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The Influence of Sex on Efficacy, Adverse Events, Quality of Life, and Delivery of Treatment in National Cancer Institute of Canada Clinical Trials Group Non-small Cell Lung Cancer Chemotherapy Trials

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Background: Female sex is a favorable prognostic factor in lung cancer. In small-cell lung cancer, women have been shown to experience greater toxicity from chemotherapy, but there are few studies of sex-related toxicity in non-small cell lung cancer (NSCLC).

Patients and Methods: This retrospective analysis evaluated the effect of sex on efficacy, adverse events (AEs), dose intensity (DI), and quality of life (QoL) in three phase III NSCLC trials conducted by the National Cancer Institute of Canada Clinical Trials Group; BR.10 (adjuvant chemotherapy), BR.14, and BR.18 (first-line advanced disease). Only patients with National Cancer Institute of Canada Clinical Trials Group data were included, and patients in the BR.10 observation arm were excluded.

Results: Of 1108 patients analyzed, 29% were female. On study entry, women were less likely to be overweight or obese (40% versus 51%, $p < 0.0001$), more likely to have adenocarcinoma (70% versus 44%, $p < 0.0001$), and less likely to be anemic at baseline (29% versus 55%, $p < 0.0001$) or have medical comorbidities. There were no significant differences in response rate to chemotherapy (27% versus 31%, $p = 0.44$ [excluding BR.10]), grade 3 or 4 AEs, DI, or QoL between sexes, although women reported more nausea and vomiting of any grade (77% versus 66%, $p = 0.0004$). In multivariate analysis, women had longer progression-free survival than men (hazard ratio 0.83, 95% confidence interval 0.71–0.97, $p = 0.02$) but not overall survival (hazard ratio 0.89, 95% confidence interval 0.75–1.05, $p = 0.17$).

Conclusion: Women demonstrate modestly longer progression-free survival than men in chemotherapy-treated NSCLC, with no differences observed in response rates, serious AEs, or QoL.

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Disclosure: The authors declare no conflicts of interest.

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ISSN: 1556-0864/10/0505-0640

Key Words: Chemotherapy, Sex, Non-small cell lung cancer.

(*J Thorac Oncol.* 2010;5: 640–648)

Lung cancer is the most common cause of cancer death worldwide, with more than one million cases annually.[1,2] In North America in 2008, there were more than 239,000 new lung cancer cases, resulting in more than 181,000 deaths.[3,4]

Sex may influence outcomes of treatment for lung cancer. In various tumor types, females have been shown to experience greater toxicity from chemotherapy.[5–10] Singh et al. reported significant differences in toxicity to chemotherapy in patients with small-cell lung cancer (SCLC) in an analysis of National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) trials, where women experienced significantly more hematologic and nonhematologic toxicity. As in other SCLC studies, women also had significantly improved response and overall survival (OS) from treatment.[9] Improved survival in women has been reported in a number of malignancies, including oral, colon, and esophageal cancer and melanoma.[11–14] Indeed, a recent analysis in the USA reported that the 10-year risk of death from all causes combined (heart disease, stroke, cancer, pneumonia, AIDS, accidents, and chronic obstructive pulmonary disease) is higher for men than women.[15]

The effect of sex on treatment outcomes in non-small cell lung cancer (NSCLC) is less clear, with some but not all studies reporting a more favorable outcome for women compared with men.[16–22] In this retrospective pooled analysis of NSCLC chemotherapy trials performed by the NCIC CTG, we investigated the influence of sex on efficacy, adverse events (AEs), dose delivery, and quality of life (QoL).

