ELSEVIER

European Journal of Cardio-thoracic Surgery 21 (2002) 319–325

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

www.elsevier.com/locate/ejcts

Do women live longer following lung resection for carcinoma?☆

Christos Alexiou*, C.V. Patrick Onyeaka, David Beggs, Ruchan Akar, Lynda Beggs, Fayek D. Salama, John P. Duffy, W. Ellis Morgan

Department of Cardiothoracic Surgery, City Hospital, Nottingham, NG5 1PB, UK

Received 19 September 2001; received in revised form 12 November 2001; accepted 19 November 2001

Abstract

Objective: To determine whether patient gender affects the outlook following lung resection for non-small cell lung cancer (NSCLC). **Patients and methods**: Prospectively collected data on 833 patients undergoing lung resection for NSCLC between 1990 and 2000 in a single unit were analysed. **Results**: 581 patients were male (mean age 64.7 ± 7 years) and 252 were female (mean age 62.6 ± 7.8 years) ($P = 0.006$). Male patients were more likely to have a history of ischaemic heart disease ($P = 0.03$), to have poorer preoperative spirometry as demonstrated by their % predicted FEV1 ($P = 0.02$) and to need pneumonectomy ($P = 0.0001$) than their female counterparts. Squamous cell carcinoma was the predominant histological cell type in men and adenocarcinoma in women ($P < 0.0001$). There was a trend towards a lower pathological stage among women, but this was not significant. Operative mortality for men was 4.6 and 1.2% for women ($P = 0.01$). Overall 5-year survival for men was 34.2 ± 2.65% and 47.5 ± 4.2% for women ($P = 0.001$) and, for the hospital survivors, was 36.5 ± 2.7% and 48.1 ± 4.2%, respectively ($P = 0.01$). On univariate analysis, older age, the need for pneumonectomy and higher pathological stage were significant adverse factors whereas squamous cell type and female gender were significant favourable factors for survival ($P < 0.05$). On Cox proportional hazards model (with and without hospital deaths), pathological stage ($P < 0.0001$), female gender ($P = 0.0006$) and squamous cell type ($P = 0.001$) were independent predictors of survival. The survival was significantly better for women having squamous cell ($P = 0.01$) or non-squamous cell cancers (adenocarcinoma and other) ($P = 0.002$). Regarding the stage, women had a significant survival advantage at pathological stage I ($P = 0.01$) and a relatively better survival at stage II and stage III disease ($P = 0.3$). **Conclusions**: This study suggests that female gender exerts a significant positive effect on survival following lung resection for NSCLC. This effect is pronounced at early disease stage and persists after adjusting for important differences in the clinical, histo-pathological features and extent of pulmonary resection between male and female patients. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Lung cancer; Gender; Survival

1. Introduction

Carcinoma of the lung remains a major health problem with an overall 5-year survival of less than 10%. Its prevalence has declined in men but continues to rise in women, being the second cause of cancer-related death in European female population [1] and the most frequent cause of cancer-related fatalities amongst North American women [2].

The identification of factors likely to influence long-term survival following lung resection for carcinoma is of interest to physicians, surgeons and patients alike. Such knowledge may facilitate the process of patient selection for certain forms of treatment, the design of clinical trials and the evaluation of their results.

The link of tumour stage to the long-term survival is well accepted but the impact of other parameters such as age, gender, cell type and extent of the resection is less clear. With regard to the gender, several studies report a better survival in women [3–11].

In light of the increasing number of women with lung cancer entering clinical trials there would seem to be a need to further study the issue of a possible effect of female gender on the late outcome. The inclusion of large numbers of patients in such studies and the analysis of sufficient number of possible predictors of survival using multivariate statistical models are highly desirable.

In this paper we analysed prospectively collected data on patients undergoing pulmonary resection for non-small cell lung cancer (NSCLC) over a 10-year period in a single unit, aiming to ascertain whether female gender affords an advantage for long-term survival.

☆ Presented at the joint 15th Annual Meeting of the European Association for Cardio-thoracic Surgery and the 9th Annual Meeting of the European Society of Thoracic Surgeons, Lisbon, Portugal, Sepetember 16–19, 2001.

* Corresponding author. Tel.: +44-116-2871471.
E-mail address: christosalexiou@hotmail.com (C. Alexiou).

1010-7940/02/$ - see front matter © 2002 Elsevier Science B.V. All rights reserved.
PII: S1010-7940(01)01114-9

Downloaded from https://academic.oup.com/ejcts/article/21/2/319/412867 by ANKARA user on 11 December 2021

2. Patients and methods

Between February 1990 and December 2000, a total of 993 patients with lung cancer underwent exploratory thoracotomy in our unit. In 116 patients (11.4%) the tumour was non-resectable. A variety of pulmonary resections were performed in 876 patients. Ten patients with small cell lung cancer and 33 patients for whom complete follow-up data was not available were excluded from the study.

