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An International Registry Study of Early-Stage NSCLC treatment variations (LUCAEUROPE) in Europe and the USA highlighting variations

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ABSTRACT

Objective: Harmonized European NSCLC incidence, treatment approach, and survival based on national tumor registries are unclear.
Summary background data: Surgery has the potential to cure NSCLC and significantly prolong survival. This large-scale international study aimed to investigate treatment variations in Europe and the USA, as well as the determinants for its utilization.
Methods: The retrospective cohort study analyzed data from six European national population-based cancer registries (Belgium, Denmark, Estonia, Germany, the Netherlands, and Slovenia) and the US SEER database from 2010–2015.
Results: The study computed cancer incidence, survival, and age-standardized proportions of the use of various therapies. Multivariable logistic regression models were used to assess associations between resection and demographic and clinical parameters. A total of 428,107 records were analyzed. Among all countries, Estonia had the highest surgical resection rate (79.3 %) and the lowest radiation rate (7.3 %) for stage I patients. The Netherlands had the highest rate of radiotherapy across all years of investigation and the lowest surgery rate between 2012 and 2015. The primary treatment for early-stage NSCLC showed significant international variation, with the USA having a decrease in surgical rates from 67.6 % to 59.5 %. Resection was less frequently performed as tumor stage increased, patients aged, other lung cancer besides adenocarcinoma was present, and when the tumor site overlapped multiple lobes.
Conclusions: Resection rates have declined in some studied European countries and the USA and resection rates vary substantially among countries. Interpretation of current scientific lung cancer evidence and international guidelines results in wide variations in patient treatment.

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1. Introduction

Lung cancer is the most deadly cancer in industrialized countries worldwide [1]. In Europe, lung cancer accounts for approximately 20 % of all cancer deaths [2]. Recent work show an overall decreasing trend in lung cancer mortality in Europe, while female cancer mortality remained stable or even increased [3]. Approximately 87 % of all tumors are non-small lung cancer (NSCLC), and 13 % are small cell lung carcinomas (SCLCs) [4]. For UICC stage I-II NSCLC, surgery is the treatment of choice if the patient is medically fit, whereas in locally advanced stages (UICC III), a multimodal treatment is recommended, which may include surgery, thoracic radiation, and systemic therapy [5,6]. Systemic therapy is the cornerstone for stage IV tumors and has experienced a highly dynamic paradigm shift in recent years with the rise of immunotherapy and targeted therapy [7–10].

Data are very limited when it comes to describing treatment and survival on the European continent. Existing large-scale comparative studies of long-term survival and treatment approaches in Europe, such as EUROCARE from the beginning of the millennium, are outdated [11]. Comparing and harmonizing multiple cancer registries poses some major challenges. For example, a recent study (ICBP SURVMARK-2) presents lung cancer data from seven countries on four continents [12]. The study does not report on how the patients were treated and only shows three-year survival. If we want to interpret the data, we have to deal with the treatment guidelines of the mentioned four continents in the study and interpret the results considering continental differences in patient and tumor characteristics such as sex, age, and histology. This is a challenge. Although there are excellent results from the individual national cancer registries on the European continent, there is no current comparative approach.

Therefore, we launched a research initiative (LUCAEUROPE) to explore and harmonize data from European national registries and study variations in NSCLC treatment patterns and survival.

2. Methods

2.1. Registries

The availability of data in the European registries was screened according to an investigation by Huang et al. [13]. Unfortunately, the Norwegian and English cancer registries were not able to comply with the protocol. As a result, information on patient treatment was obtained from six national European tumor registries (Belgium, Denmark, Estonia, Germany (selected federal states), the Netherlands, Slovenia), and US SEER data were used for comparison (Supplemental Table 1). In Germany, only three of 16 federal states were able to provide data for this analysis (Supplemental Table 1). To ensure compliance with national ethical and data protection regulations and the heterogeneity of the data sets, we developed a detailed uniform study protocol (available for third parties) with harmonized inclusion and exclusion criteria that had to be agreed upon by each participating country. Briefly, patients were excluded if the diagnosis was based on autopsy/death, if they were younger than 18 years, or if they had other invasive malignancies within 5 years before the date of diagnosis. Only the seventh edition of the TNM classification for lung cancer diagnoses (ICD C34.0-C.34.9, Behavior codes 1 or 3) between 2010 and 2015 was accepted.

Patient data were collected from the population-based cancer registries with the respective data protection regulations of the collaborating institutions. The study was conducted following the tenets of the Declaration of Helsinki and in compliance with the German Federal Data Protection Act. The protocol was approved by the local ethics committee of the University of Heidelberg (S-647/2021).

Clinical stage I included patients with T1a, T1b and T2a without known nodal involvement (N0-X). The data sets were harmonized (Table 1), and primary therapy was presented as coded by the registries. Due to different approaches to stage definition (e.g. clinical/pathological/combined) by registries, we decided to use the clinical or combined clinical/pathologic definition (Supplementary Table 1). Age-standardized rates were then derived using the age distribution of the largest group of patients (US data). Overall survival was modeled using the Kaplan–Meier method, survival was stratified by UICC-stadium and adjusted for patient age and year of diagnosis.