PATIENTS AND METHODS

Studies Included and Treatment

Studies were selected for inclusion if they were randomized phase III studies conducted by the NCIC CTG using modern chemotherapy doublets. All trials received ethics

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TABLE 1. NCIC Clinical Trials Group NSCLC Trials Included in the Analysis

Study	Treatment	Number Analyzed in Sex Analysis	
		Female	Male
BR.10 Winton et al.[23]	Cisplatin 50 mg/m^2 d1+ 8 q4 wk × 4 cycles + vinorelbine 25 mg/m^2 weekly × 16[a]	79	152
	vs		
	Observation		
BR.14 Gridelli et al.[24]	Cisplatin 80 mg/m^2 d1 + vinorelbine 30 mg/m^2 on d1+ d8 q3 wk × 6 cycles	35	57
	or		
	Cisplatin 80 mg/m^2 d1 + gemcitabine 1200 mg/m^2 d1+ 8 q3 wk × 6 cycles		
	vs		
	Vinorelbine 25 mg/m^2 + gemcitabine 1000 mg/m^2 d1+ 8 q3 wk × 6 cycles		
BR.18 Leighl et al.[25]	Carboplatin AUC 6 + paclitaxel 200 mg/m^2 d1 q3 wk, up to 8 cycles, plus oral BMS-275291 1200 mg daily (until disease progression or intolerable toxicity)	206	561
	vs		
	Carboplatin AUC 6 + paclitaxel 200 mg/m^2 d1 q3 wk, up to 8 cycles, plus oral placebo daily (until disease progression or intolerable toxicity)		

[a] 18 patients were treated with vinorelbine 30 mg/m^2 before a protocol amendment.

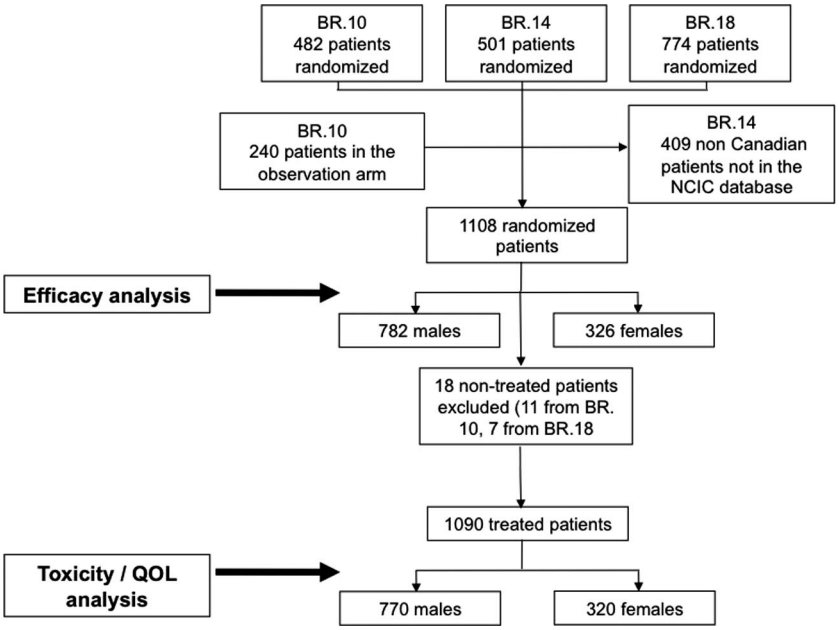

FIGURE 1. Study flow diagram.

board approval and all patients gave informed consent. All patients, except those in the observation arm of BR.10, were included for efficacy analysis if NCIC CTG held their data. Patients who were randomized to receive chemotherapy but received no cycles were excluded from the AE and QoL analyses. The studies and their treatment arms are listed in Table 1.

The BR.10 study investigated adjuvant cisplatin/vinorelbine chemotherapy versus observation in patients with resected stage IB or stage II NSCLC.[23] The BR.14 study was a three-arm study, comparing cisplatin/vinorelbine or cisplatin/gemcitabine versus vinorelbine/gemcitabine in patients with advanced (stage IIIB or IV) NSCLC. This trial was conducted by the GEMVIN investigators (Naples, Italy, and the NCIC CTG). Only the Canadian patients were included in this analysis.[24] The BR.18 study randomized patients with advanced NSCLC (stage IIIB or IV) to carboplatin/paclitaxel with either BMS-275291 (a broad-spectrum matrix metalloproteinase inhibitor) or placebo.[25] Patients included in the pooled analysis are shown in Figure 1.

