Resection Rate and Outcome of Pulmonary Resections for Non–Small-Cell Lung Cancer

A Nationwide Study From Iceland

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Background: The proportion of patients with non–small-cell lung cancer (NSCLC) who undergo surgery with curative intent is one measure of effectiveness in treating lung cancer. To the best of our knowledge, surgical resection rate (SRR) for a whole nation has never been reported before. We studied the SRR and surgical outcome of NSCLC patients in Iceland during a recent 15-year period.

Methods: This was a retrospective study of all pulmonary resections performed with curative intent for NSCLC in Iceland from 1994 to 2008. Information was retrieved from medical records and from the Icelandic Cancer Registry. Patient demographics, postoperative tumor, node, metastasis stage, overall survival, and complication rates were compared over three 5-year periods.

Results: Of 1530 confirmed cases of NSCLC, 404 were resected, giving an SRR of 26.4%, which did not change significantly during the study period. Minor and major complication rates were 37.4% and 8.7%, respectively. Operative mortality rates were 0.7% for lobectomy, 3.3% for pneumonectomy, and 0% for lesser resection. Five-year survival after all procedures was 40.7% and improved from the first to the last 5-year period (34.8% versus 43.8%, $p = 0.04$). Five-year survival for stages I and II together was 46.8%, with no significant change in stage distribution between periods. Five-year survival after pneumonectomy was 22.0%, which was significantly lower than for lobectomy (44.6%) and lesser resection (40.7%) ($p < 0.005$). Unoperated patients had a 5-year survival of 4.8%, as compared to 12.4% for all the NSCLC patients together.

Conclusion: Compared with most other published studies, the SRR of NSCLC in Iceland is high. Short-term outcome is good, with a low rate of major complications and an operative mortality of only 1.0%. Five-year survival improved significantly over the study period.

Key Words: NSCLC, Resection rate, Outcome, Complications, Survival.

(*J Thorac Oncol.* 2012;7: 1164–1169)

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Disclosure: The authors declare no conflict of interest.

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ISSN: 1556-0864/12/0707-1164

Lung cancer is the leading cause of cancer-related deaths in the western world.[1] In Iceland, the mortality from lung cancer is similar to that of breast, prostate, and colon cancer combined, and non–small-cell lung cancer (NSCLC) accounts for about 85% of lung cancer cases.[2] Although surgical resection is still the only well-defined curative treatment for NSCLC, it is only possible for the one third of patients diagnosed with stage I or stage II disease and for selected cases of stage IIIA disease.[3,4,5]

Surgical resection rate (SRR) is one measure of effectiveness in treating NSCLC, for example, in a particular geographic location. SRR has varied considerably, often ranging from 15% to 25% in European studies,[6–9] and it was 29% in a study including more than 700 hospitals in the United States.[5] However, smaller single-institution studies from the United States have found SRRs of up to 37%,[10] and there have been studies from Europe that show SRRs as low as 10%.[6,11–13] None of the previously published studies have found an SRR for a whole nation. The same applies to outcome analysis of surgical treatment of NSCLC. Numerous authors have reported short-term complications and long-term survival for lobectomies, pneumonectomies, and lesser resections separately, with only a few of the studies analyzing all the different procedures together. In these studies, the combined rate of major complications has been around or over 10%,[14–16] and operative mortality has ranged from 1.5% to 7%.[5,8,14,17–19] For pneumonectomies, the figures were often double these values.[14–16]

The aim of this study was to investigate the SRR for the whole nation of Iceland using centralized databases in the country. Another aim was to determine surgical outcomes for the different lung procedures that were performed with curative intent in NSCLC patients in Iceland as a whole.

MATERIALS AND METHODS

This was a retrospective study of all patients in Iceland who underwent pulmonary resection with curative intent for NSCLC from January 1, 1994 to December 31, 2008. Exploratory-only thoracotomies, palliative procedures, and lesser resections for biopsy purposes were excluded.

