Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences

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Surgical Treatment of Stage I Lung Cancer Patients at St. Olavs Hospital 2008-2018

Master's thesis in Medicine
Supervisor: Øystein Pettersen
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1. Abstract

Background: Lung cancer is in Norway the second most prevalent cancer type, and responsible for the highest number of cancer related deaths in Norway. Lung cancer is divided into four stages based on the TNM system. Patients with Stage I has the best prognosis and is traditionally treated with surgical removal of the tumour with the intention to cure. Improved treatment methods and diagnostics have become more available during the last years and the survival for stadium I lung cancer patients has shown promising trends during the last decades.

Patients and Methods: The aim of the study was to do a quality assurance of patients surgically treated at St. Olav's Hospital in Trondheim from 01.01.2008 – 31.12.2018 (n=587). Only patients preoperatively determined to be Stage I Non-Small Cell Lung Cancer were included. The focus has been on survival after surgery and identifying variables and their role in patient survival, as well as using descriptive statistics to survey changes in patient characteristics, treatment and diagnostics.

Results: The study shows a 30, and 90 – days, 1,3 – and 5-year survival of 99,5%, 98,3%, 94, 6%, 84,8% and 75,1% respectively. For the patients with N0 vs N1/2 disease, there was a 5-year survival difference of 76,4 %(N0) vs 57,1% (N1/2). 12% of all the patients had a pTNM stage >I, this includes 7,8% with positive N1/N2, and 4,2% patients who had a T stadium which exceeded the criteria for stage I.

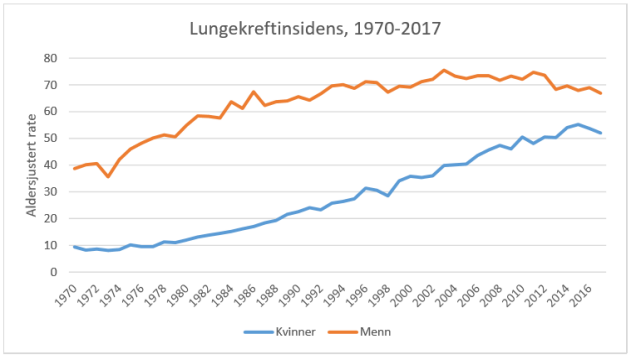
A trend of change in diagnostics and treatment was discovered. The increase in use of PET CT has changed from 27% in 2008 to be used in more than 80% of all cases from 2013. There has also been a change in the use of minimally invasive techniques, in 2008, 100% of the patients were assigned for thoracotomy. In 2018 more than 80% were assigned for thoracoscopy. Parallel to these changes the amount of harvested lymph nodes has also increased. In 2008, 27% patients had zero harvested N2-lymph nodes. In 2018 only 6,4 % of the patients had zero harvested N2 lymph nodes, whereas almost 80% had two or more harvested N2 lymph nodes.

Conclusion: The survival of surgically treated lung patients matches national and international numbers, and both diagnostics and treatment is performed according to national guidelines. There has been changes in diagnostics and surgical procedures at St. Olav's hospital from 2008 – 2018 which has shown that less invasive surgery still seems to provide increased amount of harvested N2- stations.

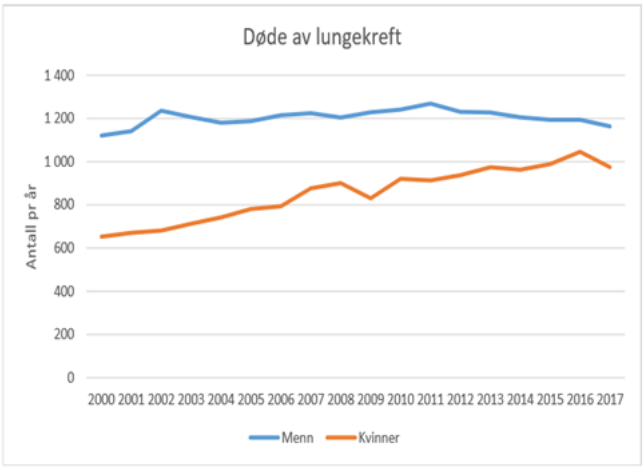
2. Introduction

In 2018, lung cancer was the second most common cancer diagnosis in Norway. It is also the type of cancer responsible for the highest numbers of deaths of all cancer types in Norway. Lung cancer makes up about 10% of all new cancer cases each year, there were 3351 cases of lung cancer in in 2018, and 666 cases of these were “localized disease” (all cases where the tumour is confined to the primary organ)(1, 2). In 2018, 2201 deaths related to lung cancer was registered (3, 4).

From 2009-2013 the prevalence for men was 72,2 cases per 100 000. From 2014 to 2018 the prevalence for men slightly decreased to 67,8 per 100 000. While for women the prevalence has increased from 49,2 per 100 000 in 2009-2013 to 54,5 per 100 000 from 2014 to 2018 (5). On world basis it is estimated that 1,6 million people die every year from lung cancer.



Incidence of lung cancer in Norway from 1970 to 2017 (6).



Figur 2 Antal dødsfall forårsaket av lungekreft i Norge (Dødsårsaksregisteret, 2018)

This graph shows the amount of people dying of lung cancer per year in Norway (6)

Smoking is well established as a dominant factor for the development of lung cancer. In the Nordic countries there is believed that tobacco can be the cause for 80 – 90 % of the cases with lung cancer (7). And the risk of developing lung cancer increases with the number of cigarettes smoked and amount of years smoking (8). Other well-known risk factors for developing lung cancer is radon, asbestos and occupational exposures, as well as both indoor and outdoor air pollution. Indoor air pollution can be a result of solid fuel combustion or environmental tobacco smoking.

