original article

Annals of Oncology 21: 2023–2028, 2010
doi:10.1093/annonc/mdq067
Published online 23 March 2010

The influence of sex and histology on outcomes in non-small-cell lung cancer: a pooled analysis of five randomized trials

P. Wheatley-Price[1]*, F. Blackhall[2], S.-M. Lee[3], C. Ma[1], L. Ashcroft[2], M. Jitlal[4], W. Qian[5], A. Hackshaw[4], R. Rudd[6], R. Booton[2], S. Danson[7], P. Lorigan[2], N. Thatcher[2] & F. A. Shepherd[1]

[1]*Princess Margaret Hospital/University Health Network, Toronto, Ontario, Canada;* [2]*Christie Hospital, Manchester;* [3]*University College Hospital, London;* [4]*Cancer Research UK and University College London Cancer Trials Centre, London;* [5]*Medical Research Council Clinical Trials Unit, London;* [6]*St Bartholomew's Hospital, London;* [7]*Weston Park Hospital, Sheffield, UK*

Received 5 January 2010; revised 2 February 2010; accepted 5 February 2010

Background: Some non-small-cell lung cancer (NSCLC) surgical series have indicated that the positive prognostic effect of female sex is limited to patients with adenocarcinoma. We carried out a retrospective analysis to investigate the role of sex and histology on efficacy, toxicity, and dose delivery after chemotherapy.

Patient and methods: Individual patient data were pooled from five randomized, phase III, advanced NSCLC chemotherapy trials. Primary outcomes were response rate, overall survival (OS), toxicity, and dose delivery. A secondary analysis examined survival by sex in histological subgroups.

Results: Of 2349 patients, 34% were women. Women had a higher response rate to chemotherapy (42% versus 40%, $P = 0.01$) and longer survival than men (median OS 9.6 versus 8.6 months, $P = 0.002$). The difference in OS remained after adjusting for age, stage, performance status, and histology (hazard ratio 0.83, 95% confidence interval 0.74–0.92, $P = 0.0005$). Upon further examination, longer survival in women was only seen in patients with adenocarcinoma (test for interaction $P = 0.006$). There were no differences in hematological toxicity or transfusions. Women experienced more grade 3–4 emesis than men ($P < 0.0001$) and more dose delays ($P = 0.02$) or dose reductions ($P < 0.0001$).

Conclusion: The positive prognostic effect among women is confirmed in patients receiving platinum-based chemotherapy but appears confined to those with adenocarcinoma histology.

Key words: chemotherapy, histology, non-small-cell lung cancer, sex

introduction

In many countries around the world, lung cancer historically has been more common in men than in women, reflecting the different rates of cigarette smoking between genders. In recent decades, in Western countries in particular, rates of cigarette smoking have fallen and are approaching parity between women and men. With this, there has been a convergence in the rates of lung cancer observed in both sexes [1, 2].

Regarding the prognostic effect of female sex, we previously reported results of a pooled analysis of 1090 patients receiving chemotherapy in non-small-cell lung cancer (NSCLC) trials carried out by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG), in which women had a significant progression-free survival advantage over men [hazard ratio (HR) 0.83, 95% confidence interval (CI) 0.71–0.97, $P = 0.02$], but the difference in overall survival (OS) did not reach statistical significance in multivariate analysis (HR 0.89, 95% CI 0.75–1.05, $P = 0.17$) [3].

However, significant prognostic effects have been reported both in surgical series and in other series of patients with advanced disease receiving palliative chemotherapy [4–8]. Furthermore, in early-stage lung cancer, some studies have indicated that the positive prognostic effect in women may be confined to those patients with adenocarcinoma histology [9, 10].

We therefore carried out this large pooled analysis of individual patient data (IPD) from chemotherapy trials from the Manchester Lung Group (MLG), London Lung Cancer Group (LLCG), and the British Thoracic Oncology Group (BTOG), to validate the results from NCIC CTG and to compare with other published analyses. We investigated the influence of sex on efficacy, toxicity, and dose delivery in these NSCLC studies, and we carried out a secondary analysis to investigate the influence of sex on outcomes in histological subgroups.

