Original Article

Gender effects on quality of life and symptom burden in patients with lung cancer: results from a prospective, cross-cultural, multi-center study

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Background: Lung cancer causes impairment of health-related quality of life (QoL), but little is known about gender aspects in QoL and symptom burden of lung cancer patients. The aim of this study was to investigate gender differences in QoL as assessed by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and the updated lung cancer module.

Methods: In a prospective, international, cross-cultural, multicenter study that was undertaken to update the lung cancer-specific module EORTC QLQ-LC13, patients filled in the core questionnaire EORTC QLQ-C30 and the updated lung cancer module. Gender differences were calculated for all QoL scores using ANCOVAs that controlled for known and suspected confounders. Comparisons with historic data were drawn.

Results: A total of 200 patients (82 female and 118 male, median age 65 years) were recruited. With the exception of coughing (estimated marginal means: women 33.86 and men 43.52, P=0.022) and diarrhea (estimated marginal means: women 26.01 and men 17.93, P=0.038) there were no significant QoL gender differences. Fatigue was the most pronounced symptom in both, men and women, outpacing typical respiratory symptoms. Quite generally, our sample of lung cancer patients showed considerably worse QoL in all scores when compared to EORTC reference data (lung cancer and combined cancer diagnoses, mean differences up to 13.70 and 21.54 score points, respectively) and to a German norm reference sample (up to 35.37 score points).

Conclusions: This study adds to the literature in showing that the typical QoL gender difference effect

(women doing worse than men) may not be generalizable across all patient samples.

Keywords: Quality of life (QoL); gender differences; lung cancer; European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30); EORTC QLQ-LC29

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Introduction

Gender aspects are becoming an increasingly important topic in the treatment of lung diseases. A number of recent clinical examples illustrate this point. Lung cancer, one of the most common cancers worldwide and the leading cause of cancer associated with death (1-3), has witnessed a growing incidence in women in recent years (1,4-6). Female patients present with more advanced disease stages and at a younger age than men, which may be attributable to time trends in smoking habits and their related effects (1). Adenocarcinoma is the most common type of lung cancer in female patients (1,7). Women respond better to various therapies in non-small cell lung cancer (NSCLC) than men with benefits in overall survival (1,5). A Japanese nationwide registry study covering 12,509 patients showed overall survival benefits for women after resection of primary lung neoplasms (5-year survival rate of women 75.6% *vs.* men 57.95%) (7). Women with chronic obstructive pulmonary disease (COPD) suffer from more exacerbations (8) and greater impairment of their health status than men (9). A recent review on asthma coined the phrase "the female lung" and came to the conclusion that women experience more asthma symptoms than men and use more rescue medications, which results in reduced quality of life (QoL) (10).

The analysis of gender differences has a long tradition in QoL research (11-17). Large-scale studies on representative samples conducted in Germany and Norway have consistently shown that women report lower levels of QoL and higher symptom burden than men as assessed by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 core questionnaire (11-17). This gender effect is relevant with regard to oncological therapy, since considerations regarding patients' QoL during and after treatment are becoming a topic of growing interest (13,18). For one, QoL contributes to increased overall survival (19), for the other improving QoL is a treatment goal on its own. In the context of clinical studies it has become standard to include QoL measures as endpoint variables (20). Therefore, for determining gender differences in patients with lung cancer is important to identify areas of need for patients and to ensure the best possible clinical outcome.

Lung cancer patients may suffer from numerous symptoms, such as dyspnea, coughing, pain and fatigue, which have a negative impact on their QoL (4,21). The EORTC QLQ-C30 is a well-known questionnaire used to assess QoL of cancer patients in oncological clinical trials (11). Additionally, as a lung cancer-specific module the QLQ-LC13 covers 13 typical symptoms of lung cancer patients. It has been used since 1994 together with the core questionnaire QLQ-C30 (22). Due to the changes in diagnostic and therapeutic options in lung cancer treatment, an international multicenter research project has been initiated to update the EORTC lung cancer module, according to the scientifically acknowledged EORTC procedure (20,22).

In the course of this project data are available that allow to investigate gender differences in QoL reporting. The goal of the present paper was to analyze whether female and male lung cancer patients differ with regard to their self-reported somatic symptoms and functional QoL outcomes, and whether certain symptoms are reported as being more intense or more frequent in women than in men. Based on the previous findings of large scale studies (11-17), we proceeded with the hypothesis that women report worse QoL and more intense symptoms than men. We present the following article in accordance with the SURGE reporting checklist (23) (available at http://dx.doi.org/10.21037/jtd-20-1054).

