Differences in therapy and survival between lung cancer patients treated in hospitals with high and low patient case volume

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Abstract

***Background*:** In light of political discussions about minimum case volumes and certified lung cancer centers, this observational study investigates differences in therapy and survival between high vs. low patient volume hospitals (HPVH vs. LPVH).

***Methods*:** We identified 12,374 lung cancer patients treated in HPVH (>67 patients) and LPVH in 2013 from German health insurance claims. Stratified by metastasis status (no metastases, nodal metastases, systemic metastases), we compared HPVHs and LPVHs regarding likelihood of resection and systemic therapy, type of systemic therapy, and surgical outcomes, using multivariate logistic models. Three-year survival was modeled using Cox regression. We adjusted all regression models for age, gender, comorbidity, and residence area, and included a cluster variable for the hospital.

***Results*:** Around 24 % of patients were treated in HPVHs. Irrespective of stratum and subgroup, three-year survival was significantly better in HPVHs. In patients with systemic metastases (OR = 1.84, CI=[1.22,2.76]) and without metastases (OR = 3.28, CI=[2.13, 5.04]), resection was more likely in HPVHs. Among patients with systemic therapy, the odds of receiving pemetrexed was higher in HPVHs, in patients with nodal metastases (OR = 1.57, CI=[1.01,2.45]). In resected patients without metastases the odds ratio of receiving a thoracoscopic lobectomy was 2.28 (CI=[1.04,4.99]) in HPVHs.

***Conclusion*:** Our data suggests that case volume is clinically relevant in resected and non-resected lung cancer patients, but optimal minimum case volumes may differ for subgroups.

Keywords: Patient volumes; Certified lung cancer center; Minimum volumes; Claims data; Secondary data; Bronchial carcinoma

1 Introduction

In medical research about cancer care and specifically lung cancer care, there is an on-going debate about the influence of hospital and surgical case volume on surgical outcomes, mortality, and care. Studies have described a relationship between surgical volume and improved short-term outcomes in lobectomy and other surgical procedures [1,2], as well as a relationship between hospital volume and mortality in common medical conditions [3]. However, regarding surgical outcomes, subsequent research challenged these results and cast doubt on the influence of surgical volume on outcomes in lung cancer resection [4–6]. Studies regarding the association between hospital volume and quality of care and processes of cancer care, have resulted in improved outcomes with higher hospital volume in different types of cancer, and support centralization of care.

In Germany, an initial step to centralization was undertaken in 2008, when in accordance with the ‘national cancer plan’ (Nationaler Krebsplan), the German Cancer Society (Deutsche Krebsgesellschaft) began to offer accreditation for cancer care centers in various types of cancer [7]. A panel of advisors representing the relevant medical associations, defined criteria including minimum case volumes, for centers to be eligible for accreditation [8]. To maintain their certified status, lung cancer centers have to treat a sufficient volume of patients, defined as at least 200 primary lung cancer cases and at least 75 anatomic resections per year. In addition centers need to meet quality of care benchmarks before being accredited [8]. Regarding surgical volumes, currently, the Federal Joint Committee (G-BA, the highest decision-making body of the joint self-government of physicians, dentists, hospitals and health insurance funds in Germany), is reviewing the implementation of minimum case volumes for lung cancer resections for hospitals [9].

The benchmarks for certification of lung cancer centers were chosen with the intention of improving quality of care but have yet to be validated. Additionally, research about the influence of hospital and surgical volumes in lung cancer so far mainly focused on patients with operable cancer. In these studies, the main outcomes were in-hospital death and survival and only some investigated complication rates or length of stay [4,10–12]. Moreover, the observation period was limited to the hospital stay of the resection in most studies [10].

Therefore, and in light of recent debates, in this observational study based on health insurance claims we aimed to compare high patient volume hospitals (HPVH) and low patient volume hospitals (LPVH) in terms of 3-year survival, and to identify possible differences in provided services to patients receiving systemic therapy or lung resection.

2 Material and methods

2.1 Data set and sample selection

We analyzed anonymized health insurance claims of 19,696 patients with a first diagnosis of lung cancer in 2013, provided by the Scientific Institute of the AOK health insurance trust (WIdO), covering about 30 % of the German population [13]. In total, around 86 % of German citizens are insured in a statutory health insurance fund (SHI). This study was carried out in accordance with Good Practice of Secondary Data Analysis guidelines [14].

Basic data contained month and year of birth, sex, postal codes, need for nursing care and nursing home residency status over the course of the disease. Additionally, we used claims for hospitalization, outpatient hospital care, outpatient doctor visits and medications for a period of three years after diagnosis. These included German International Classification of Diseases (ICD-10-GM) codes, OPS codes (German Version of the International Classification of Procedures in Medicine), and Anatomical Therapeutic Chemical (ATC) codes. Specific codes used in this study can be either found directly in the method section or in appendix table 6.