NSCLC histology was defined using ICD-O-3 morphology codes and categorized as followed: Adenocarcinoma, Squamous cell carcinoma, Other (includes large cell carcinoma, NSCLC not otherwise specified (NOS) and 'other specified' NSCLC) and unknown histology (including clinically diagnosed cases).

2.2. Statistical analysis

The association of demographic and clinical parameters with surgical resection versus non-resection for patients with NSCLC in

Table 1
Information on participating registries.

Registry	Year of diagnosis	Registered cases	Excluded cases					Analysed cases
			DCO/autopsy or with the same date of diagnosis and last follow-up time/death	Lost to follow up	UICC cTNM stage 0	UICC cTNM stage unknown	Patients who had other malignant tumours diagnosed within 5 years prior to their lung cancer diagnosis	
Belgian Cancer Registry	2010 −2015	39,754	74 (0.2 %)	9 (0.0 %)	3 (0.0 %)	4890 (12.3 %)	5059 (12.7 %)	30,399
Danish Cancer Registry	2010 −2015	23,094	19 (0.1 %)	0 (0.0 %)	14 (0.1 %)	1993 (8.4 %)	Not available	21,068
Estonian Cancer Registry	2010 −2015	3711	68 (1.8 %)[a]	5 (0.1 %)	0 (0.0 %)[b]	478 (13.1 %)	Excluded a priori by the cancer registry	3160
German Centre for Cancer Registry[c]	2010 −2015	91,551	11,352 (12.4 %)	1 (0.0 %)	3 (0.0 %)	12,656 (15.8 %)	Not excluded by the registry	67,539
Netherlands Cancer Organisation	2010 −2015	67,076	104 (0.2 %)[a]	0 (0.0 %)	25 (0.0 %)	3256 (4.9 %)	Excluded a priori by the cancer registry	63,691
Slovenian Cancer Registry	2010 −2015	6616	148 (2.2 %)[a]	0 (0.0 %)	0 (0.0 %)	460 (7.0 %)	422 (6.4 %)	5586
USA SEER Database	2010 −2015	291,195	32,810 (11,.3 %)	0 (0 %)	0 (0.0 %)	21,721 (10.9 %)	Excluded a priori by the cancer registry	236,664

[a] Cases diagnosed through DCO/autopsy had been previously excluded by the cancer registry. The reported cases were additionally excluded due to null survival (the same date of diagnosis and death).
[b] The Estonian Cancer Registry only records malignant tumors.
[c] Three federal states were able to provide data for Germany, details are presented in Supplemental Table 1.

population-based registries was estimated through multivariable logistic regression. Odds ratios (ORs) and 95 % confidence intervals (CIs) for surgical resection versus non-resection were calculated for the contributing countries, adjusted for the year of diagnosis, sex, age group, tumor location, and UICC stage.

The annual percent change (APC) was used as a summary measure of country-specific trends in age-standardized percentages of surgical resection for stage I, II, and III NSCLC. Specifically, APCs were estimated by fitting a log-linear regression model assuming homoscedasticity and first-order autocorrelation of random errors. [14,15] The 95 % CIs for the APCs were calculated using the empirical cumulative distribution function quantile method described by Kim et al. [16]. Statistical analysis was performed using Stata 16 and 17.

3. Results

A total of 428,107 patients from seven national cancer registries diagnosed with NSCLC between 2010 and 2015 were included in the analysis (Table 1).

The largest European cohort with 67,539 patients was provided by registries from Germany, followed by the Netherlands with 63,691 patients, and Belgium with 30,399 patients. The mean age distribution was

Table 2
Demographic and Clinical Characteristics of Patients with Non-Small Cell Lung Cancer Diagnosed between 2010 and 2015, by Country.

