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A nationwide population-based cohort study of surgical care for patients with superior sulcus tumors: Results from the Dutch Lung Cancer Audit for Surgery (DLCA-S)

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ABSTRACT

Objectives: Data on national patterns of care for patients with superior sulcus tumors (SST) is currently lacking. We investigated the distribution of surgical care and outcome for patients with SST in the Netherlands.
Material and methods: Data was retrieved from the Dutch Lung Cancer Audit for Surgery (DLCA-S) for all patients undergoing resection for clinical stage IIB-IV SST from 2012 to 2019. Because DLCA-S is not linked to survival data, survival for a separate cohort (2015–2017) was obtained from the Netherlands Cancer Registry (NCR).
Results: In the study period, 181 patients had SST surgery, representing 1.03% (181/17488) of all lung cancer pulmonary resections. For 2015–2017, the SST resection rate was 14.4% (79/549), and patients with stage IIB/III SST treated with trimodality had a 3-year overall survival of 67.4%. 63.5% of patients were male, and median age was 60 years. Almost 3/4 of tumors were right sided. Surgery was performed in 20 hospitals, with average number of annual resections ranging from ≤ 1 (n = 17) to 9 (n = 1). 39.8% of resections were performed in 1 center and 63.5% in the 3 most active centers. 12.7% of resections were extended (e.g. vertebral resection). 85.1% of resections were complete (R0). Morbidity and 30-day mortality were 51.4% and 3.3% respectively. Despite treating patients with a higher ECOG performance score and more extended resections, the highest volume center had rates of morbidity/mortality, and length of hospital stay that were comparable to those of the medium volume (n = 2) and low-volume centers (n = 1).
Conclusion: In the Netherlands, surgery for SST accounts for about 1% of all lung cancer pulmonary resections, the number of SST resections/hospital/year varies widely, with most centers performing an average of ≤ 1/year. Morbidity and mortality are acceptable and survival compares favourably with the literature. Although further centralisation is possible, it is unknown whether this will improve outcomes.

1. Introduction

Superior sulcus tumors (SST), also called Pancoast tumors, account for less than 5% of lung cancers, but they deserve special attention due to their anatomical location in proximity to the spine, large vessels, brachial plexus and other nerves, leading to characteristic pain and

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neurological deficits, and posing challenges for their resection. There is a long-standing view that complete surgical resection offers the best functional and oncological outcome [1]. This is reflected by national and international guidelines recommending trimodality treatment, consisting of induction chemoradiotherapy (CRT) followed by surgical resection, as the preferred treatment for fit patients with a technically resectable SST [2–4]. This multimodal regimen offers a high probability of locoregional control after radical (R0) resection, and favorable overall survival in appropriately selected patients [5,6]. For these reasons, extended resections, including (partial) removal and reconstruction of vertebrae, the subclavian artery or vein, and the superior caval vein, should be considered [7,8]. In addition, resection may be considered in selected patients with limited mediastinal nodal involvement (N2), and low-volume (oligo-) metastatic disease [9,10].

Although surgery for SST is considered complex, it can be performed with acceptable morbidity and mortality. However, due to invasion of e.g. spine and vascular structures, complete resection may require the expertise of various surgical specialists [11,12]. Such specialist teams may not be available at all centers in which lung surgery is performed. Furthermore, the low incidence of SST and especially resectable SST, implies that individual teams may have very limited experience with this disease. Analogous to other complex cancer operations, such as those for pancreatic cancer or esophageal cancer, SST surgery may reasonably be expected to be centralized, limiting the variations in patterns of care and outcome [13–18].

Although large database studies have reported outcome from selected patients with SST, there is little data on national patterns of surgical practice for SST [19]. The purpose of this study was to investigate the national distribution of surgical resections, patterns of care and outcomes for patients with resected SST in the Netherlands. Such an analysis is possible due to the combination of the Dutch National Cancer Registry (NCR), that captures more than 95% of the cancer population, and the Dutch Lung Cancer Audit for Surgery (DLCA-S), which is a national lung cancer surgery database in which all hospitals are mandated to enter details of all lung operations since 2012.

