Author/s:
Wainer, Z;Wright, GM;Gough, K;Daniels, MG;Choong, P;Conron, M;Russell, PA;Alam, NZ;Ball, D;Solomon, B

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Impact of sex on prognostic host factors in surgical patients with lung cancer

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TITLE PAGE

Full Title: The impact of sex on prognostic host factors in surgical patients with lung cancer

Short Title: Sex differences in survival in lung cancer

Authors:

1. Zoe Wainer, BMBS.
    a. The University of Melbourne, Department of Surgery, St Vincent's Hospital
    b. Department of Cancer Experiences Research, The Peter MacCallum Cancer Centre
2. Gavin Michael Wright, MBBS, FRACS,
    a. The Department of Surgery, The University of Melbourne
    b. Division of Cancer Surgery, Peter MacCallum Cancer Centre
    c. Surgical Oncology, St Vincent's Hospital, Melbourne
3. Karla Gough, Ba (Hons), PhD.
    a. The Department of Cancer Experiences Research, Peter MacCallum Cancer Centre
4. Marissa Grace Daniels, MBBS, BMedSci
    a. The University of Queensland, Thoracic Research Centre
5. Peter Choong, MBBS, FRACS,
    a. The University of Melbourne, Department of Surgery, St Vincent's Hospital
6. Matthew Conron. FRACP, MD
    a. Department of Respiratory and Sleep Medicine, St Vincent's Hospital, Melbourne
7. Prudence Anne Russell, MBBS (Hons), FRCPA,
    a. Department of Anatomical Pathology, St Vincent's Hospital Melbourne
    b. Department of Anatomical Pathology, The University of Melbourne
8. Naveed Zeb Alam, MBBS FRACS,
    a. St Vincent's Hospital, Department of Thoracic Oncology, Melbourne
9. David Ball, MD, FRANZCR
    a. Department of Radiation Oncology, Peter MacCallum Cancer Centre
10. Benjamin Solomon, MBBS, FRACP,
    a. The Peter MacCallum Cancer Centre, Division of Medical Oncology

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Dr Zoe Wainer has been the recipient of two RACS scholarships to undertake her PhD, of which this paper is a component. In 2009 she received the Foundation for Research Scholarship and in 2010 she received the Raelene Boyle Scholarship. In 2013 The University of Melbourne Melville Hughes Scholarship has also supported her PhD.

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Corresponding author:
Dr Zoe Wainer
Email: zoewainer@gmail.com
Postal Address: 5d/26 Wellington St Collingwood, Vic 3066
Mobile: 0419368949

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Abstract:

Introduction:

Lung cancer has markedly poorer survival in men. Recognised important prognostic factors are divided into *host*, *tumour*, and *environmental factors*. Traditional staging systems that use only tumour factors to predict prognosis are of limited accuracy. By examining sex-based patterns of disease-specific survival in non-small cell lung cancer (NSCLC) patients, we determined the effect of sex on the prognostic value of additional host factors.

Methods:

Two cohorts of patients treated surgically with curative intent between 2000-2009 were utilized. The primary cohort was from Melbourne, Australia, with an independent validation set from the United States Surveillance, Epidemiology and End Results database (SEER). Univariate and multivariate analyses were performed in both cohorts to investigate the differences between men and women of validated host-related prognostic factors.

Results:

The Melbourne cohort had 605 patients, (61% men) and SEER cohort comprised 55,681 patients, (51% men). Disease-specific 5-year survival showed men had statistically significantly poorer survival in both cohorts($p<0.001$), Melbourne men at 53.2% compared to women at 68.3%, and SEER 53.3% men and 62.0% women were alive at 5-years. Being male was independently prognostic for disease-specific mortality in the Melbourne cohort after adjustment for ethnicity, smoking history, performance status, age, pathological stage and histology (HR=1.54, 95% CI 1.10-2.16, $p=0.012$)

Conclusions

Sex differences in NSCLC are important irrespective of age, ethnicity, smoking, performance status and TNM stage. Epidemiological findings such as these should be translated into research and clinical paradigms to determine the factors that influence the survival disadvantage experienced by men.

