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ORIGINAL ARTICLE

Patterns of survival and surgical treatment in lung cancer patients in Estonia by histologic type and stage, 1996–2016

Kaire Innos[a], Kersti Oselin[b], Tanel Laisaar[c,d] and Tiiu Aareleid[a]

[a]Department of Epidemiology and Biostatistics, National Institute for Health Development, Tallinn, Estonia; [b]Department of Chemotherapy, Clinic of Haematology and Oncology, North Estonia Medical Centre, Tallinn, Estonia; [c]Department of Thoracic Surgery, Lung Clinic, Tartu University Hospital, Tartu, Estonia; [d]Department of Pulmonology, Faculty of Medicine, University of Tartu, Tartu, Estonia

ABSTRACT

Background: Lung cancer (LC) remains the most frequent cause of cancer death worldwide. We aimed to examine long-term trends in LC survival in Estonia by age, gender, histologic type and stage, with specific focus on surgical treatment.

Material and methods: Data on all incident cases of LC diagnosed from 1996 to 2016 were obtained from the Estonian Cancer Registry. Logistic regression was used to examine receipt of surgical treatment in localized LC. Relative survival ratios (RSR) were calculated, and excess hazard ratios (EHR) of death were estimated by stage with gender, age, histology and period of diagnosis as independent variables.

Results: Among the total of 16,423 cases, squamous cell carcinoma remained the most common histologic type. The odds of receiving surgical treatment in localized LC increased significantly over time and were associated with age, gender and histologic type. Overall, the age-standardized 5-year RSR improved significantly from 10% in 1996–2002 to 16% in 2010–2016 (from 8% to 15% in men and from 15% to 20% in women). Larger survival gain was seen in younger patients, for non-small cell LC subtypes, and for surgically treated patients. For localized disease, the 5-year RSR increased by more than 20 percentage units, reaching 50% in men and 69% in women. For all stages, the adjusted EHR of death was significantly associated with age, histologic type and period of diagnosis.

Conclusions: We observed a substantial improvement of relative survival, with considerable variations across patient groups. After adjustment for age, gender and histology, a significant survival increase over time was seen for all stages. The considerable survival gain observed for localized LC can largely be attributed to rapidly growing proportion of surgically treated patients. Further investigation of LC management practices, particularly the use of non-surgical treatment options is warranted.

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Introduction

Lung cancer (LC) remains the most frequent cause of cancer death worldwide [1]. In highly developed countries, the age-standardized LC incidence and mortality among men turned to decline already in the 1980s, while a rise among women has generally continued. In Estonia, a steady decline in male LC incidence and mortality has been observed since mid-1990s [2], but both remain among the highest in Europe [3]. Female rates in Estonia are predicted to reach a plateau in the upcoming decade [2]. In addition to gender, incidence trends vary across age groups and histologic types, as adenocarcinoma is increasingly becoming the most common histologic type in many high-income countries [4]. In Estonia, squamous cell carcinoma still largely prevails despite declining incidence [2].

LC survival has been poor compared to other common cancers and is improving slowly. The worldwide CONCORD-3 study showed that the 5-year relative survival for LC increased by 5−10 percentage units from 1995−1999 to 2010−2014 in 21 countries, reaching 33% in Japan, 20–30% in 12 countries (including five countries in Europe), and 10–20% in most countries [5]. In EUROCARE-5 (2000–2007), the 5-year survival estimates varied from 17% in Austria to 6% in Bulgaria, with the Estonian estimate (12%) being quite close to the European average of 13% [6].

LC survival is higher in women than in men [6–8], and for non-small cell lung cancer (NSCLC) than for small cell lung cancer (SCLC) [6,9]. Survival declines with advancing age [6] and is strongly dependent on stage at diagnosis [9,10]. Screening high-risk individuals to achieve earlier diagnosis is currently being considered in numerous settings [11]. For early stage NSCLC, surgical treatment is recommended, while other local therapies, e.g., stereotactic body radiation therapy (SBRT) are reserved for patients who have contraindications to surgery [11,12]. Radio-chemotherapy is the standard of care for patients with locally advanced NSCLC not amenable to surgical resection [12]. Recently, molecular targeted

CONTACT Kaire Innos kaire.innos@tai.ee Department of Epidemiology and Biostatistics, National Institute for Health Development, Hiiu 42, 11619 Tallinn, Estonia

Supplemental data for this article can be accessed here.

therapies have become available for specific subgroups of NSCLC and immunotherapy for advanced NSCLC [11]. The more aggressive SCLC is mainly treated with the combination of chemotherapy and radiation [13,14].