2. Methods

2.1. Data collection

Data was retrieved from the DLCA-S, a nationwide prospective clinical registry that started in 2012 with the aim of monitoring adherence to quality standards, and identifying variation in clinical practice and outcomes for lung operations [20]. The DLCA-S collects data from all patients undergoing surgery for malignant or benign lung and/or mediastinal disease. Participation is obligatory, and data entered into the database is verified randomly by an external party with trained personnel [20]. Unfortunately, there is no survival data in the DLCA-S. However, to place the numbers of SST patients in the DLCA-S into context of all patients diagnosed with SST, and to provide the reader with survival data with which to assess the quality of SST care, we also included data from the Netherlands Cancer Registry (NCR request K19.394), The NCR records basic data on diagnosis, stage, treatment and survival of all cancer patients in the Netherlands. Although detailed information about the surgical procedure and surgical morbidity is not recorded in the NCR, a specific code for SST was introduced in 2015. To ensure a long enough period of follow-up, data from the period 2015–2017 was used to calculate overall survival (from date of diagnosis until date of death or censoring). Survival status up to February 1, 2019 was used for this analysis.

In the first years of the DLCA-S, the item ''histopathology'' was interpreted ambiguously for patients with complete pathological response (pCR) as some hospitals selected the option "no / benign" and some recorded the pre-treatment biopsy histology (e.g. adenocarcinoma, squamous cell carcinoma, etc.). Since 2019, however, it is clearly stated in the database what to record in case of pathological complete

Table 1
Patient, tumor, surgical and pathological characteristics from patients who underwent surgery for sulcus superior tumors in the Netherlands between January 1st 2012 and December 31st 2019.

	n	%	Missing (n,%)
Patient characteristics			
Number of patients	181		
Gender (male : female)	115 : 66	63.5 : 36.5	
Age (median, IQR)	60 (53-67)		1 (0.5)
ECOG performance status			12 (6.6)
0	72	39.8	
1	77	42.5	
2 or more	20	11.0	
ASA classification			2 (1.1)
I & II	120	66.3	
III & IV	59	32.6	
FEV1 %(mean,(SD))	83.5 (18.8)		16 (8.8)
DLCO %(mean,(SD))	70.1 (17.5)		24 (13.3)
FDG-PET/CT-scan			0 (0.0)
Yes	179	98.9	
No	2	1.1	
Mediastinal evaluation Any	98	54.1	7 (3.9)
EUS	16	8.8	14 (7.7)
EBUS	63	34.8	12 (6.6)
Mediastinoscopy	43	23.8	10 (5.5)
Tumor characteristics			
Laterality			0 (0.0)
Right	132	72.9	
Left	49	27.1	
cTNM (7th edition 2012-2016)			0 (0.0)
IIb	49	27.1	
IIIa	43	23.8	
IIIb	4	2.2	
IV	5	2.8	
cTNM (8th edition 2017-2019)			0 (0.0)
IIb	33	18.2	
IIIa	29	16.0	
IIIb	13	7.2	
IIIc	4	2.2	
IV	1	0.6	
Induction treatment			1 (0.6)
Chemoradiotherapy	161	89.0	
Radiotherapy	3	1.7	
Chemotherapy	7	3.9	
Immunotherapy	1	0.6	
None	8	4.4	
Surgical characteristics			
Surgical approach			2 (1.1)
(U)VATS (conversion to open)	8 (1)	4.5 (0.6)	
Thoracotomy	159	87.8	
Other	11	6.1	
Type of resection			0 (0.0)
Pneumonectomy	1	0.6	
Bilobectomy	4	2.2	
Lobectomy	166	91.7	
Segmentectomy	4	2.2	
Wedge resection	6	3.3	
Extended resection			0 (0.0)
Yes	23	12.7	
No	158	87.3	
Intra-operative blood loss (cc)			4 (2.2)
0-500	109	60.2	
500-1000	45	24.9	
1000-2000	18	9.9	
>2000	5	2.8	
Complications	93	51.4	0 (0.0)
Prolonged air leak (>5 days)	18	9.9	
Infection			
Pneumonia (antibiotics given)	40	22.1	
Other infections (empyema, wound)	23	12.7	
Bleeding (+ reintervention)	8	4.4	
Chylothorax	6	3.3	
Atelectasis	18	9.9	
Recurrent nerve damage	1	0.6	
Phrenic nerve damage	7	3.9	
Respiratory failure			

(*continued on next page*)

