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Age and Prognosis of Non-small Cell Lung Cancer. Usefulness of a Relative Survival Model

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The aim of our study was the comparative evaluation of a relative survival model and a Cox model to determine the prognostic factors of survival for patients with surgically cured non-small cell lung cancer (NSCLC). We focused particularly on the exact role of age in this survival. 156 patients treated between 1975 and 1988 were studied. Both univariate and multivariate analyses were performed, using the actuarial method and the Cox model for crude survival and the Hakulinen model for relative survival. This study confirmed the poor prognosis of NSCLC, even if a curative surgical procedure has been possible, with a 5-year survival of 48% for stage I tumours but only 6% for stage III tumours. The most significant prognostic factor was the postsurgical TNM staging. The relative survival method of Hakulinen dismissed age as a significant prognostic factor. Our study underlines the usefulness of relative survival methods which should be more frequently employed to allow comparisons between series of different origin and to set up multicentre therapeutic trials.
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INTRODUCTION

DURING THE last 10 years, many survival studies of non-small cell lung carcinomas (NSCLC) undergoing surgical resection have been published. Data on prognosis factors of survival were frequently presented using univariate analysis models or, less often, multivariate analysis models. Survival rates were difficult to compare from one study to another because methods of recruitment of the cases were quite different between medical centres, especially regarding the age of the patients [1].

Indeed, for a NSCLC patient the risk of death results from the cancer-related risk of death and from the 'natural' risk of death from any other cause, which increases with age. Two adjusting methods can be used to take into account this 'natural' risk of death in survival analysis. The first one considers only death related to the disease currently studied and calculates the so-called 'net survival'. This method is rarely convenient and leads to underestimates of mortality [2]. The second useful method is 'relative survival', described by Berkson and Gage in 1950 [3] as an age-adjusted survival corrected for normal life expectancy [4]. The relative survival is the ratio of the survival rate of a group of diseased patients to the survival rate of a group of disease-free patients perfectly matched for age and sex. This method does not require any information on the true cause of death [4].

Multiple regression models of relative survival have been recently developed [2, 5] and they have already been used for the study of different types of cancer [6, 7]. Despite this, no clear data has been published so far on relative survival in NSCLC undergoing curative surgical resection. The aim of our study was the evaluation of a relative survival model compared with a Cox model, to determine the prognostic factors of survival for patients with surgically cured NSCLC. We focused particularly on the exact role of age in this survival.

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PATIENTS AND METHODS

Patients

The Pulmonary Diseases Department of the University Hospital of Dijon, France, has treated patients with NSCLC since 1975. This study included all patients admitted in this department who underwent surgery for NSCLC between 1975 and 1988 (n = 204). The department opened in 1975 and the 31 December 1988 was chosen as the end-point of the study because a sufficient follow-up was necessary to analyse survival. Date of point was the 31 December 1990. Criteria for analysis were (1) patients with NSCLC but no other previous personal history of cancer and chosen for surgery when clinical staging of tumours was stage I, stage II or stage IIIA, (2) no contraindications to surgery, e.g. respiratory insufficiency, deleterious clinical status (WHO >1), (3) patients who had undergone complete curative surgery for cancer, (4) patients who did not die within 30 days after surgery (considered as the postoperative period). From the original 204 patients, 48 patients were excluded from the analysis; 10 patients died during the postoperative period and 38 patients had an incomplete resection or a resection margin was involved. Therefore, the remaining 156 patients were the subject of our analysis.

Variables studied were as follows. Age: classified in six periods (less than 49, 50–54, 55–59, 60–64, 65–69 and over 70 years). Sex: male or female. Smoking history: non-smokers, current or ex-smokers. Clinical presentation: patient symptomatic or not. Surgical procedure: lobectomy or pneumonectomy. Postsurgical pathological TNM: all cases have been reviewed and retrospectively classified according to the international 1986 TNM classification [8, 9]. Histopathology: squamous cell carcinomas, adenocarcinomas and other types—undifferentiated and large cell carcinomas. Histology was performed on the whole surgically removed tumour, to decrease the risk of mistyping. Period of surgery: during the 13 years of our study, diagnostic methods have improved with the introduction of routine ultrasound techniques and computed tomography scans during 1984. To test if better selection of patients could have led to better survival, we compared the 1975–1983 and 1984–1988 periods. We must also point out that the same surgical team has been in place throughout the period of our study and that the selection for surgery has not been modified even in the presence of clinically suspected stage IIIA tumours. Data are presented using as the reference class the stratum of best prognosis.