Since early 1990s, Estonia has undergone major societal, economic and health care transition, including changes in tobacco control and increasing availability of diagnostic and treatment options. This study aimed to examine LC survival trends in Estonia over the past two decades by gender, age, histologic type and stage, with special focus on surgical treatment.

Material and methods

Data were obtained from the Estonian Cancer Registry (ECR), a population-based registry with nation-wide coverage since 1968 (population 1.3 million according to the 2011 census). Reporting to the ECR is mandatory for all physicians and pathologists. Multiple sources are used for case ascertainment, including linkages with the patient files of two cancer centers and trace-back of cases first identified from death certificates. The ECR uses ICD-O-3 for coding and adheres to international definitions and rules [15].

Thoracic surgery in Estonia is provided solely at two tertiary-care hospitals, which are also the only two cancer centers providing radiation therapy. Estonia was among countries with the lowest availability of radiotherapy equipment in Europe until 2012 [16] and the total number of megavoltage units per million inhabitants increased only in 2016 (from 3.0 to 4.6). SBRT was not available during the study period. Molecular targeted therapies for NSCLC were not reimbursed until 2010 and immunotherapy became available after 2014. Positron emission tomography (PET) became available in 2002.

The ECR provided data on all adult (age $\geq$15 years) incident cases of cancer of bronchus and lung (ICD-10 codes C34) diagnosed from 1996 to 2016, regardless of cancer sequence. Histologic types were defined as follows: NSCLC (ICD-O-3 8010–8576, except 8041–8045); SCLC (ICD-O-3 8041–8045); other or unspecified (ICD-O-3 8800–9120; 8000–8005). In the latter group, 15% of cases were microscopically verified and 35 cases had 'other specified' histology. Within NSCLC, we differentiated adenocarcinoma (ICD-O-3 8140, 8211, 8230–8231, 8250–8260, 8323, 8480–8490, 8550– 8551, 8570–8574, 8576), squamous cell carcinoma (ICD-O-3 8050–8078, 8083–8084) and other NSCLC.

Age was grouped into four categories: 15−54, 55−64, 65−74 and $\geq$75 years. Stage was categorized as localized, locally/regionally advanced (including regional lymph node metastases and/or primary tumor invasion to neighboring organs), distant metastases and unknown. Stage according to the Union for International Cancer Control TNM classification version 7 [17] was available in coded format for 2010−2016. Stage categorization was based on pathological or clinical stage reported by clinicians and/or pathologists.

Surgically treated cases included all patients for whom surgical treatment was reported on the cancer notification form, regardless of intention. It was neither possible to distinguish between cases not treated and those with treatment not reported to the registry nor between different types of surgical procedures. Reliable data on other therapies and comorbidities was not available.

Chi-square test was used to test the statistical significance of difference between proportions. Univariate and multivariate logistic regression was used to calculate odds ratios with 95% confidence intervals (CI) for receipt of surgical treatment among patients with localized LC. Cases with 'other or unspecified' histology were excluded from this model.

Follow-up for vital status from the date of diagnosis until 31 December 2016 was conducted by the ECR at the Estonian Population Registry, using unique personal identification numbers. In case of death or emigration, the respective dates were obtained. Death certificate only and autopsy cases were excluded from survival analyses. Patients who were diagnosed and died on the same calendar day were included with one day of survival time. Relative survival ratio (RSR) was calculated as the ratio of observed survival and expected survival of the underlying general population. The latter was calculated according to Ederer II method [18], based on national life tables, stratified by age, gender and calendar year. Cohort method was used for patients diagnosed during 1996−2002 and 2003−2009; period method for 2010−2016 [19]. Due to small numbers, complete analysis (1996−2016) was used to construct survival curves by histologic types and surgical treatment in localized LC. RSRs with 95%CIs were calculated using the *strs* algorithm in STATA 14 (StataCorp, College Station, TX, USA) [20]. International Cancer Survival Standards were used for age-standardization [21].

