[7] Age-standardized lung cancer mortality rates were higher in England than in the United States in 2014 for both men (72.9 versus 55.9 per 100,000 population) and women (48.4 versus 36.3 per 100,000 population).[2,8] Several population-based research studies, including EUROCARE, CONCORD, and the International Cancer Benchmarking Partnership, have revealed substantive international differences in cancer outcomes, with patients in England tending to experience lower survival.[7,9,10] Efforts to estimate and compare care and outcomes across health systems have been disjointed, however, owing to challenges in collecting comparable data that are population based and contain sufficient clinical detail. For instance, in a comparison of EUROCARE cancer registries from 17 European countries with the data from the Surveillance and Epidemiology End Results (SEER) Program in the United States, survival for most major cancers was lower in Europe. However, this study lacked information on stage and primary treatment, with many countries reporting data on only a subset of the population.[11] The CONCORD-2 global cancer surveillance study reported wide differences in 5-year age-standardized net lung cancer survival rates (9.6% in England versus 18.7% in the United States for 2005–2009),[12] a difference that was thought to be driven by the intensity of diagnostic activity, tumor staging at diagnosis, and treatment but was ultimately concluded to be due to the face that the comparability of data on cancer stage and treatment remains poor.[7,13–16] Hence, more detailed population-based comparisons between the health systems in the United States and Europe are needed.

The growing costs of cancer care, coupled with the international divide in outcomes, raises questions regarding best practices for and the value of investment in health care resources. The higher survival rates in the United States likely reflect earlier diagnosis, more aggressive treatment, and utilization of new technologies.[17] However, a better understanding of the differences between health systems is required to maximize the return on investment in cancer care. This is particularly important in older patients, as the median age at diagnosis for NSCLC is approximately 70 years.[18,19] Older patients are frequently excluded from clinical trials, reducing the generalizability of evidence-based medical practice[20] and resulting in greater variation in clinical practice.[21]

We performed a collaborative investigation of diagnostic, treatment, and survival patterns in older patients with a diagnosis of NSCLC between England and United States. Specifically, we compared the two health care systems from the standpoints of distribution of stage at diagnosis, use of cancer-directed treatment, and survival. In addition, we aimed to estimate the degree to which stage at diagnosis and receipt of cancer treatment mitigated potential differences in survival between countries.

Materials and Methods

Study Design and Data Sources

Data for this retrospective cohort study were obtained from population-based cancer surveillance registries and administrative databases in England and the United States. In England, patient-level data were identified in the combined National Cancer Analysis System (CAS), Public Health England's National Cancer Registration and Analysis Service (NCRAS), the National Lung Cancer Audit (LUCADA) database, and the Hospital Episode Statistics[22] database. The Office for Data Release in Public Health England extracted lung cancer records from the national CAS 2013 database and linked them to the LUCADA 2012[23] and Hospital Episode Statistics data sets by National Health Service number. Patient-level data from the United States were provided by the linked SEER-Medicare database maintained by the National Cancer Institute (NCI), which is responsible for linkage between the SEER database and administrative claims for Medicare-eligible persons residing in the areas covered by the 17 SEER regional cancer registries.[24] Details on data sources are available in the Supplementary Methods.

Population

We included all incident cases of invasive NSCLC diagnosed in 2008–2011 in the SEER-Medicare database

and in 2009–2012 in the LUCADA and NCRAS databases for patients age 66 years or older. We excluded patients whose tumor registration was made from a death certificate or on the basis of autopsy only, as well as patients with a pathologically confirmed diagnosis of SCLC.

Data Elements and Measures

Patient-level information included sociodemographic characteristics (year of diagnosis, age, and sex) as well as clinicopathological characteristics, including diagnostic confirmation, stage, and histologic subtype. We calculated the proportion of patients with a pathologically confirmed diagnosis of NSCLC, combining the basis of diagnosis variables in the CAS and LUCADA databases for England and using the diagnostic confirmation variable in the SEER database for the United States.

The following histologic groupings were included as NSCLC: adenocarcinoma (*International Classification of Diseases for Oncology*, *Second Edition* [ICD-O-2] codes 8140, 8141, 8143, 8147, 8200, 8250, 8251, 8252, 8253, 8254, 8255, 8260, 8310, 8480, 8481, 8490, 8550, 8560, 8570, 8571, 8572, 8573, 8574, and 8575); squamous cell carcinoma (ICD-O-2 codes 8052, 8070, 8071, 8072, 8073, 8074, 8575, 8076, and 8078); large cell carcinoma (ICD-O-2 codes 8012, 8013, 8021, 8022, 8031, 8032, and 8033); and other specified histologic code (ICD-O-2 codes 8020, 8046, 8050, 8051, 8430, 8980, 8010, and 8011). We also included tumors with nonspecific histologic codes (ICD-O-2 codes 8000, 8001, 8003, and 8004), as NSCLC constitutes the great majority of lung tumors.

We used the American Joint Committee on Cancer Staging system to classify stage at diagnosis (version 7 of the Union for International Cancer Control TNM system), either clinical or pathological, categorized as stage I, II, IIIA, IIIB, or IV. Stages IIIB and IV were combined in the survival analysis. Separate estimates are available in Supplementary Table 1. We reported the frequency and percentages of unknown stage.

