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Full title
Survival after resection for primary lung cancer.
A population-based material of 3,211 resected patients

Short title
Survival after lung cancer surgery

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Abstract

Background Very few population-based results have been presented for survival after resection for lung cancer. The purposes of this study were to present long-term survival after resection and quantify prognostic factors for survival.

Methods All lung cancer patients diagnosed in Norway 1993-2002 were reported to the Cancer Registry of Norway (n=19,582). A total of 3,211 patients underwent a surgical resection and were included for analysis. Supplementary information from hospitals including comorbidity data was collected for patients diagnosed 1993-98. Five-year observed and relative survival was analyzed for patients diagnosed and operated 1993-99. Factors believed to influence survival were analyzed by a Cox proportional hazard regression model.

Results Five-year relative survival in the period 1993-1999 was 46.4% (n=2,144); for disease in stage I 58.4% (n=1,375), II 28.4% (n=532), IIIa 15.1% (n=133), IIIb 24.1% (n=63) and IV 21.1% (n=41). The high survival in stage IIIb and IV was due to the contribution of multiple tumours. Cox regression analysis identified male sex, higher age, other procedures than upper and middle lobectomy, histologies such as adenocarcinoma and large cell carcinoma, surgery on the right side, infiltration of resection margins and larger tumour size as non-favourable prognostic factors.

Conclusions The survival was found to be favourable for resected patients in a population-based material, including subgroups such as elderly patients, advanced stage, small-cell lung cancer, tumours with nodal invasion and patients with multiple tumours. These results question the validity of the current TNM system for lung cancer with regard to tumour size and categorization of multiple tumours.

Key words: Lung neoplasm, survival analysis

Word count: 250

Introduction

The increasing incidence and poor survival of lung cancer, also in women and young people, require a reappraisal of the current strategy for diagnosis and treatment [1][2][3]. Patients are often in an advanced stage of disease and resection rates are therefore low. Improvements of surgical outcomes have been sparse but evidence of lower postoperative mortality and slightly increased survival is reported [4][5]. Former reports often originate from single institutions and there are few population-based reports on survival, especially relative survival [6][7][8][9][10].

The population-based cancer registries create a unique platform for studies of risk factors for survival. Traditionally these registries have recorded incidence of various cancers and research has been concentrated on aetiological factors and time trends in incidence. Now the registries are moving toward a trend where evaluation of treatment plays a more central role. This paper adds to a series of publications based on the evaluation of the lung cancer treatment in Norway [11][12]. The purpose of this study was to present relative and observed survival in different subgroups after resection and quantify prognostic factors in a defined population.

METHODS

All newly diagnosed cases of cancer are required by Norwegian law to be reported without patient consent to the Cancer Registry of Norway. Since 1953 the registry has collected information on all cancer patients in the population from clinical and pathology reports. The registry also routinely receives death certificates from The Cause of Death Registry of Statistics Norway. For patients whose clinical or pathology reports were not satisfactory, supplementary reports from the hospital records were requested. Electronic summary discharge files from hospitals have been available from 1998 and were used for quality assurance. Administration of radio- or chemotherapy was reported on clinical reports as "yes" or "no". Supplemental information regarding pre- and postoperative radiotherapy was obtained from the verification systems of the linear accelerators located at the 6 different oncology units in Norway (including two satellite units). For all patients diagnosed from 1993-1998 supplementary information was requested, including details of comorbidity.

We analyzed retrospectively data on all lung cancer patients diagnosed during the period 1993-2002. Cases diagnosed at autopsy or notified with death certificate only were excluded (n=704). Of the remaining 19,582 cases surgical treatment was performed in 3,211 patients and these were studied thoroughly. Twenty patients were operated twice in the period for synchronous or metachronous tumours. Observation was terminated on 31 December 2004. Patients who had emigrated (n=13) were followed up to the date of emigration or to the date of the last consultation after emigration, if known.