Excess hazard ratios (EHR) of death within five years of diagnosis were estimated in the framework of generalized linear models using a Poisson assumption for the number of observed deaths [20]. Cases with unknown stage or with 'other or unspecified' histology were excluded. Gender, age, histologic type, stage and period of diagnosis were included as independent variables. All models included year of follow-up. Due to interactions between stage and other variables (tested with likelihood ratio test), the adjusted models are presented stratified by stage.

The study protocol was approved by the Tallinn Medical Research Ethics Committee.

Results

From 1996 to 2016, 16,423 new LC cases (12,747 cases in men and 3676 cases in women) were diagnosed in Estonia (Table 1). Overall, 74% of cases were microscopically verified. On average, women were older than men (mean age 70 and 67 years, respectively), while the proportion of elderly patients ($\geq$75 years) increased significantly in both genders. The proportion of NSCLC increased mainly on the account of malignancies with 'other or unspecified' histology. Among NSCLC, adenocarcinoma became more and squamous cell carcinoma became less frequent. Overall, 17%, 33% and 41% of cases were diagnosed with localized, locally/regionally advanced and distant disease, respectively. 19% of LC

Table 1. Incidence cases of lung cancer by age, histologic type and stage, Estonia 1996–2016.

	Number (%)							
	Men				Women			
	1996–2002	2003–2009	2010–2016	*p* Value[a]	1996–2002	2003–2009	2010–2016	*p* Value[a]
Total	4351 (100)	4185 (100)	4211 (100)		995 (100)	1121 (100)	1560 (100)	
Microscopically verified	3211 (74)	3035 (73)	3252 (77)	<.001	645 (65)	766 (68)	1191 (76)	<.001
Death certificate only	92 (2)	196 (5)	129 (3)	<.001	22 (2)	55 (5)	45 (3)	.001
Autopsy cases	143 (3)	135 (3)	84 (2)	<.001	39 (4)	30 (3)	29 (2)	.007
Age at diagnosis (years)								
<55	584 (13)	451 (11)	309 (7)	<.001	121 (12)	115 (10)	122 (8)	<.001
55–64	1395 (32)	1058 (25)	1120 (27)		180 (18)	253 (23)	326 (21)	
65–74	1791 (41)	1681 (40)	1525 (36)		397 (40)	334 (30)	518 (33)	
≥75	581 (13)	995 (24)	1257 (30)		297 (30)	419 (37)	594 (38)	
Histologic type								
NSCLC	2223 (51)	2283 (55)	2594 (62)	<.001	417 (42)	577 (51)	985 (63)	<.001
Adenocarcinoma[b]	327 (15)	468 (21)	795 (31)		155 (37)	260 (45)	522 (53)	
Squamous cell carcinoma[b]	1600 (72)	1421 (62)	1314 (51)		179 (43)	183 (32)	243 (25)	
Other NSCLC[b]	296 (13)	394 (17)	485 (19)		83 (20)	134 (23)	220 (22)	
SCLC	688 (16)	607 (14)	562 (13)		160 (16)	142 (13)	175 (11)	
Other or unspecified[c]	1440 (33)	1295 (31)	1055 (25)		418 (42)	402 (36)	400 (26)	
Stage[d]								
Localized	669 (16)	613 (16)	711 (18)	<.001	160 (17)	173 (17)	299 (20)	<.001
Locally/regionally advanced	1692 (41)	1269 (33)	1109 (28)		344 (37)	314 (30)	336 (23)	
Distant metastases	1445 (35)	1618 (42)	1772 (44)		337 (36)	425 (41)	688 (46)	
Unknown	310 (8)	354 (9)	406 (10)		93 (10)	124 (12)	163 (11)	
TNM (7th edition) stage[d]								
I			496 (12)				240 (16)	
II			328 (8)				95 (6)	
III			899 (22)				273 (18)	
IV			1774 (44)				688 (46)	
Unknown			501 (13)				190 (13)	
Surgical treatment[d]	540 (13)	722 (19)	893 (22)	<.001	114 (12)	200 (19)	404 (27)	<.001

NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer.
[a]Chi-square test.
[b]Percent of all NSCLC, $p < .001$ for both genders.
[c]Includes 35 cases with other specified histology.
[d]Death certificate only and autopsy cases excluded.

patients received surgical treatment and the proportion treated increased significantly in both genders.

A significant difference in stage distribution was observed between histologic types ($p < .001$; Supplementary Figure 1). Over time, the proportion of localized tumors increased only for adenocarcinoma, reaching 28%, whereas it remained unchanged for squamous cell carcinoma (24% from 2010 to 2016).