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Introduction

Despite significant advances in oncology translational research, survival rates for patients with lung cancer are suboptimal. Fifty per cent of patients with stage I disease will have disease recurrence within 5 years.[1] Improved outcomes for patients with NSCLC will depend on the development of more accurate outcome prediction models to facilitate better selection of patient for treatment and optimal clinical trial design. The current tool, the International Union for Cancer Control (UICC), American Joint Committee on Cancer (AJCC) and International Association for the Study of Lung Cancer's (IASLC) Tumour, Node, Metastasis staging system (TNM), [2] demonstrates significant heterogeneity in outcomes for patients with non-small cell lung cancer (NSCLC) as demonstrated by the high recurrence rate for patients with stage I disease. [1]

The IASLC and UICC have defined prognostic factors in NSCLC as "tumour, host or environmental factors".[3] The TNM staging system is an anatomical tumour based staging system with powerful prognostic value but does not include host factors. Lung cancer survival, with the highest global mortality rate of any cancer,[4] is strongly influenced by the host factor sex, with markedly poorer outcomes in men. The American Surveillance, Epidemiology and End Results (SEER) database documents a mortality rate ratio for men:women of 1.82, and a hazard ratio for men of 1.17 after controlling for age and stage.[5]

As defined in the IASLC/UICC staging manual, important host prognostic factors include the age, performance status at diagnosis and smoking history.[2] This study aimed to determine whether sex was a significant and independent predictor of disease-specific survival, after accounting for other known prognostic factors, in a surgical patient cohort from the Peter MacCallum Cancer Centre and St Vincent's Hospital (Melbourne cohort) and compare this to patterns observed in a SEER cohort. It then sought to determine the prognostic value of host factors within sex groups in the Melbourne cohort after accounting for disease-related prognostic factors.

Methods

Study populations

Data was obtained from an Australian surgical database (Melbourne dataset) and from the United States of America Surveillance Epidemiology and End Results (SEER) database. Inclusion criteria were patients who had undergone a potentially curative resection for histologically confirmed NSCLC performed between 2000 and 2009.

Melbourne dataset:

Surgical database data was enriched by review of electronic and hard-copy clinical records (Refer to table 1 for data collected). Comprehensive staging data were collected according to best practice.[6] An experienced pathologist undertook pathological evaluation using the original diagnostic glass slides to determine pathologic TNM stage and histologic subtype.

Date and cause of death were recorded. Recurrence was pathologically confirmed, with unequivocal progression of radiologic findings considered an acceptable surrogate.

SEER dataset:

The population cohort comprised patients who underwent resection of NSCLC between 2000 and 2009, using SEER*Stat version 7.1.0[7]. The dataset was abridged for this cohort due to a lack of data granularity preventing more detailed comparisons and included sex, age, histology, TNM stage, survival time and disease specific mortality.

Outcomes of interest

Disease-specific survival/mortality at five years was the outcome of interest, and defined for the Melbourne cohort through detailed case review and cause of death statements on death certificates and pre-defined for the SEER dataset based on death certificates and registry entry. Throughout this analysis, all staging was performed according to the 7th edition TNM system.[9,10]

Statistical methods

Sample sizes were pragmatic based on data available that met inclusion criteria. Using the rule of ten events per predictor variable as a guide, there were a sufficient number of events per predictor for each of the Cox models described below.

Statistical analysis was performed with SPSS (Version 21, Chicago IL, USA) and R (reference index version 3.1.1 "Sock it to Me")[9] using the 'survival' package. Alpha was set at 0.05 (two-tailed) for all analyses with no adjustment for multiplicities.