The remaining 833 patients with NSCLC are the subject of this report. These patients were divided in two groups according to their gender and compared with regard to the demographic, clinical and histo-pathological features, type of pulmonary resection, operative mortality and long-term survival. There were 581 male patients and 252 female patients with a mean age of 64.7 ± 6.9 years and 62.6 ± 7.8 years, respectively ($P = 0.006$).

2.1. Preoperative evaluation

Preoperative evaluation was by means of physical examination, haematological and biochemical investigations, chest X-ray, electrocardiogram, computerised tomography (CT) of the chest and abdomen and brochoscopy. Additional investigations such as liver ultrasound, bone scan and head CT were performed if required on the basis of clinical findings and/or laboratory parameters (e.g. abnormal liver enzymes or serum calcium, skeletal symptoms, hepatomegaly, splenomegaly, lymphadenopathy, abnormal neurological examination etc).

Cervical mediastinoscopy and anterior parasternal mediastinotomy are important diagnostic and staging procedures in patients having mediastinal lymph nodes greater than 1 cm on the CT scan but not all surgeons used them routinely over the study period. Currently they are invariably employed where indicated.

All patients had spirometry and arterial blood gasses. In the patients with borderline predicted postoperative lung volumes a ventilation perfusion isotopic scan, was, also, performed. Exercise tests were carried out if a patient was older than 70 years, had lung volumes less than 60% of predicted value for age and height or had a previous history of cardiovascular disease and/or ischaemic changes on the ECG (Q waves, ST wave depression, left ventricular hypertrophy, complete right bundle branch block, premature ventricular contractions etc). Patients exhibiting an abnormal exercise test, were referred to the cardiologists for further evaluation.

Patients were considered for lung resection if there was no evidence of mediastinal involvement by the tumour or distant metastatic disease and they were deemed as having adequate cardiac reserve and a predicted postoperative FEV1 of at least 1L, as assessed by preoperative spirometry and/or ventilation/perfusion isotopic scan.

2.2. The operation

At operation the aim was to achieve complete clearance of all visible tumour mass with the least possible loss of healthy lung tissues. The hilar lymph nodes were dissected en-block routinely and sampling of the mediastinal lymph nodes was performed as appropriate. Formal mediastinal lymph nodal clearance was not performed. The types of lung resections performed are shown in Table 1. In patients having a pneumonectomy the main bronchus was closed with a stapling device applied to the main bronchus flush with the carina and was left uncovered or covered with a pleural flap depending on the operating surgeons preference. Histopathological analysis was carried out and the tumours were staged using the revised international TNM staging system for lung cancer [12]. Chemotherapy or radiotherapy preoperatively or postoperatively were only occasionally used.

Table 1
Preoperative clinical features and types of lung resections

Parameter	Male	Female	All patients	*P*-value
Age (mean ± SD)	64.7 ± 6.6	62.6 ± 7.8	64.1 ± 6.9	0.006
% Predicted FEV1 (mean ± SD)	76.8 ± 15	80.3 ± 16	77.8 ± 15.4	0.02
% Predicted FVC (mean ± SD)	88.9 ± 14	96 ± 15	91 ± 14.6	< 0.0001
Chronic obstructive airways disease	35 (6%)	17 (6.7%)	52 (6.2%)	0.8
Asthma	31 (5.3%)	16 (6.4%)	47 (5.6%)	0.7
Tuberculosis	12 (2.1%)	8 (3.2%)	20 (2.4%)	0.3
Ischaemic heart disease	88 (15.1%)	20 (7.9%)	108 (13%)	0.006
Hypertension	105 (18.1%)	41 (16.3%)	146 (17.5%)	0.6
Peripheral vascular disease	8 (1.4%)	2 (0.8%)	10 (1.2%)	0.7
Deep venous thrombosis	7 (1.2%)	3 (1.2%)	10 (1.2%)	1
Diabetes mellitus	20 (3.4%)	12 (4.7%)	32 (3.8%)	0.4
No smokers	19 (3.2%)	20 (7.9%)	39 (4.7%)	0.006
Body mass index (mean ± SD)	25.5 ± 3.1	27.2 ± 6.8	26.6 ± 4.1	0.003
Pneumonectomy	248 (42.6%)	71 (28.2%)	319 (38.3%)	0.0001
Bilobectomy	27 (4.6%)	13 (5.2%)	40 (4.8%)	0.9
Lobectomy	257 (44.2%)	137 (54.4%)	394 (47.3%)	0.2
Lesser resections	49 (8.4%)	31 (12.3%)	80 (9.6%)	0.1

Downloaded from https://academic.oup.com/ejcts/article/21/2/319/412867 by ANKARA user on 11 December 2021

2.3. Data collection and follow-up

Patients were seen in the outpatient clinic every 3 months for the first year, every 6 months for the next two years and yearly thereafter. Survival time was calculated from the time of the operation until death or until the end of the study period.