Methods

Study design

The current report is based on a prospective, international, cross-cultural, multicenter study that was designed to update the EORTC QLQ-LC13. Patients were stratified according to their primary therapy (surgery, radiochemotherapy or targeted therapy) and time frame (questionnaire

administration during or shortly after therapy) in order to pick up side effects related to the therapy when assessing QoL. The study recruitment took place in nine different geographical locations (Germany, Great Britain, Italy, Israel, Norway, Poland, Spain, Taiwan and Cyprus) from February 2014 until February 2015. The study was approved by the Ethical Committee of the University of Regensburg, Germany (reference number 11-101-0024) and by the local ethical committees of the participating centers. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All patients gave their informed consent prior to being enrolled into this study. Details of the study methodology have been reported earlier (14). The original study protocol was registered with clinicaltrials.gov (reference number NCT01434784).

Patients

The following eligibility criteria applied: histologically proven non-small cell lung cancer (NCSLC) or small cell lung cancer (SCLC), 18 years of age or older, no previous other or recurrent tumor, cognitive and physical ability to fill in a questionnaire and written informed consent. Patients were excluded from the study if any of the above criteria was not fulfilled.

Procedure

Upon being informed about the study and providing written consent, patients filled in the paper-and-pencil version of the EORTC QLQ-C30 and the updated lung cancer module QLQ-LC29 (22). Thereafter, patients participated in a structured interview to evaluate the content of the questionnaires. Clinical data were recorded by the study personnel, using a standardized case report form (CRF).

Questionnaires

The EORTC QLQ-C30 (version 3.0) is a core questionnaire designed for the use in international clinical trials and addresses issues relevant for cancer patients of any tumor type (24,25). As its name suggests, the questionnaire consists of 30 individual items that are aggregated into a global quality of life score, five multi-item function scores (social, role, physical, cognitive, and emotional functioning), three multi-item symptom scores (nausea, pain, fatigue), and five single items (diarrhea, constipation, dyspnea, appetite loss, insomnia). Items are accompanied by four-item Likert scales with the response options labeled (I) "not at all", (II) "a little", (III) "quite a bit" and (IV) "very much", with the exception of the two global quality of life items that are presented with a seven-item Likert scale (1=very poor to 7=excellent). According to the EORTC scoring manual, linear transformations are applied, resulting into scores from 0 to 100 (25). In the case of functional scores 0 denotes lowest and 100 highest functioning, in the case of symptom scales 0 denotes lowest and 100 highest symptom burden.

The updated EORTC lung cancer module consists of 29 items (22). The original QLQ-LC13 has been preserved (with the exception of one item tapping into pain medication) and amended by items assessing therapy-related side effects, existential issues and surgery-related symptoms. An initial psychometric analysis suggests that the QLQ-LC29 consists of five multi-item scales (coughing, shortness of breath, side effects, fear of progression, surgery-related symptoms) and five single items (coughing blood, pain in the chest, pain in the shoulder, bodily pain, problems with weight loss) (22).

Statistical analyses

Basic descriptive statistics included counts, percentages, medians/interquartile ranges (IQR), means and confidence intervals.

Gender differences in all QoL aspects were analyzed using univariate (*t*-test) and multivariable (analyses of covariance, ANCOVA) models. ANCOVAs adjusted for the following covariates: age, tumor type (NSCLC *vs.* SCLC), therapeutic approach (curative *vs.* palliative), living partner (with *vs.* without), education (compulsory *vs.* higher), primary therapy (surgery *vs.* chemo radiation therapy *vs.* targeted therapy), stage (NSCLC stage IV *vs.* other stages), region (English speaking *vs.* northern *vs.* southern *vs.* eastern countries) and comorbidity (yes/no). Estimated marginal means with corresponding 95%-confidence intervals were presented as effect estimates. A P value <0.05 was considered as the threshold of statistical significance. Due to the exploratory nature of all analyses, corrections for alpha-error were not applied. Furthermore, we compared descriptive data of our sample with descriptive data of historic controls, namely EORTC large scale cancer reference values (21) and representative German population values (11). Differences between our sample and historic samples were calculated using weighted means across men and women.