Characteristics	Belgium (n = 30,399)	Denmark (n = 21,068)	Estonia (n = 3160)	Germany (n = 67,539)	Netherlands (n = 63,691)	Slovenia (n = 5586)	United States (n = 236,664)
Female sex	9141 (30.1)	10,227 (48.5)	859 (27.2)	21,529 (31.9)	26,718 (41.9)	1818 (32.5)	114,301 (48.3)
Mean age (y), mean ± SD	67.7 ± 10.8	69.5 ± 9.9	68.6 ± 10.0	67.7 ± 10.3	67.8 ± 10.5	66.6 ± 10.3	69.1 ± 10.9
Age group (y)							
≤ 60	8008 (26.3)	3775 (17.9)	663 (21.0)	17,302 (25.6)	15,402 (24.2)	1676 (30.0)	51,113 (21.6)
61–74	13,469 (44.3)	10,433 (49.5)	1580 (50.0)	31,299 (46.3)	30,010 (47.1)	2499 (44.7)	107,064 (45.2)
≥ 75	8922 (29.3)	6860 (32.6)	917 (29.0)	18,938 (28.0)	18,279 (28.7)	1411 (25.3)	78,487 (33.2)
Tumor laterality							
Left	12,350 (40.6)	NA	NA	NA	25,733 (40.4)	2295 (41.1)	94,492 (39.9)
Right	16,599 (54.6)	NA	NA	NA	36,011 (56.5)	3131 (56.1)	132,253 (55.9)
Both	0 (0.0)	NA	NA	NA	82 (0.1)	64 (1.1)	2513 (1.1)
Unknown	1450 (4.8)	NA	NA	NA	1865 (2.9)	96 (1.7)	7406 (3.1)
Tumor location							
Main bronchus	1433 (4.7)	NA	221 (7.0)	6082 (9.0)	5245 (8.2)	259 (4.6)	9813 (4.1)
Upper lobe	13,522 (44.5)	NA	1373 (43.4)	31,642 (46.8)	32,858 (51.6)	2902 (52.0)	123,388 (52.1)
Middle lobe	1067 (3.5)	NA	131 (4.1)	2889 (4.3)	2424 (3.8)	306 (5.5)	10,614 (4.5)
Lower lobe	7053 (23.2)	NA	829 (26.2)	17,548 (26.0)	16,548 (26.0)	1693 (30.3)	63,555 (26.9)
Overlapping sites of lung	95 (0.3)	NA	113 (3.6)	3559 (5.3)	2531 (4.0)	69 (1.2)	2334 (1.0)
Unspecified site	7229 (23.8)	NA	493 (15.6)	5819 (8.6)	4085 (6.4)	357 (6.4)	26,960 (11.4)
TNM stage							
I	6030 (19.8)	4178 (19.8)	482 (15.3)	10,120 (15.0)	10,040 (15.8)	824 (14.8)	56,071 (23.7)
II	2763 (9.1)	1873 (8.9)	331 (10.5)	5836 (8.6)	4683 (7.4)	519 (9.3)	20,657 (8.7)
III	7202 (23.7)	4371 (20.7)	733 (23.2)	15,609 (23.1)	15,065 (23.7)	1283 (23.0)	48,752 (20.6)
IV	14,404 (47.4)	10,646 (50.5)	1614 (51.1)	35,974 (53.3)	33,903 (53.2)	2960 (53.0)	111,184 (47.0)
Pathology							
Adenocarcinoma	16,144 (53.1)	9574 (45.4)	1002 (31.7)	27,322 (40.5)	26,027 (40.9)	2627 (47.0)	117,108 (49.5)
Squamous cell carcinoma	8958 (29.5)	4486 (21.3)	1062 (33.6)	17,468 (25.9)	13,756 (21.6)	1830 (32.8)	52,775 (22.3)
Other	2453 (8.1)	2062 (9.8)	387 (12.2)	9416 (13.9)	18,193 (28.6)	750 (13.4)	55,416 (23.4)
Unknown	2844 (9.4)	4946 (23.5)	709 (22.4)	13,333 (19.7)	5715 (9.0)	379 (6.8)	11,365 (4.8)
Primary therapy							
Surgery, with or without (neo)adjuvant therapy	6635 (21.8)	4533 (21.5)	793 (25.1)	12,757 (18.9)	10,163 (16.0)	1338 (24.0)	56,896 (24.0)
Radiation only	2405 (7.9)	3724 (17.7)	270 (8.5)	9568 (14.2)	6808 (10.7)	1706 (30.5)	33,769 (14.3)
Systemic only	9452 (31.1)	3818 (18.1)	1006 (31.8)[d]	19,291 (28.6)	16,128 (25.3)	1277 (22.9)[d]	40,100 (16.9)
Systemic and radiation	4739 (15.6)	4324 (20.5)	NA	13,102 (19.4)	9881 (15.5)	NA	56,709 (24.0)
No therapy	7168 (23.6)	4669 (22.2)	1091 (34.5)	12,821 (18.9)[e]	20,711 (32.5)[e]	1265 (22.6)	49,190 (20.8)[e]
Type of surgery							
Wedge resection	NA	540 (11.9)	NA	NA	407 (4.0)	NA	10,395 (18.3)
Segmental resection	NA	91 (2.0)	NA	NA	168 (1.7)	NA	2456 (4.3)
Lobectomy	NA	3346 (73.8)	NA	NA	7890 (77.6)	NA	NA
Bilobectomy	NA	161 (3.6)	NA	NA	672 (6.6)	NA	NA
Lobectomy or bilobectomy	NA	NA	NA	NA	NA	NA	41,259 (72.5)
Pneumonectomy	NA	194 (4.3)	NA	NA	977 (9.6)	NA	2301 (4.0)
Other surgery	NA	156 (3.4)	NA	NA	49 (0.5)	NA	485 (0.9)
Unknown	NA	45 (1.0)	NA	NA	0 (0.0)	NA	0 (0.0)
Neoadjuvant systemic therapy	707 (2.3)	NA	NA	NA	615 (1.0)	42 (0.8)	NA
Neoadjuvant radiotherapy	218 (0.7)	NA	NA	NA	430 (0.7)	9 (0.2)	1851 (0.8)
Neoadjuvant systemic therapy or radiotherapy	NA	NA	71 (2.2)	NA	NA	NA	NA
Adjuvant systemic therapy	2141 (7.0)	NA	212 (6.7)	NA	2356 (3.7)	322 (5.8)	NA
ECOG score							
0	4560 (15.0)	7194 (34.1)	NA	NA	2360 (3.7)	NA	NA
1	17,686 (58.2)	6264 (29.7)	NA	NA	2447 (3.8)	NA	NA
2	3640 (12.0)	2986 (14.2)	NA	NA	917 (1.4)	NA	NA
3	1464 (4.8)	1720 (8.2)	NA	NA	508 (0.8)	NA	NA
4	443 (1.5)	783 (3.7)	NA	NA	124 (0.2)	NA	NA
Unknown	2606 (8.6)	2121 (10.1)[f]	NA	NA	57,335 (90.0)	NA	NA