We identified our study sample according to a three-step process. First, we selected all patients with any inpatient or outpatient diagnosis of lung cancer (ICD: C34) in 2013. In a second step, to avoid false positives, we only included patients with at least one inpatient principal diagnosis or at least two confirmed outpatient diagnoses in two distinct quarters in the year 2013. Third, we excluded all patients with a history of lung cancer or lung metastases in the two years prior to the 2013 diagnosis (inpatient or outpatient), as well as patients without continuous insurance in these years and in the three years after diagnosis.

In order to be certified as a lung cancer center, hospitals have to treat a minimum of 200 patients as primary cases, and perform at least 75 anatomic resections per year. As our study population represents around one third of the German lung cancer patients, we used a case volume of 67 primary cases (one third of 200) and 25 anatomic resections, as a threshold to classify hospitals as LPVH or HPVH. For this, we first identified the number of primary cases for each hospital. According to the definition for the national cancer plan, primary cases are all patients with newly diagnosed or not previously treated lung cancer presenting at a hospital and receiving lung cancer therapy there [8]. The definition of lung cancer therapy includes tumor-directed therapy as well as palliative and best supportive care. A patient can be a primary case for one hospital only. Within our sample we identified 12,374 primary cases in 721 hospitals. In a second step, we grouped hospitals with a number of patients greater than 66 and with at least 25 anatomic resections as HPVH and all others as LPVH.

2.2 Stratification and subgroups

We carried out all analyses stratified by metastases location at diagnosis, as therapy and survival is highly correlated to the stage of the disease [15]. For this we used ICD codes from hospitalizations, outpatient hospital care, and outpatient doctor visits coded in the 3 months before and after the diagnosis date, and grouped patients into no metastases, nodal metastases and systemic metastases. Nodal metastases were defined as metastases found in lymph nodes (ICD codes starting with C.77), and systemic metastases as metastases found elsewhere (ICD codes starting with C.76, C78, and C.79). Further, as we intended to compare outcomes related to surgical resection and to systemic therapy individually, we analyzed these outcomes in subgroups of patients with resection and patients with systemic therapy. Subgroups of patients with lung resection and patients with systemic therapy are not distinct, as patients with therapy before (neoadjuvant) or directly after (adjuvant) resection, or after recurrence or progress of the disease at a later time. Surgical resection was defined as anatomical resection and identified using inpatient OPS codes. We identified inpatient systemic therapy using OPS codes and outpatient therapy using ATC codes for systemic agents.

2.3 Outcome parameters

For our main analysis, we compared conduct of tumor-directed therapy (lung resection and systemic therapy) and survival time over a 3 year follow-up (right censored at three years) between HPVHs and LPVHs as follows: First, we compared the proportion of patients receiving a lung resection or systemic therapy in the 180 days after diagnosis in all patients. Second, in the subgroup of patients with a resection, we looked at the proportion of patients receiving a pneumonectomy, the proportion of broncho- or angioplastic reconstruction, and the proportion of open versus thoracoscopic resections in patients with lobectomy. These outcomes reflect some of the benchmark criteria for the evaluation of certified lung cancer centers in Germany [8]. Third, in patients in the subgroup with systemic therapy, we measured the proportion of patients receiving pemetrexed, and therapy with tyrosine kinase inhibitors in the three years after diagnosis to reflect diffusion of innovative therapies into routine care. To measure all endpoints, we used inpatient OPS codes, inpatient and confirmed outpatient ICD codes, and outpatient ATC codes. Fourth, we compared three-year survival in all patients and all subgroups.

2.4 Confounders

Confounders included in the analysis were age, sex, need for care as measured in nursing home residency and care level, the Charlson comorbidity index [16], and whether patients lived in more rural or urban areas of Germany. Gender, age, care level and nursing home residency, comorbidities, and the area of residence have been shown to influence treatment choice and outcomes in lung cancer [17,18]. Care level indicates the intensity of assistance needed to complete activities of daily living at the time of lung cancer diagnosis (higher care level = more assistance) [19]. Information on nursing home residency was taken at baseline. The Charlson comorbidity index was modified by excluding lung cancer and metastases and calculated based on all inpatient, and all confirmed outpatient ICD diagnoses (defined and adjusted by Quan et al. [16]) in the two years prior to the initial lung cancer diagnosis. The patients' residential area was classified as major city, urban, rural or remote rural based on the postal code of residence at baseline. We used district types defined by the German Federal Institute for Research on Building, Urban Affairs and Spatial Development for 2014, which are based on the population density and the proportion of the population living in large and medium-sized cities [20]. In the analysis of survival we included the type of resection (pneumonectomy, lobectomy and segmental resection) additionally, asas this factor might have an influence on survival.

2.5 Sensitivity analysis 1 (SA1): Treatment in Multiple Centers

In order to test the robustness of our results we carried out two sensitivity analyses (SA). In SA 1 we excluded all patients who were treated in more than one hospital over the course of the disease, to avoid bias from patients that have switched to another hospital during treatment.