Survival analysis

Univariate analysis. Crude survival rates were calculated by the actuarial method [10, 11]. Univariate crude survival curve comparisons were performed using the log rank test [12]. Relative survival rates for the same variables were calculated using the method developed by Hakulinen *et al.* [13]. Relative survival curves were compared using the maximum likelihood ratio test [13]. Loss in life expectancy for each category of patients was also calculated using the Hakulinen software [14] implemented in the Registre des Tumeurs Digestives de Côte d'Or, Pr Faivre, Dijon, France. Expected survival for our patients was calculated from the baseline probability of survival and life expectancy for the French population provided by sex and age through INSEE (National Institute of Statistics and Economics) [15, 16]. Not all the years from our study were available for use with the Hakulinen software. However, because the general population survival and mortality rates were constant in France between 1975 and 1988 [16], we used the 1981–1983 tables located in the middle period of our study as this has already been done by others during similar studies [6, 7].

Multivariate analysis. Multivariate analysis of crude survival was performed using the Cox model [17, 18]. The significance of the covariates was tested on the change in the log-likelihood at a 5% level, using a forward stepping procedure. As it has been recommended for studying cancer [2], multivariate analysis of relative survival was performed using the Hakulinen method [5] conceived as an additive relative survival model, and considering that the mortality due to cancer was added to the mortality due to other causes. Forward stepwise analysis was performed and significance was tested by the change in the deviance. Proportionality of risks along the studied period was assessed for both Cox and Hakulinen models for each covariate using a graphical method [19].

Variables tested in multivariate analysis were age, sex and all variables significant at the 10% level in univariate analysis. Calculations were performed using the 1L and 2L programs from the BMDP statistical software [20] for crude survival and the Hakulinen software [14], using GLIM software [21] for relative survival.

RESULTS

Population

We studied 150 male and 6 female patients with age ranging from 30 to 78 years (mean 59 years). 152 patients (97%) were smokers or ex-smokers. 98 patients (63%) were symptomatic. Squamous cell carcinomas were the most common tumours (76%); adenocarcinomas were less frequent (20%). Pneumonectomy and lobectomy were performed equally (51 and 49%). The postsurgical TNM pathological staging distribution is presented in Table 1. By 31 December 1990, 116 patients had died, 24 patients were alive and 16 patients were lost to follow-up.

Univariate analysis

Crude survival (*Table* 1). Overall crude survival was 75.8% after 1 year, 53.8% after 2 years, 28.7% after 5 years and 14.4% after 10 years (Fig. 1). Five variables had a significant influence on survival in our population: histopathology, resection procedure, tumour extension (T), node involvement (N) and postsurgical TNM staging. Mediastinal homolateral or contralateral nodes were factors of bad prognosis. Postsurgical TNM staging had a bad prognostic influence with 5-year survival of 42.2, 32.2, 4.2 and 0% for stages I, II, IIIA and IIIB tumours, respectively. The resection procedure modified survival and pneumonectomy had the worst influence on prognosis. Undifferentiated and large cell carcinomas had a significantly poorer prognosis but this had to be taken with caution because of the low number of patients concerned (5 patients). The sex or the time period of the surgical procedure did not influence survival: the 5-year survival was, respectively, 29.4% for men and 16.7% for women (P = 0.7); 29.9% before 1984 and 28.7% after 1984 (P = 0.4). Survival was not shorter in the symptomatic patients. The 1-year and 5-year survivals were not significantly different for the six age groups during univariate analysis.