Table 1 (*continued*)

	n	%	Missing (n,%)
ARDS	2	1.1	
Other	13	7.2	
Cardiac event			
Supraventricular arrhythmia	10	5.5	
Myocardial infarction	1	0.6	
Thrombotic event			
TIA/CVA	1	0.6	
Length of stay (median, IQR)	9 (7-14)		5 (2.8)
Mortality (<30days/ in hospital)	6	3.3	2 (1.1)
Pathology characteristics			
Resection margin			13 (7.2)
Complete resection (R0)	154	85.1	
Microscopically incomplete (R1)	13	7.2	
Macroscopically incomplete (R2)	1	0.6	
pTNM (7th edition 2012-2016)			37 (20.4)
0	1	0.6	
Ia	12	6.6	
Ib	2	1.1	
IIa	1	0.6	
IIb	30	16.6	
IIIa	10	5.5	
IIIb	0	0	
IV	6	3.3	
pTNM (8th edition 2017-2019)			15 (8.3)
0	17	9.4	
Ia	7	3.9	
Ib	0	0	
IIa	0	0	
IIb	28	15.4	
IIIa	11	6.1	
IIIb	1	0.6	
IV	1	0.6	
Histopathology *			0 (0.0)
No tumor/ complete response	29	16.0	
Adenocarcinoma	75	41.4	
Squamous cell carcinoma	48	26.5	
Adenosquamous carcinoma	3	1.7	
Large-cell carcinoma	9	5.0	
Not otherwise specified (NOS)	5	2.8	
Other	12	6.6	

*= In the first years of the DLCA-S, the item ''histopathology'' was interpreted ambiguously for patients with complete pathological response (pCR) as some hospitals selected the option "no / benign" and some recorded the pre-treatment biopsy histology (e.g. adenocarcinoma, squamous cell carcinoma, etc.).
ECOG = Eastern Cooperative Oncology Group, ASA = American Society of Anaesthesiologists, SD = standard deviation, FEV1 = Forced Expiratory Volume in 1 s, DLCO = diffusing capacity for carbon monoxide, FDG-PET/CT = fluoro-deoxy-glucose positron emission tomography/computer tomography. EUS = esophageal ultrasound, EBUS = endobronchial ultrasound, cTNM = clinical TNM, (U)VATS = (uniportal) video-assisted thoracoscopic surgery, ARDS = adult respiratory distress syndrome, TIA = transient ischemic attack, CVA = cerebrovascular accident

response after induction therapy.

2.2. Patient selection

All patients undergoing a resection for a clinical stage IIB-IV (TNM7 (2012–2016) and TNM8 (2017–2019)) SST, between January 1st 2012 and December 31st 2019, were identified in the DLCA-S. To analyze the possible impact of the annual number of resections for SST on morbidity and mortality, centers were divided into 3 groups: high volume (HV), medium volume (MV), and low volume (LV) hospitals. Patient characteristics, stage distribution, type of treatment, and postoperative outcome were calculated for the three groups.

2.3. Outcomes

For all hospitals, we analysed patient characteristics (age, gender, Eastern Cooperative Oncology Group (ECOG) performance status, American Society of Anaesthesiologists (ASA) classification and lung function), diagnostic work-up characteristics (FDG-PET/CT, EUS, EBUS and mediastinoscopy), tumor characteristics (tumor location, clinical stage using the TNM-classification and postoperative histopathology) and treatment characteristics (type of induction therapy, surgical approach, type of parenchymal resection and presence and type of extended resection which was defined as including pericardial resection, arterial or venous resection/reconstruction, vertebral resection), complications and mortality (in-hospital or within 30 days after resection).

2.4. Statistics

Due to the observational nature of the study, we refrained from advanced statistics. Categorical data are reported as frequency accompanied by percentage. Non-normally distributed continuous data were presented as median with interquartile ranges (IQR) or, in case of a normal distribution, a mean with standard deviation (SD). Missing data are reported per item. Differences in patient-, tumor-, and treatment characteristics between hospital groups (HV, MV, LV) were assessed by means of chi-square test or Fisher's exact test for characteristics that were categorical, and by means of independent samples *t*-test for characteristics measured on a continuous scale. Statistical significance was defined as $p < 0.05$ and overall morbidity and mortality rates are reported with 95% confidence interval (CI).

Three-year overall survival (OS) and 95% confidence interval were calculated with the Kaplan-Meier method. R Studio version 1.1.456, Integrated Development for R. RStudio, Inc., was used for statistical analysis.