2.6 Sensitivity analysis 2 (SA2): medium, small and very small centers

The primary analysis defined 30 out of 630 centers as high volume centers. However, the number of cases treated in the remaining 600 centers varied considerably. In order to further investigate the effect of case volume on medium- and small-sized centers we divided this heterogeneous group into five smaller subgroups. We classified hospitals according to the number of primary cases into hospitals with 199–150, 149–100, 99–50, 49–25, and fewer than 25 lung cancer patients per year. As with the primary analysis, we expected our dataset to capture approximately one third of patients in each bracket.

2.7 Statistical analysis

In the univariate analysis, we calculated proportions for treatments in the metastases strata and subgroups. We compared proportions using Chi^2 test, and three-year survival using Kaplan Meier curves. For our multivariate analyses, we used generalized linear mixed models (GLMM) to account for cluster effects in each hospital by including the hospital ID as random intercept. We used logistic regression models for binary outcomes (resection yes/no, systemic therapy yes/no, therapy with pemetrexed yes/no, targeted therapy yes/no, pneumonectomy yes/no, broncho- or angioplastic reconstruction yes/no, open vs. thoracoscopic lobectomy), and Cox regression for time-to-event data (survival). We compared binary outcomes from logistic regression models based on odds ratios (ORs), and time-to-event data as hazard ratios (HR). We assessed the proportional hazard assumption based on visual inspection of the Schoenfeld residuals. We used LPVH as reference group in all models and adjusted them by the confounders mentioned above. A significance threshold of 5% was applied for all analyses.

All analyses were performed using SAS 9.3 (SAS software of the SAS System for Microsoft, Version 9.3 (c) 2002–2010 by SAS Institute Inc., Cary, NC, USA.); tables and figures were created in SAS, Microsoft Excel and R Studio [21].

3 Results

3.1 Sample characteristics

We classified 30 hospitals as HPVH and 691 as LPVH. In total, around 24 % of patients were treated in HPVHs. HPVH patients were younger (66.7 vs. 67.2, p-value = 0.02), lived in nursing homes less often (2.2 vs. 3.0 %, p-value = 0.02), had less care dependency (p-value<0.0001), and lived in major cities or urban areas more often (p-value=<0.0001) compared to LPVH patients. The distribution of male patients (68.3 vs. 67.6 %, p-value = 0.47) and the Charlson comorbitity index (2.5 vs. 2.6, p-value = 0.07) was similar in HPVH and LPVH.. Metastases location differed significantly, with more patients in earlier stages in the HPVH hospitals. In the different metastases strata, the distribution of patients treated in the two hospital types was similar. Distribution of confounding variables in the whole cohort as well as metastases strata and subgroups can be found in Table 1.

alt-text: Table 1

Table 1

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Sample characteristics of patients with lung cancer in Germany treated in high vs. low patient volume hospitals, in total and across metastases strata.

	All patients			No metastases (28.9 %)			Nodal metastases (17.0 %)			Systemic metastases (54.1 %)		
	HPVH (n = 2956)	LPVH (n = 9418)	p-value	HPVH (n = 940)	LPVH (n = 2636)	p-value	HPVH (n = 573)	LPVH (n = 1525)	p-value	HPVH (n = 1443)	LPVH (n = 5257)	p-value
Mean age in years (sd)	66.7 (9.8)	67.2 (9.9)	0.02	67.7 (9.5)	68.8 (9.6)	0.002	66.6 (9.7)	66.7 (9.7)	0.82	66.0 (10.0)	66.5 (10.0)	0.12
Male gender in % (n)	68.3 (2018)	67.6 (6362)	0.47	68.1 (640)	70.6 (1860)	0.16	71.9 (412)	70.8 (1079)	0.61	66.9 (966)	65.1 (3423)	0.20
Mean Charlson index (sd)	2.5 (2.5)	2.6 (2.5)	0.07	2.8 (2.6)	3.0 (2.6)	0.12	2.4 (2.4)	2.6 (2.5)	0.20	2.4 (2.4)	2.4 (2.4)	0.24
Nursing home residence in % (sd)	2.2 (66)	3.0 (285)	0.02	2.0 (19)	2.4 (63)	0.52	0.9 (5)	1.9 (29)	0.10	2.9 (42)	3.7 (193)	0.16
No care dependancy in % (n)	82.6 (2442)	78.3 (7374)		86.7 (815)	82.1 (2164)		86.6 (496)	82.5 (1258)		78.4 (1131)	75.2 (3952)	
Care level 0 in.% (n)	0.2 (7)	0.2 (18)		0.3 (3)	0.3 (7)		0.5 (3)	0.3 (4)		0.1 (1)	0.1 (7)	
Care level 1 in.% (n)	10.0 (338)	11.0 (990)	<0.0001	9.3 (100)	10.0 (251)	0.001	8.8 (58)	10.1 (145)	0.02	10.8 (180)	11.8 (594)	0.01
Care level 2 in.% (n)	6.5 (221)	8.0 (718)		3.4 (36)	6.0 (150)		3.8 (25)	5.8 (84)		9.6 (160)	9.6 (484)	
Care level 3 in.% (n)	1.9 (64)	2.3 (202)		1.3 (14)	1.4 (36)		1.5 (10)	1.0 (15)		2.4 (40)	3.0 (151)	
District type												
Unknown % (n)	2.6 (77)	3.3 (309)		3.3 (31)	3.4 (89)		1.9 (11)	2.3 (35)		2.4 (35)	3.5 (185)	
Major city in % (n)	34.9 (1032)	26.0 (2452)		34.0 (320)	26.4 (697)		40.0 (229)	27.9 (426)		33.5 (483)	33.5 (1329)	
Urban district in % (n)	42.4 (1252)	40.9 (3853)	<0.0001	42.8 (402)	39.9 (1051)	<0.0001	39.1 (224)	40.4 (616)	<0.0001	43.4 (626)	41.6 (2186)	<0.0001
Rural districtin % (n)	14.0 (413)	15.0 (1413)		13.5 (127)	16.2 (426)		13.1 (75)	14.0 (214)		14.6 (211)	14.7 (773)	
Remote rural district in % (n)	6.2 (182)	14.8 (1391)		6.4 (60)	14.2 (373)		5.9 (34)	15.3 (234)		6.1 (88)	14.9 (784)	
No metastases	31.8 (940)	28.0 (2636)										
Nodal metastases	19.4 (573)	16.2 (1525)	<0.0001									
Systemic metastases	48.8 (1443)	55.8 (5257)										