If the patient is more than 40 years old and has a history of smoking, combined pathological findings on CT or X-ray, further examination is required. Symptoms like increased coughing or dyspnoea can be early signs, haemoptysis or metastatic symptoms from skeleton, liver, adrenal glands or general B-symptom can indicate a more advanced stage of lung cancer (9). There are also cases where the lung cancer is detected due to findings on x-rays or CT scans of lungs/ abdomen taken in other contexts (10) and the need for a screening program with low dose CT thorax has been discussed (11).

During the last 10 years PET CT has shown to be the best non-invasive method for evaluating lymph nodes and extra thoracic disease among lung cancer patients. The Norwegian guidelines from 2018 recommends that all lung cancer patients with a possible curable diagnosis is examined with PET CT (6).
Further examination of lung cancer patients is based on histopathological findings from biopsy/ cytology of tumour and possible lymph nodes. EUS, TTNA, EBUS-TBNA and FNAC are different methods go get the histological material from the tumour. All of these examinations will help the clinicians give the tumour the right stage according to the cTNM system (12).

The patients physical state pre surgery is important when deciding form of treatment. All patients who are examined for their lung tumour should have a spirometry and a CO-diffusion test done to evaluate their lung function (6). A stair test, the patient's performance status (ECOG), as well as the patient's comorbidities and the patient's own preferences are considered important when deciding treatment. A multidisciplinary meeting will use this information to decide if the patient is surgically operable or if other treatment options should be considered (6).

Possible treatment modalities for lung cancer patients are surgical resection, radiotherapy, and chemotherapy. Combinations of these modalities are also possible. Both diagnostic procedures and lung cancer therapy has changed since the beginning of the millennium. With chemotherapy widely applied since 2000 and the use of PET-CT for staging since 2006. Stereotactic body radiotherapy (SBRT) was introduced at the national level from 2008, and mutational analyses were implemented from 2010. Note that there are variations among hospitals for when these diagnostic tools and new treatments were taken into use. Immunotherapy is believed to have had an impact on the prognosis of lung cancer, but until 2016 only a small number of patients received this kind of treatment. The change in diagnostics and treatment has improved the prognosis for lung cancer patients, as well as increased the costs and resources of the health care system (13).

The standard treatment in Norway for stage I lung cancer has traditionally been surgical removal of the tumour with the intention to cure. The recommended procedure is lobectomy. This is also in line with the European guidelines where surgery is recommended as first choice of treatment (14). Radiotherapy should be considered when the tumour is technically inoperable, or the patient has an excessive surgical risk due to comorbidities.

Sublobar resections is an alternative when the patient's lung function is poor. It's usually considered for individuals who aren't suitable for lobectomies (6).
The use of sublobar resection for T1a tumours are being actively studied in large clinical trials (15). Neoadjuvant or adjuvant radiotherapy can be given before or after surgery if necessary (6).

Other studies have looked at the outcome for nonsurgical approaches such as stereotactic body radiotherapy (SBRT). Studies still show that surgical resections are the primary and preferred approach to treat stage I NSCLC for operable patients (15) (6).

With surgical treatment, video assisted thoracoscopic surgery (VATS) has become the preferred surgical access for stage I-II lung cancer at Norwegian hospitals. If VATS is not possible an anterolateral muscle spearing thoracotomy or a posterolateral thoracotomy can be performed. VATS is considered a minimal invasive technique and has shown to have less negative effect on postoperative lung function and immobilization compared to thoracotomy (6). Studies also suggests that thoracoscopy might be associated with better long-term survival (16). At the same time it is suggested that an increased use of thoracoscopy would lead to a decreased lymph node harvesting. During surgery, resection of hilar and mediastinal lymph

nodes should be performed.
The lymph nodes can either be sampled or dissected. Each station must be precisely marked with which level they are resected from. European society of thoracic surgeons (ESTS guidelines) suggests a systematic dissection of all lymph node stations if possible (6).

The combined histopathological examination of the tumour and lymph nodes determine the pTNM (pathological) stage post-surgery. The pTNM will guide further treatment and estimate prognosis for the patient (12).

The survival for lung cancer patients has for decades been considered poor but later studies suggest a trend of better survival prognosis, with the best survival prognosis for Stage I (17). Studies on survival for Stage I lung cancer was reviewed. Different studies from 1994 to 2016 showed increased survival rates for both men and women diagnosed with stage I lung cancer. These studies will be further reviewed in the discussion part of this study.

With lung cancer being such a prevalent disease with a high mortality (18), this study will focus on investigating the survival and factors contributing to differences in survival of these patients. The group of focus will be Stage I NSCLC patients surgically treated at St.Olav's Hospital in Trondheim from 01.01.2008 to 31.12.2018.

Aims of the study

1) Examine whether survival for surgically treated lung cancer patients at St. Olav's Hospital matches national and international standards.

2) Examine how well preoperative diagnostics (cTNM) is correlating with the postoperative and final staging (pTNM)

3) Examine the trends and developments in disease, patient demographics and treatment from 2008 to 2018

3. Patients and methods

3.1 Study design

The study is performed as a quality assurance with a retrospective review of all patients diagnosed with stage I NSCLC treated surgically at St.Olav hospital from 01.01.2008 – 31.12.2018. The focus has been on survival after surgery and identifying variables and their role in patient survival, as well as using descriptive statistics to survey averages of the patient population. The changes in treatment and diagnostics has also been investigated.
The project was approved by the Local Ethics Comitte (REK) with REK number 119749.