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Assessment

The primary end points of this analysis were efficacy, AE, dose delivery, and QoL. The primary efficacy end points included OS, progression-free survival (PFS), or relapse-free survival (RFS) and tumor response. Responses were measured using the World Health Organization criteria in BR.14[26] and RECIST (Response Evaluation Criteria in Solid Tumors) in BR.18.[27] PFS (BR.14 and BR.18) and RFS (BR.10) were pooled and calculated from the date of randomization until the date of the event. OS was calculated from the date of randomization until the date of death or date of last follow-up.

AEs were graded and reported using NCIC CTG expanded toxicity criteria (BR.10), World Health Organization toxicity criteria (BR.14),[26] and National Cancer Institute Common Toxicity Criteria (NCI CTC) version 2 (BR.18).[28] Both hematological (neutropenia, anemia, thrombocytopenia, and febrile neutropenia) and nonhematological (emesis, mucositis, fatigue, diarrhea and nonneutropenic infection) AEs were assessed, because these had been found to differ between sexes in previous studies.[9] All common and important AEs (grade 1 and above) and severe AEs (grade 3 and 4) were reported, regardless of their relationship to study medication.

DI was calculated by the total dose of chemotherapy delivered divided by the total planned dose. The number of treatment delays or dose reductions was calculated for each patient. For patients who received more than the planned 6 cycles in BR.18, DI was calculated by dividing the total dose given and the total dose planned by the number of weeks of treatment. The total dose of chemotherapy administered and the number of dose reductions were calculated using all included patients from the start of treatment until completion of the last cycle of chemotherapy.

QoL was assessed in all trials using the European Organization for Research and Treatment of Cancer QoL questionnaire QLQ-C30 and the lung cancer-specific QoL module QLQ-LC13.[29,30]

Statistical Methods

To evaluate an overall patient sex effect while controlling for the effect of treatment received, all analyses were performed stratified by treatment arm whenever applicable. Mantel-Haenszel tests were used to compare the characteristics of patients, response rates, AEs, and dose delivery between sexes. Stratified logistic regression was performed to examine for potentially confounding covariates including age, performance status, body surface area, pathologic subtype, and hemoglobin level at baseline. Survival curves were estimated by the Kaplan-Meier method and compared with the stratified log-rank test between different groups. Cox regression models, stratified by treatment received, were used to study the effect of patient sex while adjusting for prognostic factors.

In assessing changes in QoL, the Cochran-Armitage test was used to detect trends in QoL in each study, and the Mantel-Haenszel test was used in the pooled database to test the trend stratified by treatment received.[31] For functional domain scores, patients were classified as improved if there was a score $\geq$10 points higher than baseline at any time point in the assessment period or worsened if there was a drop in score of $\geq$10 points without the aforementioned defined improvement, and the rest were classified as stable. For symptom domains and single items, the classification of responses was reversed because lower scores from baseline indicate improvement.

RESULTS

Patients

Of 1757 patients randomized into the 3 trials, 409 Italian patients were excluded from the BR.14 study because their data were not held by NCIC CTG. The 240 patients in the observation arm of BR.10 were excluded. A total of 1108 patients were analyzed for survival, of whom there were 326 females (29%) and 782 males (71%). Eighteen patients (11 in BR.10 and 7 in BR.18) were not treated and therefore excluded from the AEs and QoL analyses (Figure 1). Baseline patient characteristics are shown in Table 2.

Women were more likely to have adenocarcinoma histology (70% versus 44%, $p < 0.0001$), and using body mass index, were more likely to be either of normal weight or underweight than men (60% versus 49%, $p < 0.0001$). Conversely, women were less likely to be anemic at baseline (29% versus 55%, $p < 0.0001$), or to have other comorbidities such as diabetes mellitus, ischemic heart disease, hypertension, or chronic obstructive pulmonary disease (32% versus 47%, $p < 0.0001$). A history of cigarette smoking was only recorded in the BR.10 study, where 7 women (9%) in the chemotherapy arm were never smokers, whereas none of the men was classified as a never smoker ($p < 0.0001$).