3. Results

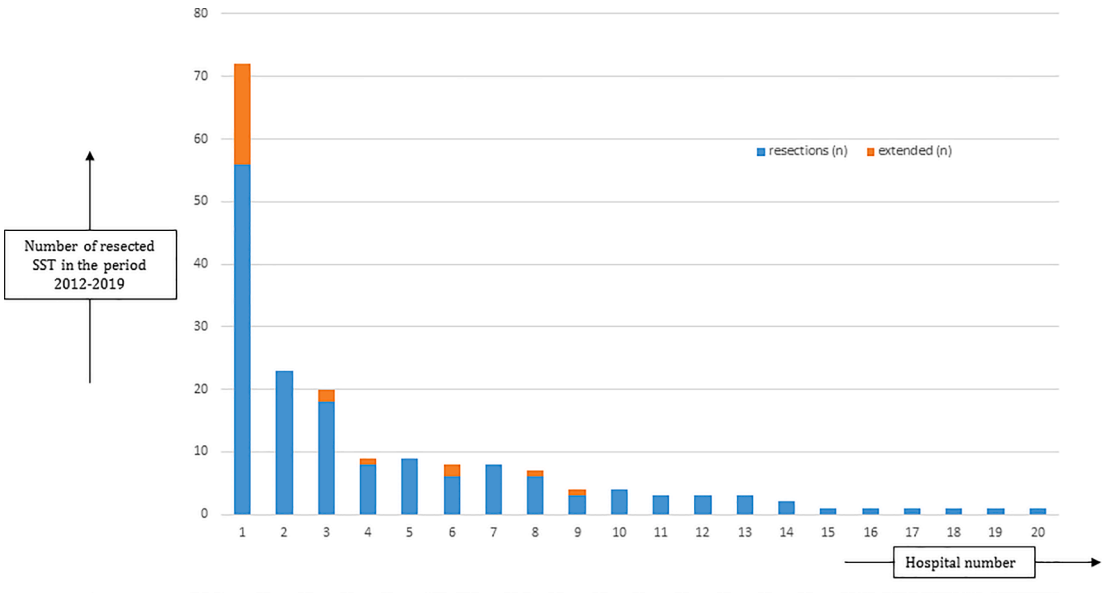
The population of the Netherlands is approximately 17.3 million [18]. During the period 2012–2019, 17.448 patients underwent a pulmonary resection for (suspected) lung cancer, of which 181 patients (1.03%) were registered as having had surgery for clinical stage IIB-IV SST. For the period 2015–2017, the NCR reported 549 SST patients, of which 239 (43.5%) were clinical stage IV. In this same period, there were 79 patients registered in the DLCA-S as having had a resection for SST, resulting in a resection rate of 14.4%.

Patient -, tumor -, treatment characteristics are summarized in Table 1. Median age was 60 years (IQR 53–67), and patients were predominantly male (63.5%). Tumors were located in the right lung in almost three quarter of the patients (72.9%). Nearly all patients (98.9%) were staged with FDG-PET-scan (in the years 2017–2019, 95.0% of all tumors were FDG positive, data not shown), and 54.1% had some form of invasive mediastinal staging: endobronchial ultrasound (EBUS: n = 63, 34.8%), esophageal ultrasound (EUS: n = 16, 8.8%) and/or mediastinoscopy (n = 43, 23.8%).

Prior to surgery, nearly all patients received some form of induction treatment, with chemoradiotherapy accounting for 89.0%. A minimally invasive surgical approach was used in 4.5% of patients (n = 8), while the vast majority had an open approach (87.8%, n = 159). Surgical treatment consisted of an anatomical oncological resection in 96.7% (n = 175) of patients.