Notes: Data are presented as n (%), unless otherwise specified.
Abbreviations: SD, standard deviation; NA, not available; ECOG, Eastern Cooperative Oncology Group.
[d] Chemoradiotherapy is included in systemic therapy.
[e] Includes unknown therapy.
[f] Includes 321 patients registered as dead (ECOG score equal to 5).

comparable across the registries. The predominant tumor laterality of the registry with available data was right (54.6–56.5 %), and the primary tumor location was most often in the upper lobe, followed by the lower lobe. The predominant tumor stage at presentation was stage IV (47.0–53.3 %), followed by stage III (20.6–23.7 %) and stage I (14.1–23.7 %). In most countries, the most commonly applied treatment was primary systemic therapy only(14.3–31.8 %), followed by surgery (16.0–25.1 %), or no therapy (20.8–34.5 %). Few registries were able to provide detailed data on type of surgery, perioperative therapy, and ECOG status (Table 2).

While the age-standardized stage distribution of NSCLC was comparable between registries, and the stage distribution remained stable over the study period (Fig. 1), we found substantial differences in the primary treatment approach for stage I patients (Fig. 2). Estonia had the highest surgical resection rate (79.3 %) and the lowest radiation rate (7.3 %) among all countries for stage I patients (Fig. 2; Supplementary Table 1). The Netherlands had the highest rate of radiotherapy across all years of investigation and the lowest surgery rate between 2012 and 2015. Therapy rates in the USA fell in the middle of the European rates (Fig. 2). Between 2010 and 2015, the USA experienced a significant decreasing trend in surgical resections for stage I (67.6 % to 59.5 %; APC = −2.7 %; 95 % CI = −3.1 %, −2.4 %) (Fig. 2). We also found that in the Netherlands, there was a significant decreasing trend in surgical resection for stage I NSCLC (69.1 % to 47.0 %; APC = −7.9 %; 95 % CI = −10.1 %, −5.7 %). In the other five registries (Belgium, Denmark, Estonia, Germany, and Slovenia), there were no significant changes in surgical resection over the study period.