A central, computerized histology database from the Department of Pathology of Landspitali University Hospital, containing details of all lung histology specimens in Iceland was used to identify cases. To minimize the risk of cases being

missed, we also reviewed the diagnosis and operation registry at Landspitali University Hospital, the only center performing cardiothoracic surgery in Iceland.

We obtained information on all cases with a histologically confirmed diagnosis of primary NSCLC from the Icelandic Cancer Registry.[2] This registry covers all cancer cases diagnosed at hospitals and other healthcare facilities in Iceland since 1955. SRR was calculated by dividing the number of all pulmonary resections with curative intent for NSCLC by the number of all histologically confirmed cases of NSCLC within the same period. One hundred and thirty-three patients (6.6% of all patients with a lung cancer diagnosis) did not have a histologically confirmed diagnosis, and 306 patients had small-cell carcinoma. These two groups were excluded from the NSCLC group that made up the denominator for the calculation of SRR. We also excluded patients with carcinoid tumors (n = 38), sarcomas, and carcinoma in situ.

Baseline demographic information and clinical data were collected from hospital charts and surgical reports using a standardized data sheet. Age, comorbidities, and presenting symptoms were collected along with data regarding the type of operation, tumor, postoperative tumor, node, metastasis (TNM) stage, complications, and survival.

Patients being considered for pulmonary resection had been reviewed by a multidisciplinary tumor board including thoracic surgeons, pulmonologists, oncologists, radiologists, and pathologists. The preoperative workup varied between patients, but usually included a chest radiograph, a computed tomography (CT) scan of the chest, upper abdomen and head, and also bone scintigraphy and spirometry. Preoperative biopsies were obtained through bronchoscopy or transthoracic CT-guided needle biopsy. Mediastinoscopy was performed preoperatively in a proportion of the cases, but positron emission tomography (PET) scan has never been available in Iceland.

Patients were staged postoperatively (pathological stage, pTNM) using both the 6th and the 7th edition of the TNM staging system,[20] but data is primarily reported for the 6th version. Preoperative clinical staging (cTNM) was not performed uniformly and is not reported in this study.

All surgical procedures were performed in general anesthesia with double lumen intubation and thoracic epidural anesthesia. The operations were performed by six surgeons using standardized techniques with intraoperative lymphadenectomy of enlarged hilar or ipsilateral mediastinal lymph nodes, but during the last 5-year period these lymph nodes were routinely removed or sampled. A posterolateral thoracotomy was most often performed, but during the last 5-year period an anterolateral approach was used.

Major complications were defined as reoperation for bleeding, heart failure, acute respiratory distress syndrome, myocardial infarction, empyema, stroke, and bronchopleural fistula. Minor complications were defined as air leakage for more than 7 days, pneumonia, intraoperative bleeding of more than 1 liter, atrial fibrillation/flutter, wound infection, and recurrent laryngeal nerve paralysis. Operative mortality was defined as death occurring within 30 days of surgery. To assess trends, the 15-year study period was divided into three 5-year periods.

Statistics

Microsoft Excel was used for descriptive statistics, and R version 2.10.1 for survival calculations. Student's t test, Fisher's exact test, and the χ^2 test were used to compare groups, and differences were considered to be statistically significant when the p value was less than 0.05. Overall survival (OS) was analyzed by the Kaplan-Meier method, and the log-rank test was used to compare survival between groups. All patients were followed up with respect to survival by using data from the Icelandic National Population Registry.[21] In this way, patients could be assigned a date of death or were identified as living on July 10, 2010. Mean follow-up time was 49 months (range, 0–194 months).

The study was approved by the Icelandic National Bioethics Committee and the Data Protection Authority. As individual patients were not identified, individual consent was waived.

RESULTS

There were 1530 histologically confirmed cases of NSCLC during the 15-year period, of which 404 underwent surgery (397 patients). The SRR was 26.4% and did not change significantly between the three 5-year periods (28.2%, 24.3%, and 26.8%, respectively; Table 1). The surgical procedures consisted of 297 lobectomies (73.5%), 60 pneumonectomies (14.9%), and 47 lesser resections (11.6%).