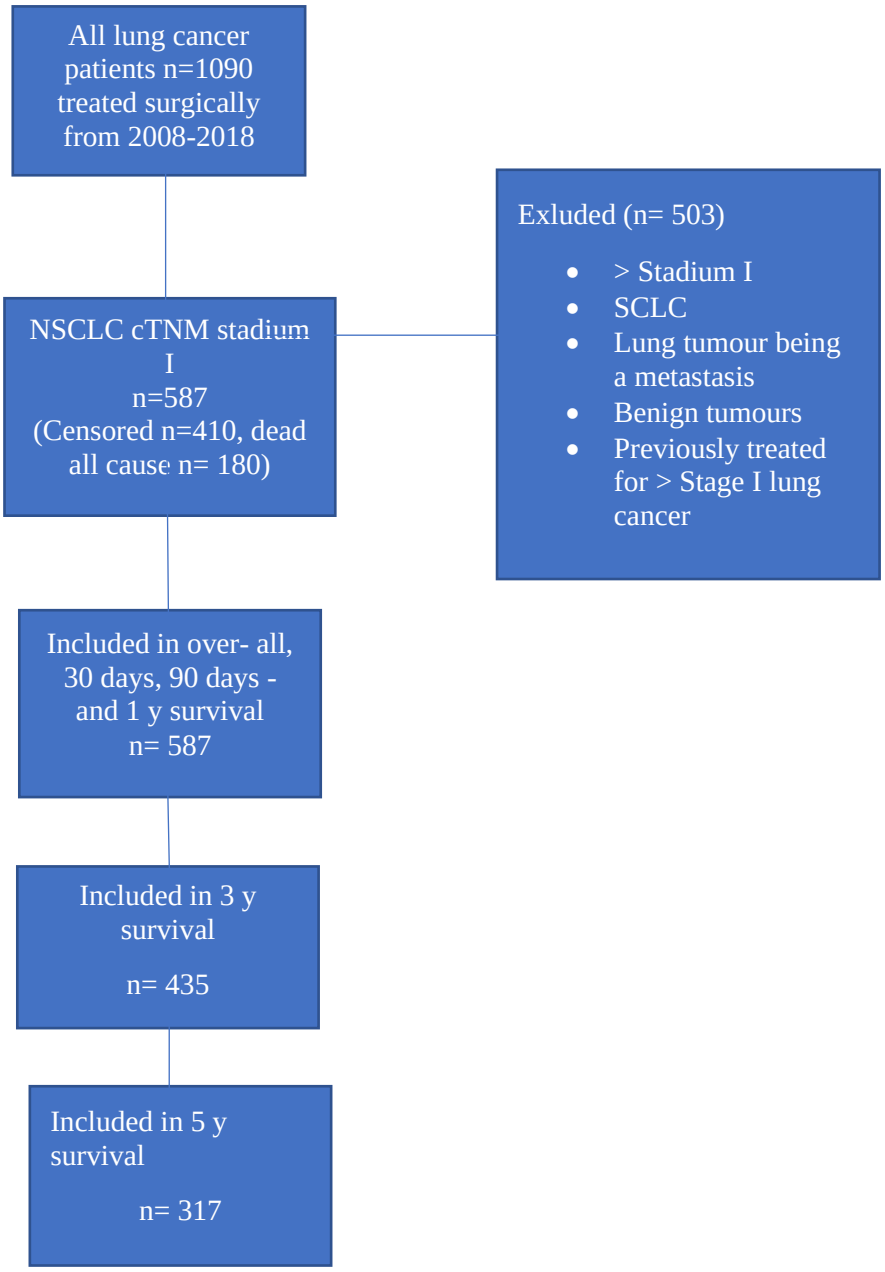
3.2 Material

All patients with NSCLC stage I treated surgically from 01.01.2008-31.12.2018 who matched the criteria for inclusion made a total of 587 patients. Because this study included patients treated until the end of 2018, only patients treated until the end of 2016 were included in the 3-year calculations (n= 435) and for the 5-year calculations only patients treated until the end of 2014 was included (n=317). This study only includes patients treated at St. Olavs Hospital. All patients treated at St.Olavs are a part of Helse-Midt which includes patients examined in hospitals in Trøndelag and Møre & Romsdal (19).

3.3 Patient selection

All patients registered from 01.01.2008 to 31.12.2018 has been registered in databases at the thoracic surgery department. They were first sorted out by their IDC-10 code, which is C34 for lung cancer (20). Patients with tracheal cancer (C33) were excluded.
All patients with the ICD-10 code C34 made a total of about 1090 patients from 2008 to 2018. For further selection, all the patients journals had to be read. cTNM was used to sort out Stadium I cancer patients. If the cTNM showed T>2a, N>0 or M>0 the patient was excluded from the material, no matter what the pTNM was post-surgery. If the cTNM suggested a benign tumour they were also excluded. Other exclusion criteria were SCLC tumours, if the patient had been treated for a > Stadium I lung cancer previously or if the tumour turned out to be a metastasis from another form of cancer.
Some patients were diagnosed and treated for more than one lung cancer during the period - they were only included the first time of treatment. Some patients had another ongoing type of cancer, and some patients had more than one lung tumour at time of surgery, but they were still included in the material.
By using cTNM and not pTNM as a standard for selection, this study can be further used when comparing the survival of surgically treated patients with stereotactic treated patients.

This because pTNM is only discovered in surgically treated patients. But note that the benign tumours were excluded which will be different from a study of stereotactic treated patients, where you do not get a correction on the histology following treatment.



An overview of how the patients for the study were selected

3.4 Variables

The following variables were registered on each patient included in the study: age, gender, place for diagnostics (which hospital), date of diagnosis, which type of diagnostic tool, date of surgery, comorbidity (CCI), former types of cancer, FEV 1%, tobacco, histology, size of tumour, ICD10-code, type of access, type of surgery, cTNM, pTNM, amount of lymph nodes harvested (and affected), place for follow up, the occurrence of metastasis/ recurrence after surgery and date of death.