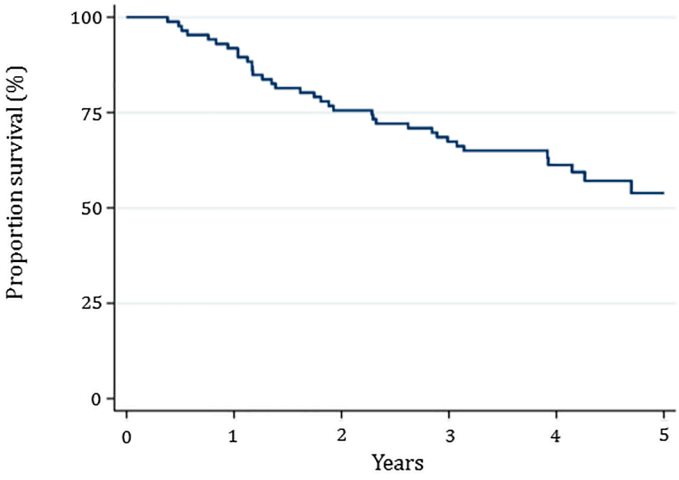
The morbidity rate was 51.1% (95%CI 43.9–58.9), resulting in an uneventful perioperative course in 48.9% of patients. Complications reported in>5% of patients were: pneumonia requiring antibiotics in 22.1% (n = 40), atelectasis in 9.9% (n = 18), prolonged air leakage (>5 days) in 9.9% (n = 18), respiratory failure in 8.3% (n = 15) of which 1.1% (n = 2) had acute respiratory distress syndrome (ARDS), and supra-ventricular arrhythmia in 5.5% (n = 10). Median duration of hospital stay was 9 days (IQR 7–14 days). The 30-day mortality was 3.3% (95%CI 1.2–7.2). Complete resection (R0) was achieved in 85.1% (n = 154), however, resection margin was not reported in 7.2% (n = 13) of patients.

In the Netherlands, pulmonary surgery is currently being performed in 43 hospitals, 20 of which were doing SST resections in the study



Total resections (n)	72	23	20	9	9	8	8	7	4	4	3	3	3	2	1	1	1	1	1	1
Extended (n)	16	0	2	1	0	2	0	1	1	0	0	0	0	0	0	0	0	0	0	0
Complications n	31	14	13	6	3	3	6	0	4	2	2	1	1	1	1	1	1	1	1	1
%	43	61	65	68	33	38	75	0	100	50	67	33	33	50	100	100	100	100	100	100
Mortality n	2	0	3	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
%	2.5	0	15	0	11.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Fig. 1. Absolute numbers of resections, extended resections, complications and mortality within 30 days (or in-hospital) after surgery for SST for individual hospitals in the Netherlands between January 1st 2012 - December 31st 2019.



Number at risk	86	79	65	57	33	14

Fig. 2. Overall survival for patients with TNM stage IIB-III treated with trimodality treatment, Netherlands Cancer Registry 2015–2017.

period. For each hospital performing SST resections, Fig. 1 shows the number of SST resections, extended SST resections, complications and 30-day mortality.

Three hospitals performed $\geq$ 20 resections during the study period, one of which accounted for 39.8% (72/181) of all resections, and was the only hospital performing an average of nearly 9/year. There were 5 hospitals in which no SST resection was performed in the last four years of the study period. The majority of hospitals (17/20 (85%), recorded an average of $\leq$ 1 resection/year. From the NCR, we identified 86/310 (28%) patients with clinical TNM stage IIB-III SST who underwent trimodality treatment during the period 2015–2017, and these patients had a three-year overall survival of 67.4% (95% CI 56.4–76.2) (Fig. 2).

Based on the annual number of resected SST, we divided hospitals in high volume (HV, n = 1), performing ~ 9 SST/year, medium volume (MV, n = 2) with ~ 3 SST/year and low volume (LV, n = 17) resecting $\leq$ 1 SST/year. Patient -, tumor -, treatment characteristics for these groups are presented in Table 2. Despite treating patients with a higher ECOG performance ($p < 0.001$) score and more extended resections ($p = 0.007$), the HV had rates of morbidity and mortality, and length of hospital stay that were comparable to those of MV and LV hospitals.

4. Discussion

In this population-level study looking at the surgical treatment of

Table 2
Patient, tumor, surgical and pathological characteristics from patients who underwent surgery in high volume hospitals (HV), medium volume (MV) and low volume (LV) hospitals for sulcus superior tumors in the Netherlands between January 1st 2012 and December 31st 2019.