The mean age of patients who underwent surgery was 65.9 years; those in the pneumonectomy group were 6 years younger on average than those in the lesser resection group (Table 2). Over 95% of the patients were current or previous smokers, and many of them had reduced pulmonary function. A history of coronary artery disease and chronic obstructive

TABLE 1. Evaluation of Trends From 1994 to 2008 for Patients in Iceland Who Underwent Surgical Resection With Curative Intent for NSCLC, Divided into Three 5-Year Periods

	1994–1998 (n = 124)	1999–2003 (n = 119)	2004–2008 (n = 161)	All Periods (n = 404)
Male sex	66 (53.2)	60 (50.4)	85 (52.8)	211 (52.2)
Mean age	64.4	65.4	67.1	65.8
Age > 69 years	46 (37.1)	48 (40.3)	74 (46.0)	168 (41.6)
Surgical resection rate (SRR), %	28.2	24.3	26.8	26.4
Adenocarcinoma histology	67 (54.0)	64 (53.8)	103 (64.0)	234 (57.4)
Incidental diagnosis	40 (32.8)	38 (31.9)	61 (37.9)	139 (34.6)
Mediastinoscopy performed	11 (8.9)	21 (17.6)	25 (15.5)	57 (14.1)
Stage I or II disease	98 (79.0)	94 (79.0)	126 (7.83)	318 (78.7)
Pneumonectomies	16 (12.9)	18 (15.1)	26 (16.1)	60 (14.9)
5-year survival, %	34.8	40.6	43.8[a]	40.7

The numbers of patients are given with percentages in parentheses, except for age, surgical resection rate, and survival, where mean and percentage are given.
[a]Statistically significant difference between groups ($p < 0.05$).
NSCLC, non–small-cell lung cancer.

TABLE 2. Patient Demographics and Comorbidities in Patients in Iceland, Who Underwent Surgical Resection With Curative Intent for NSCLC, 1994 to 2008

	Lobectomy (n = 297)	Pneumonectomy (n = 60)	Lesser Resections (n = 47)	All Procedures (n = 404)
Male sex	148 (49.9)	42 (70.0)	21 (44.7)	211 (52.2)
Age, years (range)	65.9 (37–89)	62.7 (45–83)	69.1 (43–84)	65.8 (37–89)
History of smoking	285 (96.0)	59 (98.3)	46 (97.9)	390 (96.5)
COPD	73 (24.7)	14 (23.3)	19 (40.4)[a]	106 (26.3)
FEV1 < 75% predicted	83 (27.9)	20 (33.3)	20 (42.6)	123 (30.5)
Coronary artery disease	72 (24.2)	12 (20.0)	26 (55.3)[a]	110 (27.2)
ASA score, mean	2.6	2.6	2.6	2.6

The numbers of patients are given with percentages in parentheses, except for age and ASA score where means are given.
[a] Statistically significant difference between groups ($p < 0.05$).
NSCLC, non–small-cell lung cancer; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; ASA, American Society of Anesthesiologists.

pulmonary disease was significantly more common in patients who underwent lesser resection than in patients who underwent pneumonectomy or lobectomy. A forced expiratory volume of less than 75% of the predicted value in 1 second was also identified in more patients who underwent lesser resection (42.6% versus 28.9% for the other patients, $p = 0.06$; Table 2).

Adenocarcinoma was the most common histological type of lung cancer (57.4%), whereas squamous-cell histology accounted for 31.7% (Table 3). Squamous-cell carcinoma was more frequent in those who underwent pneumonectomy than in the other patients. As shown in Table 3, almost 87% of the patients had stage I, stage II, or stage IIIA disease, but 13.9% had stage IIIB or IV disease in postoperative staging. The proportion of stage I cases was highest in the patients who underwent lesser resection (78.7%). In Table 4 the stage distribution using the 7th edition of the TNM system is also given. The stage distribution did not change significantly between periods (Table 1). A mediastinoscopy was performed preoperatively in 20 of the pneumonectomies (33.3%), in 36 of the lobectomies (12.1%), and in one of the lesser resections (2.1%).