Information on treatment, including the date of operation and type of resection performed, was derived from clinical or pathology reports. Supplementary information including operative reports was retrieved from hospitals when the information was found to be incomplete. The survival time was calculated from the date of operation to the last follow-up date.

All cases were re-staged at the Cancer Registry according to pathology TNM (pTNM) by an experienced thoracic surgeon (H.R.) [13]. For synchronous tumours with different histopathology the T-stage of the most advanced lesion determined the T category according to the current TNM system. Only the first tumour was included in analyses in patients with metachronous tumours. The tumour size (largest diameter) as measured by the pathologist was described in 97% of the pathology reports.

Surgery

Surgical procedures were carried out at 27 hospitals by general or thoracic surgeons. The usual procedure was open thoracotomy, but in recent years a few surgeons performed thoracoscopic procedures, mainly for patients with small, peripherally located tumours. When a limited resection of another lobe in addition to a lobectomy was performed, the procedure was classified as a lobectomy only. A limited resection is mainly performed in patients with severe comorbidity, as lobectomy is the standard of care. Tumours that could be diagnosed by a bronchoscope were regarded as centrally located, while others were classified as peripheral, unless the pathology report indicated the opposite.

Statistics

Descriptive analyses of survival were only carried out for patients diagnosed and operated before year 2000 in order to have at least a 5-year follow-up. Cox regression analysis was utilized for all cases.

Univariate analyses were performed with independent samples T-test and Pearson Chi square statistics including Chi Square test for trend. Included in the analyses were age, sex, side of resection, surgical procedure and technique, tumour stage and size, histopathology type and treatment volume expressed by number of resections per year on average of the treating hospital.

Relative survival was estimated using the life-table method [14], and was calculated as observed survival in the patient group divided by expected survival of a comparable group from the entire general population (Norway), matched by current age, calendar time and sex. The life-tables for each sex were obtained from the Statistics Norway, by one-year groups of age and period. The survival rates in each subgroup of patients were thus adjusted for the expected mortality that the group would have from all causes of death.

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Prognostic factors were evaluated both by analysis of crude effects and adjusted for other factors using the Cox proportional hazard regression models [15]. The statistical software SPSS version 12.0 was utilized for descriptive, univariate and multivariate analyses.

RESULTS

There were 2,061 men and 1,150 women who had resection performed. The resection rate was 16.4% for the whole country. Postoperative mortality within 30 days of surgery was 4.8 % (women 2.4%, men 6.1%). Median age was 66 years (mean 64.2, range 8-87 years). In the age group less than 50 years, 54.1% of resected patients were men, increasing to 72.3% in the age group more than 80 years. Synchronous tumours were found in 112 patients, 101 of these were satellite tumours to the index pulmonary tumour.

Adjuvant chemo- or radiotherapy or both were given to 14.2% of resected patients in the period. For 1,837 patients diagnosed 1993-98 information about comorbidity was known, 14,9% had cardiac disease only, 12,6% had respiratory disease only and 3,2% had both. Diabetes mellitus was present in 3.3%.

There was a higher proportion of squamous cell carcinoma in men compared to women, 44% and 23%, while the opposite was true for adenocarcinomas, 33% and 47%, respectively. The proportion of pneumonectomies varied greatly between different centers (range 9.5-45.0%, mean 26.5%, $p<0.001$) and declined throughout the diagnostic period with a rate of 31% in 1993 and 23% in 2002 (p for trend = 0.011). The proportion of pneumonectomies was higher in men as compared to women, 30% and 20%, respectively. Resection by minimal invasive technique was performed in 100 cases, mostly in the later years.

There were more procedures on the right side as compared to the left, 1,752 and 1,459, respectively. In 212 patients the margin was involved or possibly involved. The proportion of involved resection margins was not different between patients operated upon by thoracoscopic or open technique. The overall stage distribution as shown in table 2 was representative for all histologies except bronchioloalveolar carcinomas (BAC) and carcinoids which both had a higher proportion of patients in stage I, 79% and 91%, respectively. Of patients with small cell lung cancer (SCLC) 61% were operated with disease in pStage I.