Efficacy

Response rates, measured in BR.14 and BR.18, were not significantly different between women and men (27% versus 31%, $p = 0.44$).

PFS was significantly longer in women in both univariate (hazard ratio [HR] for disease progression 0.80, 95% confidence interval [CI] 0.69–0.93, $p = 0.003$) (Figure 2*A*) and multivariate analysis (adjusting for age, stage at randomization, treatment arm, baseline hemoglobin, body surface area, and performance status) (HR 0.83, 95% CI 0.71–0.97, $p = 0.02$).

In univariate analysis, women had a significantly longer OS than men (HR 0.81, 95% CI 0.68–0.95, $p = 0.01$) (Figure 2*B*), but this was not statistically significant in multivariate analysis (HR 0.89, 95% CI 0.75–1.05, $p = 0.17$).

In multivariate analysis (adjusting for the same factors as for PFS), only baseline anemia was a predictor of poor OS, where patients with $\geq$ grade 1 anemia at baseline had a HR for death of 1.60 (95% CI 1.37–1.86, $p < 0.0001$). Baseline anemia also predicted for shorter PFS (HR 1.34, 95% CI 1.17–1.54, $p < 0.0001$), as did nonsquamous, nonadenocarcinoma histology (HR 1.34, 95% CI 1.11–1.63, $p = 0.003$).

When assessing the effect of patient sex in the individual studies, longer PFS and OS in women was observed in all studies. In BR.10 ($n = 242$), women had longer RFS (not reached versus 72 months, HR 0.69 [0.45–1.06], $p = 0.09$) and OS (94 versus 78 months, HR 0.65 [0.40–1.05], $p =$

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TABLE 2. Comparison of Baseline Patient Characteristics by Sex

	Female $n = 320$ (29%)	Male $n = 770$ (71%)	p
Trials and treatment groups			
Trial			
BR.10 (number analyzed = 231)	79 (34%)	152 (66%)	0.02
BR.14 (number analyzed = 92)	35 (38%)	57 (62%)	
BR.18 (number analyzed = 767)	206 (27%)	561 (73%)	
Treatment group			
BR.10 Vin Cis ($n = 231$)	79 (34%)	152 (66%)	0.01
BR.14 Gem Cis ($n = 23$)	10 (43%)	13 (56%)	
BR.14 Gem Vin ($n = 46$)	18 (39%)	28 (61%)	
BR.14 Cis Vin ($n = 23$)	7 (30%)	16 (70%)	
BR.18 Pac Carbo placebo ($n = 385$)	103 (27%)	282 (73%)	
BR.18 Pac Carbo BMS ($n = 382$)	103 (27%)	279 (73%)	
Patient demographics			
Age			
≤65	209 (65%)	520 (67%)	0.40
>65	111 (35%)	250 (32%)	
Stage (at surgery in BR.10, at randomization in BR.14 and BR.18)			
I	39 (12%)	64 (8%)	Not applicable[a]
II	40 (12%)	88 (11%)	
III	40 (12%)	134 (17%)	
IV	201 (63%)	484 (63%)	
Body surface area (BSA)			
<2	305 (95%)	581 (75%)	<0.0001
≥2	15 (5%)	189 (25%)	
Body mass index (BMI) (weight [kg]/height [m^2])			
Underweight (<18.5)	28 (9%)	28 (4%)	<0.0001
Normal weight (18.5–24.9)	162 (51%)	344 (45%)	
Overweight (25.0–29.9)	81 (25%)	275 (36%)	
Obese (>30.0)	47 (15%)	111 (15%)	
ECOG performance status			
0	118 (37%)	247 (32%)	0.52
1	175 (55%)	449 (58%)	
2 or 3	27 (8%)	74 (10%)	
Pathological subtype			
Adenocarcinoma	223 (70%)	338 (44%)	<0.0001
Squamous cell carcinoma	32 (10%)	246 (32%)	
Other	65 (20%)	186 (24%)	
Baseline hemoglobin			
Grade 0	226 (71%)	346 (45%)	<0.0001
Grade 1 or more	93 (29%)	421 (55%)	
Comorbidities			
Any comorbidity	103 (32%)	363 (47%)	<0.0001
Diabetes mellitus	9 (3%)	64 (8%)	0.001
Ischaemic heart disease	4 (1%)	26 (3%)	0.06
Cerebrovascular disease	8 (2%)	14 (2%)	0.46
Hypertension	69 (22%)	219 (28%)	0.02
COPD	33 (10%)	156 (20%)	0.0002

[a] Trials were stratified by stage.