Correspondence to: Dr P. Wheatley-Price, Department of Medical Oncology, Ottawa Hospital Cancer Centre, 501 Smyth Road, Ottawa, Ontario, Canada K1H 8L6. Tel: +1-613-737-7700 ext. 70175; Fax: +1-613-247-3511; E-mail: pwheatleyprice@toh.on.ca

methods

studies included

Five randomized phase III trials conducted by the MLG, LLCG, and BTOG, investigating first-line platinum-based chemotherapy regimens in NSCLC between 1997 and 2006, were identified [11–15]. Ethics approval for a retrospective analysis was available from each trial. IPD were available from all trials and were included in the analysis. The trials are summarized in Table 1.

assessment

The primary end points of this analysis were efficacy, toxicity, and dose delivery. Efficacy and activity end points were OS, measured as the time from randomization until death of any cause, and tumor response. Because the NCIC CTG analysis had demonstrated differences in baseline rates of comorbidities between sexes, we also measured lung-cancer-specific survival (LCSS), measured as the time from randomization until death from lung cancer. Due to a lack of recording of the date of progression in many patients, progression-free survival was not included as an end point following discussion between the investigators. Responses were measured using the RECIST criteria in BTOG1 and Study 14 [16]. In Study 11, GC–MIC–MVP (*g*emcitabine and *c*arboplatin; *m*itomycin, *i*fosfamide, and *c*isplatin; *m*itomycin, *v*inblastine, and cis*p*latin), and the Gemcitabine Hospitalization studies, World Health Organization response criteria were used [17]. Toxic effects were recorded using National Cancer Institute Common Toxicity Criteria version 2.0 in all studies except GC–MIC–MVP, which used version 1.0. Laboratory results were recorded for hematological toxicity scoring. All common and important toxic effects (grade 1 and above) and severe toxic effects (grades 3 and 4) were reported for all patients who received at least one cycle of treatment. Reported hematological toxic effects included anemia, leukopenia, neutropenia, thrombocytopenia, and febrile neutropenia. Non-hematological toxic effects reported included emesis, mucositis, fatigue, diarrhea, neuropathy, and non-neutropenic infection. The rates of blood and platelet transfusions were recorded and reported.

Information on doses of drugs administered was not available for all studies. Dose intensity (DI) was calculated by the total number of chemotherapy cycles delivered divided by the planned number of cycles. The number of treatment delays and dose reductions was calculated for each patient.

statistical methods

The Pearson chi-square test was used to compare various demographic and clinical factors between the sexes. OS was examined using Kaplan–Meier curves. Univariate Cox proportional hazards regression was used to test the association of baseline factors with OS. Statistically significant prognostic factors from the univariate analysis were entered into the multivariate model. A test for heterogeneity was carried out to compare HRs from the individual trials. All statistical analyses were carried out using SAS version 9.1 (SAS Institute, Cary, NC) and R version 2.1.1.

results

patients

A total of 2349 patients were included in the analysis, with 793 women (34%). The distribution of sexes in each trial was similar. Median follow-up was 8.6 months, and there were 1988 deaths.

Baseline demographics are reported in Table 2. Women and men were well matched for stage and performance status. Women were slightly younger than men at study entry (median age 61 versus 63 years, $P < 0.0001$). Adenocarcinoma was more common in women than in men (41% versus 31%, $P < 0.0001$). Men were more likely to be anemic than women at study entry (64% versus 32%, $P < 0.0001$).

efficacy

Response and survival results are shown in Table 3. The overall response rate (complete response plus partial response) was slightly higher in women than in men (42% versus 40%, $P = 0.01$).

In the overall cohort, women had a significantly longer median survival than men (9.6 versus 8.6 months, HR for death 0.86, 95% CI 0.78–0.95, $P = 0.002$). One-year survival was 41% in women and 35% in men, and 3-year survival rates were 8% and 5%, respectively. LCSS was almost identical to OS in both sexes, favoring women (9.7 versus 8.7 months, HR 0.86, 95% CI 0.78–0.95, $P = 0.002$). The test for heterogeneity, comparing the HRs of each trial, demonstrated no significant difference in effect across the trials ($P = 0.99$).