Treatment characteristics included first-line surgery, receipt of chemotherapy or radiotherapy, and any active treatment from 1 month before through 6 months after initial diagnosis (see the Supplementary Methods). For comparisons of treatment modalities other than surgery (radiotherapy or chemotherapy and any active treatment) across the two health care systems, the U.S. sample was restricted to patients with continuous fee-for-service (FFS) Medicare coverage from 1 year before through 6 months after diagnosis to capture initial treatment. We restricted the U.S. sample to patients with continuous FFS coverage because the SEER data alone do not reliably capture chemotherapy or radiotherapy.[24,25] Date of diagnosis is defined in the English register according to European rules[26] and for the United States according to SEER-Medicare standards.[27] Survival time was calculated as the total number of months from the date of diagnosis to date of death or the censoring date of December 12, 2013.

We calculated the number of excess deaths from lung cancer that were due to differences in stage distribution at diagnosis and stage-specific survival in England versus in the United States by using observed stage distribution and the 2-year estimated stage-specific relative survival (RS). We compared the observed number of patients alive within 2 years of diagnosis with the expected number if either the stage distribution or the 2-year stage-specific RS in England mirrored the observed distribution in the United States.

Institutional review board approval for the study was obtained both in England and in the United States.

Statistical Analysis

In accordance with study protocols, the two health system databases were not combined in any analyses, and access to the data was limited to the investigators at their respective study sites. Rather than creating a joint patient-level database, summary estimates from each health system were reported and compared. Overall differences in patient and treatment-related characteristics between the two countries were assessed by chi-square and Mantel-Haenszel tests. Differences between categories were presented with their binomial 99% confidence intervals (CIs). We calculated age-standardized estimates for the proportion of patients receiving different treatment modalities by stage by using the U.S. 2000 standard population.[28]

For each country, we estimated overall survival (OS) by using the Kaplan-Meier method. Patients with a survival time of zero were included.[29] We also estimated 1- and 2-year RS rates, which were measured as the ratio of observed to expected survival by using life table methods and the Ederer II method to calculate expected survival.[30] We used country-specific life tables (for the years 2008–2013 for the United States and the years 2009–2013 for England), which included survival probability for each year by sex and single year of age from 66 to 99 years. As the English life tables were calculated by the Office for National Statistics with a period of 3 consecutive years,[31] we used the Office for National Statistics estimate for the central year of the period (e.g., for 2009 we used the 2008–2010 period estimate). We also estimated RS in subgroups according to demographic characteristics, stage, and treatment. Calculations for the number of excess deaths were produced by using 2-year RS estimates and the lower and upper limits of the 95% confidence intervals to obtain a minimum and a maximum for the predictions.

All statistical analyses were performed with SAS software (version 9.4, SAS Institute Inc., Cary, NC). Figures were produced with R software (version 3.3.0, R Foundation for Statistical Computing, Vienna, Austria).

Results

We identified a total of 91,322 patients in the English database and 101,600 patients in the U.S. database (Supplementary Fig. 1). After application of the exclusion criteria, the final samples consisted of 86,978 patients for England and 84,415 patients for the United States. Seventy-five percent (n = 65,496) of the final English sample linked to a LUCADA record, and 64%. (n = 54,318) of the final U.S. patient sample had continuous FFS Medicare coverage from 1 year before through 6 months after diagnosis.

We found slight differences in age and sex distribution between the two countries (Table 1). The proportion of patients without pathological confirmation was higher in England (37%) than in the United States (15%) (a 22.2% difference [99% CI: 22.8%–21.7%]). In England, the proportion of patients without pathological

Table 1. Cohorts of Patients with NSCLC in England and the United States

Characteristics	England (n = 86,978)	United States (n = 84,415)	% Difference (99% CI)
Patient characteristics			
Year of diagnosis			
2008	—	21,612 (25%)	
2009	20,881 (24%)	21,714 (26%)	-1.7 (-2.3 to -1.2)
2010	21,251 (24%)	21,092 (25%)	-0.6 (-1.1 to -0.0)
2011	21,960 (25%)	19,997 (24%)	1.6 (1.0-2.1)
2012	22,886 (26%)	—	
Age at diagnosis, y			
66-70	17,627 (20%)	20,478 (24%)	-4.0 (-4.5 to -3.5)
71-75	19,948 (23%)	20,170 (24%)	-1.0 (-1.5 to -0.4)
76-80	19,971 (23%)	19,257 (23%)	0.1 (-0.4 to 0.7)[a]
81-85	16,783 (19%)	14,669 (17%)	1.9 (1.4- 2.4)
>85	12,649 (15%)	9841 (12%)	2.9 (2.5-3.3)
Sex			
Male	48,888 (56%)	43,342 (51%)	4.9 (4.2-5.4)
Female	38,090 (44%)	41,073 (49%)	-4.9 (-5.5 to -4.2)
Ethnicity			
White	57,606 (97%)	71,467 (85%)	13.0 (12.6-13.3)
Black	367 (1%)	7582 (9%)	-8.4 (-8.6 to -8.1)
Other, specified	1032 (2%)	5366 (6%)	-4.6 (-4.9 to -4.4)
Clinical characteristics			
Basis of diagnosis			
Cytologic or histologic examination	54,973 (63%)	72,121 (85%)	-22.2 (-22.8 to -21.7)
Clinical	31,743 (36%)	10,098 (12%)	24.5 (24.0-25.0)
Confirmation unknown	262 (0.3%)	2196 (3%)	-2.3 (-2.5 to -2.2)
Histologic type, all patients			
Adenocarcinoma	21,315 (24%)	36,213 (43%)	-18.39 (-18.97 to -17.81)
Squamous cell	18,929 (22%)	21,024 (25%)	-3.14 (-3.67 to 2.62)
Large cell	986 (1%)	2265 (3%)	-1.55 (-1.72 to -1.38)
Other, specified	36,168 (42%)	17,392 (21%)	20.98 (20.42-21.54)
Other, NOS	9580 (11%)	7521 (9%)	2.10 (1.73-2.48)
Histologic type, MV only			
Adenocarcinoma	20,815 (38%)	35,841 (50%)	-11.8 (-12.6 to -11.1)
Squamous cell	18,579 (34%)	20,857 (29%)	4.9 (4.2-5.6)
Large cell	972 (2%)	2246 (3%)	-1.4 (-1.6 to -1.1)
Other, specified	14,302 (26%)	12,366 (17%)	8.9 (8.3-9.5)
Other, NOS	305 (1%)	811 (1%)	-0.6 (-0.7 to -0.4)
Stage	1		
I	10,176 (15%)	18,227 (25%)	-9.2 (-9.7 to -8.6)
II	5685 (8%)	3669 (5%)	3.5 (3.2-3.9)
IIIA	8543 (13%)	7030 (9%)	3.3 (2.8-3.7)
IIIB	8029 (12%)	12,622 (17%)	-4.9 (-5.4 to -4.4)
IV	35,534 (52%)	33,976 (45%)	7.3 (6.6-8.0)