Time of diagnosis was registered on the date of the multidisciplinary team (MDT). The information about date of surgery, surgical technique, ICD10-code and pTNM was found in the Thorax databases. Detailed information about the post-surgical examination of the tumour and lymph nodes were found in a database from the pathology department. All other information on each patient were obtained from their journals in DocuLive Helse Midt-Norge, with last date for observation 31.12.2018.

The classification system for staging lung cancer has changed from 2008 to 2018. The pTNM of the project is based on the pathological findings of tumour and lymph nodes, and is classified using pTNM 6 (21) for 2008 and 2009, 7 for 2010 to 2015, and 8 (12) from 2016. With these new guidelines, some changes in how the cancer was classified also occurred. The tumour staging (T) changed from T1 (0-3 cm), in the sixth classification to a more accurate staging dividing the T into T1a (1cm), T1b (1-2 cm) and T1c (2-3 cm) in the eight edition of the system. T2 was in the sixth edition 3-7 cm, while in the eight edition it was divided into T2a (3-4 cm) and T2b (4-5cm), here T2b also represented a shift into stage II lung cancer**.** From 2016 a tumour of 40mm or more equals stage II cancer.

3.5 Collection of Data

Specific parameters for each patient were registered in a database first made in the Microsoft Office program Excel. Later the statistical program SPSS (Statistical Package for the Social Sciences) version 26 was used. The variables and parameters were decided together with the supervisors. Descriptive analysis was used to calculate the frequency for gender, amount of smokers, place for diagnostics, N2-stations harvested, former cancer disease, diagnostics, N1/N2 disease, the histology of the tumour, the distribution of surgical techniques done per year, their comorbidity, the numbers of patients with recurrence/ metastasis and the correlation between cTNM and pTNM. Median, maximum and minimums values was used for their FEV1%, age, tumour size and CCI.

Survival was measured as the time interval from the day of surgery to death by all cause or

censoring. The Kaplan Meier survival analysis was used to calculate over-all, 30 – and 90 - days, 1, 3 – and 5-year survival for all groups. Clustered bar charts with years on the x-axis and percentage on the y-axis was also created in SPSS.

4. Results

4.1 Patient characteristics

VARIABLES	NUMBERS	VARIABLES	NUMBERS
Age		**Histology**	
Median (min- max)	68, 6 (27-88)	Adenocarcinoma	62,5%
		SCC	23,5%
		Others	14%
Gender		**Side**	
Male	49,5 %	Left	40%
Female	50,5 %	Right	60%
Amount of smokers		**Access**	
Smokers	82%	Thoracoscopy	46,5%
Non-smokers	8%	Thoracotomy	53,5%
No info	10%		
Hospitals for diagnostics		**Amount of patients treated each year**	n
Trondheim	39,9%		
Orkanger	4%	2008	37
Levanger	16,4%	2009	32
Namsos	2,7%	2010	38
Kristiansund	1,7%	2011	47
Molde	14,1%	2012	48
Volda	5,6%	2013	63
Ålesund	15%	2014	52
Tynset	0,3%	2015	56
Røros	0,3%	2016	62
		2017	74
		2018	78
		Total	587
FV1%		**Postoperative cancer history**	
Median (min- max)	77,5% (35-134)	None	68,1%
		Later cancer, any type	9,3%
		Recurrence/ new primary lung cancer	11,2%
		Metastasis from lung cancer	11,2%
N2-stations harvested		**Type of resection**	
0	20,1%	Lobectomy	89,4%
1	29,6%	Bilobectomy	3%
2-5	50,3%	Pulmectomy	1%
		Wedge resection	5,8%
		Sleeve resection	0,2%
Former cancer		**Multiple lung tumours**	
No	68,8%	No	97,1%
Former/ ongoing cancer any type	31,2%	Multiple lung tumours	2,9%
Diagnostics - PET		**Tumour size**	
Yes	71%	Median (min- max)	24 mm (3-127mm)
No	29%		
N1/N2 disease		**CCI**	
Yes	7,8%	Median (min- max)	5 (2-7)
No	92,2%		
T match		**Stages**	
Yes	68%	Stage I	88%
Upstage	16,6%	>Stage I	12%
Downstage	15,6%		

Table 1:
Patient characteristics for 587 patients surgically treated for Stage I NSCLC from 2008-2018.

Amount of smokers*= Few journals were marked with quantified sizes like "pack-years", so all patients are listed as either YES or NO, not based on the amount or years of smoking tobacco. Former smokers are also included in the "YES"-category. Some patients had no records of smoking in their journals, therefore 11% of the patients have an unknown smoking status.*

Former cancer *= patients with a former or ongoing cancer diagnosis in addition to their lung cancer. The types of cancer included mammae, prostate, vesica, colon, lymphoma, malignant melanoma, KLL, ovary, kidney, adrenal and larynx cancer.*
Histology = *"others" includes large cell carcinoma, carcinoid tumours, neuroendocrine tumours, adenosquamous carcinoma and bronchoalveolar carcinoma.*
Postoperative cancer history *= None: considered cancer free at death or censoring. Later cancer any type: patients who were diagnosed with another type of cancer (NOT lung cancer) during the time post-surgery. Recurrence/ new primary lung cancer: amount of patients experiencing recurrence of the lung cancer or a new primary lung cancer post- surgery. Metastasis: patients who experienced metastasis from their primary lung cancer. This included metastasis to brain, skeleton, adrenals, liver, kidney and the spinal column.*
Multiple lung tumours = *2,9% of the patients had multiple lung tumours at time of treatment. This includes two or more tumours. None of the tumours exceeded a cT > 50mm.*
CCI= *Charlson Comorbidity Scale Index is used with the intention to predict the patient's ten-year survival based on the patients age and comorbidities. For each factor, the patient gets one or two points, and a higher score indicates a decreased 10-year survival prognosis. (22). A score of 5 indicates a 10-year survival of 21%.*

4.2 Survival

Table 2:
30 and 90 -days, 1, 3, and 5-year survival for 587 patients surgically treated for Stage I NSCLC from 2008-2018.