In univariate analysis, female sex, stage III disease (compared with stage IV), and a good performance status were associated with significantly improved survival. In multivariate analysis (controlling for age, stage, performance status, sex, and histology), female sex (HR 0.83, 95% CI 0.74–0.92, $P = 0.0005$), stage III disease (HR 0.75, 95% CI 0.68–0.82, $P < 0.0001$), and

Table 1. Trials included in the analysis

Study	Author	Years	Treatment	*n* analyzed in sex analysis (%)	
				Female	Male
Study 11	Rudd et al. [14]	1999–2001	GC versus MIC	126 (30)	296 (70)
Study 14	Lee et al. [13]	2003–2005	GC + thalidomide versus GC + placebo	257 (36)	465 (64)
DOCMIC (BTOG1)	Booton et al. [11]	2001–2002	DC versus MIC or MVP	138 (32)	295 (68)
GC–MIC–MVP	Danson et al. [12]	1997–2001	GC versus MIC or MVP	138 (37)	233 (63)
Gemcitabine Hospitalization study	Blackhall et al. [15]	2002–2006	GC versus GP	134 (33)	267 (67)
Total				793 (34)	1556 (66)

GC, gemcitabine and carboplatin; MIC, mitomycin, ifosfamide, and cisplatin; DC, docetaxel and carboplatin; MVP, mitomycin, vinblastine, and cisplatin; GP, gemcitabine and cisplatin.

a good performance status (HR 0.56, 95% CI 0.49–0.63, $P < 0.0001$) remained significant predictors of longer survival.

In subgroup analysis, the extent of longer survival in women was greater among patients with adenocarcinoma (median OS 10.9 versus 8.4 months, HR 0.70, 95% CI 0.59–0.83, $P < 0.0001$) than among patients with non-adenocarcinoma histology (median OS 8.8 versus 8.5 months, HR 0.97, 95% CI 0.85–1.10, $P = 0.61$). The test of interaction between histology (adenocarcinoma versus non-adenocarcinoma) and sex was highly significant ($P = 0.006$; Figure 1).

Table 2. Baseline demographics by sex

	Women, $n = 793$		Men, $n = 1556$		P value
	n	%	n	%	
Age at randomization, years					
<65	547	69	867	56	<0.0001
≥65	246	31	689	44	
Median in years (range)	61 (34–83)		63 (23–85)		
Stage					
IIIa	58	7	90	6	0.19
IIIb	319	40	673	43	
IV	416	52	791	51	
Unknown	0		2		
Performance status					
Good[a]	636	80	1249	81	0.97
Poor	155	20	303	19	
Unknown	2		4		
Histology (reported as a percentage of those recorded)					
Adenocarcinoma	272	41	399	31	<0.0001
Squamous cell	203	31	550	43	
Large cell	35	5	41	3	
NOS	149	23	299	23	
Not recorded	134		267		
Baseline hemoglobin (reported as a percentage of those recorded)					
Normal	256	68	268	38	<0.0001
≥Grade 1 anemia[b]	120	32	481	64	
Unknown	417		807		

[a]Eastern Cooperative Oncology Group 0/1, Karnofsky 80–100.
[b]Grade 1 anemia defined as <12 g/dl in women and <14 g/dl in men.
NOS, not otherwise specified.

Table 3. Response and survival by sex

	Women, $n = 793$ (%)	Men, $n = 1556$ (%)	P value
Response rate (those evaluated received a cycle of chemotherapy)			
Overall response (CR + PR)	42	40	0.01
Stable disease	41	38	
Progressive disease	17	22	
Overall survival (all patients)			
Median survival, months (95% CI)	9.6 (9.0–10.3)	8.6 (8.1–9.0)	
One-year survival, % (95% CI)	41 (37–44)	35 (33–38)	
Hazard ratio (95% CI)	0.86 (0.78–0.95), $P = 0.002$		
Lung-cancer-specific survival			
Median survival, months (95% CI)	9.7 (9.1–10.5)	8.7 (8.4–9.1)	
One-year survival, % (95% CI)	41 (38–45)	36 (34–39)	
Hazard ratio (95% CI)	0.86 (0.78–0.95), $P = 0.002$		
Overall survival (adenocarcinoma subset, $n = 671$)			
Median survival, months (95% CI)	10.9 (9.2–12.6)	8.4 (7.5–9.0)	
Hazard ratio (95% CI)	0.70 (0.59–0.83), $P < 0.0001$		
Overall survival (non-adenocarcinoma subset, $n = 1277$)			
Median survival, months (95% CI)	8.8 (7.9–9.6)	8.5 (7.9–9.1)	
Hazard ratio (95% CI)	0.97 (0.85–1.10), $P = 0.61$		

CR, complete response; PR, partial response; CI, confidence interval.