[a]The only 99% CI that includes a zero.

CI, confidence interval; MV, microscopically verified cases; NOS, not otherwise specified.

confirmation varied by age, from 18% in patients age 66 to 70 years to 69% in patients age 85 or older. In the United States, the variation ranged from 12% in patients age 66 to 70 to 30% in patients age 85 or older. Among patients with pathologically confirmed tumors, the proportion of those with adenocarcinoma was lower in England than in the United States (38% versus 50%, for a difference of 11.8 [99% CI: 12.6%–11.1%]), whereas the percentage of those with squamous cell carcinoma was higher (34% versus 29%, for a difference of 4.9% [99% CI: 4.2%–5.6%]).

The proportion of patients for whom stage was not available was 22% for England and 11% for the United States (a difference of 11.3% [99% CI: 10.9%–11.8%]). This estimate varied by age, more than doubling from 15% in those age 66 to 70 years to 34% in those older than 85 years in England and increasing from 16% to 23% in the United States. We found differences in stage distribution at diagnosis between the two countries ($p < 0.001$). Patients in England were less likely to have their NSCLC diagnosed at stage I than were those in the United States (15% versus 24%, for a difference of 9.2% [99% CI: 8.6%–9.7%]), whereas the proportion of patients with stage IIIB or IV disease was comparable between the two countries (64% in England versus 62% in United States, for a difference of 2.0% [99% CI: 1.3%–2.6%]). The stage distribution was similar across age groups in both countries.

Treatment

The proportion of patients who received any active treatment was lower in England than in the United States (46% versus 60%, for a difference of 14.0% [99% CI: 13.3%–14.7%]) (Table 2), but it was similar when the comparison was restricted to patients with pathologically confirmed tumors (66% versus 69%, for a difference of 3.3% [99% CI: 2.5%–4.1%]). Among patients without pathological confirmation, active treatment was received by 12.1% (of 32,005) of those in England and 9.6% (of 8301 [FFS patients only]) of those in the United States. Larger differences were observed in the receipt of an operation, however, with 13% of patients in England receiving an operation compared with 20% in the United States overall (a difference of 7.4% [99% CI: 6.9%–7.8%]). Similar absolute differences were observed for the receipt of nonsurgical treatments, with 36% of patients in England receiving chemotherapy or radiotherapy compared with 45% of patients in the United States (a difference of 9.0% [99% CI: 8.4%–9.7%]). For patients with stage I disease, the difference in receipt of an operation was 8.1% (99% CI: 6.5%–9.7%), with rates of 52% for England and 60% for United States. The largest differences in receipt of

Table 2. Crude and Age-Standardized Receipt of Treatment by Stage in England and the United States