Data was obtained from the thoracic surgery audit database, entered in a prospective systematic fashion by a dedicated Thoracic Surgery Data Manager. Complete survival information (up to death or date last seen) was available for all patients. The mean follow-up was 2.3 ± 1.8 years, ranging between 0 and 10.3 years with a total of 1960 patient years.

2.4. Definitions and statistics

Operative mortality includes deaths within 30 days from the operation or during the same hospital admission irrespective of the length of time elapsed since the operation.

Continuous data are presented as means (±standard deviation) and categorical variables as percentages.

Thirty-one variables (Appendix A) were tested with univariate analysis with the end point being the long-term survival.

Continuous variables were screened with logistic regression, means were compared with unpaired *t*-test and proportions with Chi-square or Fishers exact test as appropriate. The prediction of freedom from late events (±standard error from the mean) was estimated with the Kaplan–Meier product limit method and the resulting curves compared with the log-rank test. The variables attaining a *P* value of less than or equal to 1.0 on univariate analysis, were entered into multiple logistic stepwise regression analysis and Cox proportional hazards regression models. A *P* value of <0.05 was considered statistically significant. Statistical analysis was done using the statistical package SPSS PC (version 8.0) (Chicago, IL, 60611).

3. Results

3.1. Clinical features, types of operations, histology and pathological staging

Male patients were older ($P = 0.006$) and they were more likely to have a previous history of ischaemic heart disease (stable angina requiring medical treatment with or without a previous myocardial infarction) ($P = 0.03$) (Table 1).

In addition, a higher proportion of male patients were smokers ($P = 0.006$) and they had poorer preoperative spirometry as shown by the percent predicted FEV1 ($P = 0.02$), and FVC ($P < 0.0001$) values than female patients (Table 1).

The prevalence of other risk factors and/or co-morbid conditions such as hypertension, peripheral vascular disease, deep venous thrombosis, chronic obstructive airways disease, asthma, tuberculosis and diabetes mellitus was similar in men and women (Table 1).

The most common procedure was lobectomy (47%) but men underwent more pneumonectomies than women ($P = 0.0001$). Bilobectomies, lobectomies and lesser resections (wedge resections or segmentectomies) were evenly distributed in male and female patients (Table 1).

On the histo-pathological examination of the resected specimens, squamous cell type predominated in men and adenocarcinoma in women ($P < 0.0001$) (Table 2).

There was a trend for a lower pathological tumour stage in women but this might have been due to chance alone ($P > 0.05$ for all stages) (Table 2).

3.2. Operative mortality

Overall operative mortality was 4.6% (30 patients). This was significantly higher in men (27 patients, 4.6%) than women (3 patients, 1.2%), ($P = 0.01$). This difference was due to a notably higher operative mortality following pneumonectomy in men (8.1 vs. 1.2%, $P = 0.007$). Early death

Table 2
Tumour cell types and pathological stage

Parameter	Male	Female	All patients	*P*-value
Squamous cell	376 (64.7%)	98 (39%)	474 (56.9%)	< 0.0001
Adenocarcinoma	142 (24.4%)	108 (42.9%)	250 (30%)	< 0.0001
Large cell Ca	32 (5.5%)	19 (7.5%)	51 (6.1%)	0.6
Broncho-alveolar Ca	4 (0.7%)	10 (4%)	14 (1.7%)	0.001
Mixed cell type	11 (1.9%)	10 (3.4%)	21 (2.5%)	0.1
Other	16 (2.8%)	4 (1.6%)	17 (2%)	0.5
Stage Ia	80 (13.8%)	48 (19%)	128 (15.4%)	0.06
Stage Ib	192 (33%)	95 (37.7%)	287 (34.5%)	0.2
Stage IIa	24 (4.1%)	8 (3.2%)	32 (3.8%)	0.6
Stage IIb	188 (3.2%)	70 (27.7%)	258 (31%)	0.2
Stage IIIa	86 (14.85)	28 (11.1%)	114 (13.7%)	0.2
Stage IIIb	11 (1.9%)	3 (1.2%)	14 (1.7%)	0.6

Downloaded from https://academic.oup.com/ejcts/article/21/2/319/412867 by ANKARA user on 11 December 2021

Table 3
Operative mortality by gender according to the procedure

Procedure	Male	Female	Total	P value
Pneumonectomy	20 (8.1%)	1 (1.4%)	21 (6.6%)	0.007
Lobectomy	5 (1.9%)	1 (0.7%)	6 (1.5%)	0.6
Bilobectomy	1 (3.7%)	0 (0%)	1 (2.5%)	1.0
Lesser resections	1 (2%)	1 (3.2%)	2 (2.5%)	0.5
Total	27 (4.6%)	3 (1.2%)	30 (3.6%)	0.01

rates were similar for and men and women following bilobectomy, lobectomy and lesser resections (Table 3).

