Health-Related Quality of Life in Disease-Free Survivors of Surgically Treated Lung Cancer Compared With the General Population

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Objective: We compared the health-related quality of life (HRQOL) of disease-free lung cancer survivors with those from the general population.

Background: Although clinical research usually is focused on how to better identify the lung patients most likely to benefit from surgery in terms of survival, few studies have concentrated specifically on HRQOL in disease-free lung cancer survivors compared with that of the general population.

Methods: We enrolled 830 disease-free cancer survivors (median time since diagnosis, 4.11 years) who had a past diagnosis of lung cancer and treated with curative surgery (stage from 0 to III) at either of 2 hospitals between 2001 and 2006, and 1000 subjects without a history of cancer were selected randomly from a representative sample of general Korean population. Subjects filled out a questionnaire that included the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and the lung cancer module.

Results: There were no clinically meaningful differences between the disease-free lung cancer survivors and general population in terms of any of the functioning subscales and most of the symptoms. However, survivors exhibited clinically meaningful worse dyspnea and financial problems on the EORTC QLQ-C30 subscales and dyspnea, coughing, and pain in chest wall on the EORTC QLQ-LC13 subscales than the general population. There was no clinically significant difference between the survivor groups according to the survival time. Survivors receiving lung resection, radiotherapy, and chemotherapy had clinically meaningful worse dyspnea than survivors receiving only lung resection. Lung cancer survivors with a respiratory or cardiologic comorbidity showed clinically meaningful worse social functioning, fatigue, dyspnea, and financial problems.

Conclusions: These findings afford useful information clinicians preparing patients for lung cancer treatment by providing them with an understanding of the potential outcomes, and also for potential intervention targeting supportive care needs.

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Although lung cancer has one of the worst prognoses,[1] the practice of low-dose computed tomographic scanning as an early detection tool and improvement in patient management has increased the number of long-term lung cancer survivors.[2–5] The most recent 5-year survival rate in Korea reported by the Korean Central Cancer Registry in 2009 was 16.7%.[6] Surgical resection is considered to offer the best survival outcomes for early-stage non–small-cell lung cancer.[7]

Although clinical research is usually focused on how to better identify the patients most likely to benefit from surgery in terms of survival, patients and surgeons also need information about the potential health-related quality of life (HRQOL) outcomes.[8–10] Self-reported multidimensional HRQOL data describing physical, psychological, social, and existential well-being after the diagnosis of cancer have been accumulating.[11] However, most of the literature focuses on short-term HRQOL outcomes[8,9,12] or on patients with advanced-stage disease[11,13–15] because of the poor prognosis.[15] A comparison with population-based reference data can provide greater insight into the altered HRQOL of cancer patients[16–19] and enable health care providers to set HRQOL target levels[11] and allow a precise estimation of the risk in tailored intervention strategies.[2]

We compared the HRQOL of disease-free lung cancer survivors with those from the general population and evaluate the impact of types of treatment, period after treatment, and comorbidity on survivors' HRQOL. We hypothesized that HRQOL would be poorer in lung cancer survivors than in the general population.

MATERIALS AND METHODS

Participants and Procedures

To understand lung cancer survivorship, a study was designed to identify important survivorship issues including HRQOL, health behavior, screening of a second primary cancer, and rehabilitation.

Lung Cancer Survivors

We identified 2049 patients who had been treated for lung cancer in 2 hospitals, the Samsung Medical Center (SMC) and National Cancer Center (NCC) in South Korea, from 2001 through 2006. We collected information about the primary cancer site, date of diagnosis, stage, type of treatment, and other clinical characteristics from the hospital cancer registries. Patients were eligible to participate if they (1) had a past diagnosis of lung cancer, (2) were treated with curative surgery, and (3) had no other history of cancer. Eligible subjects were contacted by telephone, and those who agreed to participate were surveyed by an interviewer with questionnaires at home or the clinic. We excluded from this analysis the subjects whose cancer had recurred at that time. Because video-assisted thoracic surgery (VATS) was not often performed from 2001 through 2006, we also excluded patients who received it. Thus, all patients in this study had undergone pulmonary resection via open thoracotomy. All participants provided written informed consent.