Vin, vinorelbine; Cis, cisplatin; Gem, gemcitabine; Pac, paclitaxel; Carbo, carboplatin; BMS, BMS-275291; ECOG, Eastern Cooperative Oncology Group; COPD, chronic obstructive pulmonary disease.

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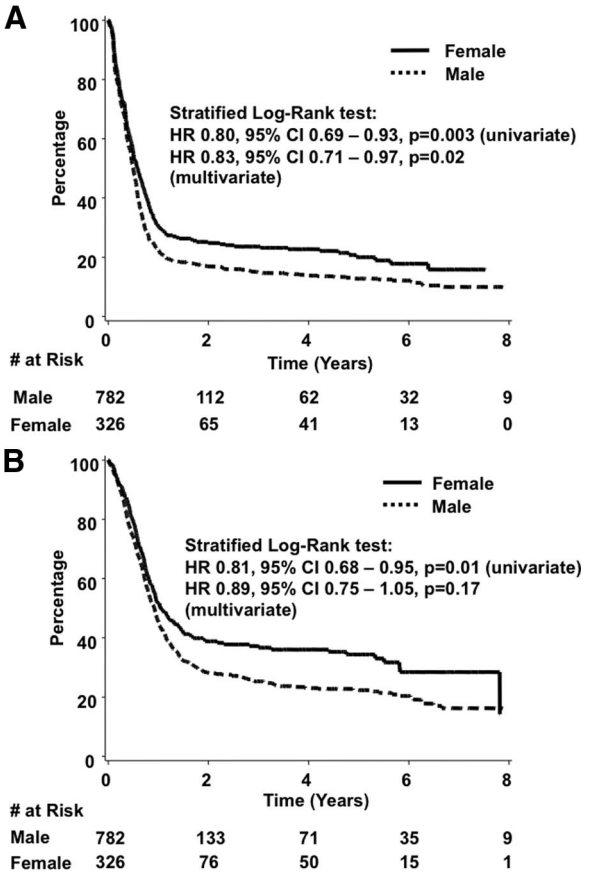

FIGURE 2. Progression-free survival (*A*) and overall survival (*B*) by sex in the pooled database.

0.08) than men. In BR.14 ($n = 92$), women had longer PFS (5.6 versus 4.1 months, HR 0.77 [0.47–1.28], $p = 0.31$) and OS (11.9 versus 8.9 months, HR 0.74 [0.39–1.44], $p = 0.38$) than men.

In BR.18 ($n = 774$), women had longer PFS (5.2 versus 4.8 months, HR 0.82 [0.70–0.97], $p = 0.02$) and OS (9.5 versus 8.8 months, HR 0.84 [0.70–1.01], $p = 0.06$) than men. In BR.18, data were also available on postprotocol lines of therapy. Second-line therapy was administered to 46% of patients, and when this was included in the multivariate analysis, female sex remained a significant predictor of longer survival (HR 0.83 [0.69–1.00], $p = 0.046$).

Adverse Events

There was no statistically significant difference in severe (grade 3 or 4) AEs between the sexes in any of the trials or in the pooled analysis (Table 3). Women were more likely to report nausea or vomiting of any grade than men (78% versus 66%, $p = 0.0004$), but the difference was only a trend when confined to grade 3 or 4 (10% versus 6%, $p = 0.077$). Women were less likely to experience anemia of any grade (91% versus 98%, $p < 0.0001$), but there was no significant difference in grade 3 or 4 anemia (9% versus 10%, $p = 0.85$). In a stepwise logistic regression analysis, patient sex and baseline hemoglobin correlated with the risk of anemia. The use of erythropoietin was reported in 81 cases in the BR.18 study only (23 women [11%] and 58 men [10%], $p = 0.74$), but this had no effect on PFS or OS. There were no significant differences between men and women in rates of thrombocytopenia, neutropenia, or febrile neutropenia. There was no significant difference in the rates of grade 5 AEs (death) of all causalities between women and men (1% versus 2%).