Causes of death in male patients were pneumonia [4], bronchopleural fistula [4], pulmonary embolism [4], myocardial infarction [4], cardio-respiratory failure [3], adult respiratory distress syndrome [2], ventricular arrythmia [1], empyema and sepsis [1] and peritonitis following unsuspected rupture of gall bladder [1].

Causes of death in female patients were intra-operative haemorrhage [1], pneumonia [1] and complications following exacerbation of pseudemembranous colitis [1].

3.3. Late survival

Overall Kaplan–Meier, survival at 1, 3, 5 and 7 years, including operative mortality, was 69.2 ± 1.7%, 46.9 ± 2, 38.1 ± 2.2% and 30 ± 3%.

Five-year survival for all male and female patients was 34.2 ± 2.6% vs. 47.5 ± 4.2% ($P = 0.001$) (Fig. 1) and for the hospital survivors this was 36.5 ± 2.7 vs. 48.1 ± 4.2%, respectively ($P = 0.01$).

On univariate analysis, higher pathological stage ($P < 0.0001$), pneumonectomy ($P = 0.005$) and older age ($P = 0.03$) were significant adverse factors for survival whereas squamous cell type ($P = 0.01$) and female gender ($P = 0.001$) were favourable factors.

On Cox proportional hazards regression model, higher pathological stage was negative ($P < 0.0001$) and female gender ($P = 0.0006$) (Fig. 1) and squamous cell type ($P = 0.001$) were positive independent predictors of survival. Tumour stage, female gender and cell type remained independent predictors of survival after the hospital mortality was excluded from the analysis.

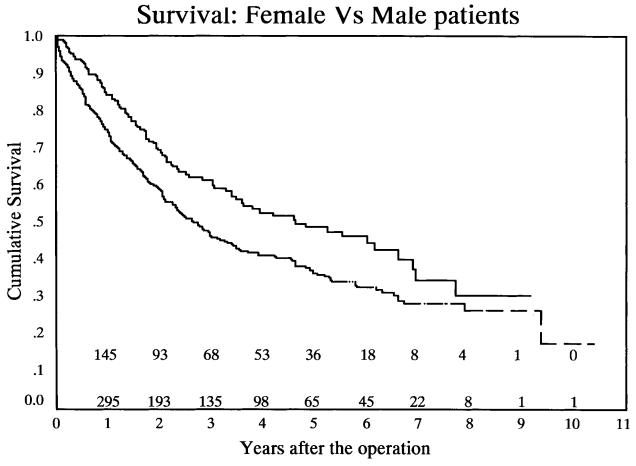


Fig. 1. Five-year survival for all male and female patients was 34.2 ± 2.6% and 47.5 ± 4.2% ($P = 0.001$) on univariate and $P = 0.0006$ on multivariate analysis).

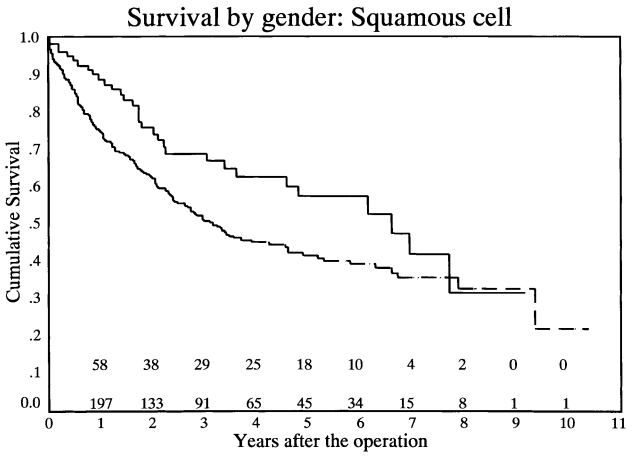


Fig. 2. Five-year survival for women (continuous line) and men (interrupted line) with squamous cell carcinoma was 57.3 ± 6.6 vs. 40.1 ± 3.3% ($P = 0.01$).

Women had a significantly better long-term outcome than men, irrespective of whether they had squamous cell carcinoma ($P = 0.01$) (Fig. 2) or other non-squamous cell type ($P = 0.002$) (Fig. 3).

Compared to men, women had significantly better 5-year survival in the pathological stage I ($P = 0.01$) (Fig. 4) and relatively better 5-year survival at stage II ($P = 0.4$) (Fig. 5) and stage III ($P = 0.3$) (Fig. 6).