YEAR n	**30 days** % n	**90 days** % n	**1 year** % n	**3 year (08-16)** % n	**5 year (08-14)** % n
2008 (37)	100% (37)	100% (37)	97,4% (36)	83,6% (31)	75,7% (28)
2009 (32)	100% (32)	100% (32)	93,8% (30)	84,4% (27)	71,9% (23)
2010 (38)	100% (38)	100% (38)	100% (38)	78,9% (30)	65,8% (25)
2011 (47)	97,9% (46)	95,7% (45)	85,1% (40)	80,9% (38)	74,5% (35)
2012 (48)	100% (48)	95,8% (46)	93,8% (45)	87,5% (42)	77,1% (37)
2013 (63)	100% (63)	98,4% (62)	96,8% (61)	87,3% (55)	74,6% (47)
2014 (52)	100% (52)	100% (52)	96,2% (50)	88,5% (46)	82,7% (43)
2015 (56)	100% (56)	98,2% (55)	98,3% (55)	83,9% (47)	
2016 (62)	96,8% (60)	96,8% (60)	90,3% (56)	85,5% (53)	
2017 (74)	100% (74)	98,6% (73)	94,6% (70)		
2018 (78)	100% (78)	98,7% (77)	94,9% (74)		
Total (587)	**99,5% (584)**	**98,3 (577)**	**94,6% (555)**	**84,8% (369)**	**75,1% (239)**

Table 2 presents 30, and 90 – days, 1,3 – and 5-year survival of 99,5%, 98,3%, 94, 6%, 84,8% and 75,1% respectively. Over-all survival for the whole material: 69,7%.

4.3 Survival based on variables

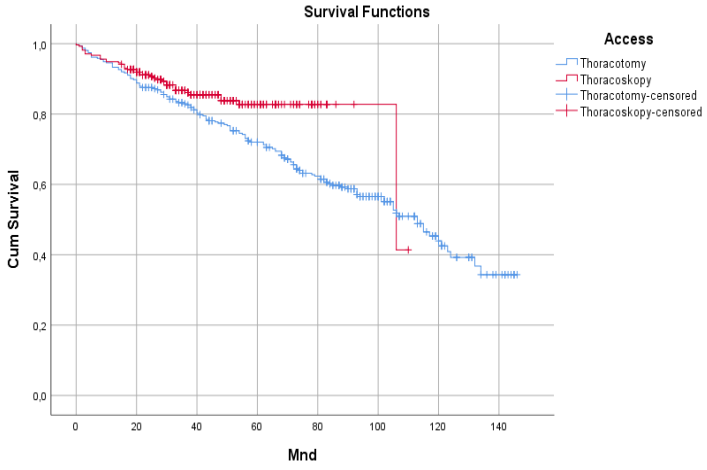
Prognostic factors are variables that can affect the course of the disease and the outcome for the patients. Variables are interesting to survey to see if some groups of patients with certain variables shows a different outcome. The factors are in this study divided into disease, treatment - and patient - related factors. Staging of the cancer (TNM), histology, tumour size, N1/N2 disease and later cancer disease are disease related factors. Treatment factors are diagnostic tools, the type of treatment modalities and types of surgical procedures. Patient factors are gender, age, smoking status and comorbidities.

4.3.1 Survival based on variables - Treatment related

Table 3 *Over-all, 3 – and 5 year survival for based on variables for 587 patients surgically treated for Stage I NSCLC from 2008-2018*

Variable	**Over-all survival (n=587)**				**3 year (n= 485)**	**5 year (n=317)**
Access	**Total (N)**	**Dead (N of events)**	**Alive (N)**	**Survival**	**Survival**	**Survival**
Thoracotomy	313	139	174	**55,6%**	**83,7%**	**72,7%,**
Thoracoscopy	274	39	235	**85,8%**	**87,0%**	**86,8%**
Amount of N2-stations harvested						
0	127	45	82	**64,6%**	**85,6%**	**73,4%**
1	190	66	124	**65,3%**	**84,7%**	**76,0%**
2-4	270	67	203	**75,2%**	**84,4%**	**75,5%**

The graphs below are results of using the Kaplan-Meier survival curve.



Graph 1

Graph 1 shows over-all survival in months for thoracotomy and thoracoscopy.

4.3.2 Survival based on variables – patient related

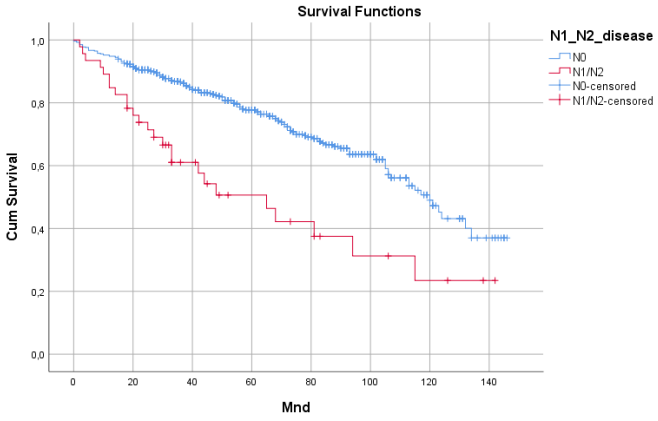
Table 4 *Over-all, 3 – and 5-year survival for based on variables for 587 patients surgically treated for Stage I NSCLC from 2008-2018*