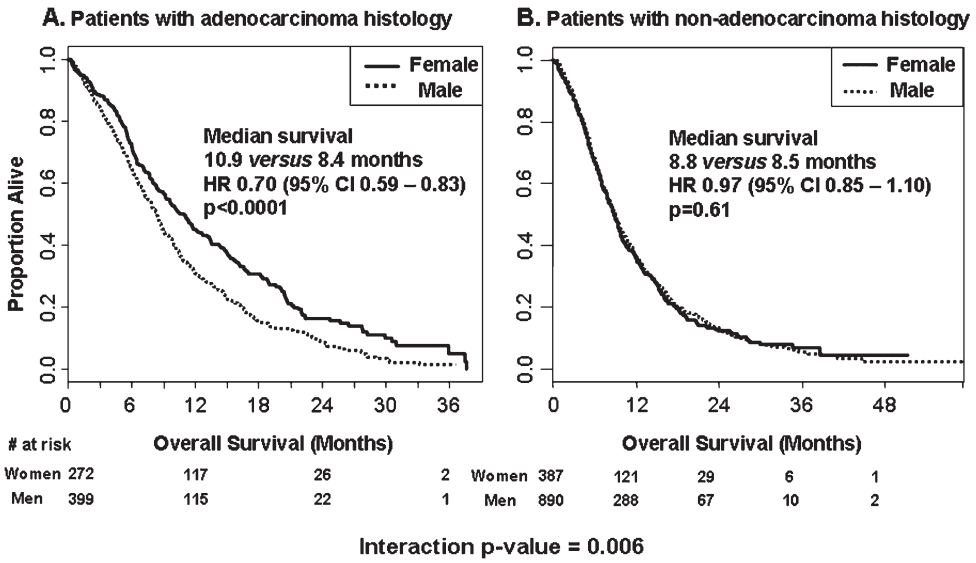

Figure 1. Overall survival by sex in adenocarcinoma and non-adenocarcinoma subgroups.

toxicity

Severe toxic effects (grades 3–4) are shown in Table 4. There were no significant differences between sexes in any measure of hematological toxicity. For non-hematological toxicity, women experienced greater levels of nausea and vomiting of any grade (62% versus 54%, $P = 0.0004$) and severe grades (11% versus 6%, $P < 0.0001$). Women experienced more mucositis of any grade (39% versus 34%, $P = 0.03$), but there was no difference in the rates of grade 3 or 4 mucositis (2% versus 1%, $P = 0.10$). Eleven men (2%) experienced grade 3 or 4 peripheral neuropathy, compared with no women ($P = 0.02$). There were no significant differences in the rates of infection between sexes, and there was no difference in treatment-related death rates (0.6% versus 0.7%, $P = 0.97$).

treatment delivery and DI

DI, calculated as the number of cycles received divided by the number of cycles planned, was not statistically different between women and men (0.85 versus 0.83, $P = 0.50$). More women required at least one dose reduction (32% versus 23%, $P < 0.0001$) or experienced more than one treatment delay (39% versus 32%, $P = 0.02$), when compared with men. At least one blood transfusion was given in 38% of women and in 37% of men ($P = 0.78$). Platelet transfusions were administered in 12% of women and in 11% of men ($P = 0.43$).

discussion

In this retrospective pooled analysis, we report the results based on IPD from 2349 patients from randomized trials, who all received first-line platinum-based chemotherapy as treatment for advanced or unresectable NSCLC.

This is the largest series to date reporting sex differences in chemotherapy-treated patients with NSCLC, and the number of patients available for this analysis allowed us to carry out a subgroup analysis according to histological subtype, despite one of the trials not recording histology (Gemcitabine Hospitalization study).