4. Discussion

The reported differences in the presentation, management and survival between men and women raise certain ques-

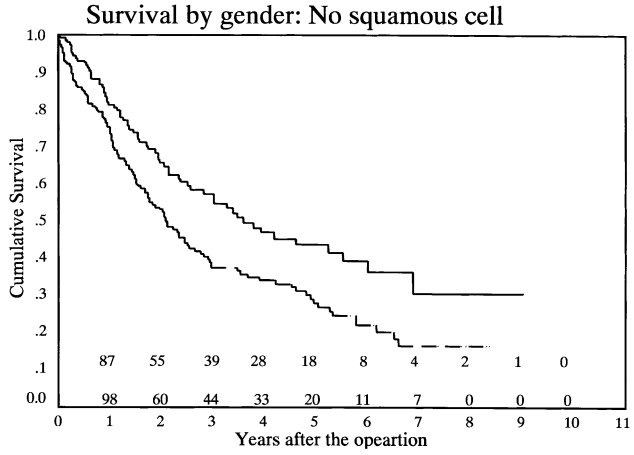


Fig. 3. Five-year survival for women (continuous line) and men (interrupted line) with non-squamous cell type was 43.7 ± 5.3 vs. 24.6 ± 3.9% ($P = 0.002$).

Downloaded from https://academic.oup.com/ejcts/article/21/2/319/412867 by ANKARA user on 11 December 2021

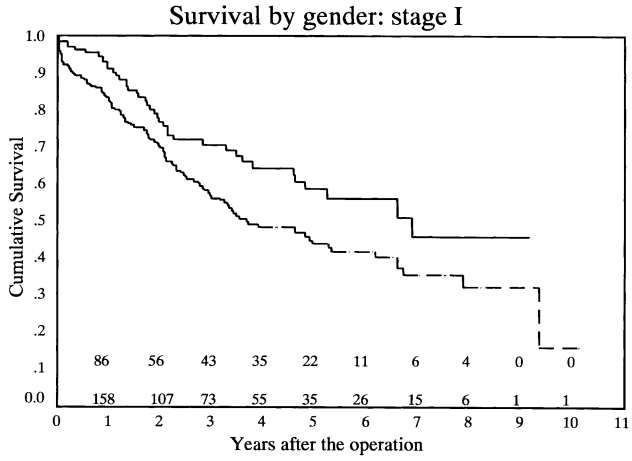


Fig. 4. Five-year survival for women (continuous line) and men (interrupted line) at pathological stage I was 56.4 ± 5.9 vs. 41.9 ± 4% ($P = 0.01$).

tions [3–11]. If women do live longer than men, an improved survival with the modern treatment regimens might simply reflect the increased proportion of women entering the trials [9]. Also, if the natural history of lung cancer in women does differ from that in men, women should, perhaps, have access into other types of treatment [3].

Our study identified notable differences between men and women in demographics, the clinical and histo-pathological features, the type of surgery and the early and late post-operative outcome.

Women were younger, a finding similar to that reported by others for patients undergoing lung resection for carcinoma [3] and in population based studies [13,14]. The reasons for this disparity are not well understood but it has been suggested that women might be more susceptible to the adverse effects of smoking cigarettes and other unknown factors possibly responsible for the lung carcinogenesis [13,14]. In other studies, men and women had similar age [4–7].

In agreement with several previous reports, women were significantly less likely to be active or former smokers [3,4,7,13]. The rate of smoking amongst women in this series (92%) is higher than the 75% reported from Japan [7] and Switzerland [4] and it is similar to 90% reported from the US [3]. These figures may reflect national epidemiological variations and/or the different eras covered in these studies.

The differences in age and smoking habits between men and women may contribute to the higher prevalence of ischaemic heart disease and the poorer preoperative spirometry in our male patients. Information on the preoperative clinical features in previous reports is limited but in one study men had, also, a poorer preoperative spirometry [3].

In keeping with a multitude of previous reports, squamous cell carcinoma predominated in men and adenocarcinoma in women [3–11,13]. Smoking is believed to account partly for this and it has been suggested that sexual hormones may promote the development of adenocarcinoma in women [15].

The propensity of squamous cell carcinomas to grow more centrally would explain the higher proportion of men having a pneumonectomy in our series.

Squamous cell type was as an independent favourable predictor of survival in this study and patients with this histology fared better than the patients having non-squamous type of NSCLC. There is uncertainty regarding the impact of the tumour histology on survival, but where a survival difference was demonstrated this was usually in favour of the squamous cell type [16,17]. Others showed no survival difference on the basis of the cell type [17,18] whereas Ferguson et al have found a superior late survival for patients having adenocarcinomas [3].