Based on the multivariable logistic regression analysis to investigate

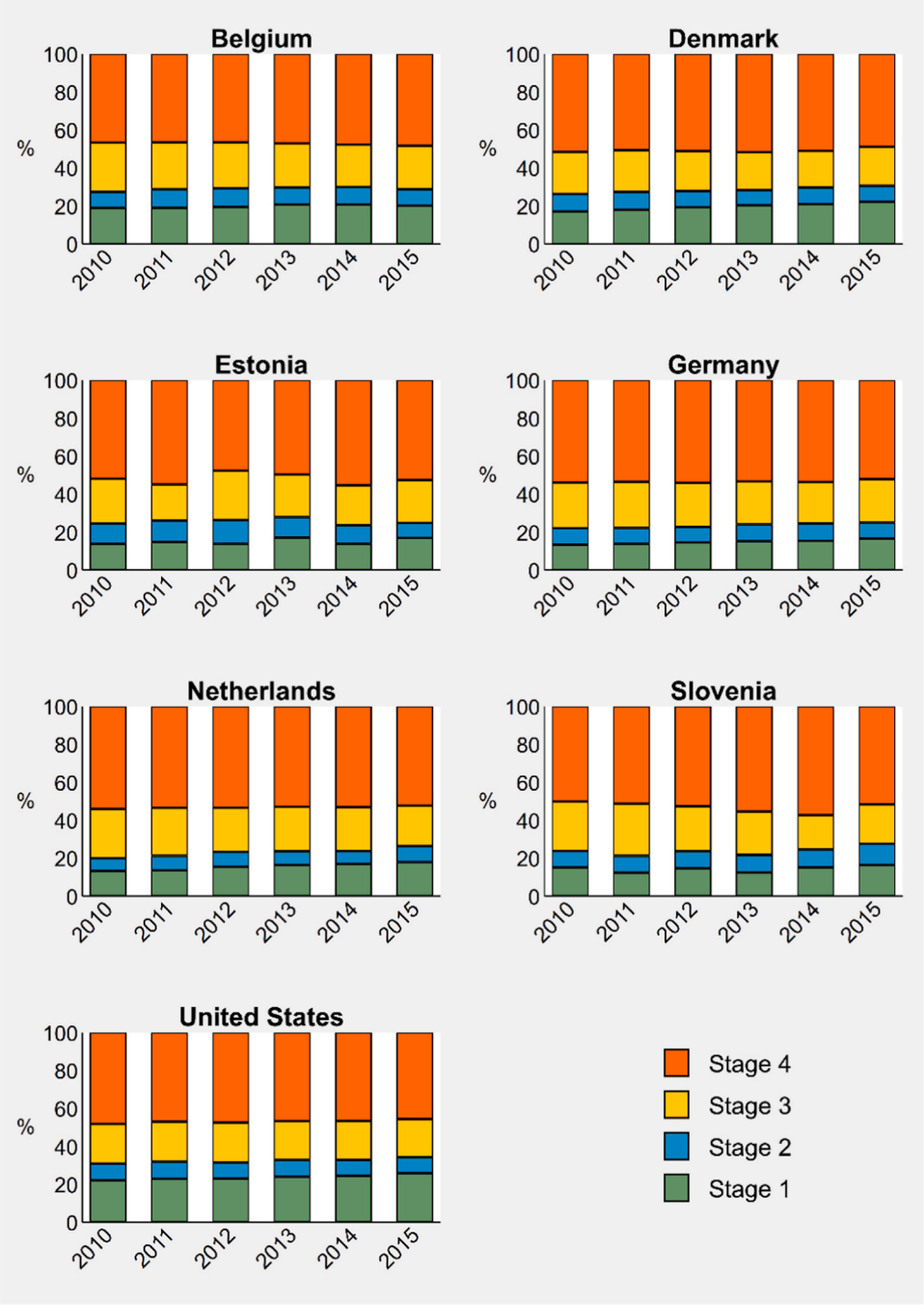

Fig. 1. Stage distribution of age-standardized non-small cell lung cancer incidence between 2010 and 2015, by country.

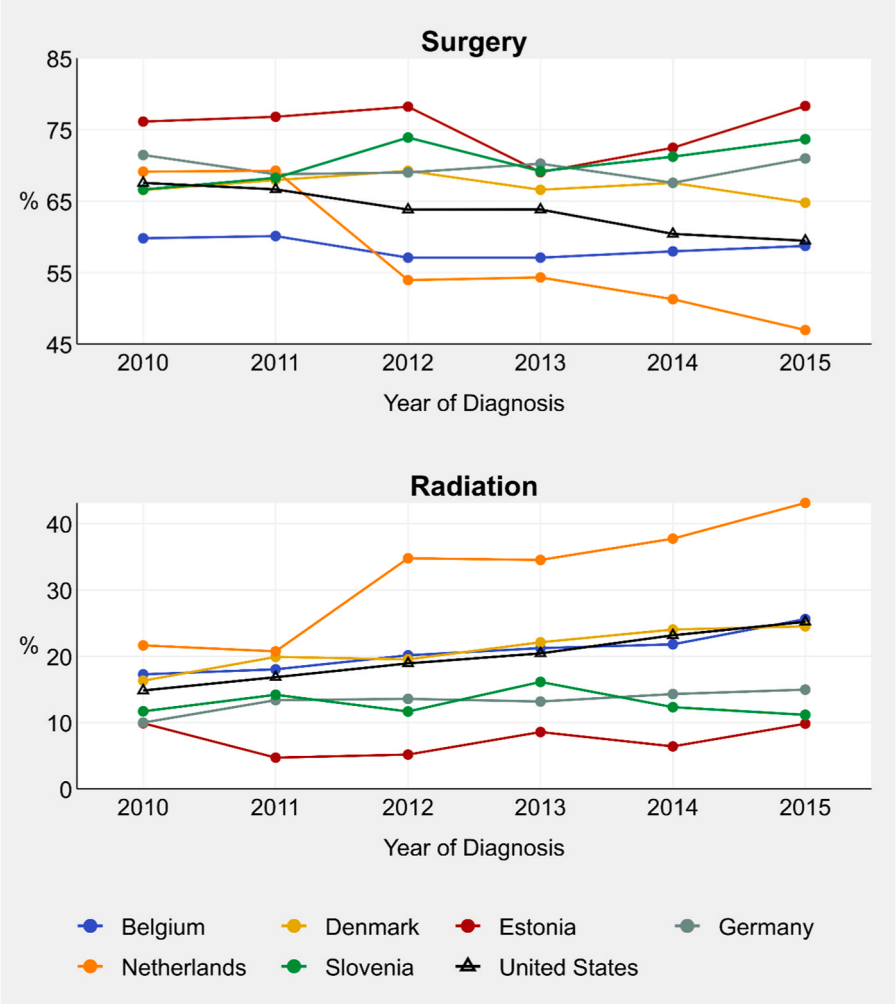

Fig. 2. Trends in age-standardized proportions of primary surgical resection and primary radiation for stage i non-small cell lung cancers diagnosed between 2010 and 2015, by Country. *Notes:* The Netherlands (−7.9 % [95 % CI −10.1, −5.7]) and the United States (−2.7 % [95 % CI −3.1, −2.4]) had a significant annual % decrease in resection rates.

the association of demographic and clinical factors with surgical resection versus non-resection (Table 3), older age, unknown histology and higher UICC stadium were strongly associated with lower resection rates. Trends were consistent in between countries, however, age > 75 years in particular was rated very differently for a decision in favor of an operation (age >= 75 years vs. <=60 years within surgical resection versus non-resection: e.g Germany OR 0.85 (95 % CI 0.79 −0.91), Slovenia OR 0.15 (95 % CI 0.11–0.20)).