Treatment Delivery and DI

In the pooled analysis, there was no significant difference in the number of dose reductions or dose delays required between women and men. In BR.18, women were more likely to have carboplatin doses omitted (8% versus 3%, $p = 0.002$) or treatment delays because of hematological toxicity (16% versus 10%, $p = 0.02$). There was no difference in the DI of cisplatin, carboplatin, vinorelbine, or paclitaxel between the sexes.

Quality of Life

There were no major differences in compliance between women and men at baseline or at any time point in each of the trials. In the pooled analysis, there were no significant differences in any QoL measures between women and men. In the global QoL score, 50% of women reported improvement compared with 42% of men ($p = 0.11$). There were no significant differences in rates of improvement of the main lung cancer symptoms between women and men (cough: 37% versus 41%, $p = 0.97$; dyspnea: 35% versus 34%, $p = 0.98$; pain: 59% versus 60%, $p = 0.83$). In addition, no significant differences between sexes were seen in cognitive, emotional, financial, role, or social function (Table 4).

In BR.10, women reported more improvements in dyspnea (38% versus 26%, $p = 0.03$), cognitive function (38% versus 20%, $p = 0.02$), emotional function (62% versus 36%, $p = 0.004$), social function (69% versus 48%, $p = 0.04$), and global QoL (62% versus 39%, $p = 0.007$) than men.

DISCUSSION

In this retrospective pooled analysis of NCIC CTG NSCLC phase III trials, we demonstrate only small efficacy and AE differences between women and men. No significant difference in response rate was observed between sexes, and although a modest improvement in PFS was seen among women, OS was not significantly different in multivariate analysis. This is in contrast to our analysis of the influence of sex in NCIC CTG SCLC trials where we demonstrated a clear efficacy benefit for women,[9] a finding that has been demonstrated in other SCLC studies.[32,33] Given the difference in observations of PFS and OS, postprotocol therapy was investigated in BR.18 (the only study that collected such data). When second-line therapy was included in the multivariate model, female sex remained a predictor of longer OS.

Evidence that treatment with chemotherapy may be more effective in women with NSCLC is increasing. Although two previous analyses of the role of sex on outcomes from chemotherapy showed no significant difference in response rates,[18,22] a number of studies have shown an OS benefit to women. Two published series from the Southwest Oncology Group reported female sex to be a positive prog-

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TABLE 3. Comparison of Adverse Events by Sex

Grade	Adverse Event Variable	Female	Male	*p*
Hematological parameters				
≥ Grade 1	Hemoglobin	291 (91%)	753 (98%)	<0.0001
	Platelets	172 (54%)	412 (54%)	0.72
	Neutrophils	273 (86%)	624 (81%)	0.14
≥ Grade 3	Hemoglobin	30 (9%)	78 (10%)	0.85
	Platelets	22 (7%)	46 (6%)	0.49
	Neutrophils	207 (65%)	465 (61%)	0.18
	Febrile neutropenia	22 (7%)	65 (8%)	0.42
Nonhematological parameters				
≥ Grade 1	Stomatitis	69 (22%)	139 (18%)	0.17
	Nausea/vomiting	249 (78%)	506 (66%)	0.0004
	Infection (nonneutropenic)	97 (30%)	217 (28%)	0.53
	Fatigue	261 (82%)	615 (80%)	0.57
	Renal	37 (12%)	117 (15%)	0.06
	Neuropathy	180 (56%)	452 (59%)	0.98
	Anorexia	151 (47%)	377 (49%)	0.78
≥ Grade 3	Stomatitis	4 (1%)	9 (1%)	0.84
	Nausea/vomiting	31 (10%)	48 (6%)	0.08
	Infection (nonneutropenic)	19 (6%)	66 (9%)	0.20
	Fatigue	56 (17%)	129 (17%)	0.67
	Renal	3 (1%)	16 (2%)	0.22
	Neuropathy	29 (9%)	92 (12%)	0.33
	Anorexia	13 (4%)	40 (5%)	0.35
Grade 5 adverse events (death) of all causalities		2 (1%)	15 (2%)	0.18