	England (n = 86,978)			United States (n = 84,415[a]/54,318[b])				
Treatment	n	Crude %	Standardized %	n	Crude %	Standardized %	% Difference Crude (99% CI)	*p* Value[c]
Surgery[a]	11,224	13%	15%	17,113	20%	21%	-7.4 (-7.8 to -6.9)	<0.001
Stage I	5284	52%	55%	10,940	60%	60%	-8.1 (-9.7 to -6.5)	<0.001
Stage II	2353	41%	45%	2062	56%	54%	-14.8 (-17.5 to -12.1)	
Stage IIIA	1312	15%	17%	1416	20%	20%	-4.8 (-6.4 to -3.2)	
Stage IIIB	289	4%	4%	1258	10%	11%	-6.4 (-7.3 to -5.5)	
Stage IV	1088	3%	3%	1131	3%	3%	-0.3 (-0.6 to 0.1)	
Chemotherapy or radiotherapy[b]	31,596	36%	39%	24,647	45%	47%	-9.1 (-9.7 to -8.4)	<0.001
Stage I	2638	26%	26%	3652	30%	30%	-4.4 (-6.0 to -2.9)	<0.001
Stage II	2477	44%	45%	1393	59%	59%	-15.8 (-18.9 to -12.6)	
Stage IIIA	4836	57%	59%	2992	67%	67%	-10.0 (-12.3 to -7.7)	
Stage IIIB	4542	57%	59%	4101	51%	54%	5.6 (3.6-7.7)	
Stage IV	14,696	41%	44%	11,076	51%	53%	-9.8 (-10.9 to -8.7)	
Any active treatment[b]	40,084	46%	50%	32,623	60%	62%	-14.0 (-14.7 to -13.3)	<0.001
Stage I	7356	72%	74%	9888	82%	82%	-9.9 (-11.4 to -8.5)	<0.001
Stage II	3959	70%	72%	1959	83%	82%	-13.8 (-16.4 to -11.3)	
Stage IIIA	5501	64%	67%	3250	72%	72%	-7.9 (-10.1 to -5.7)	
Stage IIIB	4700	59%	61%	4513	56%	59%	2.5 (0.5-4.5)	
Stage IV	15,383	43%	46%	11,442	53%	54%	-9.6 (-10.7 to -8.5)	

Note: The U. S. 2000 standard population was used for standardization. Overall includes patients with no staging data: for surgery, n = 898 for England and n = 306 for the United States; for chemotherapy or radiotherapy, n = 2407 for England and n = 1433 for the United States; for any active treatment, n = 3185 for England and n = 1571 for the United States.

[a]Number of patients available to evaluate surgery.

[b]Number of patients available to evaluate medical treatment.

[c]From chi-square or Mantel-Haenszel test.

CI, confidence interval.

all treatment modalities were observed for patients with stage II disease (see Table 2). Compared with the United States, England had an approximately 7% smaller absolute difference in the proportion of patients receiving an operation in all age classes (from a 6.8% difference in the 66–70 years age group to a 7.7% difference in the 76–80 years age group) (Table 3), with the exception of patients older than 85 years (a difference of 2.5% [99% CI: 1.9%–3.2%]). In contrast, the difference between the two countries in receipt of chemotherapy or radiotherapy was smaller for younger patients (4.6% difference between patients age 66–75, 99% CI: 3.5%–5.7%) compared to older patients (11.6% difference for those age 76 or older, 99% CI: 10.8%–12.5%).

Survival

The 1- and 2-year OS rates for England were 29.2% (95% CI: 28.8%–29.5%) and 17.0% (95% CI: 16.7%–17.2%), respectively. In the United States, the 1- and 2-year OS rates were 40.1% (95% CI: 39.8%–40.4%) and 27.1% (95% CI: 26.8%–27.4%), respectively. The 1-year RS estimates (Table 4) by sex showed a survival advantage for women compared with men in the United States (48.0% [95% CI: 47.5%–48.5%] for women versus 41.2% [95% CI: 40.7%–41.7%] for men) and in England (32.4% [95% CI: 31.9%–32.9%] for women versus 29.5% [95% CI: 20.0%–29.9%] for men) (Fig. 1). When the confidence intervals for the first and last year of diagnosis were compared, an improvement in 1-year RS was observed for all age and sex subgroups in England, but only for women age 66 to 80 years in the United States (Supplementary Table 2).

The disparity in survival rates between the two countries varied according to stage at diagnosis. For instance, the 1- and 2-year RS rates for stage I disease were similar between England and the United States for patients with pathological confirmation and for patients receiving treatment (see Table 4). Although the 1-year RS rate for patients with stage II disease who underwent an operation was similar between England and the United States (83.6% [95% CI: 81.9%–85.2%] versus 84.0% [95% CI: 82.1%–85.7%]), survival was significantly lower among patients in England with stage IIIA and IIIB or IV disease, regardless of the type of treatment received, as shown by the nonoverlapping confidence intervals (see Table 4 and Supplementary Table 1). Although the RS rate was higher in the United States, when the confidence intervals for the first and last year of diagnosis were compared, the 2-year stage-specific RS rate in England increased from 2009 to 2011 among stage I patients undergoing any active treatment and overall, whereas estimates remained stable for the United States in the same period (see Supplementary Table 3).

In a random sample of 1000 patients with pathological confirmation from each country, a total of 246 patients from England and 344 from the United States were

Table 3. Distribution of treatment receipt by age in England and the United States

Treatment	England (n = 86,978)		United States (n = 84,415[a]/54,318[b])		% Difference (99% CI)	*p* Value[c]
	n	Crude %	n	Crude %		
Surgery by age, y[a]	11,224	13%	17,113	20%	-7.4 (-7.8 to -6.9)	<0.001
66-70	3587	20%	5551	27%	-6.8 (-7.9 to -5.6)	<0.001
71-75	3494	18%	4930	24%	-6.9 (-8.0 to -5.9)	
76-80	2718	14%	4096	21%	-7.7 (-8.7 to -6.7)	
81-85	1133	7%	2059	14%	-7.3 (-8.2 to -6.4)	
>85	292	2%	477	5%	-2.5 (-3.2 to -1.9)	
Chemotherapy or radiotherapy by age, y[b]	31,596	36%	24,647	45%	-9.1 (-9.7 to- 8.4)	<0.001
66-70	9192	52%	6742	56%	-3.5 (-5.0 to -2.0)	<0.001
71-75	9260	46%	6702	52%	-5.5 (-7.0 to -4.0)	
76-80	7131	36%	5824	46%	-10.8 (-12.2 to -9.3)	
81-85	4272	25%	3707	38%	-12.2 (-13.7 to -10.7)	
>85	1741	14%	1672	24%	-10.4 (-12.0 to -8.9)	
Any active treatment by age, y[b]	40,084	46%	32,623	60%	-14.0 (-14.7 to -13.3)	<0.001
66-70	11,594	66%	8888	73%	-7.6 (-8.9 to -6.2)	<0.001
71-75	11,831	59%	8894	69%	-9.6 (-11.0 to -8.2)	
76-80	9349	47%	7919	63%	-16.4 (-17.8 to -15.0)	
81-85	5300	32%	4935	50%	-18.6 (-20.2 to -17.0)	
>85	2010	16%	1987	29%	-12.8 (-14.5 to -11.2)	