Finally, we present a comprehensive analysis of adjusted five-year overall survival estimates for all patients at all tumor stages, demonstrating survival differences stratified by stage (Supplementary Figure 1).

4. Discussion

LUCAEUROPE demonstrates the feasibility of conducting a large-scale comparative study of national lung cancer outcomes in Europe. We found high variations in the management of stage I to stage III NSCLC, particularly in the rates of surgical resection for early-stage disease.

Variations in resection rates between European countries and over time have not been studied. Approximately 20 % of all NSCLC patients underwent surgery, and particularly in stage I, we found high variations in surgical resection rates (58.5–79.3 %). This is influenced by different interpretations of the current scientific evidence. In addition to surgery, stereotactic body radiation therapy (SBRT) has been introduced as the standard of care for high-risk surgical patients [17]. The ESMO guideline states that surgery should be offered to all patients with stage I and II NSCLC, and SBRT to patients with comorbidities or other reasons for inoperability. However, there '*is currently no evidence to routinely recommend SABR (*Comment: stereotactic ablative radiotherapy) *for patients who are at low risk for surgical complications*' [18]. Because high-quality randomized trials comparing surgery and SBRT have not been feasible in the past, [19–21] treatment decisions depend mainly on the judgment of the patient and their treating physician [22–25]. The wide variation in interpretation of the ESMO guideline and current scientific evidence is reflected in our study. In the Netherlands, following the introduction of national guidelines for SBRT in 2010, there was a sharp 20 % reduction in resection rates and a large increase in SBRT [26]. The Netherlands have a strong history and tradition of implementing SBRT. Compared with all other European countries and the USA, the Netherlands have the relatively highest SBRT rates and the lowest resection rates for stage I NSCLC. Specifically, the Netherlands and Belgium had the strongest association of increasing age with non-resection, but the radiation rate in Belgium was significantly lower than in the Netherlands. This is in contrast to Estonia (7.3 %), Slovenia (10.1 %) and Germany (12.1 %), where much lower rates of SBRT were reported. Interestingly, these treatment variations do not seem to be reflected in the overall survival.