The mean tumour size was 4.1 cm (range 0.3–16.5) for all cases and it was larger in the lower lobe as compared to the upper lobe, 4.2 cm and 3.2 cm, respectively (p-value <0.001). For 1,835 patients sufficient information was collected to decide the location of the tumour as central or peripheral, 1,120 (61 %) tumours were localized peripherally. Adenocarcinomas and BACs were peripherally located in 74% and 83% patients, respectively, while squamous cell carcinoma and carcinoids had such location in 48%.

Survival

Observed survival at one, three, and five years were 74.4%, 50.9% and 40.9%, respectively (Figure 1). Subgroup analysis with both relative and observed survival for patients diagnosed and operated in the period 1993-1999 is presented in Table 1. There was no trend towards a change in survival throughout the period and the 5-year survival for each diagnostic year varied between 37.9% and 41.2%.

The pneumonectomy procedure was associated with the poorest prognosis, while lobectomies had the highest observed survival (Figure 2). Survival after upper lobectomy was significantly better than after lower lobectomy in multivariate analysis (p=0.017).

According to the principles of the TNM staging system the survival rate should decrease with higher stages (Figure 3). Patients with disease in stage IIIb and IV had a better prognosis than IIIa, but this was not significant. This difference was caused by cases with satellite tumours. Synchronous tumours of same histology in the same lobe are classified as T4 (stage IIIb), while tumours in different lobes are designated M1 (stage IV). When patients with synchronous tumours in the same lobe were analyzed separately (1993-99), they had a 30.0% (95% CI 16.2 – 43.7%) (n=43) observed 5-year survival, while this was 8.0% (95% CI 0.0 – 18.5%) (n=25) for patients with one T4 tumour due to other reasons. Likewise for patients in stage IV, no patients with extra-thoracic metastasis to liver, brain or adrenal gland (n=9) lived more than 5 years (only two patients lived more than 1 year), while patients with synchronous tumours in different lobes (n=35) had a 5-year observed survival rate of 22.9 %.

For patients with nodal stage N0 the 5-year observed survival was 49.3% (n=2,247), for N1 24.0% (n=750) and for N2 13.1% (n=212).

Large tumour size as presented in Table 1 was significantly associated with reduced long-term survival. The corresponding 5-year relative survival rates for patients in stage I were 69.7% (95% CI 65.4 - 74.0), 55.3% (95% CI 49.8 – 60.8) and 36.9% (95% CI 30.4 - 40.3) for tumour size ≤3.0, >3.0-5 cm and >5 cm, respectively.

Cox regression analysis for all patients identified male sex, higher age and stage, other procedures than upper and middle lobectomy, histologies such as adenocarcinoma and large cell carcinoma, surgery on the right side, infiltration of resection margins and larger tumour size as prognostic factors for non-favourable survival (Table 2).

The effect of comorbid disease (classified as presence of cardiac disease, lung disease or diabetes) on survival was analysed with Cox proportional hazard regression in the subset of patients for whom this variable was available (patients diagnosed 1993-1998). Comorbid disease was significantly associated with inferior survival, hazard ratio 1.21 (p=0.001), but when adjusting for this variable the effect of the other independent risk factors were not changed. In particular, the effect of hospital volume was unchanged after adjustment for comorbidity (data not shown).

DISCUSSION

This population-based study of all lung cancer patients resected during a 10-year period in Norway demonstrates favourable long-term survival. Even cases of elderly patients, advanced stage and subgroups with SCLC, nodal invasion (N1-N2) and patients with multiple tumours may be cured with surgery. A high proportion of patients had substantial comorbidity and few received adjuvant treatment.