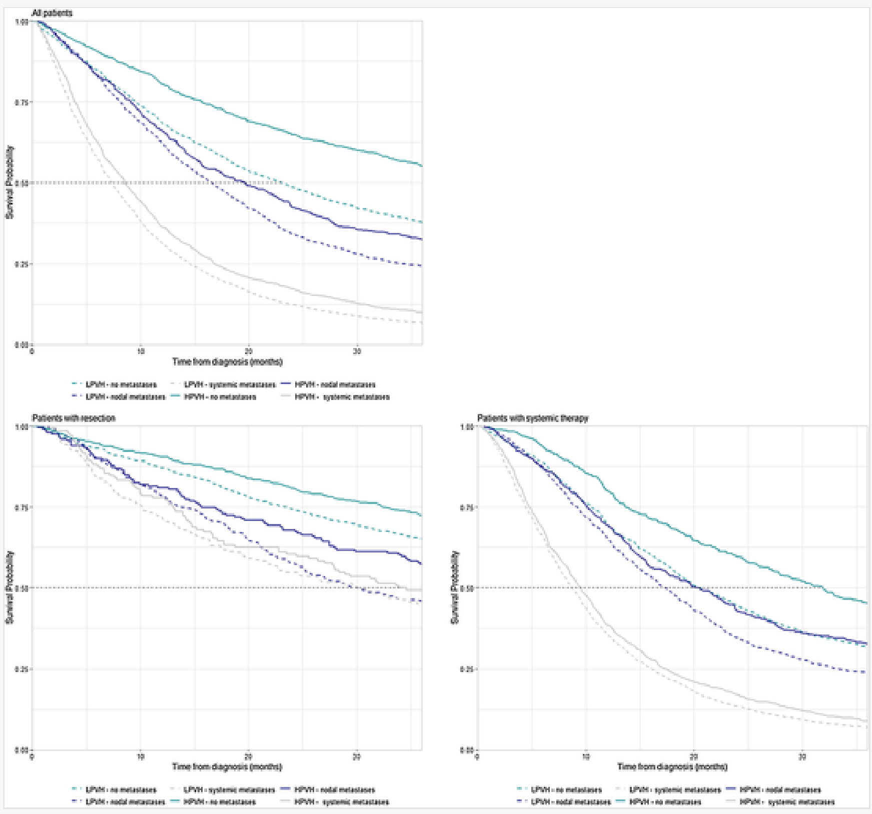
Notes: Sample characteristics of patients with lung cancer in Germany treated in high (>67 patients) vs. low patients volume hospitals. Means with standard deviation and proportions with numbers of sample characteristics. P-values from chi² test for proportions and *t*-test for means. Metastases status at initial diagnosis. HPVH = high patient volume hospital, LPVH = low patient volume hospital, sd = standard deviation.

3.2 Univariate analysis

The Kaplan Meier curves in Fig. 1 show a higher survival probability over the three-year follow-up in patients treated in HPVHs compared to LPVH in all subgroups and all strata.

alt-text: Fig. 1

Fig. 1



Kaplan-Meier curves in cohort of patients with lung cancer in Germany treated in high vs. low patient volume hospitals, in therapeutic subgroups and metastases strata. Notes: Survival curves of lung cancer patients treated in treated in high (>67 patients) vs. low patients volume hospitals across therapeutic subgroups. LPVH = low patient volume hospital, HPVH = high patient volume hospital~~Fig~~.