Descriptive statistics were used to summarise patient characteristics for both cohorts. Pearson's chi-square test for nominal variables and independent samples t-tests for continuous variables were used to compare patient and tumour characteristics by sex. The Kaplan-Meier method was used to calculate estimates of disease-specific survival at 1, 2, 3, 4 and 5 years for the full sample and for men and women separately for both cohorts. Cox proportional hazards regression was used to assess the prognostic importance of sex (female, male) in the Melbourne cohort after adjustment for ethnicity (non-Asian, Asian), smoking history (never, ever/current if more than 100 cigarettes had been consumed), Performance status (Eastern Cooperative Oncology Group (ECOG) score)[10] was defined as 0 or >0, age (mean-centred and re-scaled, so coefficients provided an estimate for each 5-year increase in age from average age), pathological TNM stage (1A, 1b, 2A, 2B, 3A/3B/4) and histology (adenocarcinoma, squamous cell carcinoma, large cell/other). Cox proportional hazards regression was also used to assess prognostic value of host factors within sex groups in the Melbourne cohort after disaggregating the data by sex.

Results

Patient characteristics

Inclusion criteria were met by 605 patients in the Melbourne cohort and 55,681 patients in the SEER. Demographic and clinical characteristics of both cohorts are presented in Table 1. In

both cohorts, there were more women with adenocarcinoma than men and in the Melbourne cohort, more women were never smokers than men.

Sex-based patterns of survival

Five-year disease-specific survival was similar in both cohorts; 59.0% (95%CI: 54.6 to 63.9) for Melbourne and 57.5% (95%CI: 57.0 to 58.1) for SEER. Disease-specific survival estimates for both cohorts are shown in Table 2. Survival estimates for both cohorts for men and women were notably different at one, two, three, four and five years. Men had statistically significant worse five-year survival in both the Melbourne cohort ($\chi^2 = 14.0$, $p < 0.001$) and the SEER cohort ($\chi^2 = 451.0$, $p < 0.001$).

Prognostic value of sex

Being male was a strong independent poor prognostic factor for disease-specific mortality in the Melbourne cohort after adjustment for ethnicity, smoking history, ECOG performance status, age, pathological TNM stage and histologic subtype (Table 3; hazard ratio = 1.54, 95%CI: 1.10 to 2.16, $p = 0.012$).

Prognostic value of host factors for men and women

Results for multivariate Cox models assessing the prognostic value of host factors within sex groups are provided in Table 3. Host factors were not independently prognostic for disease-specific mortality in males (all $p > 0.05$). Increased age was independently prognostic for disease-specific mortality in women only ($p = 0.001$); but ethnicity, smoking and performance status were not (all $p > 0.05$). As expected advanced pathologic TNM stage was independently prognostic for disease-specific mortality in both males and females ($p < 0.001$).

Discussion

The UICC/AJCC/IASLC lung cancer staging recommendations [9, 10] further classify host, tumour and environmental factors into categories of clinical significance as 'essential', 'additional' and 'new and promising'. Essential prognostic factors are fundamental to clinical algorithms while additional factors provide more refined prognostic information.(3) We investigated whether sex should be considered an 'essential' host factor in addition to other validated prognostic host variables.

Subgroup prognostic factor analyses performed during development of the 7th edition UICC/AJCC/IASLC TNM staging system confirmed male sex as an independent poor prognostic factor with HR of 1.17 (p<0.001),(11) and 1.32 (p<0.001)(12). Population-based data from the World Health Organisation verifies poorer outcomes for men with lung cancer.(13) Irrespective of stage, histology or treatment, many studies have demonstrated that for patients with NSCLC men have a poorer prognosis than women as demonstrated by the meta-analysis of 86,800 patients in 2011 by Nakamura *et al.*(14)

In line with previous studies, our findings demonstrated that, despite controlling for known TNM stage, male sex remained an important prognostic factor, with the log rank test for both cohorts showing men had a worse survival at 5 years, (p<0.001) (Table 2) and on multivariate analysis for the Melbourne cohort the hazard ration for being male was 1.54, (95% CI 1.10-2.16; p=0.012) (Table 3).