Almost 9% of the patients had major complications, of which reoperation for bleeding (n = 9), reoperation for empyema and/or bronchopleural fistula (n = 7), heart failure (n = 7), and myocardial infarction (n = 6) were the most common (Table 5). The rate of major complications was significantly higher for the patients who underwent pneumonectomy (18.3%) than for those who underwent lobectomy (7.1%) and lesser resection (6.4%) ($p = 0.01$; Table 5).

Two patients died within 30 days of lobectomy and two others died after pneumonectomy, but there was no operative mortality after lesser resection. Operative mortality for the whole group was therefore 1.0%.

Five-year OS for the whole group was 40.7%. It was significantly higher for the last 5-year period than for the first (43.8% versus 34.8%; log-rank test, $p = 0.039$) (Table 1). Figure 1 shows OS for the different procedures. Survival at 5 years was 44.6% after lobectomy, 40.7% after lesser resection,

TABLE 3. Tumor Histology, Disease Stage (pTNM), and Other Pathological Data for Patients in Iceland, Who Underwent Surgical Resections (Lobectomy, Pneumonectomy, and Lesser Resections) with Curative Intent for NSCLC, 1994 to 2008

	Lobectomy (n = 297)	Pneumonectomy (n = 60)	Lesser Resections (n = 47)	All Procedures (n = 404)
Tumor histology				
Adenocarcinoma	179 (60.2)	22 (36.7)[a]	31 (66.0)	138 (57.4)
Squamous-cell	85 (28.6)	32 (53.3)[a]	11 (23.4)	128 (31.7)
Large-cell	19 (6.4)	3 (5.0)	1 (2.1)	23 (5.7)
Other (including adenosquamous)	13 (4.3)	3 (5.0)	4 (8.5)	20 (5.0)
Disease stage (pTNM)				
I	179 (60.2)	8 (13.3)[a]	37 (78.7)	224 (55.4)
II	59 (19.9)	27 (45.0)[a]	8 (17.0)	94 (23.3)
IIIA	19 (6.4)	9 (15)	2 (4.3)	30 (7.4)
IIIB	22 (7.4)	13 (21.7)	0	35 (8.7)
IV	18 (6.1)	3 (5.0)	0	21 (5.2)
Mean size of tumor, mm (range)	39 (4–190)	57 (20–150)	23 (8–50)	40 (4–190)
Positive surgical margins	27 (9.1)	7 (11.7)	9 (18.8)	43 (10.6)

The numbers of patients are given with percentages in parentheses, except for tumor size where means with range are given.
[a] Statistically significant difference between groups ($p < 0.05$).
TNM, tumor, node, metastasis; NSCLC, non–small-cell lung cancer.

TABLE 4. Overall 5-Year Survival According to Both the 6th and 7th Edition of the TNM Staging System for Patients in Iceland With NSCLC Who Underwent Surgical Resection With Curative Intent, 1994 to 2008

TNM Stage	6th Edition (*n*)	Survival at 5 Years (%)	7th Edition (*n*)	Survival at 5 Years (%)
I	224	55.3	194	58.1
II	94	26.6	128	29.4
IIIA	30	19.9	61	22.1
IIIB	35	23.8	3	NA[a]
IV	21	7.1	18	5.4
I + II	318	46.8	322	46.7
III + IV	86	18.4	82	17.8

[a] Only three patients, calculations therefore not available.
NA, not available.

and significantly lower (22.0%) after pneumonectomy (p = 0.006). The NSCLC patients who did not undergo surgery had a much less favorable survival: only 4.8% after 5 years. Survival for all NSCLC patients together was 12.4% at 5 years, but 46.8% for stages I and II together for the operated patients. Survival for the different stages is shown in Table 4 and Figure 2.