Relative survival (*Table* 1). Overall relative survival was 77.5% after 1 year, 56.0% after 2 years, 32.5% after 5 years and 18.9% after 10 years (Fig. 1). Variables which were significant during relative survival analysis were the same as for crude survival, except for the resective procedure (P = 0.002 in crude survival, non-significant in relative survival). Survival remained

Table 1. Results of univariate crude and relative survival (n = 156)

	Number of cases	Crude survival 1 year (± SE)	Crude survival 5 years (± SE)	*P* value*	Relative survival 1 year (± SE)	Relative survival 5 years (± SE)	*P* value†	Years of life lost	% of life lost
Age									
30–49	25	72.0 ± 9	22.0 ± 10	NS	72.3 ± 9	23.4 ± 10	NS	22.2	73.0
50–54	31	74.2 ± 8	21.0 ± 9		75.0 ± 8	24.0 ± 9		16.1	69.9
55–59	25	80.0 ± 8	33.9 ± 10		81.0 ± 8	37.2 ± 10		11.5	57.0
60–64	29	86.2 ± 6	35.9 ± 9		88.0 ± 6	40.5 ± 10		8.9	53.1
65–69	27	64.9 ± 9	33.4 ± 10		67.3 ± 10	41.3 ± 11		7.1	53.7
>70	19	77.1 ± 10	18.4 ± 11		82.0 ± 10	27.0 ± 15		5.6	59.2
Patient	(153)								
Symptomatic	98	71.2 ± 5	30.3 ± 5	NS	72.8 ± 4	34.4 ± 5	NS	11.7	63.1
Asymptomatic	55	84.9 ± 5	26.4 ± 7		86.5 ± 5	30.2 ± 7		12.4	61.9
Histopathology									
Squamous cell	119	77.6 ± 3	35.3 ± 5	0.004	79.4 ± 4	40.2 ± 5	0.05	10.1	55.8
Adenocarcinomas	32	75.0 ± 8	9.4 ± 6		76.0 ± 7	11.0 ± 6		17.5	79.0
Others‡	5	40.0 ± 22	0		40.5 ± 22	0		24.3	95.7
Resective procedure									
Pneumectomy	79	69.3 ± 5	20.7 ± 5	0.002	70.7 ± 5	23.3 ± 5	NS	14.8	74.0
Lobectomy	77	82.6 ± 4	36.8 ± 6		84.5 ± 4	42.0 ± 6		9.4	51.5
T									
1	29	88.9 ± 6	44.9 ± 11	$<10^{-3}$	90.7 ± 6	51.3 ± 11	0.03	9.0	48.5
2	105	75.5 ± 4	27.9 ± 5		77.3 ± 4	31.8 ± 5		11.7	61.9
3	14	64.3 ± 13	0		65.5 ± 13	0		19.2	85.7
4	8	50.0 ± 18	0		50.8 ± 17	0		19.4	93.9
N									
0	82	82.5 ± 4	43.4 ± 6	$<10^{-4}$	84.2 ± 4	49.0 ± 6	$<10^{-3}$	9.4	48.1
1	29	81.2 ± 8	22.9 ± 9		83.6 ± 8	26.1 ± 10		12.2	67.4
2	42	59.5 ± 8	3.0 ± 3		60.7 ± 7	3.8 ± 4		17.3	89.8
3	3	66.7 ± 27	0		67.4 ± 22	0		21.9	94.9
TNM staging									
I	79	82.9 ± 4	42.2 ± 6	$<10^{-4}$	84.7 ± 5	47.9 ± 7	$<10^{-3}$	9.2	48.3
II	23	85.7 ± 8	32.2 ± 12		87.9 ± 8	37.0 ± 13		10.3	58.0
IIIA	44	63.6 ± 7	4.2 ± 4		64.9 ± 7	6.2 ± 4		17.5	88.3
IIIB	10	50.0 ± 16	0		50.8 ± 7	0		19.4	94.2

SE : standard error. * Logrank test. † Maximum likelihood ratio test. ‡ Others = undifferentiated and large cell carcinomas.

poorer in undifferentiated and large cell carcinomas as compared to squamous cell carcinomas or adenocarcinomas. Five-year relative survival was, respectively, 47.9, 37.0, 6.2 and 0% for stage I, II, IIIA and IIIB tumours. Compared to stage I, mean relative risk was 1.58 (0.66–3.76) for stage II, 4.28 (2.20–8.34) for stage IIIA and 4.89 (1.75–13.7) for stage IIIB. Age did not influence relative survival.

Loss in life expectancy. Mean life expectancy for a normal population matched for age and sex was 19.21 ± 0.7 years and only 5.50 ± 0.7 years in our patients, corresponding to a loss in life expectancy of 71.4%. Loss in life expectancy was, respectively, 48.3, 58.0, 88.3 and 94.2% for stage I, II, IIIA, IIIB tumours corresponding to 9.2, 10.3, 17.5 and 19.4 years of life lost. Loss in life expectancy was minimal (53.1%) for the 60–64 years group and maximal (73.0%) for the youngest group 30–49 years (Table 1 and Fig. 2).