We also analyzed age effects on QoL reporting. In

Table 1 Patient characteristics

Characteristics	Total (n=200)	Women (n=82)	Men (n=118)
Age, median [IQR]	65 [57–71]	63.5 [56–69]	65 [58–71]
Smoking status			
Non-smoker	26 (13%)	17 (65.4%)	9 (34.5%)
Smoker	42 (21%)	15 (35.7%)	27 (64.3%)
Ex-Smoker	132 (66%)	50 (37.9%)	82 (62.1%)
Disease			
SCLC (all stages)	35 (17.5%)	18 (22.0%)	17 (14.4%)
NSCLC (all stages)	165 (82.5%)	64 (78%)	101 (85.6%)
Therapeutic approach			
Curative	88 (44%)	35 (39.8%)	53 (60.2%)
Palliative	112 (56%)	47 (42.0%)	65 (58.0%)
Comorbidity			
Yes	133 (66.5%)	49 (36.8%)	84 (63.2%)
No	67 (33.5%)	33 (49.3%)	34 (50.7%)
Karnofsky performance status, median (IQR)	80% (70–90%)	80% (70–90%)	80% (70–90%)

accordance with the EORTC reference data manual (15), we applied the following age cut-offs: <50, 50–59, 60–69, >70 years.

Analyses were performed using the software packages SPSS Statistics 23.0 (IBM Corporation, Armonk, NY, USA) and SAS 9.4 (SAS Institute, Cary NC).

Results

Patient characteristics

A total of 200 patients (82 female and 118 male) were enrolled (*Table 1*). Median age was 65 years (range, 39–91 years). Most patients had advanced disease (NSCLC stage IV n=77, 38.5%) and suffered from comorbidities (n=133, 66.5%). Non-small cell lung cancer was the predominant histological type (SCLC 17.5% *vs*. NSCLC 82.5%). Primary treatment at the time of questionnaire completion was either surgery (n=58), radio-chemotherapy (n=113) or targeted therapy (n=29).

Gender differences regarding functional and symptom scores

Table 2 presents the estimated marginal means (EMM) of QoL for women and men and the respective P values. Statistically significant differences were found only in two scales: cough severity was higher in men (EMM =43.52) than in women (EMM =33.86), P=0.022, and diarrhea was more pronounced in women (EMM 26.01) than in men (EMM 17.93), P=0.038. Other sizeable differences were observed with regard to nausea/vomiting (women EMM 26.10 and men EMM 18.58, P=0.053) and financial difficulties (women EMM 19.92 and men EMM 28.23, P=0.066), but the effects just fell short of the conventional level of statistical significance.

Gender differences and intensity of symptoms

Figure 1 presents the five most prominent symptoms in descending order among women and men. Fatigue was the most pronounced symptom in women and men (EMM 51.32 and 51.29, respectively), followed by dyspnea (EMM 38.88 and EMM 44.70, respectively). Men, more so than women, reported higher symptom burden with regard to typical sensations related to lung cancer, such as dyspnea (EMM 44.70 *vs.* 38.88), coughing (EMM 43.52 *vs.* 33.86) and shortness of breath (EMM 34.44 *vs.* 32.99).

Table 2 Estimated marginal means regarding quality of life of lung cancer patients broken down by gender

Quality of life scores	Women* (n=82)	Men* (n=118)	P	Lung cancer reference values (15)		Cancer reference values (15)		R. Schwarz, A. Hinz (11)	
				Women (n=830)	Men (n=1,925)	Women (n=9,028)	Men (n=13,225)	Women (n=1,139)	Men (n=889)
Global quality of life	51.84 (45.02–58.66)	47.69 (40.16–55.22)	0.201	56.1	56.9	59.3	62.9	69.2	72.7
Physical functioning	62.35 (54.73–69.96)	60.80 (52.39–69.21)	0.670	69.3	72.9	74.7	78.5	88.7	92.0
Role functioning	52.03 (42.10–61.95)	53.06 (42.09–64.02)	0.828	60.7	63.6	67.1	73.4	86.6	89.8
Emotional functioning	66.65 (58.08–75.22)	69.87 (60.40–79.34)	0.430	65.7	71.6	67.8	73.9	76.3	81.8
Cognitive functioning	73.54 (66.60–80.48)	73.88 (66.21–81.54)	0.918	80.7	82.7	80.9	83.7	90.1	92.7
Social functioning	58.66 (48.12–69.21)	61.47 (49.83–73.11)	0.576	67.4	72.7	72.9	76.3	90.3	92.0
Fatigue	51.32 (42.46–60.19)	51.29 (41.50–61.08)	0.994	44.2	39.8	37.7	32.4	19.5	14.0
Nausea/vomiting	26.10 (17.97–34.22)	18.58 (9.61–27.55)	0.053	13.8	9.5	11.1	7.7	3.6	1.8
Pain	32.47 (22.67–42.27)	33.54 (22.72–44.36)	0.819	30.7	27.4	29.3	25.4	17.2	13.0
Dyspnea	38.88 (28.73–49.03)	44.70 (33.50–55.91)	0.228	38.2	38.2	20.3	21.1	9.1	6.9
Appetite loss	34.78 (24.46–45.10)	33.43 (22.04–44.83)	0.784	30.2	26.8	23.8	19.2	6.3	4.2
Insomnia	36.14 (25.04–47.24)	28.08 (15.83–40.34)	0.128	32.7	29.7	31.8	26.7	19.1	13.0
Constipation	24.18 (13.93–34.42)	16.63 (5.31–27.94)	0.122	20.6	20.1	19.9	16.2	4.3	2.5
Diarrhea	26.01 (17.89–34.13)	17.93 (8.96–26.90)	0.038	8.1	7.3	9.3	8.7	3.1	2.5
Financial difficulties	19.92 (10.47–29.37)	28.23 (17.79–38.67)	0.066	17.7	18.2	17.5	15.6	6.3	5.5
LC29 cough	33.86 (25.07–42.66)	43.52 (33.80–53.23)	0.022						
LC29 short breath	32.99 (25.41–40.57)	34.44 (26.07–42.81)	0.688						
LC29 side effects	21.32 (16.97–25.66)	21.33 (16.54–26.13)	0.994						
LC29 progression	56.63 (45.57–67.69)	51.05 (38.83–63.26)	0.289						
LC29 surgery	33.62 (8.82–58.42)	35.72 (7.22–64.21)	0.832						
LC29 coughing blood	1.86 (–4.02–7.73)	2.46 (–4.03–8.95)	0.829						
LC29 pain in the chest	17.68 (8.08–27.28)	19.52 (8.95–30.08)	0.687						
LC29 pain in the shoulder	14.77 (5.27–24.28)	13.95 (3.45–24.45)	0.855						
LC29 pain in the body	22.50 (12.46–32.54)	28.06 (16.94–39.18)	0.246						
LC29 weight loss problems	11.36 (1.15–21.58)	15.63 (4.39–26.87)	0.386						