Treatment for older patients with early-stage disease varies due to

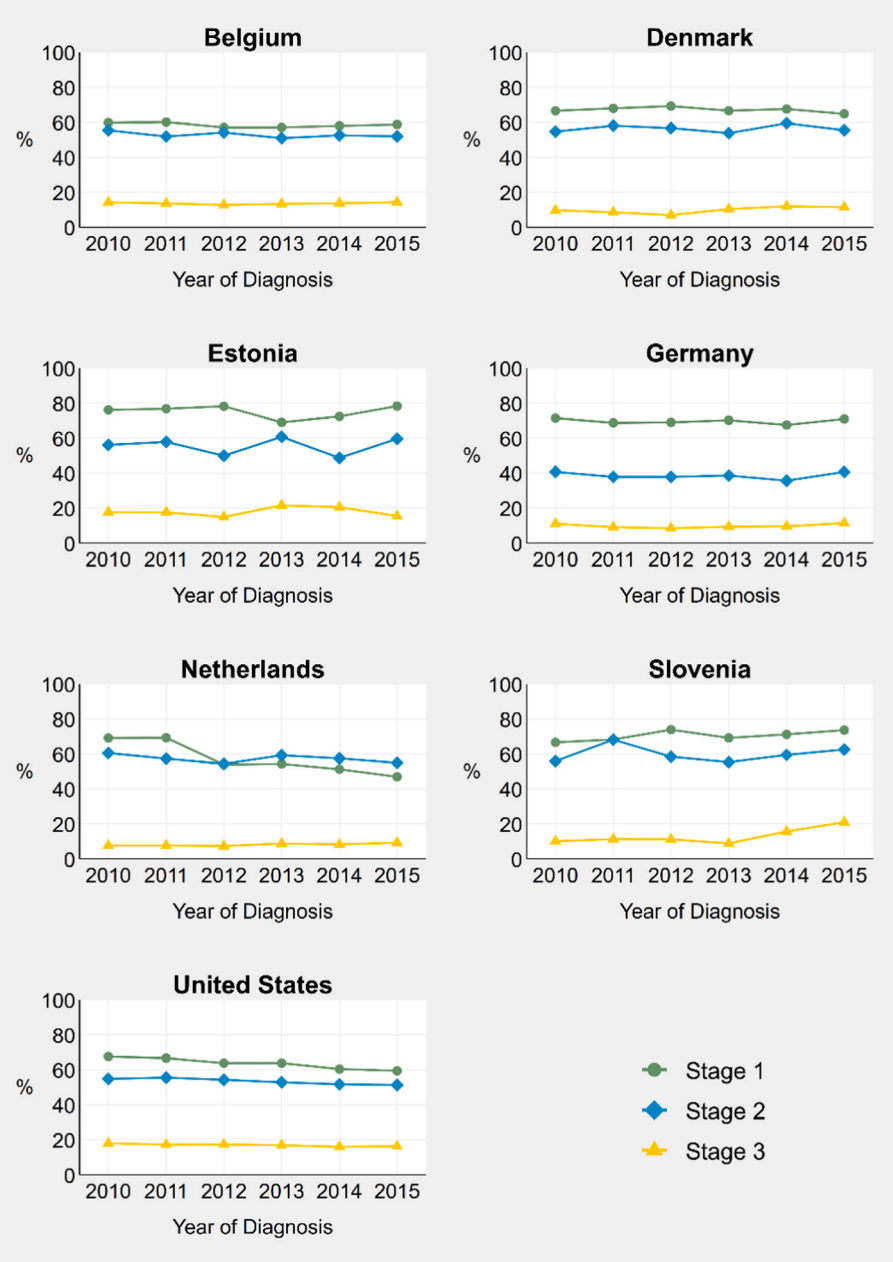

Fig. 3. Age-Standardized Surgical Resection Rates for Stage I, II and III Non-Small Cell Lung Cancers from 2010 to 2015, by Country. *Notes:* The Netherlands (−7.9 % [95 % CI −10.1, −5.7]) and the United States (−2.7 % [95 % CI −3.1, −2.4]) had a significant annual % decrease in resection rates for Stage I cancers. The United States had a significant annual % decrease in resection rates for Stage II cancers (−1.7 % [95 % CI −2.4, −0.9]). The Netherlands had a significant annual % *increase* in resection rates for Stage III cancers (4.1 [95 % CI 0.3, 7.6]), while the United States exhibited a significant decrease (−2.2 % [95 % CI −2.8, −1.7]).

different treatment policies, which depend on the medical fitness judgment for surgery [23–25,27,28]. European guidelines state that pre-treatment pathology may not be necessary if the likelihood of lung cancer is high. Therefore, pathological confirmation of a suspicious lung tumor is often lacking in some countries—in a recent analysis, only half of SBRT patients in England and the Netherlands, and two-thirds of patients in Norway had pathological confirmation [6,23]. This explains the very wide range of unknown histology associations with surgical resection versus non-resection in our multivariable analysis, as pathology confirmation varies between countries.

We found that the USA were the only country with a significant decreasing resection trend (APC −2.2 %) in stage III lung cancer. Conversely, the Netherlands was the only country with a significant increasing resection rate (APC 4.1 %). The different treatment approaches in stage III tumors might be caused by differing interpretations of multimodal treatment, in the American and European stage III NSCLC guidelines. [29,30] While the Americans seem to tend towards a non-operative approach over time, the European variation in resection rates is high (3.4–21.6 %). Of note, the new emerging systemic therapy options are currently leading to strong paradigm changes and new standards of care in this stage [31]. .

Except Germany, all countries included in this analysis have a solid nationwide lung cancer database and are reporting very encouraging results in terms of quality control and survival improvements [32–34]. Centralization of thoracic surgery to improve quality has often been discussed, so the question arises: Is there a link in our data? [35,36] In the study period, only Denmark [37], Estonia [38], and partly Netherlands (only robotic surgery) [39], but not Belgium [40], Germany

Table 3
Association of demographic and clinical parameters with surgical resection versus non-resection with for patients with NSCLC in population-based registries estimated by multivariable logistic regression.