Multivariate analysis

Cox model of crude survival (Table 2). Sex, age, year of surgical procedure and variables significant at the 10% level in univariate analysis (clinical presentation, histopathology, type of surgery, T, N, TNM staging) were tested in the multivariate

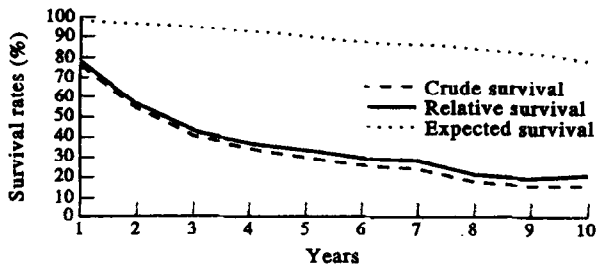

Fig. 1. Crude, relative and expected overall survival rates

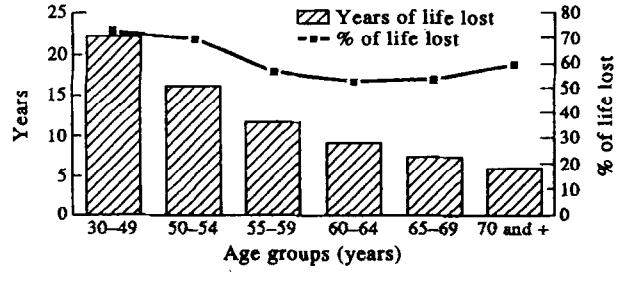

Fig. 2. Life lost (years and % of life expectancy)

Table 2. Multivariate analysis of crude survival — final Cox model (n = 156)

Variables	Relative risk	95% confidence interval	*P* value
TNM staging			
I	1		
II	1.60	0.87–2.94	NS
IIIA	4.16	2.50–6.95	$<10^{-4}$
IIIB	4.16	1.93–9.01	$<10^{-4}$
Histopathology			
Squamous cell	1		
Adenocarcinomas	1.29	0.81–2.06	NS
Others*	3.14	1.11–8.92	0.05
Age			
30–49	1.48	0.76–1.47	NS
50–54	1.28	0.71–2.33	NS
55–59	1.05	0.54–2.03	NS
60–64	1		
65–69	2.18	1.13–4.23	0.04
>70	1.99	0.99–4.00	0.05

NS : not significant. * Others = undifferentiated and large cell carcinomas.

model. We tested both the TNM staging and the T and N involvement. The TNM staging was a better predictor for survival than the more detailed staging with T and N. Age had a bad influence on prognosis only when patients were over 65 years [relative risks were 2.18 in the 65–69 years group ($P = 0.04$) and 1.99 in the >70 years group ($P = 0.05$)]. Histopathology was the third significant prognostic factor. However, this result must be treated with caution because only 5 patients had undifferentiated or large cell carcinomas.

Multivariate analysis of relative survival. The final Hakulinen model is presented in Table 3. Only TNM staging had a significant role in this final model. Histopathology and age were no longer significant.

DISCUSSION

This study confirmed the poor prognosis of our patients with NSCLC despite a carcinologically complete curative surgical resection [22–35]. The 5-year survival of our patients had a maximum value of 42.2% for stage I and was less than 5% for stage III tumours. Overall crude survival of our population was 28.7% after 5 years and 14.4% after 10 years. This was a lower figure than the 5-year overall survivals published in other series: 42% by Benichou who studied 219 patients in a medical centre [22], 39% by Roeslin who studied 645 patients in a surgical department [23] and 48% by Ishida [24]. In agreement with the French series of Benichou [22], our series included an equal number of lobectomies and pneumonectomies. Usually in the literature, lobectomy appears to be the most common procedure. On the contrary, in our series, pneumonectomy was more frequent. These differences in surgical procedure and in survival could be related to higher TNM stages in our series as compared to the literature. Stage IIIA and IIIB tumours represented 35% of our group and only 23% in the French series of Benichou [22]. These differences in recruitment have led us to emphasise again the importance of using multivariate models to report survival factors. The 10 patients who died during the postoperative period represented 6.4% of our patients while this mortality was generally lower in other series: 8% [29], 4.3% [23], 3% [24] and 2.9% [30]. This mortality was possibly related to a heavy surgical procedure because most of the 10 patients had a postsurgical T4 or N3 staging. This early mortality was related neither to age nor to the year of surgery.