Proportions and means of all unadjusted outcomes for all subgroups in each stratum are displayed in Table 2. Results for the whole cohort are presented in Appendix Table 1.

alt-text: Table 2

Table 2

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Means and proportions of therapies of patients with lung cancer in Germany treated in high vs. low patient volume hospitals, among therapeutic subgroups and metastases strata from univariate analysis.

Proportion in % (n) / mean (sd)	No metastases			Nodal metastases			Systemic metastases		
All patients	HPVH (n = 940)	LPVH (n = 2636)	p-value	HPVH (n = 573)	LPVH (n = 1525)	p-value	HPVH (n = 1443)	LPVH (n = 5257)	p-value
Initial therapy [a]									
Resection	64.9 (610)	44.4 (1169)	**<0.0001**	34.9 (200)	32.5 (495)	0.29	10.0 (144)	7.4 (390)	**0.002**
Chemotherapy	38.1 (358)	48.5 (1278)	**<0.0001**	79.4 (455)	77.6 (1184)	0.38	81.2 (1172)	79.2 (4164)	0.09
Subgroup of patients with systemic therapyb	HPV (n = 451)	LPV (n = 1600)	p-value	HPV (n = 485)	LPV (n = 1249)	p-value	HPV (n = 1203)	LPV (n = 4255)	p-value
Therapy with pemetrexed	10.2 (46)	7.6 (122)	0.08	10.9 (53)	7.9 (98)	**0.04**	20.0 (240)	15.1 (641)	**<0.0001**
Targeted therapy	6.7 (30)	6.8 (108)	0.94	7.0 (34)	7.3 (91)	0.84	9.8 (118)	9.8 (418)	0.99
Subgroup of patients with resection [a]	HPV (n = 610)	LPV (n = 1169)	p-value	HPV (n = 199)	LPV (n = 494)	p-value	HPV (n = 144)	LPV (n = 389)	p-value
Pneumectomy	5.4 (33)	6.2 (72)	0.52	19.6 (39)	16.6 (82)	0.35	10.8 (14)	10.8 (42)	0.72
Broncho- or angioplastic reconstruction	7.4 (45)	5.5 (64)	0.11	11.1 (22)	8.9 (44)	0.38	7.6 (11)	8.2 (32)	0.83
Proportion of VATS among lobectomies	18.9 (100)	14.2 (139)	**0.02**	6.5 (10)	5.5 (22)	0.65	9.9 (11)	9.4 (28)	0.88

Notes: Care patterns of lung cancer patients treated in treated in high (>67 patients) vs. low patients volume hospitals. Means and proportions of treatments in subgroups and metastases strata. P-values from Chi^2 test for binary variables and *t*-test continuous variables. Metastases status at initial diagnosis. HPVH = high patient volume hospital, LPVH = low patient volume hospital, sd = standard deviation, VATS = video assisted thoracic surgery.
[a] in the first 180 days after diagnosis, [b] in the 3 years after diagnosis.

3.3 All patients

We found significantly higher resection rates in HPVHs in patients without metastases (64.9 vs. 44.4 %, p-value < 0.0001), and in patients with systemic metastases (10.0 vs. 7.4 %, p-value = 0.002). Among patients without metastases, treatment with systemic therapy was significantly more likely in LPVHs (38.1 vs. 48.5 %, p-value < 0.0001).

3.4 Subgroup of patients with systemic therapy

When patients had nodal or systemic metastases, a significantly higher proportion of patients treated in HPVH received pemetrexed compared to smaller hospitals (nodal metastases: 10.9 vs. 7.9 %, p-value = 0.04; systemic metastases 20.0 vs. 15.1 %, p-value < 0.0001).

3.5 Subgroup of patients with resection

In patients without metastases receiving a lobectomy, the proportion of thoracoscopic lobectomies was significantly higher in patients treated in HPVHs than in those treated in LPVHs (18.9 vs. 14.2 %, p-value = 0.02).

4 Multivariate analysis

4.1 Survival

The visual inspection of Schoenfeld residuals did not reveal a violation of the proportional hazard assumption. In the group of all patients and in the subgroup of patients with systemic therapy, the hazard of dying in the three-year observation period was significantly lower in patients treated in HPVHs compared to LPVHs among all metastases strata. In the subgroup of patients with resection this was only true for patients with nodal metastases.

All ORs, IRR and HR with 95 % confidence intervals are presented in Table 3.

alt-text: Table 3

Table 3

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Adjusted therapies and mortality of patients with lung cancer in Germany treated in high vs. low patient volume hospitals, among therapeutic subgroups and metastases strata from multivariate analysis.