[a]Number of patients available to evaluate surgery.
[b]Number of patients available to evaluate medical treatment.
[c]From chi-square or Mantel-Haenszel test.
CI, confidence interval.

Table 4. Relative Survival Estimates for Patients in England and the United States

	1-year Relative Survival		2-year Relative Survival	
Patients Group	England	United States	England	United States
Overall, n range	30.8 (30.4-31.1)	44.5 (44.1-44.9)	18.9 (18.6-19.2)	31.2 (30.8-31.5)
Male	29.5 (29.0-29.9)	41.2 (40.7-41.7)	17.7 (17.3-18.1)	27.4 (27.0-27.9)
Female	32.4 (31.9-32.9)	48.0 (47.5-48.5)	20.4 (20.0-20.9)	35.1 (34.6-35.6)
66-80 years old	34.7 (34.3-35.1)	48.1 (47.6-48.5)	21.8 (21.5-22.2)	34.0 (33.6-34.4)
>80 years old	22.5 (22.0-23.0)	35.0 (34.4-35.7)	12.6 (12.2-13.0)	23.5 (22.9-24.1)
With tissue confirmation, n (range)				
Overall	38.6 (38.2-39.0)	48.6 (48.2-49.0)	24.5 (24.1-24.9)	34.5 (34.1-34.9)
Stage I	87.6 (86.7-88.4)	86.1 (85.5-86.7)	75.7 (74.5-76.9)	76.1 (75.3-76.9)
Stage II	70.1 (68.6-71.5)	73.1 (71.5-74.7)	50.9 (49.2-52.6)	55.1 (53.3-56.9)
Stage IIIA	52.1 (50.8-53.4)	59.7 (58.5-61.0)	29.0 (27.8-30.2)	38.3 (37.1-39.6)
Stage IIIB-IV	21.3 (20.9-21.8)	29.9 (29.4-30.3)	9.0 (8.6-9.3)	15.7 (15.4-16.1)
Surgery, n (range)				
Overall	80.2 (79.4-80.9)	88.1 (87.5-88.6)	68.6 (67.6-69.6)	79.3 (78.6-80.0)
Stage I	92.4 (91.5-93.2)	93.7 (93.0-94.2)	84.8 (83.5-86.0)	88.5 (87.7-89.3)
Stage II	83.6 (81.9-85.2)	84.0 (82.1-85.7)	69.0 (66.8-71.2)	69.3 (67.0-71.5)
Stage IIIA	74.7 (72.1-77.0)	81.8 (79.5-83.9)	54.1 (51.0-57.0)	64.6 (61.8-67.3)
Chemotherapy or radiotherapy, n (range)				
Overall	40.9 (40.4-41.5)	50.9 (50.2-51.5)	21.9 (21.5-22.4)	31.6 (30.9-32.2)
Stage I	83.9 (82.3-85.5)	83.2 (81.8-84.6)	63.9 (61.7-66.1)	65.7 (63.8-67.4)
Stage II	71.1 (69.2-73.0)	78.4 (76.0-80.7)	47.4 (45.2-49.6)	58.2 (55.3-61.0)
Stage IIIA	56.1 (54.7-57.6)	65.9 (64.0-67.6)	30.7 (29.3-32.2)	42.1 (40.2-44.0)
Stage IIIB-IV	27.7 (27.0-28.3)	37.4 (36.6-38.2)	11.4 (11.0-11.9)	18.9 (18.2-19.5)
Any active treatment, n (range)				
Overall	49.3 (48.8-49.8)	60.3 (59.7-60.8)	32.3 (31.8-32.8)	44.2 (43.6-44.8)
MV	51.0 (50.5-51.6)	60.6 (60.0-61.2)	33.6 (33.0-34.1)	44.5 (43.9-45.1)
Not MV	33.1 (31.5-34.6)	46.9 (43.2-50.5)	20.7 (19.3-22.1)	30.5 (27.1-34.1)
Stage I	89.4 (88.6-90.2)	89.9 (89.2-90.6)	78.1 (76.9-79.2)	80.8 (79.8-81.7)
Stage II	74.8 (73.3-76.2)	78.5 (76.4-80.4)	55.0 (53.2-56.8)	60.2 (57.8-62.6)
Stage IIIA	57.7 (56.4-59.1)	66.5 (64.7-68.2)	33.1 (31.8-34.5)	43.2 (41.4-45.1)
Stage IIIB-IV	27.7 (27.0-28.3)	38.9 (38.1-39.7)	11.8 (11.3-12.2)	20.7 (20.0-21.3)