The identification of factors predisposing to an early post-operative death is beyond the scope of the present study but older age, higher prevalence of cardiovascular co-morbidity, poorer spirometry and a higher number of pneumonectomies should all account for the higher operative mortality

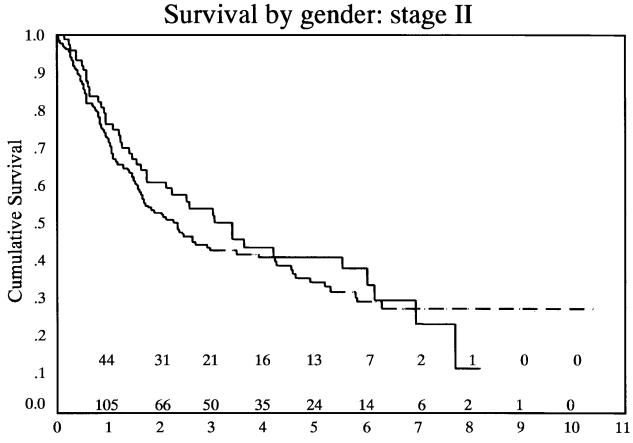


Fig. 5. Five-year survival for women (continuous line) and men (interrupted line) at pathological stage II was 41.3 ± 6.6 vs. 32.1 ± 4.1% ($P = 0.4$).

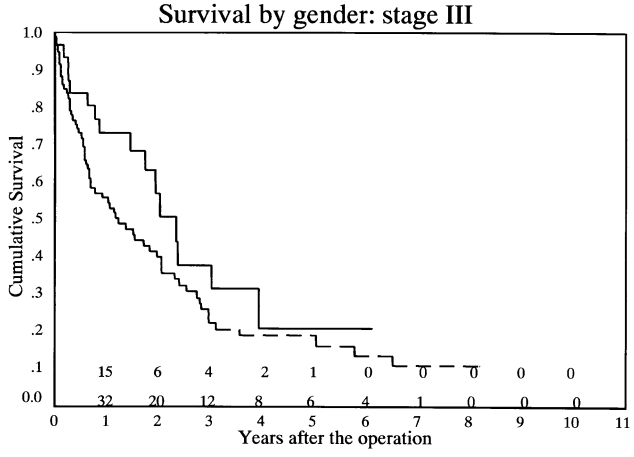


Fig. 6. Five-year survival for women (continuous line) and men (interrupted line) at pathological stage III was 21.1 ± 11.3 vs. 16.3 ± 4.9% ($P = 0.3$).

Downloaded from https://academic.oup.com/ejcts/article/21/2/319/412867 by ANKARA user on 11 December 2021

amongst men in this series. Even early mortality in both genders [3] and higher early mortality in men [4] have been previously quoted.

We observed an important overall survival advantage for women. This was unaffected by the tumour histology but it was related to the tumour stage with women living significantly longer than men at pathological stage I. At stages II and III women had a better survival but this was not statistically significant. A superior survival for women has been documented by other institutions and in population based studies following pulmonary resection for NSCLC [3–5,8,10,11]. In some of these reports, the survival benefit for females was pronounced in certain tumour stages. In the study of Perott et al [4] women had a significantly better survival at stages I and II, in the report of Ferguson et al. [3] at stages I and IIIb and in the study of Mitsudomi et al .at stage III disease [5].

Also, women lived longer than men in cohorts of patients having either inoperable NSCLC, treated with radiotherapy or chemotherapy [19,20], or small cell lung cancer [9].

The marked differences in some of the clinical features and management between men and women in our study merit further discussion. It could be argued that poorer preoperative spirometry, higher prevalence of cardiovascular comorbidity and higher proportion of pneumonectomies in men might have all biased the results in favour of women. However, in our analysis the preoperative cardio-respiratory status did not appear to influence the long term-survival and female gender remained an independent favourable factor after the hospital mortality was excluded from the analysis. Pneumonectomy was an adverse univariate but not multivariate predictor of survival and, in any case, women lived longer than men following both pneumonectomy and smaller resections. The predominance of the squamous cell type in the male population should have benefited the men and it is remarkable that women had a better outlook despite having a higher proportion of non-squamous histology.

Previous studies have been criticised for including small numbers of women, for analysing insufficient number of variables, for lacking information on co-existing cardiovascular, respiratory and other conditions and for covering a long time-period during which the management protocols might have changed. We believe that such shortcomings are not present in this report.

A probable weakness, though, is the lack of knowledge of the precise cause of late deaths and it is possible that the exclusion of non-cancer related deaths from the analysis might have helped to better clarify the issues discussed in this paper. Such an attempt could, however, introduce bias as it may be difficult to rule out the contribution of an underlying uncovered malignancy in an apparently non-cancer related death [21]. Also, in the UK a patient who has been treated for lung cancer would have lung cancer as the cause of death in his death certificate even if he died on a road traffic accident making it almost impossible to extract such data from Public health sources.