	No metastases				Nodal metastases				Systemic metastases			
	HPV vs. LPV volume				HPV vs. LPV volume				HPV vs. LPV volume			
All patients	OR/HR	CI low	CI up	P-value	OR/HR	CI low	CI up	P-value	OR/HR	CI low	CI up	P-value
Initial therapy [a]												
Resection	3.28	2.13	5.04	**<.0001**	1.19	0.85	1.65	0.31	1.84	1.22	2.76	**0.003**
Systemic therapy	0.54	0.40	0.72	**<.0001**	1.00	0.73	1.37	0.99	1.04	0.80	1.35	0.77
3-year mortality	0.57	0.48	0.69	**<.0001**	0.83	0.72	0.96	**0.01**	0.87	0.80	0.94	**0.001**
Subgroup of patients with systemic therapyb	OR/HR	CI low	CI up	P-value	OR/HR	CI low	CI up	P-value	OR/HR	CI low	CI up	P-value
Therapy with pemetrexed	1.42	0.86	2.36	0.18	1.57	1.01	2.45	**0.04**	1.47	0.99	2.19	0.06
Targeted therapy	0.97	0.63	1.51	0.90	0.92	0.51	1.65	0.78	1.07	0.79	1.44	0.66
3-year mortality	0.65	0.54	0.78	**<.0001**	0.80	0.68	0.94	**0.01**	0.90	0.83	0.99	**0.02**
Subgroup of patients with resection [a]	OR/HR	CI low	CI up	P-value	OR/HR	CI low	CI up	P-value	OR/HR	CI low	CI up	P-value
Pneumectomy	0.83	0.50	1.36	0.45	1.20	0.73	1.98	0.47	0.89	0.46	1.73	0.73
Broncho- or angioplastic reconstruction	1.41	0.91	2.18	0.12	1.32	0.73	2.39	0.35	0.94	0.39	2.28	0.90

Proportion of open vs. thoracoscopic lobectomies	2.28	1.04	4.99	**0.04**	1.35	0.42	4.37	0.62	1.17	0.45	3.06	0.75
3-year mortality	0.75	0.61	0.92	**0.01**	0.73	0.56	0.94	**0.01**	0.90	0.66	1.23	0.50

Notes: Adjusted care patterns and 3-year mortality of lung cancer patients treated in treated in high (>67 patients) vs. low patients volume hospitals. Odds ratios from logistic regression and Hazard ratios from Cox-regression models. All regressions were modeled as mixed model with hospital ID as random intercept. HPVH = high patient volume hospital, LPVH = low patient volume hospital, OR = Odds ratio, HR=Hazard ratio, IRR = Incidence rate ratio.
[a] in the first 180 days after diagnosis, [b] in the three years after diagnosis.

4.2 All patients

In the strata of patients without metastases and patients with systemic metastases, the odds of receiving a resection were significantly higher in patients treated in HPVHs compared to LPVHs (nodal metastases: OR = 3.28, CI= [2.13, 5.04]; EM: OR = 1.84, CI = [1.22, 2.76]). Additionally, in patients without metastases, the odds of receiving systemic therapy was significantly lower in HPVHs (OR = 0.54, CI = [0.40, 0.72]).

4.3 Therapy-based subgroups

In patients with nodal metastases who received systemic therapy, the odds of receiving therapy with pemetrexed were 1.57 (CI = [1.01, 2.45]) times higher in HPVHs compared to LPVHs. All other outcomes were not significantly associated with hospital volume.

In the subgroup of patients with resection in patients without metastases, the odds of receiving a thoracoscopic lobectomy was 2.28 (CI=[1.04, 4.99]) times higher in HPVHs. All other outcomes related to surgical resection were not significantly associated with hospital case volume.

4.4 Sensitivity analysis

In SA1 we excluded the 2010 patients who were treated in multiple hospitals. SA 1 resulted in small changes compared to the primary analysis. For detailed results please refer to Appendix Table 2.

In SA 2 comparing different hospital sizes, we found a general gradient towards more extreme effect estimates with lower patient volume. 3-year mortality consistently increased with decreasing hospital case volume. Adjusted HRs underlined this effect. Detailed results can be found in Appendix table 3 and 4.

5 Discussion

Our study revealed some differences in treatment patterns as well as in patient survival between HPVH and LPVHs. Three-year survival probability was significantly higher in patients treated in HPVHs. This observation was statistically significant for all subgroups of patients treated with systemic treatment as well as for patients with no systemic metastases treated with surgery. Patients without documented nodal metastases were more likely to be treated with resection in HPVH compared to similar patients in LPVH. The observation that patients with systemic metastases were also more likely to receive surgery in HPVHs may reflect a multimodal approach to oligometastatic disease in this setting. In addition, the use of minimally invasive surgical techniques in patients without metastases was higher in HPVHs. However, other measures of surgical outcome quality, such as rates of pneumonectomy, broncho-angioplastic procedures, did not differ between HPVHs and LPVHs. We performed a sensitivity analysis aimed at examining the effect of intermediate and lower case volumes on care provision and outcomes. In this analysis the proportion of patients receiving a resection, thoracoscopic lobectomy, or therapy with pemetrexed or tyrosine kinase inhibitors was higher with increasing hospital case volume. The majority of these subgroup differences reached statistical significance. As in the primary analysis comparing LPVH and HPVH, the analysis of surgical outcome quality did not show significant differences in the intermediate patient volume subgroups. In general, there was a consistent trend to improved 3-year survival with increasing case volume across most subgroups and strata. In particular, it was noteworthy that this survival advantage was statistically significant in favor of treatment in HPVHs with over 200 cases per year compared to all subgroups of LPVH for patients with no metastases or only nodal metastases. For patients with systemic metastases the 3-year survival advantage of treatment in higher volume centers reached statistical significance for the smallest centers, with less than 100 lung cancer patients per year. However, there was no difference in survival between centers with 100−150 or 150−200 cases/year. This suggests that patient volume cut offs should not be broadly tied to the diagnosis itself but rather tailored to the clinical situation and type of treatment provided.