Data are percent relative survival (95% confidence interval).
MV, microscopically verified.

estimated to be alive 2 years from diagnosis; resulting in 98 (minimum of 97–maximum of 99) excess deaths for every 1000 patients in England versus in the United States. If the stage distribution at diagnosis in England were equivalent to that in the United States, however, the number of excess deaths would decrease to 54 per 1000 (a 44.9% difference [minimum of 42.3%–maximum of 45.5%]). Further, if the 2-year stage-specific RS were the same as in the United States, the number of excess deaths in England versus in the United States would decrease to 36 deaths per 1000 patients (a 63.3% difference [minimum of 61.9%–maximum of 64.6%]) (Fig. 2). The latter would be due almost entirely to the larger proportion of patients with a diagnosis of stage IIIA or IV disease surviving to 2 years (see Table 4).

Discussion

In a population-based sample of approximately 170,000 older patients with cancer diagnosed as NSCLC, we identified substantive differences between England and the United States regarding diagnostic approach, stage at diagnosis, treatment patterns, and survival. Across the study period, the rate of pathological confirmation and the proportion of patients with missing stage at diagnosis were key process of care indicators in our study. We found lower rates of pathological confirmation in England versus in the United States, particularly among the oldest patients, with a concomitant higher rate of patients with no recorded stage at diagnosis in England. These findings may reflect differences between the two countries in terms of the level of awareness of and approach to the diagnosis and treatment of older, and particularly very old, patients,[23] and these differences should be taken into consideration when interpreting comparisons limited to patients for whom there was pathological confirmation.

We observed a lower rate of diagnosis of stage I disease in England than in the United States. Policies targeting early detection and diagnosis are imperative, as 44 deaths for every 1000 patients could be avoided at

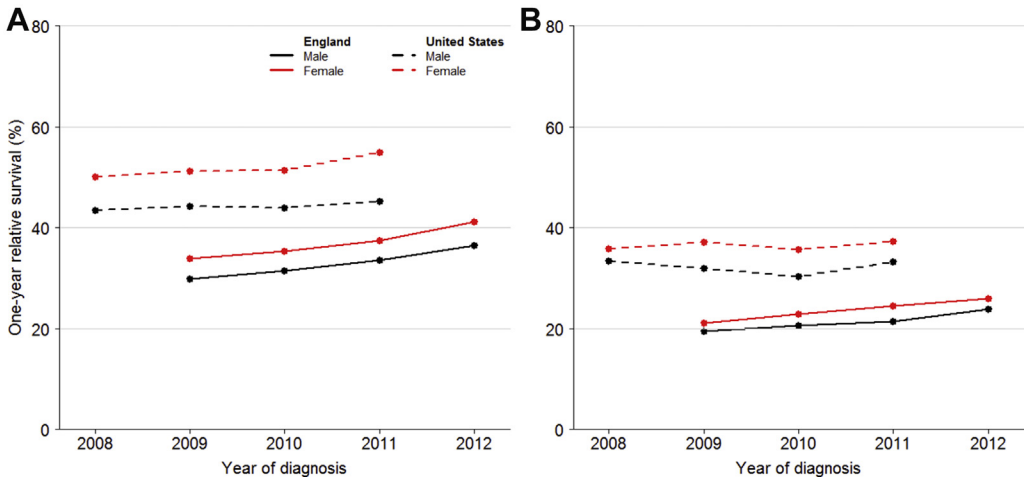

Figure 1. One-year relative survival for sex and age groups according to year of diagnosis: 66- to 80-year-old patients (*A*) and patients older than 80 years (*B*).

2-years after diagnosis if the stage distribution in England were to mirror that in the United States. In England, the Routes to Diagnosis study[32,33] has demonstrated that for approximately 40% of patients lung with cancer, diagnosis is first made as part of an emergency hospital admission. The rate of emergency presentation is higher in older patients, and the 1-year survival rate is significantly lower in those whose disease is diagnosed at emergency presentation across all ages than in those whose disease is diagnosed by other routes.[33] Stage distribution is a particularly important public health concern in lung cancer, given the recent evidence that computed tomography–based screening can decrease lung cancer mortality.[34,35] The dissemination of screening into clinical practice has occurred within the last 5 years in some countries, including in the United States.[34–36] Therefore, it is possible that differential screening practices across countries could exacerbate existing differences in early-stage diagnosis in the near future.

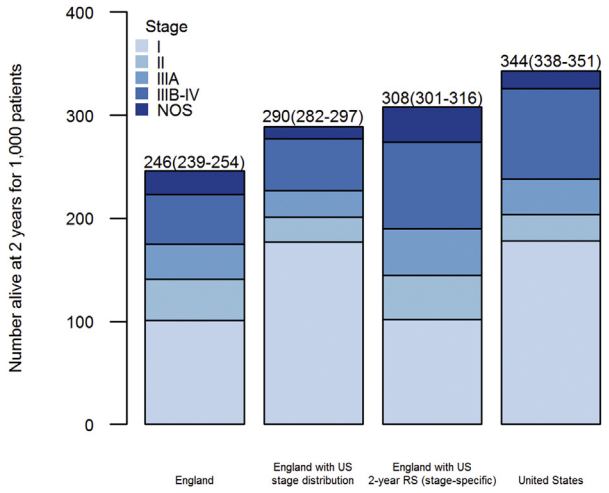

Figure 2. Variation in a sample of 1000 patients in England surviving at 2 years if the stage or stage-specific relative survival (RS) distribution of pathologically verified tumors was matched with the rates in the United States (US). Numbers in brackets were obtained by using 2-year RS lower and upper confidence interval limits. Abbreviation: NOS, not otherwise specified.