Control Subjects

Our goal was to survey 1000 members of the general adult population distributed over 15 geographic districts. In each district, the survey was conducted in age strata according to guidelines of the 2000 Korean census. We selected villages and streets by using a

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probability-proportional-to-size technique, which is widely used and is the recommended method for obtaining a representative national sample.[20] The probability-proportional-to-size technique considers the size of individual groups and corrects for differences in the probability of larger and smaller groups being sampled. All participants provided written informed consent. The control group population and data collection methods have previously been described elsewhere.[21] The institutional review board of the NCC and the SMC reviewed and approved the protocol of our study.

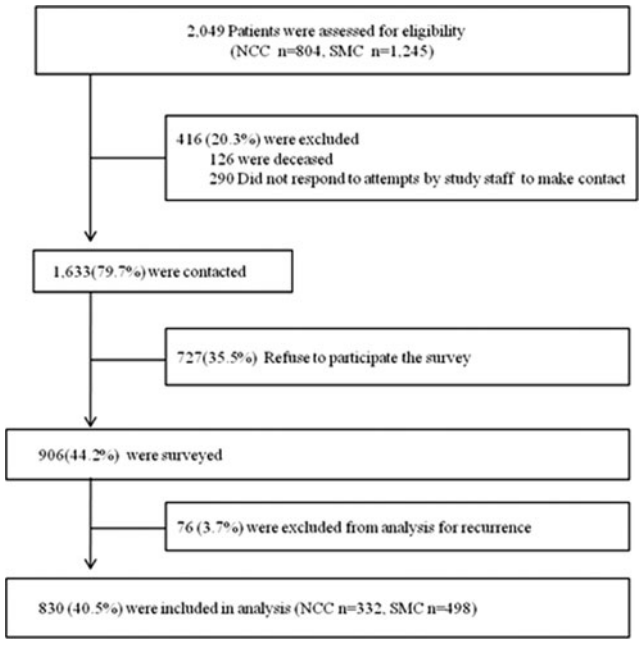

FIGURE 1. Flow of the participants through the study.

Instruments

Patients completed a questionnaire that covered demographic and clinical characteristics, and a number of standardized instruments designed to assess the HRQOL, existential well-being, fatigue, and depression. We constructed 1 questionnaire to examine HRQOL for lung cancer survivors. Questions covered the following topics: the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 item (EORTC QLQ-C30) and lung cancer module (QLQ-LC13).

The EORTC QLQ-C30 is a 30-item cancer-specific questionnaire for assessing the general HRQOL of cancer patients.[22] The questionnaire incorporates 5 functioning domains (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), global health and overall HRQOL scales, and several single items that assess additional symptoms commonly reported by cancer patients (eg, dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea) along with the perceived financial impact of disease and treatment. The QLQ-LC13 was designed to assess the impact of common lung cancer treatment modalities. The QLQ-LC13 has 1 multi-item scale (dyspnea) and 9 single items (pain in the arm/shoulder, chest, and other organs; cough; hemoptysis; dysphagia; peripheral neuropathy; alopecia; and mouth sores). The Korean version of QLQ-C30 was validated, and the QLQ-LC13 was

TABLE 1. Characteristics of Surveys of Lung Cancer Patients Before and After Adjustment for Propensity Score

	Before adjustment			After Adjustment			
Characteristics	**Survey Agree (n = 830)**	**Survey Disagree (n = 803)**	***P***	**Percentage of Survey Agree***	**Percentage of Survey Disagree†**	**Wald *F*‡ (*P*)**	**Wald *F*‡ Adjusted for Propensity Score (*P*)‡**
Age							
<55	157 (18.9)	178 (22.2)		20.4	20.4		
≥55	673 (81.1)	625 (77.8)	0.104	79.6	79.6	0.104	0.986
Gender							
Male	637 (76.8)	577 (71.9)		74.6	74.6		
Female	193 (23.3)	226 (28.1)	0.024	25.5	25.4	0.024	0.999
Region							
Metropolitan area	349 (42.1)	189 (29.4)		36.2	35.9		
City/country	481 (58.0)	454 (70.6)	<.001	63.8	64.1	<.001	0.960
Hospital							
SMU	498 (60.0)	469 (58.4)		54.3	54.1		
NCC	332 (40.0)	334 (41.6)	0.512	45.7	45.9	0.512	0.998
Stage							
0–I	526 (63.4)	506 (63.0)		63.1	63.3		
II–III	304 (36.6)	297 (37.0)	0.880	36.9	36.7	0.880	0.990
Survival times (yr)							
<5	611 (73.6)	507 (63.1)		70.5	70.5		
≥5	219 (26.4)	296 (36.9)	<.001	29.5	29.5	<.001	0.993
Type of treatment							
OP	491 (59.6)	548 (68.2)		63.5	62.8		
OP + RT	51 (6.2)	61 (7.6)		5.7	7.3		
OP + Chemo	226 (27.4)	154 (19.2)		25.4	24.5		
OP + RT + Chemo	56 (6.8)	40 (5.0)	<.001	5.4	5.4	<.001	0.934