	HV	MV	LV	
Patient characteristics				*p*
Number of hospitals (n)	1	2	17	
Total number of resections (n)	72	43	66	
Average number of resection SST/year (n)	**~9**	**~3**	**≤1**	
Age (median, IQR)	58 (53-64)	61 (55-70)	62 (52-69)	0.057
ECOG performance status (n (%))				<0.001
0	17 (23.6)	27 (62.8)	28 (42.4)	
1	43 (59.7)	10 (23.3)	24 (36.4)	
2 or more	12 (16.7)	2 (4.7)	6 (9.1)	
NA	0 (0.0)	4 (9.3)	8 (12.1)	
ASA classification (n (%))				0.255
I & II	50 (69.4)	23 (53.5)	47 (71.2)	
III & IV	22 (30.6)	19 (44.2)	18 (27.3)	
Missing	0 (0.0)	1 (2.3)	1 (1.5)	
FEV1%(mean, (SD))	84.6 (19.5)	82.8 (17.0)	83.1 (19.6)	0.844
DLCO%(mean, (SD))	68.7 (14.0)	69.3 (17.2)	72.0 (20.4)	0.551
Tumor characteristics				
cTNM (7th edition 2012-2016) (n (%))				0.161
IIb	19 (44.2)	12 (60.0)	18 (47.4)	
IIIa	21 (48.8)	6 (30.0)	16 (42.1)	
IIIb	2 (4.7)	2 (10.0)	0 (0.0)	
IV	1 (2.3)	0 (0.0)	4 (10.5)	
cTNM (8th edition 2017-2019) (n (%))				0.715
IIb	10 (34.5)	11 (47.8)	12 (42.9)	
IIIa	12 (41.4)	9 (39.1)	8 (28.6)	
IIIb	4 (13.8)	3 (13.0)	6 (21.4)	
IIIc	2 (6.9)	0 (0.0)	2 (7.1)	
IV	1 (3.4)	0 (0.0)	0 (0.0)	
Induction treatment (n (%))				0.329
Chemoradiotherapy	68 (94.4)	39 (90.7)	58 (81.8)	
Radiotherapy	1 (1.3)	0 (0.0)	2 (3.0)	
Chemotherapy	2 (2.8)	1 (2.3)	4 (6.1)	
Immunotherapy	0 (0.0)	1 (2.3)	0 (0.0)	
None	1 (1.4)	2 (4.7)	5 (7.6)	
Missing	0 (0.0)	0 (0.0)	1 (1.5)	
Surgical characteristics				
Surgical approach (n (%))				0.054
(U)VATS	0 (0.0)	0 (0)	7 (10.6)	
(U)VATS, conversion to open	0 (0.0)	1 (2.3)	0 (0.0)	
Thoracotomy	66 (91.7)	38 (88.4)	55 (83.3)	
Other	6 (8.3)	3 (7.0)	2 (3.0)	
Missing	0 (0.0)	0 (0.0)	2 (3.0)	
Type of resection (n (%))				0.213
Pneumonectomy	0 (0.0)	0 (0.0)	1 (1.5)	
Bilobectomy	1 (1.4)	1 (2.3)	2 (3.0)	
Lobectomy	66 (91.7)	39 (90.7)	61 (92.4)	
Segmentectomy	1 (1.4)	3 (7.0)	0 (0.0)	
Wedge resection	4 (5.6)	0 (0.0)	2 (3.0)	
Extended resection (n (%))				0.007
Yes	16 (22.2)	2 (4.7)	5 (7.6)	
No	56 (77.8)	41 (95.3)	61 (92.4)	
Intra-operative blood-loss (cc) (n (%))				0.019
0-500	38 (52.8)	27 (62.8)	44 (66.7)	
501-1000	23 (31.9)	14 (32.6)	8 (12.1)	
1001-2000	9 (12.5)	1 (2.3)	8 (12.1)	
>2000	2 (2.8)	1 (2.3)	2 (3.0)	
Missing	0 (0.0)	0 (0.0)	4 (6.1)	
Complications (n (%))	31 (43.1)	27 (62.8)	35 (53.0)	0.116
Length of stay (median, IQR)	9 (7-14)	9 (6-15)	11 (7-16)	0.709
Mortality (<30 days/in-hospital) (n (%))				0.201
Yes	2 (2.8)	3 (7.0)	1 (1.5)	
No	70 (97.2)	40 (93.0)	63 (95.5)	
Missing	0 (0.0)	0 (0.0)	2 (3.0)	
Pathology characteristics				
Resection margin (n (%))				0.338
Complete resection (R0)	60 (83.3)	38 (88.4)	56 (84.8)	
Microscopically incomplete (R1)	5 (6.9)	1 (2.3)	7 (10.6)	
Macroscopically incomplete (R2)	0 (0.0)	0 (0.0)	1 (1.5)	
Missing	7 (9.7)	4 (9.3)	2 (3.0)	
pTNM (7th edition 2012-2016) (n (%))				0.089
0	1 (2.3)	0 (0.0)	0 (0.0)	
Ia	8 (18.6)	1 (5.0)	4 (7.9)	
Ib	0 (0.0)	0 (0.0)	2 (5.3)	
IIa	1 (2.3)	0 (0.0)	0 (0.0)	
IIb	10 (23.3)	7 (35.0)	13 (34.2)	
IIIa	3 (7.0)	1 (5.0)	6 (15.8)	
IIIb	0 (0.0)	0 (0.0)	0 (0.0)	
IV	0 (0.0)	2 (10.0)	4 (10.5)	
Missing	20 (46.5)	9 (45.0)	10 (26.4)	
pTNM (8th edition 2017-2019) (n (%))				0.138
0	6 (20.7)	4 (17.4)	7 (25.0)	
Ia	2 (6.9)	2 (8.7)	3 (10.7)	
Ib	0 (0.0)	0 (0.0)	0 (0.0)	
IIa	0 (0.0)	0 (0.0)	0 (0.0)	
IIb	7 (24.1)	9 (39.1)	12 (42.9)	
IIIa	2 (6.9)	5 (21.7)	4 (14.3)	
IIIb	1 (3.4)	0 (0.0)	0 (0.0)	
IV	0 (0.0)	1 (4.3)	0 (0.0)	
Missing	11 (37.9)	2 (8.7)	2 (7.1)	
Histopathology* (n (%))				0.006
No tumor/complete response	20 (27.8)	4 (9.3)	5 (7.6)	
Adenocarcinoma	25 (34.7)	18 (41.9)	32 (48.5)	
Squamous cell carcinoma	17 (23.6)	8 (18.6)	23 (34.8)	
Adenosquamous carcinoma	0 (0.0)	3 (7.0)	0 (0.0)	
Large-cell carcinoma	2 (2.8)	4 (9.3)	3 (4.5)	
Not otherwise specified (NOS)	1 (1.4)	2 (4.7)	2 (3.0)	
Other	7 (9.7)	4 (9.3)	1 (1.5)	