*, data are presented as estimated marginal means and 95% CI. Means were adjusted by age, tumor type, therapeutic approach, education, primary therapy, tumor stage, region and comorbidity. All scales range from 0 to 100. In the symptom scales a higher score is associated with a higher symptom burden. In the functioning scales the reverse is true, higher scores denote better performance.

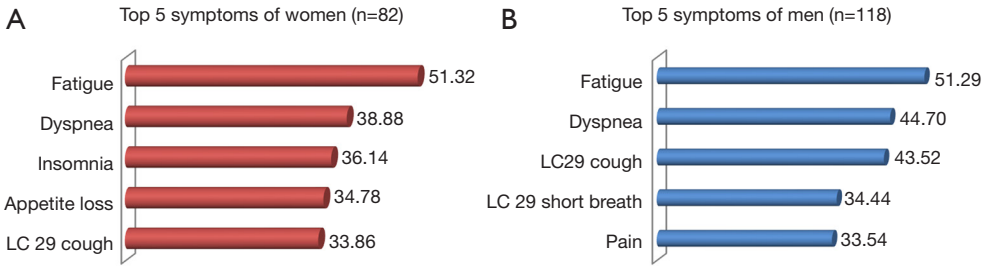

Figure 1 Most common symptoms among women (A) and men (B) (intensity of symptoms in descending order among women and men). Symptom scales range from 0 (lowest) to 100 (highest) with a higher score denoting higher symptom burden.

Comparisons with reference values

Table 2 depicts the original results of our study broken down by women and men, as well as historic QoL reference values (11,21).

The EORTC reference value manual contains QoL data from 9,028 female and 13,225 male patients pooled from numerous international studies with diverse cancer diagnoses (brain, breast, colorectal, gastric, genitourinary, gynecological, head and neck, leukemia, liver/bile/pancreas, lung, malignant lymphoma, malignant melanoma, mesothelioma, myeloma, non-Hodgkin lymphoma, esophageal, prostate, testicular) (15).

Table 2 reveals that our sample has higher symptom burden/worse functional QoL values than the EORTC lung cancer reference sample, particularly in the areas of diarrhea (mean difference between samples =13.70), nausea/vomiting (mean difference =10.87), social functioning (mean difference =–10.79), and physical functioning (mean difference =–10.38). Even more differences emerge with regard to the entire sample of cancer patients.

The highest differences were observed in comparison to the German reference data from a normal population. The most striking differences are found regarding role functioning (mean difference between samples =–35.37), fatigue (mean difference =34.21), dyspnea (mean difference =34.21), and social functioning (mean difference =–30.73).

All reported mean differences between samples considerably exceeded 10 score points, a commonly accepted criterion for a clinically meaningful difference (15).