Norway is a small country with about 4.5 million inhabitants and hospital health services are free of charge. The use of multiple sources of information in the Cancer Registry makes reporting of incidence for various cancers reliable and complete, and it is believed that all new cancers are reported to the registry [16]. We have no exact knowledge of the policy at each hospital in Norway regarding selection of patients for surgery. Similarly, we do not know how the relative contraindications are determined. A decision to offer surgery is generally based on the technical feasibility of resection and evaluation of the patient's comorbidity provided that the patient consents to undergo a surgical procedure.

Relative survival in lung cancer is useful in making comparisons between different series of different origins possible [8]. However, there are few population-based reports on long-term relative survival after lung cancer surgery in the literature and detailed subgroup analyses have not been presented [9] [17]. Some of the hospitals in Norway have presented their survival results which partly- or completely overlap this time period, and hence include the same patients. Their results correspond to ours when stratifying on these hospitals (data not shown) [18][19].

The survival rates in Norway are slightly inferior to those published in other comparable reports [10] [20]. Higher postoperative mortality could explain some of this but the main reason is probably that the patients operated upon are unselected in this population-based material [21].

The poor prognosis after sublobar resection compared to lobectomy, particularly evident in the multivariate analysis, was probably caused by local recurrence and comorbidity [22]. Survival after lower lobectomy was significantly reduced as compared to upper lobectomy in univariate and multivariate analysis of all patients. To the authors' knowledge this finding has not been formerly reported. Involved resection margins were an independent adverse risk factor, confirming findings in other reports [10].

Adenocarcinomas, which are more frequent in women, were identified as a prognostic risk factor for reduced survival; in other studies this effect seems uncertain [23][24][25]. In a previous report we found that 5-year survival was about 45% in patients resected with SCLC, which was remarkable and superior compared to other treatment modalities [12]. This is a highly selected group since few patients present in a limited stage. The favourable survival rates in patients with BAC could be explained by the high proportion in limited stage. This might explain why BAC was not an independent risk factor for survival in

multivariate analysis. Carcinoids, not surprisingly, represent a tumour group with excellent prognosis [26].

Patients with advanced disease should be carefully examined and evaluated with the aim of performing a resection if technically possible. In our unselected series there seems to be a role for surgery in patients with N2 disease, 13.4% lived more than 5 years, although inferior to series with survival as high as 20-26% [27][28]. Also for multiple tumours with same histology the results indicate that surgery is a curative treatment and it may be questioned if they should be categorized as stage IIIb and IV [29].

Tumour size (≤3, >3) seems to be insufficiently accounted for in the current TNM classification system and a 5-centimeter limit has been suggested as a new category [30]. Our data support the conclusion that patients with tumours >5cm have a significantly poorer prognosis compared to those with smaller tumours.

Large hospital volume has been found to give a positive influence on long-term survival [31]. This was not supported in our multivariate model of hospitals performing more or less than 20 procedures per year on average. Similarly, surgeon volume has been shown to play an important role for outcome [32]. At some small volume hospitals in Norway there are high volume surgeons that could interfere with the hospital volume effect. Another source of confusion is the difference in selection of patients at the different centers. Small units may perform resection only in patients without major risk factors for surgery, although analysis of the subset of patients with comorbidity data did not change the absence of hospital volume effect.

In conclusion, we found that in a population-based material there was a favourable long-term survival after lung cancer surgery. Even subgroups with high age, advanced stage, SCLC, nodal involvement and patients with multiple tumours at diagnosis should be operated upon when technically possible because the survival is superior compared to other treatment modalities. These results could therefore stimulate to a more aggressive approach in the selection of patients for surgery.