Resection vs. non-resection	Belgium		Denmark		Estonia		Germany		Netherlands		Slovenia		USA	
	OR	[95 % CI]	OR	[95 % CI]	OR	[95 % CI]	OR	[95 % CI]	OR	[95 % CI]	OR	[95 % CI]	OR	[95 % CI]
Year of diagnosis	**0.98**	0.95 0.99	0.98	0.96 1.01	**0.94**	0.88 1.01	**0.95**	0.93 0.96	**0.95**	0.94 0.97	**1.05**	1.00 1.11	**0.93**	0.92 .932
Sex (ref: male)								. .						
female	1.00	0.91 1.10	1.05	0.96 1.15	1.16	0.89 1.53	1.01	0.96 1.07	**0.89**	0.83 0.95	1.10	0.91 1.33	**1.06**	1.04 1.09
Age (ref <= 60)								. .						
61 –74	**0.69**	0.63 0.77	**0.67**	0.59 0.76	**0.69**	0.52 0.92	1.00	0.94 1.07	**0.59**	0.55 0.64	**0.67**	0.55 0.82	**0.78**	0.75 0.80
> = 75	**0.20**	0.17 0.22	**0.26**	0.22 0.30	**0.35**	0.24 0.50	**0.85**	0.79 0.91	**0.16**	0.15 0.18	**0.15**	0.11 0.20	**0.34**	0.33 0.35
Histology (ref: Adeno-CA)								. .						
Squamous	**0.70**	0.64 0.77	**0.75**	0.66 0.84	**0.44**	0.33 0.58	**0.86**	0.81 0.91	**0.69**	0.64 0.74	**0.62**	0.51 0.76	**0.47**	0.45 0.48
Other	**0.37**	0.31 0.45	**0.29**	0.23 0.36	**0.17**	0.11 0.26	**0.49**	0.45 0.53	**0.21**	0.19 0.23	**0.51**	0.38 0.67	**0.15**	0.14 0.15
Unknown	**0.02**	0.01 0.03	**0.50**	0.45 0.57	**0.03**	0.02 0.05	**0.63**	.058 0.68	**0.03**	0.03 0.04	**0.26**	0.16 0.42	**0.24**	0.23 0.26
Site (ref: Upper Lobe)														
Main Bronchus	**0.28**	0.21 0.37	NA		**0.32**	0.17 0.62	**0.46**	0.39 0.53	**0.27**	0.22 0.32	**1.64**	0.96 2.78	**0.26**	0.24 0.30
Middle lobe	1.13	0.90 1.42	NA		**0.55**	0.31 1.00	**1.22**	1.08 1.37	0.91	0.78 1.07	1.40	0.73 2.68	**1.30**	1.23 1.38
Lower lobe	1.05	0.95 1.16	NA		0.993	0.76 1.30	**1.19**	1.12 1.26	0.98	0.91 1.06	**2.00**	1.10 3.41	**1.18**	1.15 1.21
Overlapping Sites	0.59	0.21 1.63	NA		0.88	0.45 1.74	**0.99**	0.86 1.15	**1.50**	1.28 1.85	1.52	0.54 4.29	**2.55**	2.27 2.88
Unspecified Site	**0.59**	0.52 0.65	NA		**0.69**	0.45 1.06	**0.55**	0.47 0.64	**0.34**	0.27 0.44	1.13	0.55 2.30	**0.49**	0.45 0.52
cTNM-Stage (ref: I)												.		
II	**0.60**	0.54 0.67	**0.66**	0.58 0.74	**0.38**	0.27 .55	**0.35**	0.32 0.37	**0.85**	0.78 0.93	**0.55**	0.42 0.72	**0.74**	0.72 0.77
III	**0.06**	0.05 0.07	**0.05**	0.04 0.05	**0.05**	0.04 .07	**0.08**	0.07 0.08	**0.04**	0.04 0.05	**0.04**	0.03 0.05	**0.13**	0.13 0.14

Odds ratios (ORs) shown in bold are statistically significant.
Confidence Intervals (CI).

[41], Slovenia [42], or the USA [43], reported thoracic surgery centralization. Due to the very different health care structures, one cannot argue for or against it.

Comparing NSCLC incidence and overall survival, a recent study found discrepancies with higher survival observed in Canada and Norway, and lower survival in the UK, New Zealand, and Ireland [12]. We do not go into detail about why survival is higher in one country than another, as the reasons are many and do not automatically reflect the quality of care. Differences in sex, [44,45] incidence [3], and survival progress [46] are all well-known and, therefore, not discussed further here.

A limitation of the study is the heterogeneity of treatment reporting across countries, affected by the high effort to gather all the data in accordance with each country/institution privacy regulations. Comparative data were only available in a limited number of countries for the period 2010–2015, when the TNM-7 staging system was in use. Many countries were unable to comply with the study protocol. Despite improvements in registry procedures and data collection over time, there are intercountry differences in stage definition (clinical vs. combined, which can bias especially earl-stages), and microscopic verified cases that should be kept in mind.

The strengths of our study include the use of high-quality data from several population-based cancer registries, the large sample size, strict inclusion criteria, careful case selection, and consistent definition and standardization of variables across registries as defined in our protocol. The complex process of harmonization and data collection should lead to the establishment of common standardized dataset criteria from registries in Europe with standard definitions to avoid complex data harmonization and facilitate data protection restrictions.

In conclusion, this large international population-based study shows that early-stage NSCLC resection rates vary significantly in Europe and the USA. Different interpretation of guidelines leads to large international variations in surgical vs. non-operative treatments, with a country specific approach to guideline-conform treatment.

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CRediT authorship contribution statement

Hauke Winter: Conceptualization, Investigation, Methodology, Supervision, Validation, Writing – review & editing. **Hermann Brenner:** Conceptualization, Data curation, Investigation, Methodology, Supervision, Validation, Writing – review & editing. **Tina Zagar:** Formal analysis, Supervision, Validation. **Vesna Zadnik:** Data curation, Formal analysis, Validation. **Jacopo Lenzi:** Formal analysis, Methodology, Software, Supervision, Validation. **Rafael Cardoso:** Conceptualization, Data curation, Investigation, Methodology, Writing – review & editing. **Kersti Oselin:** Supervision, Validation. **Kaire Innos:** Data curation, Investigation, Validation. **Niel L Christensen:** Data curation, Formal analysis, Validation. **Paul De Leyn:** Validation. **Hanna Peacock:** Validation. **Cindy De Gent:** Formal analysis, Supervision, Validation. **Ad FTM Verhagen:** Supervision. **Ronald A.M. Damhuis:** Conceptualization, Supervision, Validation, Writing – review & editing. **Philip Baum:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Software, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114233.

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