The reasons for the better survival reported for women are not completely understood but there is evidence suggesting that the growth of lung cancer cells may be in part dependent on reproductive hormones. In vitro research on human tissue with NSCLC has documented the presence of an abundance of estrogen receptors [22] and demonstrated an anti-proliferative effect mediated by the binding of tamoxifen to these receptors [23]. Moreover, the oestrogen metabolite 2-methoxyoestradiol was shown to inhibit angiogenesis, to suppress tumour growth [24] and induce apoptosis in human lung cancer cells in vitro [25].

The available epidemiological and molecular data prompted some authors to suggest that hormonal treatment with tamoxifen may be appropriate [7,22]. In agreement with others [26], we feel that the current knowledge does not fully support the clinical use of anti-oestrogen treatment or differing treatment strategies in men and women, but stresses the need for the stratification of lung cancer trials by gender including a sufficient number of women. This would allow a valid assessment of the outcome of various treatment protocols for both men and women.

5. Conclusions

This study suggests that female gender exerts a significant positive effect on survival following lung resection for NSCLC. This effect is pronounced at early disease stages and persists after adjusting for important differences in the clinical, histo-pathological features and extent of pulmonary resection between male and female patients.

References

[1] La Vecchia C, Lucchini F, Negri E, Boyle P, Maisonneuve P, Levi F. Trends in cancer mortality in Europe 1955–1989: II. Respiratory tractbone, connective and soft tissue sarcomas, and skin. Eur J Cancer 1922;28:514–599.
[2] Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1998. CA Cancer J Clin 1998;48:6–29.
[3] Ferguson MK, Wang J, Hoffman PC, Haraf DJ, Olak J, Masters GA, Vokes EE. Sex-associated differences in survival of patients undergoing resection for lung cancer. Ann Thorac Surg 2000;69:245–250.
[4] De Perrot M, Licker M, Bouchardy C, Usel M, Robert J, Spiliopoulos A. Sex differences in presentation, management ,and prognosis of patients with non-small cell lung carcinoma. J Thorac Cardiovasc Surg 2000;119:21–26.
[5] Bouchardy C, Fioretta G, De Perrot M, Obradovic M, Spiliopoulos A. Determinants of long term survival after surgery for cancer of the lung. Cancer 1999;86:2229–2237.
[6] Ouellette D, Desbiens G, Emond C, Beauchamp G. Lung cancer in women compared with men; stage, treatment, and survival. Ann Thorac Surg 1988;66:1140–1144.
[7] Mitsudomi T, Tateishi M, Oka T, Yano T, Ishida T, Sugimachi K. Longer survival after resection of non-small cell lung cancer in Japanese women. Ann Thorac Surg 1989;48:639–642.
[8] Williams DE, Pairolero PC, Davis CS, Bernatz PE, Payne WS, Taylor WF, Uhlenhopp MA, Fontana RS. Survival of patients surgically treated for stage I lung cancer. J Thorac Cardiovasc Surg 1981;82:70–76.

Downloaded from https://academic.oup.com/ejcts/article/21/2/319/412867 by ANKARA user on 11 December 2021