Table 1: 5-year relative and observed survival, patients diagnosed and operated between 1993-1999, n=2,144

	No. patients	Survival		95% CI of relative survival
		Observed (%)	Relative (%)	
Total	2144	40.6	46.4	[44.0 - 48.8]
Sex				
Female	741	51.7	55.8	[51.9 - 59.7]
Male	1403	34.8	41.0	[38.1 - 43.9]
Age				
< 50	217	55.2	55.9	[49.2 - 62.6]
50-59	421	46.2	47.9	[43.0 - 52.8]
60-69	775	41.1	45.5	[41.6 - 49.4]
70-79	687	33.2	42.9	[38.4 - 47.4]
80-89	44	22.7	41.6	[18.9 - 64.3]
Side				
Left	966	41.5	47.4	[43.9 - 50.9]
Right	1178	39.9	45.6	[42.5 - 48.7]
Surgical procedure				
Upper lobectomy	702	48.8	55.6	[51.5 - 59.7]
Middle lobectomy	60	53.3	61.8	[47.1 -76.5]
Lower lobectomy	473	44.0	51.3	[46.0 - 56.6]
Bilobectomy	202	43.1	49.2	[41.4 - 57.0]
Pneumonectomy	589	26.3	29.5	[25.6 - 33.4]
Sublobar resection	118	39.0	46.3	[35.9 - 56.7]
Surgical technique				
Open thoracotomy	2089	40.4	46.2	[65.4 - 74.0]
VATS	55	47.3	54.2	[39.1 - 69.3]
Resection margin				
Free	1993	42.0	48.0	[45.5 - 50.5]
Involved	142	23.2	26.2	[18.4 - 34.0]
Possibly involved or not described	9	11.1	13.7	[0.0 - 39.0]
Histopathology type				
Squamous cell	804	37.9	44.5	[40.6 - 48.4]
Adenocarcinoma	783	36.1	40.7	[37.0 - 44.4]
Bronchioloalveolar	72	59.7	68.0	[55.1 - 80.9]
Carcinoid	102	94.1	99.0	[94.1 - 103.9]
Small cell	33	42.4	49.3	[29.7 - 68.9]
Large cell	150	36.7	41.5	[32.7 - 50.3]
Other	200	37.5	42.7	[35.1 - 50.3]
pStage				
I	1375	50.8	58.4	[55.3 - 61.5]
1a	559	63.5	71.9	[67.4 - 76.4]
1b	816	42.1	48.9	[45.0 - 52.8]
II	532	25.1	28.4	[24.3 - 32.5]
IIa	122	28.7	32.0	[23.0 - 41.0]
IIb	410	24.0	27.4	[22.7 - 32.1]
III	196	15.8	17.9	[12.0 - 23.8]
IIIa	133	13.5	15.1	[8.6 - 21.6]
IIIb	63	20.6	24.1	[12.5 - 35.7]
IV	41	19.5	21.1	[8.0 - 34.2]
Hospital volume				
< 20	869	41.5	47.8	[44.1 - 51.5]
≥ 20	1274	40.0	45.5	[42.3 - 48.5]
Tumour size				
≤3cm	857	51.6	58.3	[54.6 - 62.0]
>3-5cm	710	37.8	43.7	[39.6 - 47.8]
>5cm	498	25.1	28.9	[24.6 - 33.2]
Unknown	79	44.3	49.9	[37.6 - 62.2]

CI: confidence interval; VATS: Video assisted thoracic surgery

Table 2: Univariate and multivariate analysis of risk factors affecting survival after surgery for lung cancer, patients diagnosed between 1993-2002, n=3,211