*Sample size = 830; weighted = 1469.5.
†Sample size = 803; weighted = 1462.6.
‡*F* statistic based on Wald χ^2. The propensity score that summarizes collection of different observable characteristics between surveys agree and disagree.
Percentage weighted to reflect all eligible cancer survivors. OP indicates operation; RT, radiotherapy; Chemo, chemotherapy.

TABLE 2. Characteristics of Lung Cancer Survivors and the General Population Before and After Adjustment for Propensity Score

Characteristics	Cancer Survivors (n = 830)	General Population (n = 1000)	*P*	Percentage of Cancer Survivors*	Percentage of General Population†	Wald F‡ (*P*)	Wald F‡ Adjusted for Propensity Score (*P*)§
Age							
<55	157 (18.9)	804 (80.4)		54.5	52.6		
≥55	673 (81.1)	196 (19.6)	<0.001	45.5	47.4	<0.001	0.904
Gender							
Male	637 (76.8)	500 (50.0)		57.2	60.3		
Female	193 (23.3)	500 (50.0)	<0.001	42.8	39.7	<0.001	0.932
Region							
Metropolitan area	349 (42.1)	484 (48.4)		41.3	48.9		
City/country	481 (58.0)	516 (51.6)	0.007	58.7	51.2	0.007	0.712
Marital (living with spouse)							
Yes	764 (92.1)	712 (71.2)		84.2	79.4		
No	66 (8.0)	288 (28.8)	<0.001	15.8	20.6	<0.001	0.567
Education							
≤Middle school	387 (46.7)	162 (16.2)		31.5	30.4		
≥High school	441 (53.3)	838 (83.8)	<0.001	68.5	69.6	<0.001	0.913
Income (USD)¶							
<3000	603 (72.7)	614 (61.8)		68.8	64.3		
≥3000	226 (27.3)	379 (38.2)	<0.001	31.2	35.7	<0.001	0.848
Job							
Yes	322 (38.8)	635 (63.5)		49.7	55.4		
No	507 (61.2)	365 (36.5)	<0.001	50.3	44.6	<0.001	0.555
BMI							
<25	595 (72.9)	785 (78.6)		76.4	74.8		
≥25	221 (27.1)	214 (21.4)	0.005	23.6	25.2	0.005	0.895
Alcohol (current)							
Yes	188 (22.7)	660 (66.0)		49.6	46.4		
No	642 (77.4)	340 (34.0)	<0.001	50.4	53.6	<0.001	0.171
Smoking (current)							
Yes	60 (7.2)	308 (30.8)		25.6	19.9		
No	770 (92.8)	692 (69.2)	<0.001	74.4	80.1	<0.001	0.326
Comorbidity							
Yes	452 (54.7)	257 (25.7)		37.3	42.8		
No	375 (45.3)	743 (74.3)	<0.001	62.7	57.2	<0.001	0.821

*Cancer Survivors' sample size = 830; weighted = 1892.0.
†General population's ample size = 1000; weighted = 1789.8.
‡*F* statistic based on Wald χ^2.
§The propensity score that summarizes collection of different observable characteristics between cancer patients and general population.
¶1 US$ 1020 won.
Percentage weighted to reflect all eligible cancer patients.

translated into Korean by the forward–backward translation process and was pilot-tested with the original author's approval.

In addition to the previously described measures, the full survey instrument also included items concerning the utilization of cancer information and complementary and alternative medicine needs after treatment, health behavior, and screening for a second primary cancer, return to work, posttraumatic growth, fatigue, distress, and sexuality. We will publish these findings in the future. The feasibility and comprehensibility of the survey instrument were pretested with 20 lung cancer survivors. Completing the entire questionnaire took approximately 50 minutes.