Additional analyses

The gender differences observed with regard to diarrhea and coughing triggered additional subgroup analyses. We compared the use of targeted therapy (which would explain differences in diarrhea) between women and men. It turned out that women (18/29, 62.1%) received targeted therapy more frequently than men (11/29, 37.9%), chi^2 =6.22, P=0.013, which corresponds with differences in diarrhea.

Furthermore, we calculated gender differences in smoking. Men are more likely to have a smoking history (either actual smokers or ex-smokers), with the proportion of non-smokers being lower (9/118, 7.6%) than in women (17/82, 20.7%) chi^2 =6.22, P=0.025. Consequently, the number of packyears was higher in men (mean rank =96.76) than in women (mean rank =66.38), Mann-Whitney U =4.56, P<0.001. This corresponds with the higher self-reported coughing among men.

We also analyzed age effects on QoL reporting, since age is consistently and inversely (higher age, lower QoL) associated with QoL (11-17). There was not a single difference that approached statistical significance. A marginal and clinically plausible difference was obtained with regard to physical functioning with means being (P=0.069).

Discussion

Gender differences have been a subject of many analyses in QoL research (11-17). Based on a number of published large-scale studies we started with the notion that women would show lower levels of QoL (or, in reverse, higher symptom burden) than men.

In contrast to this hypothesis, we observed only one statistically significant difference to the disadvantage of women (diarrhea), whereas men reported significantly more coughing. This is at odds with other studies showing that women with lung cancer coughed significantly more than men (26,27). Subanalyses may help to explain these

findings: women were more likely to receive targeted therapy, and targeted therapy, in turn, is associated with heightened levels of diarrhea (28). In our sample, most men were smokers and ex-smokers and had a higher number of packyears than women, which is a plausible precursor of coughing. However, coughing remains a symptom that is underresearched and poorly understood in the context of lung cancer. Other observational studies have failed to demonstrate an association with smoking (27). Further research is required in this area.

All other differences in functional and symptom scores were statistically not significant. Only one other study is in line with our results. In this study of 249 patients who had undergone lung surgery, no significant gender-associated difference in QoL was demonstrated (29).

Large scale population-based studies consistently reported gender differences. An investigation on the QoL of the general German population using the EORTC QLQ-C30 found that men reported consistently better functioning and less symptoms than women (11), and these findings were confirmed in a follow-up study (13). Population-based studies in Norway, Sweden and The Netherlands came to the same conclusion (14,16).

A Swedish population study on elderly cancer patients found that women reported more loneliness and fear than men (30). These population-based findings are echoed by an American NSCLC patient study, showing that men reported better QoL 12 weeks later after receiving early palliative care than women (31).

When it comes to the most common symptoms of lung cancer patients, earlier studies suggested tumor site-specific symptoms such as dyspnea, coughing, hemoptysis and pain (4,32). The present analysis portrayed a different picture; irrespective of gender, the number one symptom was fatigue. This is an important finding, since fatigue is increasingly being recognized as an unmet need of cancer patients (33). Cancer-related fatigue can occur at any time, at diagnosis, during treatment or even after treatment and is not only a burden on its own but is also associated with an increase in mortality (34,35).

A particularly striking finding is the difference in QoL scores of our sample of patients and reference data. Our patients report much worse QoL scores than the EORTC reference sample of lung cancer patients and even worse than a reference sample representing various cancer diagnoses. Even more pronounced are differences between our sample and data obtained in a German norm data survey. This pattern of result might help to explain the lack of gender differences: the reduced variation of QoL scores in our sample made the detection of group differences between women and men less likely.

The present analysis has several limitations. First, the study was not designed to detect gender differences; it was originally conducted to revise the EORTC questionnaire for QoL of lung cancer patients. Second, experience suggests that patients with advanced stages are less likely to complete questionnaires. Therefore, a specific gender difference study would require well-defined inclusion/exclusion criteria, allowing for the recruitment of patients across a wide range of disease and performance states, as well as an appropriate power calculation.

Conclusions

The present study adds to the literature in showing that the typical gender difference effect on QoL (women doing worse than men) may not be a universal phenomenon. Future studies have to show whether this lack in gender differences can be replicated, and whether it is due to considerable impairments in QoL, as may have been the case in our sample of patients with lung cancer undergoing treatment.

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Footnote

Reporting Checklist: The authors have completed the SURGE reporting checklist. Available at http://dx.doi.org/10.21037/jtd-20-1054

Data Sharing Statement: Available at http://dx.doi.org/10.21037/jtd-20-1054

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Ethical Committee of the University of Regensburg, Germany (reference number 11-101-0024) and by the local ethical committees of the participating centers if required. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All patients gave their informed consent prior to being enrolled into this study.

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