In our analysis we did not identify certified lung cancer centers but rather all hospitals with a high enough patient volume to be eligible for accreditation as a certified center. Based on the number of such centers in Germany, it is very likely that we captured most certified lung cancer centers. We categorized 30 hospitals as HPVH, which roughly corresponds to the 35 centers certified at the end of 2013 in Germany. Moreover, the percentage of patients treated in HPVHs was around 24 % in our study, while in 2011 and 2016 the percentage of patients treated in certified lung cancer centers was 20 % [23] and 32 % [24], respectively.

Our results show that especially in early stages (reflected by no or nodal metastases), receiving a lung cancer resection is significantly associated with being treated in a HPVH. Compared to reports by the German Cancer Society, the proportion of patients receiving an anatomical resection in a HPVH in our analysis is similar to the proportion of patients treated in certified centers (38 % vs. 31 %) [25]. In total, the proportion of patients receiving resection was higher (10 % points) in HPVHs. In patients with early stage lung cancer (no metastases) this difference was more pronounced (20 % points). Surgical resection is the mainstay of curative treatment for early stage lung cancer [15]. Whether the lower rates of surgical resection in smaller centers reflect clinically relevant differences in patient characteristics (ECOG (eastern cooperative oncology group status), pulmonary function) or technical operability cannot be fully addressed in this data set. However, we did adjust for patient age and for documented comorbidities, suggesting that at least part of the observed difference may be due to case volume itself. The clinical relevance of this issue is underlined by the finding that patients with nodal metastases receiving a resection had a significantly higher 3-year survival probability when treated in HPVHs.

When a lobectomy was performed the odds of a (less invasive) thoracoscopic compared to an open lobectomy was significantly higher in HPVHs in all patients and in patients without metastases. Overall, the proportion of thoracoscopic lobectomies was around 15 % in HPVHs and 11 % in LPVHs which is slightly higher than the mean rate of 11 % across European countries [26]. In patients without metastases rates even reached around 19 %. Thoracoscopic lobectomies are associated with shorter length of stay, reduced overall complications, improved quality of life, and less postoperative pain [27,28]. Evidence on survival benefits is inconsistent [29,30]. Despite the proven efficacy of thoracoscopic lobectomy adaption of the procedure has been rather slow, as the new approach still poses a challenge for many surgeons who have been trained in thoracotomy before [31,32]. This could explain why smaller hospitals with lower resection rates did not perform thoracoscopic lobectomies as often.

However, other outcomes in the subgroup of patients with resection did not result in significant differences between the two hospital groups. We did not find studies analyzing the association between hospital case volumes and the proportion of patients with pneumectomies specifically, so a comparison to our results was not possible.

Survival in patients with resection was significantly associated with hospital size in the stratum of patients without metastases and patients with nodal metastases. Other studies report similar effects concerning short- and long-term survival. A meta-analysis of 19 studies found significant differences in postoperative mortality, but no difference in in-hospital survival [35]. A study conducted in Florida did not find differences in in-hospital mortality [4], and researchers from England found significant differences in 30 and 90 day mortality only between patients in the highest and lowest quintiles of hospital case volume [12]. Regarding 5-year survival a study from Spain found no differences [36] and a study from Japan only found differences between the highest and the lowest volume hospitals [37]. Researchers from the USA found a significant association between hospital case volume and 5-year survival in a study, however data used was from 1985 to 1996 [1]. A German study analyzing 25 different surgical interventions including lung cancer resection did find significant differences in in-hospital survival, however they excluded pneumonectomies from their analysis so a direct comparison to our results is not feasible [10].