Survival analyses were based on 15,424 cases (11,968 men and 3456 women) (Table 2). For men and women combined, the age-standardized 5-year RSR increased significantly from 10% (95%CI 9–11) from 1996 to 2002 to 16% (95%CI 15–17) from 2010 to 2016. Improvements were observed for both genders, particularly for localized cancer. For LC patients with distant metastases, the 5-year RSR remained very low, but the 1-year RSR increased over the study period from 9% to 12% in men and from 16% to 21% in women.

The overall surgical treatment rate was 40% for adenocarcinoma, 28% for squamous cell carcinoma and 6% for SCLC. The proportion of surgically treated in localized LC increased from 38% during 1996–2002 to 74% during 2010–2016 (Figure 1(A)). Increases were significant overall as well as for adenocarcinoma and squamous cell carcinoma ($p < .001$). Surgical treatment also became more common among patients with locally/regionally advanced LC (Figure 1(B)). The 5-year RSR increased for localized tumors in all histologic subgroups, but the largest change was seen for localized SCLC, from 20% (95%CI 9–33) to 45% (95%CI 23–67) (Figure 1(C)). For locally/regionally advanced LC, the 5-year RSR reached 16% for adenocarcinoma and SCLC, and 22% for squamous cell carcinoma (Figure 1(D)). The 5-year RSR for surgically treated patients increased from 64% to 69% in localized disease and from 31% to 45% in locally/regionally advanced disease (Figure 1(E)). Due to small numbers, the 5-year survival curves by histologic type and surgical treatment are shown for localized cases diagnosed during the whole study period (Figure 1(F). For all histologic types, the difference in 5-year RSR between surgical and non-surgical patients was statistically significant. In surgically treated patients, the 5-year RSR was significantly higher for adenocarcinoma (73%, 95%CI 67–78) than for squamous cell carcinoma (61%, 95%CI 56–65) and SCLC (43%, 95%CI 26–60). Among non-surgical patients, there were no significant differences between histologic types.

The odds of receiving surgical treatment in localized LC increased more than fivefold after adjustment for gender, age and histologic type (Table 3). Patients with adenocarcinoma were over two times more likely and those with SCLC 70% less likely to undergo surgical treatment compared to patients with squamous cell carcinoma. The odds of receiving surgical treatment was higher in women and decreased significantly with age.

Table 2. Five-year relative survival ratio for lung cancer by age, histologic type and stage, Estonia 1996–2016.

	5-year RSR (95%CI)							
	Men				Women			
	1996–2002	2003–2009	2010–2016	Change[a]	1996–2002	2003–2009	2010–2016	Change[a]
Crude	8 (7–9)	12 (10–13)	13 (12–14)	**+5**	14 (11–16)	15 (12–17)	18 (16–20)	+4
Age-standardized	8 (7–8)	12 (11–14)	15 (13–16)	**+7**	15 (12–18)	17 (14–19)	20 (17–23)	+5
Age at diagnosis (years)								
<55	9 (6–11)	17 (14–21)	20 (16–25)	**+11**	21 (14–29)	29 (21–38)	29 (21–37)	+8
55–64	10 (8–12)	14 (12–17)	16 (14–18)	**+6**	17 (11–23)	15 (11–20)	24 (19–30)	+7
65–74	8 (7–10)	10 (9–12)	13 (11–15)	**+5**	8 (5–11)	15 (11–20)	20 (16–24)	**+12**
≥75	6 (3–9)	7 (5–9)	7 (6–9)	+3	17 (11–23)	9 (6–13)	10 (7–13)	−7
Histologic type								
NSCLC	12 (11–14)	17 (15–19)	19 (18–21)	**+7**	16 (13–20)	21 (17–24)	26 (23–29)	**+10**
Adenocarcinoma	12 (8–16)	20 (16–25)	22 (19–26)	**+10**	19 (13–26)	25 (20–31)	27 (22–32)	+8
Squamous cell carcinoma	13 (11–15)	18 (16–21)	22 (19–24)	**+9**	9 (5–14)	14 (9–20)	22 (16–28)	**+13**
Other NSCLC	11 (7–15)	9 (6–13)	9 (7–12)	−2	28 (18–39)	20 (14–28)	26 (20–32)	−2
SCLC	4 (2–6)	5 (3–7)	6 (4–8)	+2	7 (3–12)	8 (4–14)	10 (5–15)	+3
Other or unspecified	4 (3–6)	3 (2–5)	2 (1–3)	−2	14 (10–18)	7 (4–11)	3 (2–5)	**−11**
Stage								
Localized	30 (26–34)	44 (40–49)	50 (45–55)	**+20**	38 (30–47)	58 (50–66)	69 (61–75)	**+31**
Locally/regionally advanced	7 (6–9)	12 (10–14)	18 (15–20)	**+11**	10 (7–14)	8 (5–12)	15 (11–20)	+5
Distant metastases	1 (0–2)	1 (0–2)	1 (0–1)	0	3 (1–5)	3 (2–5)	4 (3–6)	+1
Unknown	4 (2–7)	3 (1–5)	3 (1–4)	−1	24 (15–36)	11 (5–18)	7 (4–11)	**−17**