		Univariate			Multivariate		
	N	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Sex				<0.001			<0.001
Female	1150	1.00	ref		1.00	ref	
Male	2061	1.56	[1.42 – 1.71]		1.41	[1.28 – 1.56]	
Age				<0.001			<0.001
< 50	292	1.00	ref		1.00	ref	
50-59	670	1.37	[1.12 – 1.67]		1.09	[0.89 – 1.33]	
60-69	1105	1.72	[1.42 – 2.07]		1.45	[1.20 – 1.75]	
70-79	1061	2.23	[1.85 – 2.68]		1.95	[1.62 – 2.36]	
80-89	83	3.11	[2.30 – 4.20]		3.23	[2.38 – 4.40]	
Side				0.33			0.028
Left	1459	1.00	ref		1.00	ref	
Right	1752	1.04	[0.96 – 1.14]		1.11	[1.01 – 1.22]	
Surgical procedure				<0.001			<0.001
Upper lobectomy	1058	1.00	ref		1.00	ref	
Middle lobectomy	82	0.90	[0.66 – 1.23]		1.24	[0.90 – 1.70]	
Lower lobectomy	741	1.17	[1.03 – 1.32]		1.16	[1.02 – 1.32]	
Bilobectomy	298	1.33	[1.13 – 1.57]		1.25	[1.05 – 1.49]	
Pneumonectomy	851	1.98	[1.78 – 2.21]		1.57	[1.39 – 1.78]	
Sublobar resections	181	1.20	[0.98 – 1.47]		1.41	[1.15 – 1.74]	
Surgical technique				0.077			0.91
Open thoracotomy	3111	1.00	ref		1.00	ref	
VATS	100	0.78	[0.59 – 1.03]		0.98	[0.74 – 1.31]	
Resection margins				<0.001			<0.001
Free	2999	1.00	Ref		1.00	ref	
Involved	199	1.82	[1.55 – 2.13]		1.49	[1.26 – 1.76]	
Possibly involved or unknown	13	1.59	[0.88 – 2.88]		1.44	[0.79 – 2.64]	
Histopathology type				<0.001			<0.001
Squamous cell	1167	1.00	ref		1.00	ref	
Adenocarcinoma	1225	1.05	[0.95 – 1.16]		1.44	[1.30 – 1.61]	
Bronchioloalveolar	128	0.64	[0.50 – 0.82]		0.95	[0.73 – 1.24]	
Carcinoid	139	0.09	[0.06 – 0.16]		0.19	[0.11 – 0.32]	
Small cell	51	1.15	[0.83 – 1.59]		1.33	[0.96 – 1.86]	
Large cell	223	1.10	[0.92 – 1.32]		1.33	[1.11 – 1.59]	
Other	278	1.09	[0.93 – 1.28]		1.29	[1.09 – 1.51]	
pStage				<0.001			<0.001
I	2087	1.00	Ref		1.00	ref	
II	749	1.96	[1.77 – 2.17]		1.73	[1.55 – 1.92]	
III	311	2.83	[2.47 – 3.24]		2.32	[2.01 – 2.68]	
IV	64	3.20	[2.46 – 4.16]		2.47	[1.88 – 3.24]	
Hospital volume				0.78			0.48
< 20	1227	1.00	ref		1.00	ref	
≥ 20	1984	0.99	[0.90 – 1.08]		0.97	[0.88 – 1.06]	
Tumour size				<0.001			<0.001
≤3 cm	1295	1.00	ref		1.00	ref	
>3-5 cm	1035	1.49	[1.34 – 1.66]		1.21	[1.08 – 1.35]	
>5 cm	773	2.13	[1.91 – 2.39]		1.62	[1.44 – 1.83]	
Unknown	108	1.41	[1.10 – 1.80]		1.28	[0.99 – 1.64]	

HR: Hazard ratio; CI: confidence interval; VATS: Video assisted thoracic surgery

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Figure legends

Figure 1: Kaplan-Meier survival plot for patients resected for lung cancer in Norway, patients diagnosed between 1993-2002, n=3,211

Figure 2: Kaplan-Meier survival plot for patients resected for lung cancer in Norway according to procedure, patients diagnosed between 1993-2002, n=3,211

Figure 3: Kaplan-Meier survival plot for patients resected for lung cancer in Norway according to stage, patients diagnosed between 1993-2002, n=3,211

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Figure 1: Kaplan-Meier survival plot for patients resected for lung cancer in Norway, patients diagnosed between 1993-2002, n=3,211