Variable	**Censored**					
	Over-all survival (n=587)				3-year survival (n=485)	5-year survival (n=317)
Gender	**Total (N)**	**Dead (N of events)**	**Alive (N)**	**Survival**	**Survival**	**Survival**
Male	289	104	185	**64,0%**	**79,5%**	**69,8%**
Female	298	74	224	**75,2%**	**90,0%**	**80,4%**
CCI						
2,00	13	0	13	**100,0%**	**100,0%**	**100,0%**
3,00	37	4	33	**89,2%**	**93,3%**	**90,9%**
4,00	124	29	95	**76,6%**	**90,4%**	**85,5%**
5,00	189	56	133	**70,4%**	**85,8%**	**69,5%**
6,00	145	55	90	**62,1%**	**79,6%**	**69,6%**
7,00	79	34	45	**57,0%**	**77,8%**	**69,6%**
Tobacco						
Non-smoker	49	7	42	**85,7%**	**97,4%**	**96,8%**
Smoker	480	153	327	**68,1%**	**83,9%**	**72,6%**
No info	58	18	40	**69,0%**	**80,5%**	**73,9%**

4.3.3 Survival based on variables – disease related

Table 5 *Over-all, 3 – and 5-year survival for based on variables for 587 patients surgically treated for Stage I NSCLC from 2008-2018*

Variable	**Censored**					
	Over-all survival (n=587)				3-year survival (n=485)	5-year survival (n=317)
	Total (N)	**Dead (N of events)**	**Alive (N)**	**Survival**	**Survival**	**Survival**
Affected lymph nodes						
N0	541	153	388	**71,7%**	**86,6%**	**76,4%**
N1/N2	46	25	21	**45,7%**	**61,3%**	**57,1%**
Tumour size						
0-10 mm	46	5	41	**89,1%**	**97,1%**	**92,0%**
11-20mm	192	44	148	**77,1%**	**89,2%**	**77,3%**
21-30mm	223	77	146	**65,5%**	**81,4%**	**73,3%**
31-40mm	73	28	45	**61,6%**	**81,8%**	**73,9%**
41-50mm	40	17	23	**57,5%**	**81,8%**	**62,5%**
>50mm	13	7	6	**46,2%**	**69,2%**	**66,7%**
Later cancer diseas						
None	399	78	321	**80,5%**	**88,9%**	**83,2%**
Later cancer, not lung	55	21	34	**61,8%**	**84,4%**	**81,1%**
Recurrence/ new lung cancer	66	34	32	**48,5%**	**89,5%**	**68,8%**
Metastasis from lung cancer	66	45	21	**31,8%**	**58,5%**	**40,5%**

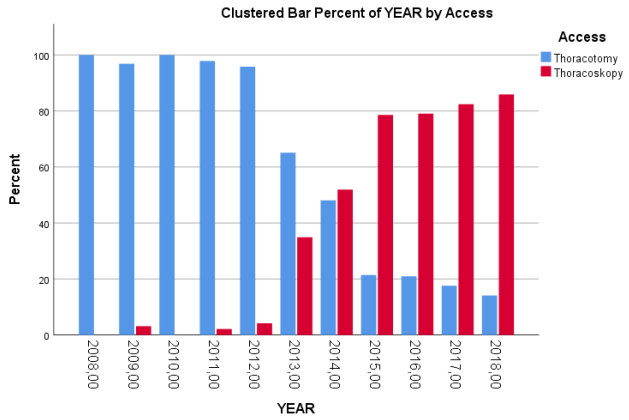


Graph 2
Graph 3 shows over-all survival in months for patients with N0 vs positive N1/N2 status post-surgery.

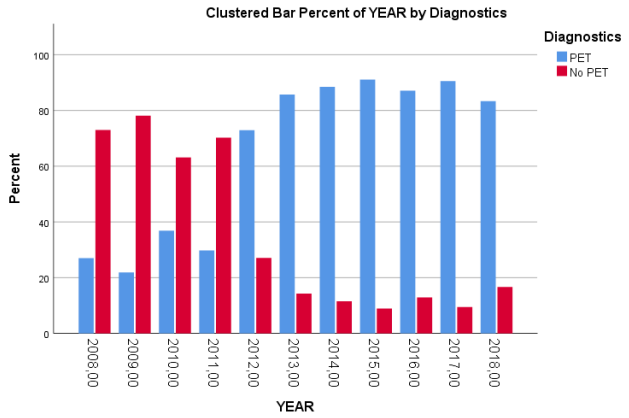
4.4. Treatment

The following bar charts shows the development and changes in treatment for surgically treated lung cancer patients at St. Olavs hospital from 2008 to 2018.

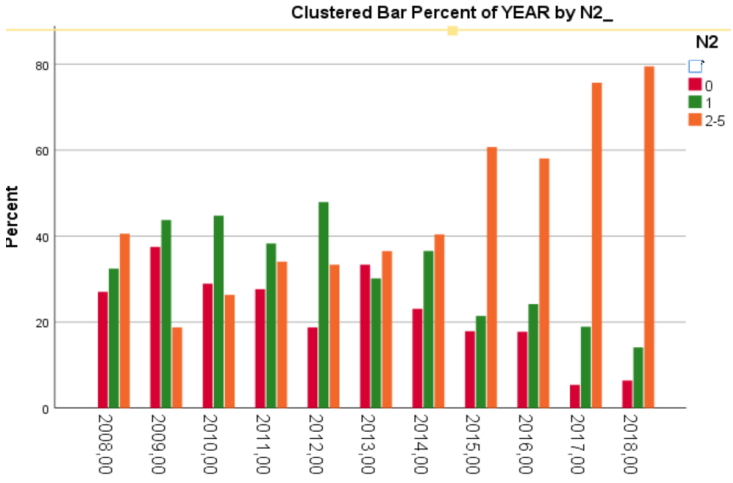
Bar chart 1: *Shows the use thoracoscopy vs thoracotomy in percent per year from 2008 to 2018.*



Bar chart 2: *Shows the use of PET CT in percent per year from 2008 to 2018.*



Bar chart 3: *Shows the percent of N2-lymph nodes harvested per year from 2008 to 2018.*



5. Discussion

5.1 Patient characteristics

Lung cancer is histologically broadly divided in to two main groups: NSCLC – Non-Small Celled Lung Cancer and SCLC - Small-cell Lung Cancer. NSCLC is further divided into adenocarcinoma, squamous cell carcinoma and large cell carcinoma (23). NSCLS represents about 80-85% of all lung cancer diagnoses (24).