RSR: relative survival ratio; CI: confidence interval; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer.
[a]From 1996–2002 to 2010–2016, statistically significant findings are given in bold.

Compared to patients with squamous cell carcinoma, the EHR of death in univariate analysis was lower for patients with adenocarcinoma and higher for those with all other histologic types (Table 4). The univariate EHR was also significantly associated with gender, age, period of diagnosis and stage. Due to interactions between stage and other variables, adjusted models were stratified by stage. The effect of histologic type was most pronounced in localized LC, as adenocarcinoma showed significantly lower and SCLC significantly higher EHR compared to squamous cell carcinoma. For other stages, a 20% higher EHR was observed for SCLC compared to squamous cell carcinoma. Compared to men, women had significantly lower EHR for localized and metastatic LC. The effects of age and period of diagnosis were consistent across stages, but the strength of the association weakened with advancing stage. Nevertheless, the risk of dying decreased significantly over time for all stages, after adjustment for other covariates.

Discussion

In this population-based study, we observed a substantial improvement of LC survival over the past two decades, but the advances varied across histologic types and stage. A rapidly growing proportion of surgically treated patients was apparent for all major histologic types, including SCLC. The largest survival increases were seen in younger patients, NSCLC subtypes, localized disease and surgically treated patients.

We observed a shift in histologic distribution toward NSCLC and among NSCLC cases toward adenocarcinoma. Previously, increasing incidence of adenocarcinoma was demonstrated for both the genders in Estonia, despite a noticeable decline in overall LC incidence in men [2]. It is difficult to quantify to what extent the increase in NSCLC is due to true risk increase and to what extent to diagnostic shift from the category of unspecified tumors. Nonetheless, squamous cell carcinoma remained the largest group within NSCLC, contrary to the findings in England and the US [22]. The changes in the proportion of adenocarcinoma in women in Estonia were similar to those observed in Norway [10], but the proportion in men remained considerably lower.

The shift in stage distribution was unfavorable, particularly for SCLC, which may have been partly due to classification changes [17], but also to increased detection of distant metastases owing to more meticulous diagnostic workup and improved radiological staging [23]. Better diagnostic accuracy was also reflected in increasing proportion of microscopic verification (77% from 2010 to 2016), although this indicator remained lower than in Europe (87%) and North-America (95%) from 2000 to 2014 [5]. Among cases with known stage, we observed a higher percentage of patients with distant metastases than that found in Norway [10]. The proportion of localized cases increased only for adenocarcinoma. However, there has probably been a shift toward smaller tumors within this rather broad category, possibly related to more frequent use of chest computed tomography for other indications and resulting incidental detection of early tumors. From 2010 to 2016, the proportion of T1 tumors among localized cases increased from 27% to 47% ($p = .003$, data not shown). TNM stage distribution in Estonia from 2010 to 2016 was similar to that reported for other countries [24,25].