Statistical Methods

Propensity-Based Weighting, Propensity Adjustment

We performed all analyses using data weighted to the population of eligible patients because half of the patients did not respond, and those who did respond might have differed significantly from those who did not, causing a selection bias. To adjust for observed differences between survey participants and nonparticipants, we used a weighting method based on propensity scores.[23] Propensity scores were defined as the conditional probability of being a respondent given all covariates available from both responding and nonresponding survivors (age, gender, region, hospital, survival times, and type of treatment), which we collected from hospital cancer registries. After propensity scores were assigned, subjects were grouped into quintiles and given the weight, which was the inverse of the mean propensity score for the stratum. In addition to propensity-based weights, we used 2 different propensity scores to control for differences in the characteristics: (1) between survey participants and nonparticipants in the lung cancer patients (age, gender, region, hospital, survival times, and type of treatment) and (2) between lung cancer patients and the general population group (age, gender, region, marital status, education, house income, occupational status, BMI [body mass index], alcohol use, smoking status, and comorbidity).

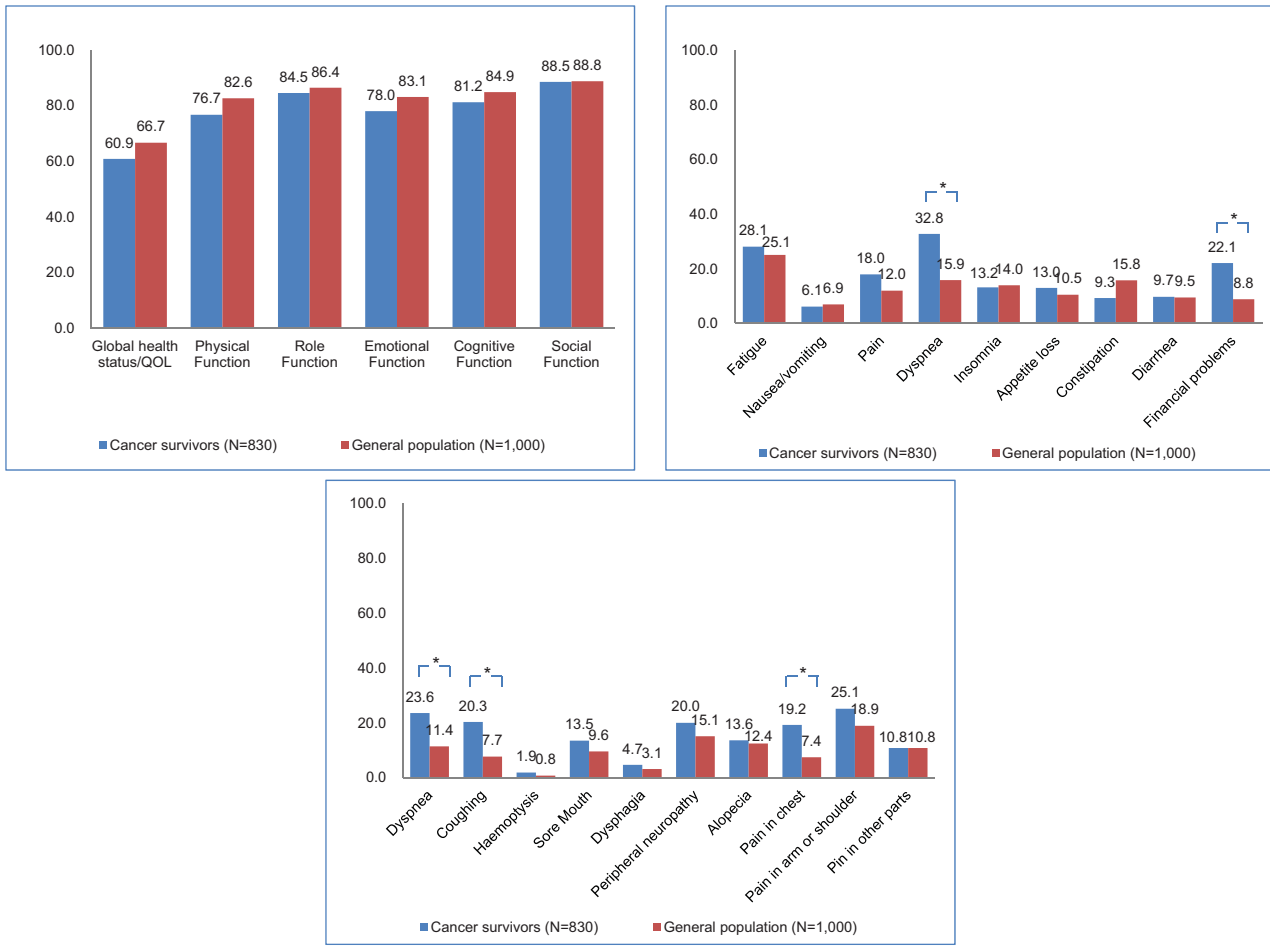

FIGURE 2. Least squares mean scores (adjusted for age, sex, comorbidity) of EORTC QLQ-C30 and QLQ-LC13 among the lung cancer survivors population and general population EORTC QLQ-C30. $^{*}P < 0.01$ from analysis of covariance with a generalized linear model and are for the comparison between cancer survivors and general population and clinical meaningful difference as 10-point difference.

Analysis of Outcomes

We scored the QLQ-C30 and QLQ-LC13 items according to the EORTC scoring manual. We linearly transformed the QLQ-C30 and QLQ-LC13 data to yield scores from 0 to 100; a higher score represented a better level of functioning or a higher level of symptoms respectively. We handled incomplete questionnaires according to the developers' recommendations.

We used descriptive statistics for clinical, socioeconomic, and therapeutic variables and t and χ^2 tests. We compared lung cancer survivors with the general population controls on the basis of multivariate (age, marital status, education, religion, and employment status)-adjusted HRQOL means and the proportion of "problematic groups" in each HRQOL scale. We defined a problematic group as one with a global HRQOL or functioning scale score of 33 or less, or a symptom scale score of 66 or more, on the QLQ-C30 and QLQ-LC13, respectively.