Age is considered an essential prognostic factor by the UICC and IASLC,(2) however there is conflicting evidence concerning the its significance(15) and clinical utility. Pallis *et al.* speculate

that comorbid illness is the poor prognostic factor that confounds studies investigating the prognostic impact of age, given that the presence of comorbid conditions occurs more commonly with increasing age.[16] The interaction between age and sex as prognostic factors in NSCLC has been previously investigated. In a review of over 300,000 patients who underwent NSCLC resection, Owinokoko *et al.* demonstrated superior survival for women regardless of age ($p<0.0001$).[17] In an investigation of the impact of prognostic factors during development of the UICC/AJCC/IASLC 7th edition TNM staging system, Chansky *et al.* demonstrated that patients ≥ 70 years of age,[12] were at greater risk of death (HR 1.51; $p<0.0001$), controlling for sex and stage.

Fu *et. al*. determined that the survival benefit for females was more pronounced over the age of 50 years.[18] This reported stronger survival benefit in older women has since been replicated in a Japanese cohort.[19] Indeed, Wisnivesky and colleagues specifically examined the impact of women's greater life expectancy on survival in lung cancer.[20] In a cohort of older patients, the survival advantage for women persisted after controlling for unrelated deaths and treatment.[20]

Despite some conflicting studies, the weight of evidence suggests that age is prognostic in NSCLC. Consistent with the literature, increased age was independently prognostic for disease-specific mortality in the Melbourne cohort (per 5-year increase –HR 1.11 95% CI 1.03-1.20; p=0.01). Notably however, after disaggregating the data by sex, increased age conferred a survival disadvantage in women only (HR 1.29, 95%CI 1.10-1.51; p=0.001).

A number of factors may have contributed to differences between our findings and earlier studies. Previous studies have not collected data on potentially confounding variables, such as comorbid illness and treatment paradigms, that are recognised factors that influence survival

outcomes. It is possible that pre-menopausal status may be associated with a worse survival in more advanced disease, which is under-represented in our study on early stage resectable NSCLC. Systematic differences between these highly selected surgical cohorts may not be applicable to more general lung cancer populations with a larger burden of comorbidities, in turn which may act as surrogates of age. Whilst age appears to be important, it both demonstrated sex differences in our study as well as inconsistent findings internationally and as such given this variability in findings it may be more appropriate as an 'additional' prognostic factor, than an 'essential' one.

Performance status is considered an "essential" prognostic factor by the UICC and IASLC,[2] and is a robust clinical tool because it incorporates both symptoms caused by cancer and the impact of comorbid illness. Studies have demonstrated the prognostic value of ECOG performance status in NSCLC.[21, 22] This is consistent with our findings, whereby an ECOG ≥1 had a hazard ratio of 1.36 (95%CI 1.01-1.82; p=0.037).

Kawaguchi *et al.* analysed a Japanese population dataset of 26,957 patients with NSCLC, most of whom were treated surgically, and found those with ECOG performance status of 0 were likely to be younger with stage I disease, never smokers, and female.[23] In an analysis of 2349 patients enrolled in chemotherapy trials, Wheatley-Price *et al.*,[24] demonstrated equivalent proportions of men and women with good performance status. Our study demonstrated that men were more likely to have ECOG performance status ≥1 (39% vs. 29%, p=0.016), corroborating the findings of Kawaguchi *et al*. However in the multivariate Cox model whilst ECOG was statistically significant for the whole cohort, it did not reach statistical significance as an independent prognostic factor for either men or women when data was disaggregated. It is important to acknowledge that this was a surgical study with a large bias towards patients well enough for

surgical resection. In addition these results may reflect a small sample size or that aggregating men and women may effect the estimate as the confidence intervals for women are very wide (95% CI 0.86-2.70), however this question is beyond the scope of this study.