TABLE 4. Comparison of Quality of Life by Sex

	Female (%)			Male (%)			
	Improved	Stable	Worse	Improved	Stable	Worse	*p*
Cognitive function	33	30	37	28	34	38	0.44
Emotional function	53	27	20	45	32	24	0.21
Physical function	39	22	39	32	27	42	0.38
Role function	47	20	34	35	27	38	0.11
Financial concerns	21	61	17	22	56	22	0.60
Nausea	27	39	34	22	44	34	0.54
Cough	37	39	24	41	33	26	0.97
Dyspnea	35	35	30	34	38	29	0.98
Pain	59	16	26	60	13	27	0.83
Global QoL	50	21	28	42	23	35	0.11

QoL, quality of life.

nostic factor, although in the more recent analysis, the effect seemed to be limited to women older than 60 years.[16,17] Retrospective analyses of the E1594 study of four chemotherapy regimens in advanced NSCLC, the European Organization for Research and Treatment of Cancer 08975 study (cisplatin/gemcitabine, cisplatin/paclitaxel, or gemcitabine/paclitaxel in advanced NSCLC), and a Mayo Clinic series all reported a small median survival advantage for women over men.[21,22,34] HRs reported in these series are similar to that found in our analysis, although the difference in our study was not statistically significant (HR 0.89, 95% CI 0.75–1.05, $p = 0.17$), perhaps due to slightly smaller numbers. Although there are three other series that do not report a statistically significant survival advantage for women (one of which was a pooled analysis that included the previously mentioned E1594 study),[18,20,35] it would seem that women with NSCLC likely do experience modestly longer survival than men when treated with chemotherapy.

In our analysis, some AE differences were observed between sexes. Women experienced more nausea and vomiting of any grade, although differences in grade 3 or 4 emesis did not reach statistical significance. Our similar analysis of

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SCLC trials from NCIC CTG reported that women experienced more hematological and nonhematological toxicities than men.[9] When comparing the two analyses, the proportions of women and men experiencing nausea or vomiting of any grade are similar (NSCLC: 78% versus 66%; SCLC: 77% versus 67%), and in both studies, the difference in grade 3 and 4 emesis outcomes just failed to reach statistical significance (NSCLC: $p = 0.08$; SCLC: $p = 0.06$). Higher rates of nausea and vomiting in women were also reported in the E1594, TAX 326, and NCCTG publications.[18,20,22] It is interesting to note that in phase III trials investigating the neurokinin-1 antagonist, aprepitant, in chemotherapy-induced nausea and vomiting, women had lower rates of emesis control in the control arm, but with the addition of aprepitant, the rates of chemotherapy-induced nausea and vomiting fell in both men and women and there was no longer a significant difference between sexes.[36] We observed no difference in the rates of stomatitis in this study, although previous studies have reported that women may expect higher rates of stomatitis/mucositis.[9,10]

As expected, given the relatively small differences in AEs, there were no significant differences seen in dose delays or dose reductions between sexes. We could find no previous reports of DI differences in NSCLC, but our SCLC analysis demonstrated that women were more likely to have treatment delays of more than 2 weeks (52% versus 43%, $p = 0.02$),[9] although an older analysis of 1521 patients with SCLC reported no sex differences in DI.[33]

To our knowledge, this is the first analysis that has examined QoL differences between sexes in a pooled dataset of lung cancer trials. In the adjuvant BR.10 study, among those patients in the chemotherapy arm, women reported greater improvements in dyspnea, cognitive function, emotional function, social function, and global QoL than men. However, when combined with the data from the BR.14 and BR.18, studies of chemotherapy in advanced disease, the benefits were no longer seen. Caution is needed in this mixed dataset, however, because QoL in the adjuvant setting may be quite different to the palliative setting. One might expect QoL to deteriorate in the adjuvant setting because of toxicity of treatment, whereas in the metastatic setting this may be offset by an improvement in cancer symptoms if the cancer burden is reduced. It would be interesting to see if more QoL differences would be reported in a situation where there was a clearer difference in either efficacy or toxicity between sexes.