We report the primary finding that women have improved efficacy outcomes, with a modestly improved response rate when compared with men (42% versus 40%, $P = 0.01$). Women had a longer OS compared with men (9.6 versus 8.6 months, $P = 0.0005$), but this was confined to patients with adenocarcinoma (median survival 10.9 versus 8.4 months, $P < 0.0001$). For patients with non-adenocarcinoma histology, there was no difference in survival between women and men (8.8 versus 8.5 months, $P = 0.61$). This difference was highly significant (test of interaction $P = 0.006$).

When comparing these findings with other, smaller, published series of sex differences in outcomes from NSCLC chemotherapy, this UK-based series supports the previous literature. Most of these previous analyses have demonstrated a modest survival advantage to women, with HRs in the range 0.75–0.99 favoring women [3, 6–8, 18, 19]. There are no published series that show an advantage to men (Table 5).

Although the improved response rate we observed in women may suggest that it is this response to chemotherapy that leads to the survival benefit, the difference is actually quite small and in fact previous analyses of patients treated surgically for early-stage NSCLC, or not receiving chemotherapy at all in advanced disease, also report longer survival in women [4, 5, 9, 20–25]. Our previous analysis of chemotherapy trials conducted by NCIC CTG did not demonstrate a difference in response rates, and although the HR for death of 0.89 favored women, it did not reach statistical significance ($P = 0.17$).

Therefore, looking at patients with NSCLC of all stages, it is clear that female sex is a positive prognostic factor, although the differences are of questionable clinical relevance. However, although there is no placebo-controlled clinical trial data to confirm the hypothesis, it would appear that treatment with chemotherapy is not predictive of a further incremental benefit for women.

This is the first analysis by sex in chemotherapy-treated patients with NSCLC that has reported that longer survival in women is confined to an adenocarcinoma subgroup. Visbal et al. [9] reported a case series of 4618 newly diagnosed patients with NSCLC from the Mayo clinic, where men had a poorer OS (HR 1.23, 95% CI 1.14–1.33, $P < 0.01$). They further reported

Table 4. Severe toxic effects (National Cancer Institute Common Toxicity Criteria grade 3 or 4)

Toxicity variable	Women (%), $n = 793$	Men (%), $n = 1556$	P value
Hematological toxic effects			
Anemia	7	7	1.00
Leukopenia	22	21	0.88
Neutropenia	31	30	0.73
Thrombocytopenia	13	13	0.79
Non-hematological toxic effects			
Nausea and vomiting	11	6	<0.0001
Infection	6	7	0.45
Anorexia	5	6	0.67
Mucositis	2	1	0.10
Lethargy	1	1	0.69
Neuropathy	0	2	0.02
Tinnitus or deafness	<1	<1	0.56

Table 5. A comparison of pooled analyses reporting the prognostic effect of female sex in non-small-cell lung cancer chemotherapy trials

Author	Source	Year	n	Hazard ratio (95% CI)	P value
Mandrekar et al. [19]	NCCTG	2006	1053	0.99 (0.84–1.17)	0.92
Belani et al. [18]	TAX326	2006	1218	0.88	0.18
Efficace et al. [7]	EORTC	2006	391	0.75 (0.59–0.97)	0.03
Wakelee et al. [8]	ECOG	2006	1157	0.84 (0.74–0.94)	0.004
Albain et al. [6]	SWOG	2007	1324	0.86 (0.75–0.98)	0.02
Wheatley-Price et al. [3]	NCIC	2008	1090	0.89 (0.75–1.05)	0.17
Wheatley-Price et al. (this analysis)	UK	2010	2349	0.83 (0.74–0.92)	0.0005

CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; ECOG, Eastern Cooperative Oncology Group; NCIC, National Cancer Institute of Canada.

that among patients with adenocarcinoma, this effect favoring women was even greater (HR 1.37, 95% CI 1.23–1.53, $P < 0.01$) but not as strong in patients with squamous histology (HR 1.11, 95% CI 0.96–1.30, $P = 0.17$). Keller et al. [10] reported a sex analysis of an adjuvant trial in resected stage II and IIIa NSCLC, where patients were randomly assigned to receive either radiotherapy or chemoradiotherapy. Overall, there was no observed difference in survival between sexes (41 versus 35 months, $P = 0.12$), but in the non-squamous histology subset, a significant and clinically relevant survival advantage was observed in women (43 versus 25 months, $P < 0.01$).