The probability of receiving surgical treatment in localized LC increased markedly, in contrast with findings from Norway where the percentage operated decreased for three major histologic types [10]. Our findings suggest that the rate of surgical treatment tends to be higher in Estonia than in several other countries. The percentage of surgically treated localized tumors was higher in Estonia than in Norway for both adenocarcinoma and squamous cell

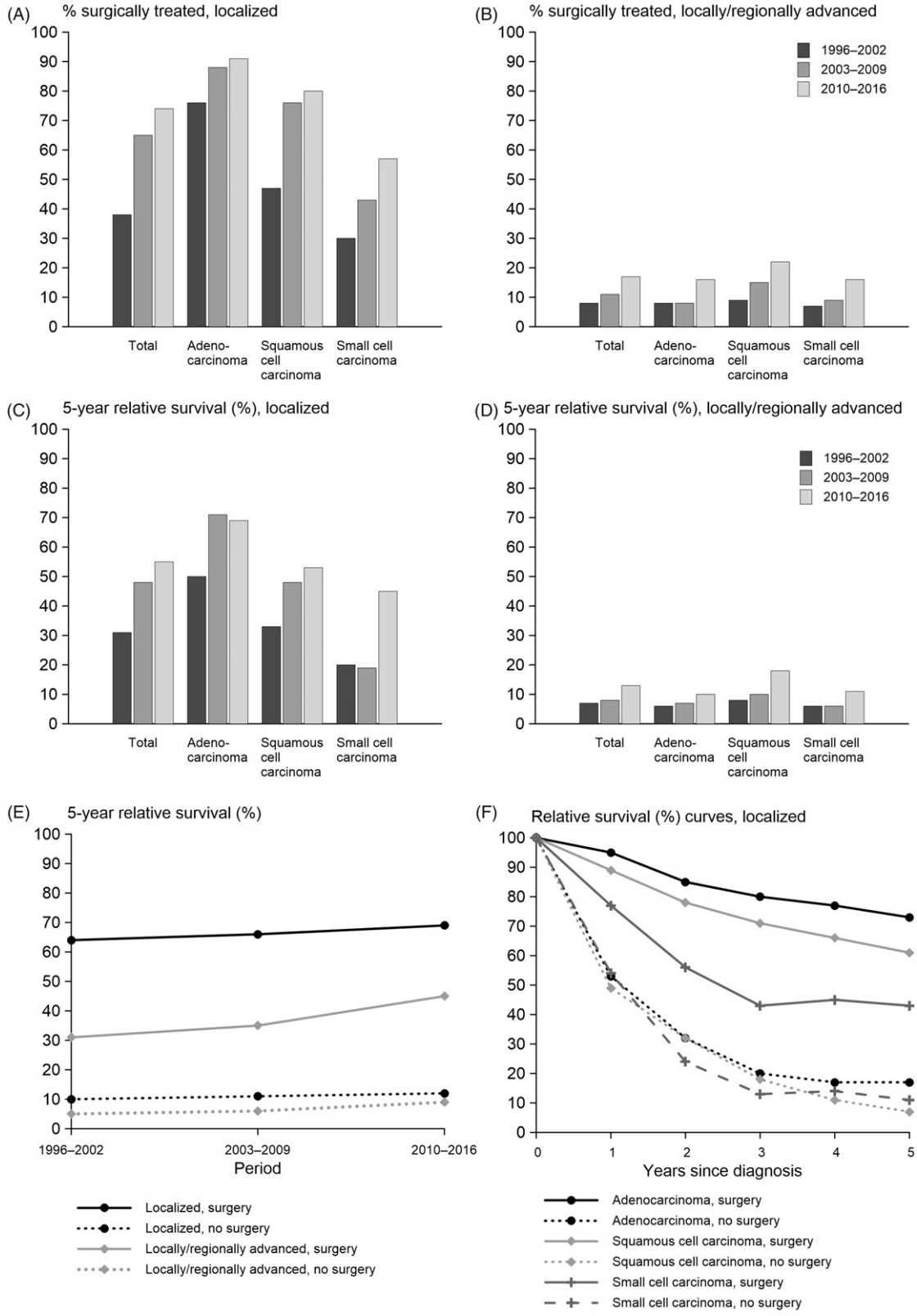

Figure 1. (A) Percentage of lung cancer patients treated surgically by histologic type and period of diagnosis, Estonia 1996–2016, localized; (B) Percentage of lung cancer patients treated surgically by histologic type and period of diagnosis, Estonia 1996–2016, locally/regionally advanced; (C) 5-year relative survival by histologic type and period of diagnosis, Estonia 1996–2016, localized; (D) 5-year relative survival by histologic type and period of diagnosis, Estonia 1996–2016, locally/regionally advanced; (E) 5-year relative survival by stage, surgical treatment and period of diagnosis, Estonia 1996–2016; (F) Relative survival curves by histologic type, surgical treatment and time since diagnosis, Estonia 1996–2016.

carcinoma [10]. In England and in the US, 13% and 20% of older (age >65 years) patients with NSCLC received an operation in 2008–2012 [22]; the respective rate (2010–2016) was 22% in our data (for stage I, the proportions were 52% for England, 60% for the US and 75% for Estonia, data not shown). According to data from one cancer center in Estonia,

Table 3. Odds ratios for receiving surgical treatment in patients with localized lung cancer, Estonia 1996–2016.