The dominating type of NSCLC has previously been squamous cell carcinoma, but the percentage of adenocarcinoma has increased and is now the most common form of all cases of NSCLC in Norway. Squamous cell now counts for 25% of all NSCLC, while adenocarcinoma makes up around 60% of all cases (6).

The ratio of the histological types of NSCLC in this study showed that adenocarcinoma was most common, affecting 62,5% of the patients, SCC counted for 23,5% and 14% were marked as "others". Shown in table 1. These ratios seem to match well with the average distribution of histological classifications found in other studies (6). Studies suggest that a shift from SCC to Adenocarcinoma could be because of differences in smoking habits, as usage of non-filtered cigarettes has decreased substantially over the latest decades (13).

5.2 Survival

5.2.1 Comparing survival with national and international standards

The survival for patients treated at St. Olav's Hospital is presented in **table 2**. The table shows a 30, and 90 – days, 1 – 3 – and 5-year survival of 99,5%, 98,3%, 94, 6%, 84,8% and 75,1% respectively. A summary of the studies mentioned in the introduction and a comparison with our results is created below.

Former studies	**St. Olav's Hospital**
1: St. Olav's Hospital (1994-2001) (25)	
5-year over-all survival: **55,9%**	**75, 1%** 5-year survival
2: Oslo University Hospital (2007-2015) (6, 26)	
1-year cumulative survival: **96%** (IA+IB)	**95,6%** 1-year survival
5-year cumulative survival: **72%** (IA), **62%** (IB)	**75,1%** 5-year survival
3: "Survival among Norwegian cancer patients from 2000 to 2016" (13)	
5-year relative survival men: **50%-75%**	**69,8%** 5-year survival men
5-year relative survival women: **75%-85%**	**80,4%** 5-year survival women

4: “Cancer In Norway 2018” (2014-2018) (27)

5-year relative survival men **59%**	**69,8%** 5-year survival men
5-year relative survival women **69,2**	**80,4%** 5-year survival women

5: American studies (2009-2015) (28) (29)

5-year survival**: 61%.**	**75, 1%** 5-year survival
5-year relative survival for stage IA was **92%**	
5-year relative survival for IB it was **68%**	

These former studies are performed differently with different variables and focus. Study 1, 2 and 3 are investigating surgically treated Stage I NSCLS, while study 4 does not include information about type of treatment. This lack of information is also the case for the American studies. It will therefore be difficult to state something significant concerning our results vs the results from the four studies if the premises are not the same. But there seem to be a trend of matching survival rates when comparing our study with the former studies which could suggest that the treatment methods used at St. Olavs are satisfying.

5.2.2 – Changes in Survival

The 30 and 90 days, 1 year, 3 year and 5-year survival were all analysed with the Kaplan Meier survival analysis from 2008 to 2018 shown in **table 2.** The survival seem quite stable and no prominent deviations between the years was observed. The 3-and 5-year survival includes a smaller amount of patients, which means that the patients treated from 2015 is not included in the five year survival analysis, and the patients treated from 2017 is not included in the three year survival analysis. As many of the diagnostic and surgical changes happened later on in this study, the effect of these changes might not be prominent yet.

5.3. Survival based on variables

5.3.1 How treatment-related variables are affecting the survival

The treatment-related variables were analysed and presented in **table 3.** To investigate if the different surgical access options provided had caused any effect on survival, a Kaplan Meier survival analysis was used. Former studies suggest that minimal invasive techniques could cause a better survival prognosis (28). The 3-year survival showed a difference 87,0% for thoracoscopy vs 83,7% for thoracotomy. The 5-year survival also showed a better prognosis with a survival rate of 86,8% for thoracoscopy vs 72,7% for thoracotomy. The over-all

survival showed a difference for thoracotomy vs thoracoscopy with 85,8% vs 55,6% respectively. This difference is most likely a result of the fact that most of the thoracotomy patients were treated many years before the thoracoscopy patients (shown in Bar Chart 1), and therefore naturally will have a worse survival rate.

Adequate lymph node harvesting is a fundamental part of surgical treatment of lung cancer patients and is believed to could improve the patients survival (30). There were however no clear changes in survival for either over-all, 3-year and 5-year survival based on the amount of N2 stations harvested. This was primarily a study with no expected N1/N2 affection, and the amount of harvested N2 nodes has increased over the years as shown in **Bar chart 3,** so the results might not be that prominent in survival yet.

5.3.2 How patient-related variables are affecting the survival

Kaplan Meier survival analysis shows differences between male and female survival for 3-year, 5 year and over-all survival with 64 % vs 75,2%, 79,5% vs 90%, and 69, 8% vs 80,4% for men and women receptively as shown in **table 4.** Former studies have also showed tendencies of better survival rates for women (13). Differences in male and female survival is multifactorial and complex. WHO suggests that women's longevity advantage becomes most apparent in old age. This may be the result of lower lifetime risk behaviours such as smoking and alcohol use. Alternatively, it may be the effect of harder-to-identify biological advantages that result in relatively lower rates of cardiovascular disease and cancer in women (31)**.**

The CCI (22) prognosis seems to match quite well with over-all and 5-year survival in **table 4** which shows a gradually decreased survival with an increased CCI score. A score of 2 points seem to give a 100% over-all, 3 year and 5-year survival prognosis while 7 points gives an over-all survival of 57% and a 5-year survival of 69,6 %.