We demonstrated in this analysis, and from our analysis of NCIC CTG trials and in other published series, that adenocarcinoma is more common in women than in men [3, 26–29]. It would seem plausible, therefore, that the entire prognostic benefit seen in women in NSCLC is accounted for by the improved survival in the adenocarcinoma subset.

Adenocarcinoma has always been the most common histological NSCLC subtype in women, and it has only overtaken squamous cell cancer as the most common type in men in recent years [30]. It is thought that this change occurred when filters were routinely added to cigarettes, resulting in deeper inhalation of smoke and peripheral tumors (that are more commonly adenocarcinoma) becoming more prevalent.

Cigarette smoking history was not available in the trials included in this analysis, as the concept of lung cancer in never smokers as a separate entity was not yet established when these trials were designed. Therefore, it is plausible that the lack of these data has biased our results. It is known that women and adenocarcinoma are overrepresented in the subgroup of never smokers with lung cancer [8, 31], and recent reports have demonstrated that never smokers with NSCLC survive longer than smokers with NSCLC [31, 32]. Therefore, one could hypothesize that female sex *per se* is not a positive prognostic factor, but rather cigarette smoking history is more important. This could be tested in an analysis of chemotherapy trials where cigarette smoking data are available, and future randomized trials in NSCLC should consider stratification of patients by sex, histological subtype, and smoking history.

Why women are more prone to adenocarcinoma than men is unclear, and an explanation of this may unlock the key to the interplay of sex, histology, smoking, and outcomes. The role of genetic, biological, or hormonal factors in this difference is not well understood [33]. Although not all series agree, it has been postulated that women are more prone to the carcinogenic effect of cigarette smoke than men [34, 35]. As squamous cell cancers are thought to require a relatively heavy smoking history to develop, a lower exposure but increased susceptibility to cigarette carcinogens may explain the higher prevalence of adenocarcinoma in women. Women may be more likely to smoke cigarettes with lower tar or nicotine content, with resulting deeper inhalation and holding of smoke in the lung to achieve the nicotine effect. The mutational spectrum of transversion mutations in the p53 gene varies by sex, supporting epidemiological data suggesting that women are more at risk from carcinogens of cigarette smoking [36, 37]. It is also clear that mutations in the epidermal growth factor receptor gene (EGFR) are more common in women, and patients with *EGFR* mutations are more likely to benefit from EGFR inhibitors than chemotherapy [38]. However, on further analysis the actual rates of *EGFR* mutations in never smokers are similar between the sexes but more common in women than in men among ever smokers [39]. It has also been reported that *EGFR* mutation status is a more powerful predictor of response to gefitinib than sex or smoking history [40].

It would have been preferable to report post-protocol therapy in this study, to examine the influence of second- and third-line therapies on the primary end point of OS. In particular, patients with adenocarcinoma may benefit from pemetrexed or one of the EGFR inhibitors, erlotinib or gefitinib. However, these data were not available for analysis from the pooled dataset. Furthermore, for the time period of these trials (1997–2006), these drugs were not funded for routine use in the UK, and therefore, it is unlikely that the results would have been significantly different.

Increasingly, the treatment of advanced lung cancer is tailored according to tumor histology, with pemetrexed and the EGFR inhibitors demonstrating better efficacy in patients with adenocarcinoma [41, 42]. Therefore, a better understanding of the interaction between patient sex, smoking history, and histology is important in planning and interpreting future NSCLC trials.

In conclusion, this analysis validates previous research demonstrating longer survival for women with NSCLC treated with chemotherapy, but the benefit seems confined to those with adenocarcinoma histology.

funding

Princess Margaret Hospital Oberlander Lung Cancer Research Fellowship to PW-P.

disclosure

None of the authors declare conflicts of interest.