DISCUSSION

Our results show that the SRR for NSCLC in Iceland (at 26.4%) is higher than in other European studies, where SRR has usually been reported to be in the 15% to 25% range.[6–9] To the best of our knowledge, this is the first report of SRR for a whole nation. Short-term outcome for all procedures was excellent, with low rates of major complications and an operative mortality of only 1.0%; other studies have found figures between 1.5% and 7%.[5,8,14,17–19]

The rate of major complications was 8.7%, which is low compared to other studies. However, comparisons between studies can be difficult because of the different criteria used. In the study by Myrdal et al.[14] the rate of major complications was 8.8%, and it was 12.4% in the study by Yano et al.[15] In another study, the major complication rate was 13%, but the authors' definition of major complications was wider than that in the present study.[16]

Five-year survival in this study was 40.7% for the whole study period and it improved from 34.8% during the first 5-year period to 43.8% for the last 5-year period (p = 0.04). Survival figures from other studies have ranged from 30% to 60% at 5 years,[10,22–24] and from around 50% to 60% for patients with stage I and II disease, which are somewhat higher than observed for stage I and II patients in our study, or 47%.[20]

Few studies evaluating surgical outcomes of NSCLC have included all three types of operations. In this study, survival after lesser resection was similar to that after lobectomy, even though a higher proportion of patients in the lesser resection group had underlying cardiopulmonary disease. There was, however, a higher proportion of patients with stage I disease in the lesser-resection group. The low complication rate and low mortality rate in the lesser-resection group raises the question of whether some of these patients could have

TABLE 5. Minor and Major Complications in Patients in Iceland Who Underwent Different Lung Operations With Curative Intent for NSCLC, 1994 to 2008

	Lobectomy (*n* = 297)	Pneumonectomy (*n* = 60)	Lesser Resections (*n* = 47)	All Procedures (*n* = 404)
Minor complications	105 (35.4)	30 (50.0)	16 (34.0)	151 (37.4)
Intraoperative bleeding > 1 l	24 (8.1)	20 (33.3)[a]	0 (0)	44 (10.9)
Atrial fibrillation/flutter	18 (6.1)	15 (25.0)[a]	1 (2.1)	34 (8.4)
Recurrent laryngeal nerve paralysis	5 (1.7)	2 (3.3)	0 (0)	7 (1.7)
Air leakage for > 7 days	63 (21.2)	1 (1.7)	6 (12.8)	70 (17.3)
Pneumonia	16 (5.4)	3 (5.0)	7 (14.9)[a]	26 (6.4)
Wound infection	5 (1.7)	1 (1.7)	2 (4.3)	8 (2.0)
Major complications	21 (7.1)	11 (18.3)[a]	3 (6.4)	35 (8.7)
ARDS	6 (2.0)	3 (5.0)	0	9 (2.2)
Reoperation for bleeding	6 (2.0)	3 (5.0)	0	9 (2.2)
Reoperation for empyema and/or BPF	3 (1.0)	4 (6.7)	0	7 (1.7)
Heart failure	6 (2.0)	0	1 (2.1)	7 (1.7)
Myocardial infarction	4 (1.3)	1 (1.7)	1 (2.1)	6 (1.5)
Empyema	3 (1.0)	3 (5.0)	0	6 (1.5)
Bronchopleural fistula	1 (0.3)	1 (1.7)	0	2 (0.5)
Stroke	0	0	1 (2.1)	1 (0.2)

A patient could have more than one complication. The numbers of patients are given with percentages in parentheses.
[a] Statistically significant difference between groups ($p < 0.05$).
NSCLC, non–small-cell lung cancer; ARDS, acute respiratory distress syndrome; BPF, bronchopleural fistula.

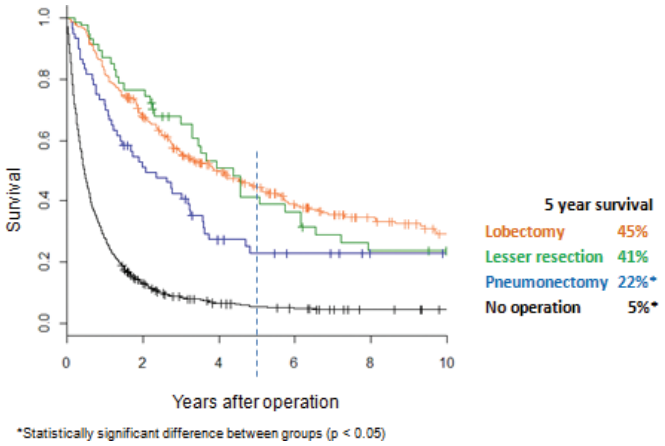

FIGURE. 1. Kaplan-Meier graph showing overall survival of patients with NSCLC who underwent surgical resection (lobectomy, pneumonectomy, or lesser resections) with curative intent in Iceland from 1994 to 2008. Patients who did not undergo surgery are also shown. NSCLC, non–small-cell lung cancer.