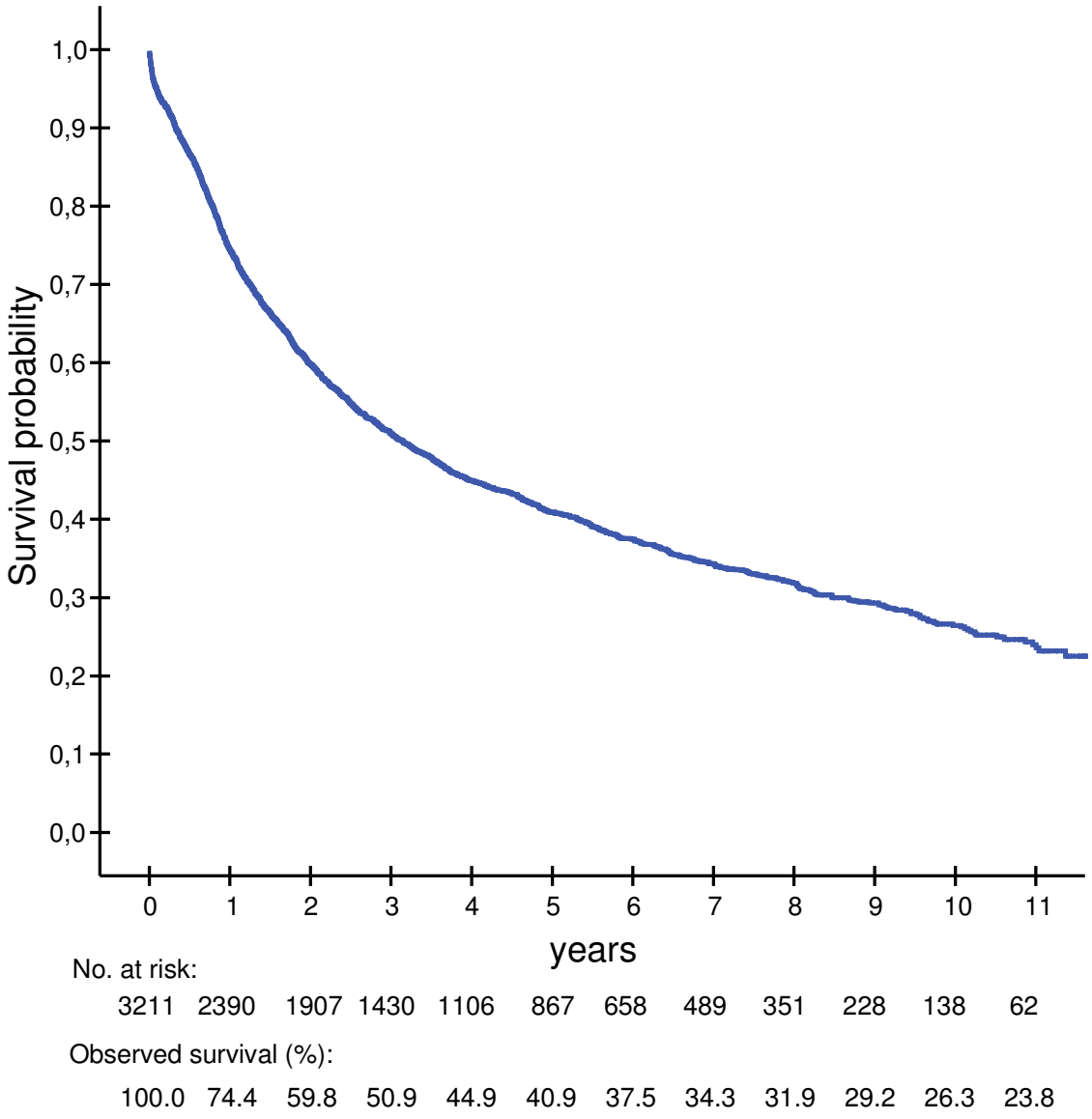

Figure 2: Kaplan-Meier survival plot for patients resected for lung cancer in Norway according to procedure, patients diagnosed between 1993-2002, n=3,211