For patients receiving systemic therapy, being treated in a HPVH was beneficial with respect to survival probability. Hazard ratios in all strata significantly favored HPVHs over LPVHs ranging from 0.65(CI=[0.54, 0.978) in patients without metastases, to 0.80 (CI=[0.68, 0.94]) in patients with nodal, and to 0.90 (CI=[0.83, 0.99]) in patients with systemic metastases. One reason for this can be found in the therapies we analyzed for this subgroup. Patients with nodal but not systemic metastases had higher odds of receiving therapy with pemetrexed in HPVHs. The likelihood of receiving pemetrexed for systemic metastases also seemed to be higher in HPVH, with a p-value just below statistical significance. Pemetrexed was initially authorized as first line treatment in NSCLC in 2008 in combination with platinum-based chemotherapy. Since 2011 it is additionally authorized as maintenance therapy (monotherapy). In general, frequency of administration of newer agents was low in our study. Compared to a study from the US where around 40 % of patients received pemetrexed in 2011 [38], in our sample it was administered to only 20 % of patients in HPVHs and 15 % of patients in LPVH in patients with systemic metastases. A similar trend can be seen in the treatment with tyrosine kinase inhibitors, as in our study around 10 % of patients with systemic metastases received tyrosine kinase inhibitors (all available agents combined) compared to 20 % receiving erlotinib (one of the agents alone) in the USA [38].

Further aspects that possibly explain survival benefits in patients receiving systemic therapy in HPVHs relate to better opportunities for multidisciplinary cooperation in bigger hospitals. For example, big hospitals often have their own palliative care ward and can offer psycho-oncological therapy alongside the oncological treatment. Further, tumor boards discussing treatment option in all patients from different perspectives (internal, surgical, palliative etc.) can have an effect on therapy choices. Unfortunately, information on these types of services were not available in our dataset.

A major challenge when analyzing claims data relates to the lack of clinical information, as information in claims data are restricted to the needs of reimbursement. For example, we did not have direct information on stage and histology of the lung cancer cases but rather relied on documented ICD codes to describe clinical states of disease. As such, we defined three strata (no metastases, nodal metastases, and systemic metastases) to approximate disease stages and defined broad therapy based on resection or systemic therapy. Another weakness in this context refers to underreporting and incorrect data. If a specific test, diagnostic code, or code for medication use is not relevant for reimbursement purposes it is less likely to be reported. Further, data can be entered incorrect e.g. by the administrative clerk. However, specifically outcomes related to surgery used in this study are relevant for certification as lung cancer center, therefore we believe that these outcomes are reflected well in our dataset. Claims data do also not include information on why specific procedures like resection and or systemic therapy were or were not carried out (e.g. patient preferences for or against a distinct therapeutic approach). This has to be kept in mind when interpreting differences in outcomes between different hospital sizes. As we identified hospitals by anonymized IDs we did not have information on the geographic location of the specific hospitals. For this reason, we could not calculate the distance from patient residence to the next high volume center.

Although the lack of detailed individual case documentation limits some conclusions, our study represents a comprehensive nationwide overview of care, outcomes and hospital size in Germany. Our study included patients from all districts in Germany and the study population represents around 36 % of all incident lung cancer cases in Germany in 2013 [42] Additionally, so far our study is the first to not only look at patients with operable lung cancer, but also include difference in treatment and survival in patients receiving systemic therapy, who are the majority of lung cancer patients and have the worst prognosis.

6 Conclusion

The minimum case volume criterion established for the accreditation of certified lung cancer centers in Germany correlates with overall 3-year survival. The quality of care benchmark criterion relating to thoracoscopic resection also differed with case volume. Other quality of care benchmarks used in the accreditation process did not differ significantly between LPVHs and HPVHs. These data suggest that case volume is clinically relevant in both surgically resected and non-resected lung cancer patients, although the optimal minimum case volumes may differ for these subgroups.

Ethical approval

Data was completely anonymized and the Ethics Committee of the Medical Faculty of the Ludwig-Maximilians-University of Munich did not have any ethical or legal concerns against the analysis of the data (Votum-number: 88–15).

Consent for publication

Not applicable.

Availability of data and materials

The authors confirm that the data utilized in this study cannot be made available in the manuscript, the supplemental files, or in a public repository due to German data protection laws (‘Bundesdatenschutzgesetz’, BDSG). Therefore, they are stored on a secure drive in the senior author’s institution to facilitate replication of the results.

Generally, access to data of statutory health insurance funds for research purposes is possible only under the conditions defined in German Social Law (SGB V § 287). Requests for data access can be sent as a formal proposal specifying the recipient and purpose of the data transfer to the appropriate data protection agency. Access to the data used in this study can only be provided to external parties under the conditions of the cooperation contract of this research project and after written approval by the sickness fund. For assistance in obtaining access to the data, please contact the corresponding author.

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Uncited references

[~~22~~,~~33~~,~~34~~,~~39~~,~~40~~,~~41~~].

Declarations of Competing Interest

The authors declare that they have no competing interests.

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Appendix A Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.healthpol.2020.07.012.

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The corrections made in this section will be reviewed and approved by a journal production editor. The newly added/removed references and its citations will be reordered and rearranged by the production team.

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Highlights

- We found significant associations between hospital size and survival.
- We did not find significant differences in quality criteria for surgical resection.
- Optimal minimum case volumes may differ depending on the intended and indicated therapy.

Appendix A Supplementary data

The following are Supplementary data to this article:

Multimedia Component 1

Multimedia Component 2

Multimedia Component 3

Multimedia Component 4

Multimedia Component 5

Multimedia Component 6

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Q1

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