references

1. Cancer Research UK. UK Lung Cancer and Smoking Statistics. 2006. http://info.cancerresearchuk.org/cancerstats/types/lung/ (last accessed 11 March 2010).
2. Polednak AP. Lung cancer incidence trends in black and white young adults by gender (United States). Cancer Causes Control 2004; 15: 665–670.
3. Wheatley-Price P, Le Maitre A, Ding K et al. The influence of sex on efficacy, toxicity and delivery of treatment in National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) non-small cell lung cancer (NSCLC) chemotherapy trials. J Clin Oncol 2008; 26: (Abstr 8054).
4. Batevik R, Grong K, Segadal L, Stangeland L. The female gender has a positive effect on survival independent of background life expectancy following surgical resection of primary non-small cell lung cancer: a study of absolute and relative survival over 15 years. Lung Cancer 2005; 47: 173–181.
5. Wisnivesky JP, Halm EA. Sex differences in lung cancer survival: do tumors behave differently in elderly women? J Clin Oncol 2007; 25: 1705–1712.
6. Albain KS, Unger J, Gotay CC et al. Toxicity and survival by sex in patients with advanced non-small cell lung carcinoma (NSCLC) on modern Southwest Oncology Group (SWOG) trials. J Clin Oncol 2007; 25: (Abstr 7549).
7. Efficace F, Bottomley A, Smit EF et al. Is a patient's self-reported health-related quality of life a prognostic factor for survival in non-small-cell lung cancer patients? A multivariate analysis of prognostic factors of EORTC study 08975. Ann Oncol 2006; 17: 1698–1704.