Published data demonstrates conflicting evidence of the prognostic value of smoking. Chansky *et al.* examined the impact of smoking and reported poorer outcomes in current smokers compared with former (HR=1.21; $p<0.0001$) and never smokers (HR=1.41, $p=0.0017$).[12] In contrast and consistent with our findings whereby smoking was not correlated with survival (p=0.26), a Japanese retrospective analysis of 12,509 cases found smoking status was not a statistically significant prognostic factor.[25]

With respect to sex differences and smoking women with NSCLC are more likely to be non-smokers[26], consistent with our data: 4% of men were non-smokers compared with 26% of women (p<0.001). This has raised the question as to whether the poorer survival rate in men with NSCLC is related to their higher smoking rates. There is no consensus in the literature on the influence of smoking on the survival benefit observed in women with some studies demonstrating equivalent outcomes for male and female smokers,[27] whilst others contradict this. [26]

In 2011, Cong *et al.* published statistical modelling of lung cancer and smoking encompassing 1.2 million subjects in the USA, and demonstrated no survival difference between men and women in either the smoking or the non-smoking groups.[28] In our study multivariate modelling demonstrated that smoking was neither prognostic in the whole cohort (p=0.26) nor in men (p=0.94) or women (p=0.081) when disaggregated by sex (Table 3).

Lung cancer in Asian women has been noted to be 2-3 times higher, commonly adenocarcinoma subtype, and displays a distinct disease pattern which is more frequent in non-smokers and has a more favourable prognosis in part due to higher rates of targetable mutations.[29] Due to this profile it is hypothesised that ethnicity may add to the survival benefit seen in women with NSCLC. Ethnicity was not statistically significant in our study for all patients (p=0.67), men (p=0.41) or women (p=0.80). In addition whilst our study was not sufficiently powered for conclusive findings, the poorer survival experienced by men was a statistically significant findings despite the low numbers of Asian women and men in the cohort.

Conclusion:

Sex has been categorised by the UICC/IASLC as an additional host factor in the Staging Manual in Thoracic Oncology.[2] We believe this categorisation should be reviewed and that sex should be considered an essential prognostic factor and hence seen as vital to review in all research and clinical paradigms and importantly sex disaggregation must occur at the beginning of any clinical algorithm to ensure differences between men and women are identified and investigated to the benefit of both sexes and good science and medicine.

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Table 1 Patient characteristics

	Melbourne cohort (N=605)				SEER cohort (N=55,681)			
Characteristic	All patients	Women	Men	p-value†	All patients	Women	Men	p-value†
Sex								
Female	238 (39)				27069 (49)			
Male	367 (61)				28612 (51)			
Age				.12				.09
M	66.7	65.9	67.2		66.4	66.3	66.5	
SD	9.9	10.4	9.5		10.4	10.6	10.1	
Mdn	68	67	68		67	67	67	
IQR	61 - 74	60 - 73	61 - 74		59 - 74	59 - 74	60 - 74	
Ethnicity				.21				
Asian	34 (6)	17 (7)	17 (5)					
Caucasian	571 (94)	221 (93)	350 (95)					
Smoking status				< .001				
Never	76 (13)	63 (26)	13 (4)					
Ever/current	529 (87)	175 (74)	354 (96)					
ECOG performance status				.016				
0	392 (65)	168 (71)	224 (61)					
1 or more	213 (35)	70 (29)	143 (39)					
Pathologic TNM stage				.61				< .001
1A	155 (26)	70 (29)	85 (23)		17281 (31)	9521 (35)	7760 (27)	
1B	146 (24)	56 (24)	90 (25)		12446 (22)	6014 (22)	6432 (23)	
2A	80 (13)	27 (11)	53 (14)		6489 (12)	2744 (10)	3745 (13)	
2B	88 (15)	30 (13)	58 (16)		5072 (9)	2090 (8)	2982 (10)	
3A	107 (18)	44 (19)	63 (17)		8621 (16)	3947 (15)	4674 (16)	
3B	10 (3)	4 (2)	6 (2)		772 (1)	346 (1)	426 (2)	
4	19 (3)	7 (3)	12 (3)		5000 (9)	2407 (9)	2593 (9)	
Histology				< .001				< .001
Adenocarcinoma	335 (55)	158 (66)	177 (48)		31779 (57)	17686 (65)	14093 (49)	
Squamous cell carcinoma	189 (31)	50 (21)	139 (38)		15658 (28)	5747 (21)	991 (35)	

Large cell carcinoma	52 (9)	21 (9)	31 (8)		2874 (5)	1235 (5)	1639 (6)	
Other	29 (5)	9 (4)	29 (5)		5370 (10)	2401 (9)	2969 (10)	
Surgery				.70				< .001
Anatomic	556 (92)	220 (92)	336 (92)		48627 (87)	23442 (87)	25185 (88)	
Non-anatomic	49 (8)	18 (8)	31 (8)		7054 (13)	3627 (13)	3427 (12)	

† P-value from tests of differences between men and women or associations between sex and other characteristics.