*= In the first years of the DLCA-S, the item ''histopathology'' was interpreted ambiguously for patients with complete pathological response (pCR) as some hospitals selected the option "no / benign" and some recorded the pre-treatment biopsy histology (e.g. adenocarcinoma, squamous cell carcinoma, etc.).
ECOG = Eastern Cooperative Oncology Group, ASA = American Society of Anaesthesiologists, SD = standard deviation, FEV1 = Forced Expiratory Volume in 1 s, DLCO = diffusing capacity for carbon monoxide, FDG-PET/CT = fluorodeoxy-glucose positron emission tomography/computer tomography. EUS = esophageal ultrasound, EBUS = endobronchial ultrasound, cTNM = clinical TNM, (U)VATS = (uniportal) video-assisted thoracoscopic surgery, ARDS = adult respiratory distress syndrome, TIA = transient ischemic attack, CVA = cerebrovascular accident

SST, we analysed the DLCA-S and NCR databases, both of which include at least 95% of all lung cancer patients. Our main findings were: (1) surgery for SST was a relatively uncommon procedure, comprising an average of 25 resections per year in the Netherlands, and (2) although SST surgery was being performed in a large number of hospitals, the vast the majority only occasionally performs such operation (17/20, 85% doing on average ≤ 1/year), indicating that SST surgery has 'spontaneously centralized' (i.e. without a specific drive to centralization). The overall morbidity and 30-day mortality rates were 51.4% and 3.3% respectively, numbers that are higher than the 34.4% and 1.9%, respectively, reported for all non-small cell lung cancer (NSCLC) operations in the Netherlands [22]. The results from the highest volume hospital (accounting for 39.8% of all resections) showed that even with a substantial proportion of patients (22.2%) treated with extended resections, high radical resection rates (83.3%), acceptable morbidity (43.1%) and low mortality rates (2.5%) can be achieved. Although the 83.3% radical margin rate could be influenced by incomplete data capture, these outcomes compare favourably with radical margin rates

reported from other high-volume centers [5,11].