	No of patients[a]		OR (95%CI)	
	Surgery	No surgery	Univariate OR	Adjusted OR[b]
Gender				
Men	1156	501	1.00	1.00
Women	403	100	**1.75 (1.37–2.23)**	**1.34 (1.01–1.78)**
Histologic type				
Squamous cell carcinoma	739	361	1.00	1.00
Adenocarcinoma	562	77	**3.56 (2.72–4.67)**	**2.51 (1.88–3.38)**
Other NSCLC	209	92	1.11 (0.84–1.46)	0.84 (0.62–1.15)
SCLC	49	71	**0.34 (0.23–0.50)**	**0.30 (0.20–0.45)**
Age at diagnosis (years)				
<55	203	36	1.38 (0.92–2.07)	1.32 (0.85–2.05)
55–64	494	121	1.00	1.00
65–74	596	269	**0.54 (0.42–0.69)**	**0.44 (0.34–0.58)**
≥75	266	175	**0.37 (0.28–0.49)**	**0.21 (0.15–0.29)**
Period of diagnosis				
1996–2002	307	288	1.00	1.00
2003–2009	509	157	**3.04 (2.39–3.87)**	**3.58 (2.74–4.66)**
2010–2016	743	156	**4.47 (3.53–5.66)**	**5.13 (3.92–6.70)**

OR: odds ratio; CI: confidence interval; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer.
[a]Cases with 'other or unspecified' histology excluded ($n = 465$).
[b]Adjusted for gender, histologic type, age at diagnosis, period of diagnosis; statistically significant findings are given in bold.

Table 4. Relative excess hazard ratio of death within five years of diagnosis among lung cancer patients, Estonia 1996–2016.

	Univariate EHR (95%CI)	Adjusted EHR (95%CI)[a]		
		Localized	Locally/regionally advanced	Distant metastases
Gender				
Men	1.00	1.00	1.00	1.00
Women	**0.82 (0.78–0.87)**	**0.63 (0.51–0.78)**	0.92 (0.83–1.01)	**0.78 (0.73–0.85)**
Histologic type				
Squamous cell carcinoma	1.00	1.00	1.00	1.00
Adenocarcinoma	**0.87 (0.82–0.92)**	**0.65 (0.53–0.81)**	1.04 (0.93–1.15)	**0.87 (0.79–0.95)**
Other NSCLC	**1.25 (1.17–1.34)**	0.94 (0.75–1.19)	**1.37 (1.22–1.53)**	**1.16 (1.05–1.28)**
SCLC	**1.68 (1.58–1.78)**	**1.87 (1.46–2.39)**	**1.20 (1.09–1.31)**	**1.17 (1.08–1.28)**
Age at diagnosis (years)				
<55	0.97 (0.90–1.05)	0.94 (0.72–1.24)	0.90 (0.81–1.01)	0.95 (0.86–1.06)
55–64	1.00	1.00	1.00	1.00
65–74	**1.11 (1.05–1.17)**	**1.43 (1.20–1.71)**	**1.14 (1.05–1.24)**	**1.16 (1.08–1.26)**
≥75	**1.22 (1.14–1.31)**	**2.00 (1.60–2.48)**	**1.53 (1.37–1.71)**	**1.33 (1.21–1.47)**
Period of diagnosis				
1995–2002	1.00	1.00	1.00	1.00
2003–2009	**0.83 (0.79–0.88)**	**0.66 (0.55–0.78)**	**0.77 (0.71–0.83)**	**0.80 (0.74–0.87)**
2010–2016	**0.68 (0.64–0.72)**	**0.48 (0.39–0.58)**	**0.55 (0.50–0.60)**	**0.68 (0.63–0.74)**
Stage				
Localized	1.00			
Locally/regionally advanced	**3.35 (3.08–3.64)**			
Distant metastases	**7.56 (6.96–8.22)**			