Table 2 Disease-specific survival estimates at 1, 2, 3, 4 and 5 years

Survival estimate	All patients		Men		Women	
	%	95% CI	%	95% CI	%	95% CI
Melbourne cohort (N=605)†						
1-year	84.7	81.9–87.7	80.8	76.8–85.0	90.8	87.1–94.6
2-year	75.3	71.8–79.0	70.0	65.3–75.1	83.8	79.0–88.9
3-year	69.3	65.4–73.4	63.8	58.8–69.3	77.9	72.3–83.9
4-year	62.8	58.5–67.4	55.9	50.4–62.1	73.6	67.5–80.3
5-year	59.0	54.6–63.9	53.2	47.5–59.5	68.3	61.5–75.9
SEER cohort (N=55,681)‡						
1-year	86.3	86.0–86.6	83.5	83.0–83.9	89.3	88.9–89.7
2-year	74.9	74.5–75.3	70.9	70.3–71.5	79.1	78.6–79.7
3-year	67.1	66.6–67.5	62.7	62.0–63.3	71.7	71.1–72.3
4-year	61.6	61.1–62.1	57.3	56.7–58.0	66.1	65.4–66.8
5-year	57.5	57.0–58.1	53.3	52.5–54.0	62.0	61.3–62.7

† The number of deaths observed among males and females was 142 and 57 respectively. Using the logrank method, the expected number of deaths were 116 and 83 respectively.
‡ The number of deaths observed among males and females was 9852 and 7430 respectively. Using the logrank method, the expected number of deaths were 8464 and 8818 respectively

Table 3 Multivariate model for disease-specific mortality to assess the prognostic importance of host factors, Melbourne cohort

	All Patients			Male patients			Female patients		
Covariate	Hazard ratio	95%CI	p-value	Hazard ratio	95%CI	p-value	Hazard ratio	95%CI	p-value
Sex			0.01						
Female	(1.00)								
Male	1.54	1.10-2.16							
Ethnicity			0.67			0.41			0.80
Non-Asian	(1.00)			(1.00)			(1.00)		
Asian	1.16	0.59-2.28		1.39	0.64–3.06		0.85	0.23–3.09	
Smoking			0.26			0.94			0.08
Never	(1.00)			(1.00)			(1.00)		
Ever/current	1.36	0.79-2.34		1.04	0.41–2.59		1.87	0.93–3.79	
Performance status			0.04			0.11			0.14
0	(1.00)			(1.00)			(1.00)		
1 or higher	1.36	1.01-1.82		1.32	0.94–1.85		1.54	0.86–2.70	
Age (per 5-year increase)	1.11	1.03-1.20	0.01	1.06	0.97–1.15	0.23	1.29	1.10–1.51	0.001
TNM stage			< 0.001			< 0.001			< 0.001
1A	(1.00)			(1.00)			(1.00)		
1B	1.40	0.85-2.30		1.32	0.75–2.34		1.48	0.54–4.10	
2A	2.41	1.42-4.09		2.03	1.09–3.77		3.19	1.14–8.89	
2B	2.42	1.43-4.08		1.86	1.01–3.44		5.12	1.87–14.03	
3A/3B/4	4.75	3.02-7.49		3.66	2.14–6.27		8.71	3.65–20.79	
Histology			0.02			0.10			0.34
Adenocarcinoma	(1.00)			(1.00)			(1.00)		

Squamous cell carcinoma	0.92	0.65-1.29	0.98	0.67–1.44	0.37	0.37–1.69
Large cell & other	1.59	1.08-2.32	1.59	1.00–2.53	0.74	0.74–3.05