Nausea as a QoL measure was not different between genders in this analysis, although women reported more nausea and vomiting as an AE. This discrepancy is most likely explained by timing of the measurements. QoL measures were recorded as how the patient felt when the questionnaire was administered just before chemotherapy. AE recording accounts for nausea occurring at any point in each cycle, which was more likely in the first days after treatment. It is possible that although women may report more nausea than men, it may not particularly affect their daily QoL.

There is little comparable data on gender differences in QoL outcomes in cancer. Female terminal care cancer patients have reported higher rates of nausea and vomiting than men, using the QLQ-C30 questionnaire.[37] In patients with locally advanced NSCLC, assessed before treatment using the Functional Living Index-Cancer scale, women reported lower scores, i.e., worse QoL, than men.[38] Elderly women with cancer have reported lower QoL scores, lower sense of coherence, and greater economic and social concerns than elderly men with cancer.[39] Women have also reported worse global health and physical functioning after rectal cancer surgery or coronary artery bypass surgery,[40,41] and worse health-related QoL scores in chronic obstructive pulmonary disease patients.[42] In addition, women have reported higher fatigue scores and more depression than men in a number of studies.[43–47]

Survival advantages for women are more clearly seen in SCLC rather than NSCLC. As both types of cancer are treated most commonly with platinum-based chemotherapy, it would seem less likely that sex-based differences in drug metabolism contribute a great deal, although variable drug distribution because of body habitus differences between sexes, and sex differences in cytochrome P450 activity have been proposed as hypotheses.[48] There is little evidence available to support clear differences in drug metabolism of specific cancer drugs. Methods of calculating glomerular filtration rate used in carboplatin dosing include the Cockroft-Gault, Calvert, Chatelut, and the Jelliffe formulae. Depending on which formula is used, the doses may vary between sexes.[49,50] A study of pharmacokinetics in 168 patients with solid tumors, including 84 NSCLC patients, demonstrated that sex significantly and independently affected paclitaxel distribution and elimination, where males had a 20% higher maximal elimination capacity.[51] We could find no reports of sex differences in drug metabolism of cisplatin, vinorelbine, or gemcitabine. Therefore, the hypothesis that women have higher DI, perhaps due to pharmacokinetic or pharmacodynamic differences, leading to greater toxicity and improved survival remains plausible, although this analysis cannot strongly support it.

The trials we reviewed in this retrospective analysis were heterogeneous, containing patients treated in both the adjuvant and metastatic setting. However, it would seem unlikely that tumor biology differences in early stage and late stage disease would vary by patient sex; indeed numerically longer PFS/RFS and OS for women were seen in each of our trials analyzed, even if this only reached statistical significance in BR.18, the study that contributed the largest number of patients. Furthermore, cigarette smoking history was not widely available, particularly in the metastatic trials. Women with lung cancer are more likely to be never smokers, and a history of never smoking is a positive prognostic factor.[52] We were unable to control for this in our analysis, and the interplay among patient sex, smoking history, histology, and outcomes is clearly an area for future research. Concomitant medications may differ between sexes, particularly as we demonstrated a higher level of comorbidities in men. The potential influence of these drugs on chemotherapy and the measured outcomes is unknown. The role of activating *EGFR* mutations is also of interest following observations that

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responses to the EGFR tyrosine kinase inhibitors are more common in women and never smokers. In an exploratory analysis from the BR.10 study, activating *EGFR* mutations were not found to be prognostic for OS or predictive of a benefit from adjuvant chemotherapy.[53]

In conclusion, this analysis demonstrates modest differences in efficacy and toxicity outcomes between women and men receiving chemotherapy for NSCLC. Decisions regarding the choice of chemotherapy should not be influenced by patient sex.

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