Table 3. Multivariate analysis of relative survival — final Hakulinen model (n = 156)

Variables	Relative risk	95% confidence interval	*P* value
TNM staging			
I	1		
II	1.58	0.66–3.76	NS
IIIA	4.28	2.20–8.34	$<10^{-4}$
IIIB	4.89	1.75–13.7	$<10^{-4}$

NS: not significant.

Our results are consistent with published series in terms of histopathology (67–77% squamous cell carcinomas, 16–19% adenocarcinomas, less than 10% undifferentiated and large cell carcinomas) [31]. We did not observe in France and also in our database of 700 patients (1975–1988), the same shift from squamous cell carcinoma to adenocarcinoma as described in the U.S.A. series. Adenocarcinomas in our group represented only 5% in 1975 and reached around 22% during the last years of the study. It is also important to point out that the same team of pathologists had taken care of our patients during the years of our study.

During univariate analysis of prognostic factors, the following variables came out as significant: staging (postsurgical TNM or separately T and N involvement), surgical procedure and histopathology. TNM staging is usually considered as the most important prognostic factor [25–28]. Our series confirmed that using TNM staging (i.e. stage I, II, IIIA and B) was more discriminant than considering separately T and N. As far as surgery is concerned, lobectomy is usually considered to produce a better prognosis than pneumonectomy [23, 24, 29, 30, 31]. The surgical procedure was no longer significant during our multivariate analysis, probably because the choice of the surgical procedure was highly correlated to the suspected clinical T and N. With regard to histology, we confirmed during univariate analysis the poorer prognostic value of adenocarcinomas as compared to squamous cell carcinomas [31, 32], but this was no longer significant during multivariate analysis or in the Hakulinen model. In fact, there was no real difference in relative risk between squamous and adenocarcinoma and, because undifferentiated or large cell carcinomas were too scarce in our study, no firm conclusions could be drawn about the exact role in survival of these histologies. The very bad prognosis of undifferentiated or large cell carcinomas, even in multivariate Cox analysis (relative risk = 3.1), should prompt multicentre studies to evaluate non-surgical and new therapeutic management techniques for these tumours.

Clinical presentation, symptomatic occurrence vs. detection by chance, was never a significant prognostic factor during univariate or multivariate analysis. X-ray detection of lung tumours is considered to be useless at a population range [36] but our result could be a matter for debate. In fact, we studied the impact of clinical presentation only in a group of patients fit for surgery and it is well known that the ability for a tumour to be surgically removed remains the main factor for long-term

survival in lung cancer. Clinical presentation, as tumour bulk, might be of significance for the NSCLC population unfit for surgery but this remains to be demonstrated.

Discussion about prognostic significance of age brings out the real value of relative survival models. Usually, age is considered to have a bad prognostic influence in most cancers. In NSCLC, age could be responsible for a less active surgical attitude. It is important to point out that older patients have a 'natural' lower life expectancy than younger patients. When corrected for the natural mortality of the population, survival of patients with NSCLC, in case of curative surgery, appears to be equivalent in all our age groups, when expressed in terms of loss in life expectancy (Fig. 2). This equivalence of survival, in addition to improved postsurgical management of elderly patients, should lead to a more frequent curative attitude whenever possible in these patients.

It was disappointing to realise that no real progress has been made in terms of survival in the last 15 years despite the real advance of diagnostic techniques. Theoretically, better selection of patients for surgery could have produced better survival. This point of view was not confirmed in our study as the period of surgery corresponding to modified diagnostic procedures never appeared as a significant factor in survival.

Survival of NSCLC relies mainly on the possibility of curative surgery because these types of tumours are only moderately sensitive to radiotherapy and chemotherapy. Obviously, there is a need for more effective neoadjuvant or adjuvant treatments and collaborative protocols because the rate of real cure of those tumours remains extremely low. The use of multivariate models of relative survival should be of increasing importance in comparing results from series of different origins and with different recruitment.

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