Treatment rates also differed: we found that the difference in rate of receipt of chemotherapy or radiotherapy, which was lower in England than in the United States, widened in patients age 75 or older. Among very old patients, access to treatment is generally reduced not only because of comorbidities and social difficulties[37,38] but also because of refusal of treatment despite evidence of a survival benefit.[39,40] The circumstances surrounding perceptions of and preferences for cancer treatment at the end of life among the oldest patients may vary across countries.

Intensity of treatment and management of care are fundamental across all stages of disease. If England were to have the same stage-specific 2-year RS rate as the United States, a total of 62 deaths for every 1000 patients could be avoided, primarily for patients with stage IIIA, IIIB, or IV disease. The lower 2-year RS rates found in England for more advanced stages can probably be attributed to lower treatment rates, both in terms of surgery for stage IIIA and IIIB disease and in terms of medical oncologic treatment.

Differences in population demographics are unlikely to explain the results, as relative-survival rates were used to compare survival outcomes. In addition, the estimated prevalence of smoking by sex in the 1980s was similar between the two countries (35% in the United Kingdom in 1986 versus 34% in the United States in 1985 for men and 31% versus 28% for women),[41,42] leading to similar incidence rates in both sexes.[43]

One limitation of this study is that we did not perform pooled analyses of the data from England and the United States because of the different protection laws. Care was taken, however, to define variables and perform analogous statistical analysis with use of identical procedures and software. Second, the available databases did not include comparable information on specific chemotherapy agents, type of radiotherapy, or curative versus palliative intent of treatment for the analyzed years, potentially confounding comparisons for this group of patients. Similarly, we did not have access to information on performance status or comorbidities, both of which may have differed between England and the United States, and as indicators of general fitness of the populations, both could be factors explaining, at least in part, the differences in treatment rates.

Overall, we have demonstrated the ability to compare two large health care systems across process and outcome measures for NSCLC in England and the United States by utilizing databases containing data from cancer registries that are linked to clinical and administrative data sets. Our results underscore the importance of performing like-with-like comparisons between patient groups, which requires data relating to pathological confirmation of the tumor, staging data at diagnosis, and receipt of treatment. We found a lower proportion of older patients with advanced-stage lung cancer who were receiving care and lower RS rates in patients whose NSCLC was diagnosed in England versus in the United States, even when comparing groups receiving the same type of treatment. These important findings demand future research to disentangle potential causes by incorporating comorbidity and socioeconomic variables into comparisons and extending comparisons to other cancer sites and countries so as to better understand the determinants of differences in care and outcomes of patients with cancer across health systems.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2018.04.022.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65:87–108.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin*. 2017;67:7–30.
3. Office for National Statistics. Death registrations summary tables—England and Wales. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathregistrationssummary

tablesenglandandwalesreferencetables. Accessed July 3, 2017.
4. Kruse GR, Rigotti NA, Raw M, et al. Tobacco dependence treatment training programs: an international survey. *Nicotine Tob Res*. 2016;18:1012–1018.
5. Johnson DH, Schiller JH, Bunn PA. Recent clinical advances in lung cancer management. *J Clin Oncol*. 2014;32:973–982.
6. Hasan N, Kumar R, Kavuru MS. Lung cancer screening beyond low-dose computed tomography: the role of novel biomarkers. *Lung*. 2014;192:639–648.
7. Walters S, Maringe C, Coleman MP, et al. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004–2007. *Thorax*. 2013;68:551–564.
8. Cancer Research UK. Lung cancer mortality statistics. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/mortality. Accessed July 3, 2017.
9. Francisci S, Minicozzi P, Pierannunzio D, et al. Survival patterns in lung and pleural cancer in Europe 1999–2007: results from the EUROCARE-5 study. *Eur J Cancer*. 2015;51(15):2242–2253.
10. Coleman MP, Quaresma M, Berrino F, et al. Cancer survival in five continents: a worldwide population-based study (CONCORD). *Lancet Oncol*. 2008;9:730–756.
11. Gatta G, Capocaccia R, Coleman MP, et al. Toward a comparison of survival in American and European cancer patients. *Cancer*. 2000;89:893–900.
12. Allemani C, Weir HK, Carreira H, et al. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). *Lancet*. 2015;385:977–1010.
13. Khakwani A, Rich AL, Tata LJ, et al. The pathological confirmation rate of lung cancer in England using the NLCA database. *Lung Cancer*. 2013;79:125–131.
14. Richards MA. The size of the prize for earlier diagnosis of cancer in England. *Br J Cancer*. 2009;101(suppl 2):S125–S129.
15. Walters S, Benitez-Majano S, Muller P, et al. Is England closing the international gap in cancer survival? *Br J Cancer*. 2015;113:848–860.
16. Riaz SP, Linklater KM, Page R, Peake MD, Møller H, Lüchtenborg M. Recent trends in resection rates among non-small cell lung cancer patients in England. *Thorax*. 2012;67:811–814.
17. Stevens W, Philipson TJ, Khan ZM, MacEwan JP, Linthicum MT, Goldman DP. Cancer mortality reductions were greatest among countries where cancer care spending rose the most, 1995-2007. *Health Aff (Millwood)*. 2015;34:562–570.
18. Royal College of Physicians. NLCA annual report 2016. https://www.rcplondon.ac.uk/projects/outputs/nlca-annual-report-2016. Accessed June 19, 2017.
19. National Cancer Institute Surveillance, Epidemiology, and End Results Program. SEER cancer statistics review, 1975-2014. https://seer.cancer.gov/csr/1975_2014/. Accessed June 21, 2017.
20. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: race-, sex-, and age-based disparities. *JAMA*. 2004;291:2720–2726.
21. Bunn PA, Lilenbaum R. Chemotherapy for elderly patients with advanced non-small-cell lung cancer. *J Natl Cancer Inst*. 2003;95:341–343.
22. NHS Digital. Hospital episode statistics (HES). http://content.digital.nhs.uk/hes. Accessed April 13, 2017.
23. Beckett P, Woolhouse I, Stanley R, Peake MD. Exploring variations in lung cancer care across the UK—the "story so far" for the National Lung Cancer Audit. *Clin Med (Lond)*. 2012;12:14–18.
24. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. *Med Care*. 2002;40(suppl 8):IV-3-18.
25. Virnig BA, Warren JL, Cooper GS, Klabunde CN, Schussler N, Freeman J. Studying radiation therapy using SEER-Medicare-linked data. *Med Care*. 2002;40(suppl 8):IV-49-54.
26. Tyczynski JE, Démaret E, Parkin DM. *Standards and Guidelines for Cancer Registration in Europe: The ENCR Recommendations*. Vol I. Lyon, France: International Agency for Research on Cancer; 2003. IARC Technical Publication No. 40.
27. Lin CC, Virgo KS. Diagnosis date agreement between SEER and Medicare claims data: impact on treatment. *Med Care*. 2014;52:32–37.
28. National Cancer Institute Surveillance, Epidemiology, and End Results Program. Standard populations (millions) for age-adjustment. https://seer.cancer.gov/stdpopulations/. Accessed June 19, 2017.
29. United Kingdom of Ireland Association of Cancer Registries. Guidelines on population based cancer survival analysis. http://ukiacr.org/publication/guidelines-population-based-cancer-survival-analysis. Accessed June 19, 2017.
30. Dickman PW. Estimating and modelling relative survival using SAS. http://biostat3.net/download/sas/relative_survival_using_sas.pdf. Accessed June 19, 2017.
31. Office for National Statistics. National life tables, UK Statistical bulletins: Trends for the UK and constituent countries in the average number of years people will live beyond their current age measured by "period life expectancy", analysed by age and sex. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/previousReleases. Accessed June 19, 2017.
32. Elliss-Brookes L, McPhail S, Ives A, et al. Routes to diagnosis for cancer—determining the patient journey using multiple routine data sets. *Br J Cancer*. 2012;107:1220–1226.
33. Tataru D, Jack RH, Lind MJ, Møller H, Lüchtenborg M. The effect of emergency presentation on surgery and survival in lung cancer patients in England, 2006-2008. *Cancer Epidemiol*. 2015;39:612–616.
34. Bach PB, Mirkin JN, Oliver TK, et al. Benefits and harms of CT screening for lung cancer: a systematic review. *JAMA*. 2012;307:2418–2429.
35. Humphrey LL, Deffebach M, Pappas M, et al. Screening for lung cancer with low-dose computed tomography: a

systematic review to update the US Preventive services task force recommendation. *Ann Intern Med*. 2013;159:411–420.
36. O'Dowd EL, Baldwin DR. Lung cancer screening—low dose CT for lung cancer screening: recent trial results and next steps [e-pub ahead of print]. *Br J Radiol*. https://doi.org/10.1259/bjr.20170460. Accessed May 22, 2018.
37. Ludbrook JJS, Truong PT, MacNeil MV, et al. Do age and comorbidity impact treatment allocation and outcomes in limited stage small-cell lung cancer? A community-based population analysis. *Int J Radiat Oncol Biol Phys*. 2003;55:1321–1330.
38. Nadpara P, Madhavan SS, Tworek C. Guideline-concordant timely lung cancer care and prognosis among elderly patients in the United States: a population-based study. *Cancer Epidemiol*. 2015;39:1136–1144.
39. Langer CJ. Elderly patients with lung cancer: biases and evidence. *Curr Treat Options Oncol*. 2002;3:85–102.
40. Dawe DE, Pond GR, Ellis PM. Assessment of referral and chemotherapy treatment patterns for elderly patients with non-small-cell lung cancer. *Clin Lung Cancer*. 2016;17:563–572.e2.
41. Fiore MC, Novotny TE, Pierce JP, Hatziandreu EJ, Patel KM, Davis RM. Trends in cigarette smoking in the United States. The changing influence of gender and race. *JAMA*. 1989;261:49–55.
42. Office for National Statistics. Adult smoking habits in Great Britain. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/drugusealcoholandsmoking/datasets/adultsmokinghabitsingreatbritain. Accessed June 19, 2017.
43. Ferlay J, Shin H-R, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*. 2010;127:2893–2917.