8. Wakelee HA, Wang W, Schiller JH et al. Survival differences by sex for patients with advanced non-small cell lung cancer on Eastern Cooperative Oncology Group trial 1594. J Thorac Oncol 2006; 1: 441–446.
9. Visbal AL, Williams BA, Nichols FC 3rd et al. Gender differences in non-small-cell lung cancer survival: an analysis of 4,618 patients diagnosed between 1997 and 2002. Ann Thorac Surg 2004; 78: 209–215; discussion 215.
10. Keller SM, Vangel MG, Adak S et al. The influence of gender on survival and tumor recurrence following adjuvant therapy of completely resected stages II and IIIa non-small cell lung cancer. Lung Cancer 2002; 37: 303–309.
11. Booton R, Lorigan P, Anderson H et al. A phase III trial of docetaxel/carboplatin versus mitomycin C/ifosfamide/cisplatin (MIC) or mitomycin C/vinblastine/cisplatin (MVP) in patients with advanced non-small-cell lung cancer: a randomised multicentre trial of the British Thoracic Oncology Group (BTOG1). Ann Oncol 2006; 17: 1111–1119.
12. Danson S, Middleton MR, O'Byrne KJ et al. Phase III trial of gemcitabine and carboplatin versus mitomycin, ifosfamide, and cisplatin or mitomycin, vinblastine, and cisplatin in patients with advanced nonsmall cell lung carcinoma. Cancer 2003; 98: 542–553.
13. Lee S-M, Woll PJ, Rudd RM et al. A phase III randomised, double blind, placebo controlled trial of gemcitabine/carboplatin with or without thalidomide in advanced non-small cell lung cancer (NSCLC): C1-03. J Thorac Oncol 2007; 2: S359.
14. Rudd RM, Gower NH, Spiro SG et al. Gemcitabine plus carboplatin versus mitomycin, ifosfamide, and cisplatin in patients with stage IIIB or IV non-small-cell lung cancer: a phase III randomized study of the London Lung Cancer Group. J Clin Oncol 2005; 23: 142–153.
15. Blackhall F, Taylor P, Ashcroft L et al. A pragmatic, randomised study to compare the hospitalisation rates of two platinum-based outpatient regimens (gemicitabine/cisplatin vs. gemcitabine/carboplatin) in non-small cell lung cancer (NSCLC)—UK Swiss collaboration. J Thorac Oncol 2007; 2: 338.
16. Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92: 205–216.
17. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981; 47: 207–214.
18. Belani CP, Von Pawel J, Pluzanska A et al. Phase III study of docetaxel-cisplatin (DC) or docetaxel-carboplatin (DCb) versus vinorelbine-cisplatin (VC) as first-line treatment of advanced non-small cell lung cancer (NSCLC): analyses by gender. Lung Cancer 2006; 49S: 235–236.
19. Mandrekar SJ, Schild SE, Hillman SL et al. A pooled analysis of 11 NCCTG advanced stage non-small cell lung cancer (NSCLC) trials reveals the importance of baseline blood counts on clinical outcomes. J Clin Oncol 2005; 23: (Abstr 7193).
20. Chatkin JM, Abreu CM, Fritscher CC et al. Is there a gender difference in non-small cell lung cancer survival? Gend Med 2004; 1: 41–47.
21. 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.
22. Asamura H, Goya T, Koshiishi Y et al. A Japanese Lung Cancer Registry study: prognosis of 13,010 resected lung cancers. J Thorac Oncol 2008; 3: 46–52.
23. Campione A, Ligabue T, Luzzi L et al. Impact of size, histology, and gender on stage IA non-small cell lung cancer. Asian Cardiovasc Thorac Ann 2004; 12: 149–153.
24. Moore R, Doherty D, Chamberlain R, Khuri F. Sex differences in survival in non-small cell lung cancer patients 1974–1998. Acta Oncol 2004; 43: 57–64.
25. Palomares MR, Sayre JW, Shekar KC et al. Gender influence on weight-loss pattern and survival of nonsmall cell lung carcinoma patients. Cancer 1996; 78: 2119–2126.
26. Barsky SH, Cameron R, Osann KE et al. Rising incidence of bronchioloalveolar lung carcinoma and its unique clinicopathologic features. Cancer 1994; 73: 1163–1170.
27. Caldarella A, Crocetti E, Comin CE et al. Gender differences in non-small cell lung cancer: a population-based study. Eur J Surg Oncol 2007; 33: 763–768.
28. Li X, Mutanen P, Hemminki K. Gender-specific incidence trends in lung cancer by histological type in Sweden, 1958-1996. Eur J Cancer Prev 2001; 10: 227–235.
29. Radzikowska E, Glaz P, Roszkowski K. Lung cancer in women: age, smoking, histology, performance status, stage, initial treatment and survival. Population-based study of 20 561 cases. Ann Oncol 2002; 13: 1087–1093.
30. Thun MJ, Lally CA, Flannery JT et al. Cigarette smoking and changes in the histopathology of lung cancer. J Natl Cancer Inst 1997; 89: 1580–1586.
31. Toh CK, Gao F, Lim WT et al. Never-smokers with lung cancer: epidemiologic evidence of a distinct disease entity. J Clin Oncol 2006; 24: 2245–2251.
32. Ou SI, Ziogas A, Zell JA. Epidemiology study of never-smokers with non-small cell lung cancer (NSCLC): high percentages of Asian and Hispanic female never-smokers and the significance of Asian ethnicity. J Clin Oncol 2008; 26: (Abstr 8004).
33. Patel JD. Lung cancer in women. J Clin Oncol 2005; 23: 3212–3218.
34. Henschke CI, Yip R, Miettinen OS. Women's susceptibility to tobacco carcinogens and survival after diagnosis of lung cancer. JAMA 2006; 296: 180–184.
35. Risch HA, Howe GR, Jain M et al. Are female smokers at higher risk for lung cancer than male smokers? A case-control analysis by histologic type. Am J Epidemiol 1993; 138: 281–293.
36. Kure EH, Ryberg D, Hewer A et al. p53 mutations in lung tumours: relationship to gender and lung DNA adduct levels. Carcinogenesis 1996; 17: 2201–2205.
37. Toyooka S, Tsuda T, Gazdar AF. The TP53 gene, tobacco exposure, and lung cancer. Hum Mutat 2003; 21: 229–239.
38. Mok TS, Wu YL, Thongprasert S et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009; 361: 947–957.
39. Toyooka S, Matsuo K, Shigematsu H et al. The impact of sex and smoking status on the mutational spectrum of epidermal growth factor receptor gene in non small cell lung cancer. Clin Cancer Res 2007; 13: 5763–5768.
40. Toyooka S, Takano T, Kosaka T et al. Epidermal growth factor receptor mutation, but not sex and smoking, is independently associated with favorable prognosis of gefitinib-treated patients with lung adenocarcinoma. Cancer Sci 2008; 99: 303–308.
41. Scagliotti G, Hanna N, Fossella F et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two phase III studies. Oncologist 2009; 14: 253–263.
42. Wheatley-Price P, Shepherd FA. Epidermal growth factor receptor inhibitors in the treatment of lung cancer: reality and hopes. Curr Opin Oncol 2008; 20: 162–175.