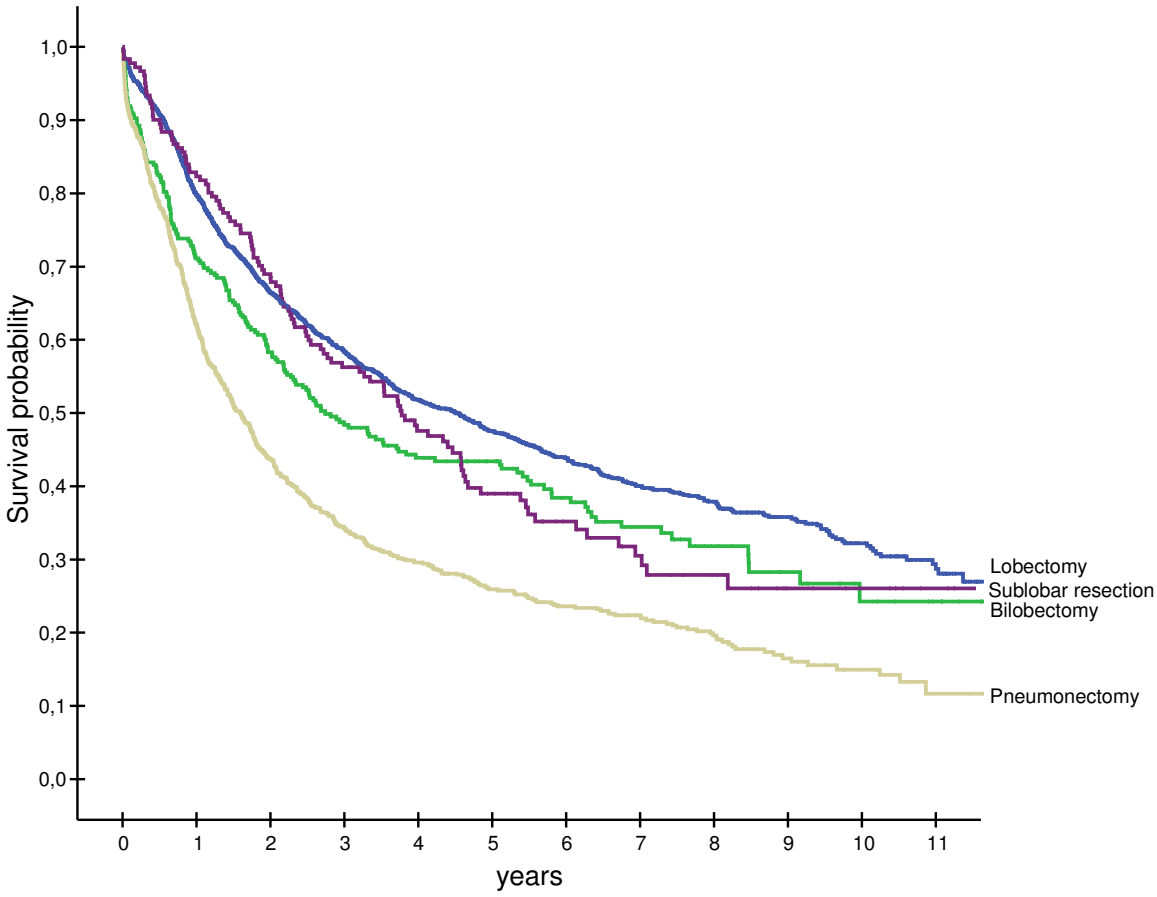

Figure 3: Kaplan-Meier survival plot for patients resected for lung cancer in Norway according to stage, patients diagnosed between 1993-2002, n=3,211