EHR: excess hazard ratio; CI: confidence interval; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer.
[a]Adjusted for gender, histologic type, age at diagnosis, period of diagnosis, year of follow-up; statistically significant findings are given in bold.

the largest group of LC cases undergoing radical resection was stage IA, but a substantial number of stage IB–III patients were also resected [26]. In Iceland, 15% of patients who underwent lobectomy had stage IIIA disease, which was usually detected postoperatively [27]. Treatment complications and comorbidities have been shown to be important causes of death in early stage LC [28]. During the study period, there have been considerable changes toward less invasive surgery in Estonia and an increasing number of LC resections is now performed thoracoscopically. Rapid evolution of minimally invasive surgery along with improved preoperative assessment and management of comorbidities have made surgery an acceptable treatment choice even for elderly and frail patients and could explain the high surgical resection rate. The unavailability of SBRT may have contributed to some extent.

Studies have suggested that SCLC patients may also benefit from surgical treatment [13,29]. Due to small numbers, caution should be exercised when interpreting SCLC data, but a large difference was seen in surgical treatment rate of localized SCLC between Norway (around 20%) [10] and Estonia (increase from 30% to 57%). A study in California reported a 2% surgical treatment rate among all SCLC patients [30], while our respective rate was 6%. According to unpublished data, only 29% of SCLC patients who underwent surgery in Estonia had preoperative morphological confirmation of SCLC. In England, 43% of SCLC patients undergoing surgical treatment were estimated to

have had a known SCLC diagnosis before surgery was planned [29].

Our latest survival estimates are quite well comparable to those observed in the Nordic countries [31], Germany [9] and the US [32]. The survival gap between men and women is narrowing, but multivariate analysis still revealed a significant female survival advantage. Female NSCLC patients in Nevada had an 18% lower risk of death after adjusting for several tumor- and patient-related characteristics [32]. In England, women were significantly more likely than men to receive surgery after adjustment for comorbidities both in early and advanced stage [33]. In our data, receipt of surgical treatment differed between the genders with borderline significance, but we were not able to account for comorbidities. Unfavorable health behavior might be a factor explaining male survival disadvantage in LC [34], along with treatment compliance and comorbidities.

The large age gradient in survival was not completely explained by differences in histology or stage. Among patients with known stage, the proportion of metastasized LC did not differ between age groups; however, the proportion of cases with unknown stage was significantly higher in patients age $\geq$75 years (16%) than in younger patients (7%), suggesting less rigorous diagnostic procedures among the elderly. The consistent survival disadvantage of older patients across stages may suggest disparities in treatment strategies. Receipt of surgical treatment in localized LC was strongly dependent on age. Comorbidities, socioeconomic factors and place of residence are important barriers to surgical treatment [32,33,35]. Our data suggest positive changes though, as the proportion of patients with localized LC who received surgical treatment increased from 10% to 56% in age group $\geq$75 years (from 71% to 86% in age group $<$55 years, data not shown). In contrast with previous findings [10], we observed only a slight survival increase in patients with localized disease who did not receive surgery, most likely due to limited availability of other treatment options.

The main strength of the study was the use of nationwide population-based data from a good quality cancer registry [36]. The main limitation was the rather broad stage categorization, which may have obscured some changes in stage distribution, particularly within the category of localized tumors. The overall proportion of tumors with unknown stage was 9%. The definition of surgical treatment was rather broad owing to data availability, surgery data may have been somewhat underreported and some of the reported surgical operations may not have been conducted during the first course of treatment.

Conclusions

We observed diverse LC survival trends across patient groups. The considerable survival gain observed for localized LC can largely be attributed to growing proportion of surgically treated patients, emphasizing the central role of surgery in the treatment of all major histologic types of LC. The accuracy of preoperative workup is crucial for achieving optimal treatment results. The proportion of cases with no microscopic verification, unspecified histology and unknown stage, particularly among the elderly, may indicate shortcomings in diagnostic approaches. As the absolute number of new LC cases will continue to be large due to demographic changes, improving outcomes for LC patients remains a challenge in terms of earlier detection and incorporating new treatment options into clinical practice. Further analysis is needed to shed light on the barriers to the application of curative-intent treatment, non-surgical treatment options and respective outcomes in different patient groups.

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ORCID

Kaire Innos http://orcid.org/0000-0003-0120-2213

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