[9] Johnson BE, Steinberg SM, Phelps R, Edison M, Veach SR, Ihde DC. Female patients with small cell lung cancer live longer than male patients. Am J Med 1988;85:194–196.
[10] Ferguson MK, Skosey C, Hoffman PC, Golomb HM. Sex associated differences in presentation and survival in patients with lung cancer. J Clin Oncol 1990;8:1402–1407.
[11] Wolf M, Holle R, Hans K, Drings P, Havemann K. Analysis of prognostic factors in 776 patients with small cell lung cancer: the role of sex as a predictor for survival. Br J Can 1991;63:986–992.
[12] Mountain CF. Revisions in the international system for staging lung cancer. Chest 1997;111:1710–1717.
[13] McDuffie HH, Klaassen DJ, Dosman JA. Female–male differences in patients with primary lung cancer. Cancer 1987;59:1825–1830.
[14] Greenberg R, Korson R, Baker J, Barrett J, Bron A, Yates J. Incidence of lung cancer by cell type: a population-based study in New Hampshire and Vermont. J Natl Inst 1984;72:599–603.
[15] Chaudhuri PK, Thomas PA, Walker MJ, Briele HA, Gupta TKD, Beattie CW. Steroid receptors in human lung cancer cytosols. Cancer Lett 1982;16:327–332.
[16] Alexiou C, Beggs D, Rogers ML, Beggs L, Asopa S, Salama FD. Pneumonectomy for non-small cell cancer: predictors of operative mortality and survival. Eur J Cardiothorac Surg 2001;20:476–480.
[17] Mountain CF, Lukeman JM, Hammar SP, Chamberlain DW, Coulser DL, Victor TA, Weiland LH. Lung cancer classification: the relationship of disease extent and cell type to survival in a clinical trials population. J Surg Oncol 1987;35:147–156.
[18] Kadri MA, Dussek JE. Survival and prognosis following resection of primary non small cell bronchogenic carcinoma. Eur J Cardiothorac Surg 1991;5:132–136.
[19] O'Connell JP, Kris MG, Gralla RJ, Groshen S, Trust A, Fiore JJ, Heelan RT, Golbey RB. Frequency and prognostic importance of pretreatment clinical characteristics in patients with advanced non-small cell lung cancer treated with combination chemotherapy. J Clin Oncol 1986;4:1604–1614.
[20] Ruckdeschel JC, Finkelstein DM, Ettinger DS, Creech RH, Mason B, Vogl S. A randomised trial of the four most active regimens for metastatic non-small cell lung cancer. J Clin Oncol 1986;4:14–22.
[21] Goldstraw P. Editorial on: age does not influence early and late tumor-related outcome after surgery for bronchogenic carcinoma. Ann Thorac Surg 2000;69:678–679.
[22] Canver CC, Memoli VA, Vanderveer PL, Dingivan CA, Mentzer Jr RM. Sex hormone receptors in non-small cell lung cancer in human beings. J Thorac Cardiovasc Surg 1994;108:153–157.
[23] Caltagirone S, Ranelletti FO, Rinelli A, Mggiano N, Colasante A, Aiello FB, Piantelli M. Interaction with type II estrogen binding sites and antiproliferative activity of tamoxifen and quercetin in human non-small-cell lung cancer. Am J Respir Cell Mol Biol 1997;17:51–59.
[24] Fotsis T, Zhang Y, Pepper MS, Aldercreutz H, Montesano R, Schweigerer L. The endogenous oestrogen metabolite 2-methoxyoestradiol inhibits angiogenesis and supresses tumor growth. Nature 1994;368:237–239.
[25] Mukhopadhyay T, Roth JA. Induction of apoptosis in human lung cancer cells after wild-type p53 activation by methoxyestradiol. Oncogene 1997;14:379–384.
[26] Albain KS. Invited commentary on: Ferguson MK, Wang J, Hoffman PC, Haraf DJ, Olak J, Masters GA, Vokes EE. Sex-associated differences in survival of patients undergoing resection for lung cancer. Ann Thorac Surg 2000;69:245–50.

Appendix A. List of tested variables

Age, history of smoking, squamous cell carcinoma, adenocarcinoma, t-stage, lymph nodal involvement, pTNM stage, previous history of respiratory disease, previous history of cardiovascular disease, diabetes mellitus, hypertension, peripheral vascular disease, plasma haemoglobin, plasma urea, plasma creatinine, liver function tests (normal or abnormal), FEV1, % of the predicted FEV1, FVC, % of the predicted FVC, FEV1/FVC ratio, peak flow, pCO2, pO2, pH, body mass index, pneumonectomy, bilobectomy, lobectomy, lesser resection, operating surgeon.

Appendix B. Conference discussion

Dr U. Stammberger (*Berne*, *Switzerland*): A very interesting study, however, as you have shown in your last slide, outcome is very dependent on tumour stage. So is it possible that your results are explained not by gender but by the fact that women go earlier to their physicians, are regularly checked up due to screening for mammary carcinoma etc.? So these are really early stage I patients, whereas men often come later to their physicians. If, on the other hand, there is a genetic explanation I would also expect a better survival in stage II or III.

Mr Alexiou: This is a valid point. We did not look at gender associated differences in the time elapsed between the onset of symptoms and the medical examination but in a study from Canada, showing also a better survival for women, there were not differences in the timing or modus of presentation and the management between men and women. We found that women had a significantly better survival in stage I. In other studies from Japan, USA and Switzerland women lived significantly longer in stages II or III but not in stage I. This, probably, has to do with the numbers of patients available for analysis at each stage in various papers.

Dr Stammberger: Maybe it is a sampling error.

Mr Alexiou: I think that 830 patients would be a sufficient sample. I should, also, point out that although women did not have a significantly better survival at stages II and III, in our series, they did have a relatively better survival than men. Also, I am not aware of a recent similar study showing better survival in men.

Dr Stammberger: Do you have any good hypothesis for this?

Mr Alexiou: Laboratory research has demonstrated the presence of estrogen receptors on human tissue with NSCLC and an anti-proliferative effect of tamoxifen. Also, oestrogen metabolites were shown to inhibit angiogenesis and tumour growth. Some authors have suggested that hormonal treatment with tamoxifen in lung cancer patients may be appropriate. We do not go that far. What we are saying is that this study supports previous reports suggesting that female gender has a positive effect on survival and, therefore, further work to examine this would be justified. Also, the clinical trials should be gender-stratified including sufficient numbers of women, and their results should be reported according to the patient gender.

Downloaded from https://academic.oup.com/ejcts/article/21/2/319/412867 by ANKARA user on 11 December 2021