For non-smokers/ smokers the over-all and 5-year survival showed a difference in survival between the groups with over-all survival for non-smokers of 85,7% vs 68,1% for smokers. 5-year survival showed 96,8% for non-smokers vs 72,6% for smokers.
As mentioned, tobacco is a clear etiologic factor for developing lung cancer, but many other comorbidities could occur due to tobacco. Examples are increased risk of heart disease, stroke and peripheral vascular disease among others (32). Only 8% of the patients were marked as non-smokers, so the number of patients might not be enough to generalize the answer.

5.3.3 How tumour-related variables are affecting the survival

A higher stage of lung cancer with affected lymph nodes is believed to worsen a lung cancer patients prognosis (29). A total of 46 patient turned out to have affected N1/N2 stations post-surgery. Of these 46 patients 36 turned out to have affected N1 stations and 10 patients turned out to have affected N2 stations. The amount of affected N2 patients were considered small and N1 and N2 patients were therefore combined. For the patients with N0 vs N1/2 disease, there was a difference in survival with an over-all survival of 71,7 %(N0) vs 45,7 (N1/2), 3-year of 86,6% (N0) vs 61,3% (N1/2) and 5-year of 76,4% (N0) vs 57,1% (N1/2). This could confirm that more advanced cancer disease could cause higher mortality.
Note that as this is primarily a study on lung cancer stadium I, all patients with a positive N-staging prior to surgery was excluded from the study. The 46 N1/N2-positive patients makes up 7,8% of the total amount of patients which could make the results somewhat limited.

The size of the tumour could also predict the prognosis. The median tumour size for the material was 24 mm, ranging from 3-127 mm as shown in **table 1**. Studies suggest that a tumour less than 20mm could lead to survival of more than 90%, but a bigger tumour could worsen the prognosis significantly (33). The over-all survival analysis presented in **table 5** shows a change in survival, with a 89,1% survival rate for patients with tumour of 0-10 mm, vs 46,2% survival rate for patients with a tumour >50 mm. This also seem to be the trend in 3-year and 5-year survival as well.

5.4 Examine how well preoperative diagnostics (cTNM) is correlating with the postoperative and final staging (pTNM)

The clinicians try to estimate the cTNM as precise as possible before surgery, still upstaging and downstaging of the cancer diagnosis can occur. This is when there is a discrepancy between cTNM and pTNM. This means that the tumour could be larger/ smaller than expected, or that lymph nodes are affected/ not affected after all. This can affect the prognosis and treatment of the patient. Studies show that upstaging occurs in 14-25% of lung cancer cases (34). The accuracy and availability of the diagnostic tool, and other pre-surgical examinations, as well as changes in how TNM was classified from 2008-2018 can be factors contributing to discrepancy

As **7,8 %** of the patients turned out to have a N1/N2 disease, some of the pre and post-surgical T-stages also showed a difference as shown in **table 1.** 68% of the patients matched

their pre-operative T stadium, while 16,6 % had a tumour larger than expected, and 15,6 % had a tumour smaller than expected. In some of the cases (4,2%) the tumour size exceeded the criteria for stage I cancer. This together with the positive N1/N2 patients showed that a total of **12%** of all the patients had a pTNM stage >I. Discovering upstaging and giving the correct staging post-surgery seem to be one of the advantages with surgery vs non-surgical cancer treatment. With non-surgical cancer treatment, the possibility of discovering pTNM is difficult, and an incorrect staging won't be discovered.

5.5 Trends and changes in treatment

Bar chart 2 shows that in 2008 27% of all patients were diagnosed with PET CT. From 2012 the use of PET gradually increased and was used in more than 80% of all examinations from 2013 until 2018. All patients with curable disease are recommended having PET-CT performed according to guidelines (6).

The number of patients treated with either thoracoscopy or with thoracotomy seems to be quite equal, with 46, 5% for thoracoscopy vs 53,5% for thoracotomy as shown in **table 1.** But **Bar chart 1** shows that there has been a change in the preferred access technique. In 2008, 100% of the patients were assigned for thoracotomy. From 2013 thoracoscopy was used more frequent, and seem to be the preferred procedure during the last couple of years being performed in more than 80% of the surgeries from 2016. Minimally invasive techniques is also the recommended procedure according the Norwegian guidelines (6).

An optimal harvesting of lymph nodes is recommended and is believed to show better results in survival (30). **In Bar Chart 3,** it is shown that in 2008 27% patients had 0 harvested N2-lymph nodes. In 2018 only 6,4 % of the patients had 0 harvested N2 lymph nodes. In 2008 40,5 % of all patients had 2 or more N2- lymph nodes removed. In 2018, 79,5% of all patients had 2 or more N2 nodes removed. It has been suggested that when converting to a minimally invasive technique, the amount of N2-stations harvested would decrease. Interestingly this study shows the opposite, as the amount of N2-stations harvested has increased with the increased amount of thoracoscopy. Whether this translates to an increased survival for patients operated using thoracoscopic procedures is not known. The use of thoracoscopy may also have improved the surgeons skills harvesting lymph nodes, which is likely to transfer to open surgery as well

6. Conclusion

- **The survival rate of surgically treated patients matches national and international numbers on survival**
- **Diagnostics and treatment at St. Olav's is performed according to national guidelines**
- **Despite increased use of less invasive surgery the amount of N2 lymph node stations has increased**

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