During the last decade, a number of studies have reported on the possible correlations between hospital volume, surgeon volume, or both, and outcomes in lung surgery. The results of these studies, which are sometimes conflicting, have fuelled the discussion on centralization and procedure concentration [17,23–26]. The threshold volume above which morbidity and mortality decrease and outcome improves, is an issue of ongoing debate for both hospital and surgeon volume. A recent study arbitrarily categorized hospitals into three groups, based on the number of resections per year: low-volume (≤30 procedures), intermediate-volume (31-≤95 procedures) and high-volume centers (>95 procedures). The authors reported a 26% drop in mortality rate when lung resections were performed in high volume centers compared to low volume centers [26]. In most reports no clear distinction is made regarding the complexity of the operation, however, pulmonary (cancer) surgery involves a wide range of procedures, with higher reported morbidity and mortality rates for patients undergoing complex resections such as salvage resections after definitive chemoradiotherapy, surgery for complications after (chemo)radiotherapy and extended resections with arterial reconstructions or vertebral involvement [27,28]. It is unclear whether centralization of complex surgical procedures will have a bigger impact on outcomes, when compared with less complex surgical interventions. While we have interpreted spontaneous centralization as positive, one consequence of concentrating care in a small number of centers is that vigilance is imperative to ensure that the quality of care in these centers, and their outcomes are comparable. Identifying the reasons for, and drivers of, spontaneous centralization were beyond the scope of this study.

The treatment of SST can be challenging. With this in mind, it is reasonable to assume that outcomes reflect the composition and expertise of the treatment team. For example, a recent study showed considerable variation in clinical staging and treatment recommendation among multidisciplinary tumor boards (MTB), largely attributable to T- staging, in particular in patients with locally advanced lung cancer, which is the case for most SST patients [29]. The input of experienced and knowledgeable clinicians during MTB discussions is important, especially when deciding things like the feasibility and usefulness of an extensive operation after multi-modal induction treatment [30]. Beyond the MTB discussion, intensivists, dieticians, physiotherapists, and specialised nurses all add to the success of treatment, especially in complex pulmonary surgery [31,32].

In a previous single-center report on SST over a 10-year period (1994–2004), 14/40 patients staged M0 were judged inoperable because of factors like involvement of N2/N3 lymph nodes, the brachial plexus, great vessels and/or neural foramina [33]. Arguably, some of these patients may have been deemed resectable by an expert team comprising of lung cancer surgeons, neurosurgeons, orthopedic and cardiac/vascular surgeons as we believe that for rare clinical conditions like SST, a low-threshold for referral to highly specialized thoracic units, might increase resection rates, result in improved outcomes for some patients, and offer the best chance for cure. In addition, higher institutional volumes might facilitate set-up and accrual to trials and the organization of cancer care in clinical networks can increase trial recruitment [34]. Unfortunately, in the present study, specific reasons for not offering surgery are unknown as they are not recorded in the DLCA-S or NCR.

The most important limitation of the current analysis is the completeness and reliability of a self-reported registry. Several items may have been incorrectly registered, and key parameters that are important for outcome measures, such as resection margin status, have substantial proportions of incomplete or missing data. This may be explained by the large number of database items that have to be recorded, which is time-consuming and arguably, more error prone: it takes at least 20–30 min to complete a patient's record after anatomical resection for cancer, significantly adding to the administrative burden of clinicians. In addition, a few of the items, such as histopathology, have had to be fine-tuned via continuous feed-back from users of the database, which makes it harder to interpret them. Nevertheless, despite these concerns the registry has been validated by external, independent parties and shown to be reliable [35]. The amount of data that clinicians have to input, the proportion of missing data, and the lack of survival data in DLCA-S all deserve attention.

5. Conclusion

In the Netherlands, surgery for SST accounts for about 1% of all lung cancer pulmonary resections, the number of SST resections/hospital/year varies widely, with most centers performing an average of ≤ 1/year. Surgery has spontaneously centralized, with a considerable majority of operations being done in 3 centers. Morbidity and mortality are acceptable, and survival compares favourably with the literature. Although further centralisation is possible, it is unknown whether this will improve outcomes. Strategies to share best-practice, ensure access to the necessary surgical expertise, and maximise outcomes are warranted. [21].

CRediT authorship contribution statement

J.A. Winkelman: Conceptualization, Methodology, Investigation, Writing - original draft, Visualization. **L. van der Woude:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing - original draft, Visualization. **D.J. Heineman:** Writing - review & editing. **I. Bahce:** Writing - review & editing. **R.A. Damhuis:** Validation, Resources, Writing - review & editing. **E.A.F. Mahtab:** Writing - review & editing. **K.J. Hartemink:** Writing - review & editing. **S. Senan:** Writing - review & editing. **A.P.W.M. Maat:** Writing - review & editing. **J. Braun:** Writing - review & editing. **M.A. Paul:** Writing - review & editing. **M. Dahele:** Writing - review & editing. **C. Dickhoff:** Conceptualization, Writing - original draft, Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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