tolerated a lobectomy. Alternatively, this could also be an argument for greater use of lesser resections in patients with small tumors. This question is being actively studied, as there is growing evidence that lesser resections are a reasonable approach for small peripheral tumors (of < 2 cm) and also for small ground-glass opacity lesions detected by CT imaging.[25]

As expected, survival after pneumonectomy was significantly lower than after lobectomy and lesser resection. Our result of 22% 5-year survival after pneumonectomy seems disproportionately low when compared to the results of other studies that have shown rates from 27% to 40%.[26–29] The reason for the low survival after pneumonectomy is open to debate, but understaging because of a low rate of mediastinoscopies

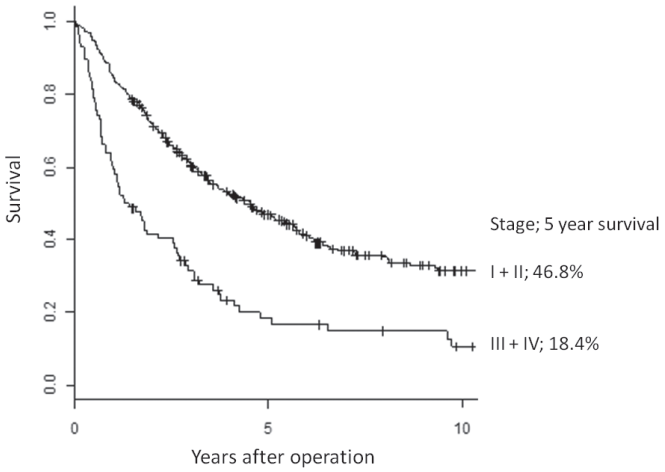

FIGURE. 2. Kaplan-Meier graph showing overall survival of patients with NSCLC, both for stages I and II, and III and IV together, who underwent surgical resection with curative intent in Iceland from 1994 to 2008. NSCLC, non–small-cell lung cancer.

may have had a role. Tumors requiring pneumonectomy are often large and centrally located, and spread more often to the mediastinal lymph nodes, making mediastinoscopy even more important in the workup of these patients.[30] The use of PET scans, which was not available for this patient population, is also known to improve preoperative staging and to prevent unnecessary surgery.

As shown in Table 1, it is unlikely that stage distribution explains improved survival, as it did not change significantly during the study period. A number of advances have been made in the preoperative evaluation and staging of patients with NSCLC in recent years. Improvements in imaging techniques and increased use of mediastinoscopy may have resulted in more patients being excluded from surgical resection because of advanced disease. This could have contributed to the fact that survival improved during the last 5-year period of this study. Improvements in surgical techniques, with increases in the number of cases operated on per surgeon, are also known to play a role.[24] Finally, more frequent use of adjuvant chemotherapy for stage II disease during the last period might also have contributed to improved survival.[31]

This is a retrospective study with the potential bias that it can introduce, problems like lack of a complete preoperative stage and documentation of complications. Furthermore, PET scan was not available in Iceland for staging, and mediastinoscopy was used routinely for mediastinal staging during the last 5 years of the study. The strength of this study is that our cohort consisted of patients from a whole population, all of whom were operated on in a single center. The results were therefore less likely to be affected by tertiary referral.

We have reported resection rate, rates of complications, and survival rates for all patients who underwent surgery with curative intent for NSCLC in the Icelandic population during a 15-year period. In our opinion, these data should be reported together in context to help evaluate the outcome of surgical care for patients with NSCLC. Furthermore, we have reported survival of patients with NSCLC who were not operated on, which is important for comparison.

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