[24] We also compared multivariate-adjusted means (age, sex, type of treatment, time since surgery, and comorbidity) of HRQOL between the treatment subgroups. We used analysis of covariance with a generalized linear model to determine significant differences between groups. We used multiple regression analysis to examine the impact of demographic and clinical characteristics on HRQOL. Because there were multiple comparisons, we considered a P value less than 0.01 to be statistically significant on the univariate and multivariate analyses, and we defined a "clinically meaningful" difference in HRQOL as a 10-point difference in the mean score.[22,24] All statistical tests were 2-sided. All statistical tests were 2-sided and performed using SAS version 9.2 (SAS Institute, Inc, Cary, NC).

RESULTS

Subjects and Recruitment Results

We identified 2049 potentially eligible lung cancer survivors from the participating registries. Of these, 126 (6.1%) had died. We made multiple attempts to contact the others by postcard or telephone but were not able to reach 290 (14.2%) of them; the most frequent reason for contact failure was a change of address or telephone number. Of the 1633 (79.7%) patients who were contacted, 727 (35.5%) refused to participate. The reasons given most frequently were that the survey was inconvenient, that it took too long to complete, or that the patient felt too ill. Ultimately, 906 (44.2%) patients consented to participate to the survey. Of these, we excluded 76 patients who had

recurrent cancer at the time, 830 patients remained in the study and 803 patients did not participate in survey (Fig. 1).

About the control group, 1483 refused to participate or did not complete the survey among 2483 eligible persons; 1000 did complete the survey, yielding a response rate of 40.3%. The most frequent reasons people gave for refusing to participate were that they felt too busy to complete the questionnaire (n = 670), that the survey was inconvenient (n = 332), and that they did not want to provide personal information (n = 165).

Sociodemographic and Clinical Characteristics

Compared with patients who did not respond to the questionnaire, responders who lived in metropolitan areas had shorter survival times and received combined treatment with chemotherapy and/or radiation therapy along with the operation ($P < 0.01$). After adjustment for the propensity score, however, no significant differences were evident between them (Table 1).

The lung cancer group differed significantly from the general population control group in several sociodemographic and health-related characteristics. After adjustment for the propensity score, however, no significant differences were evident (Table 2).

Comparison of HRQOL Between Lung Cancer Survivors and the General Population

Figure 2 presents a comparison of least mean square score (adjusted for age, sex, and comorbidity) of subscales of the EORTC QLQ-C30 and QLQ-LC13 between the lung cancer survivors and general population groups. Lung cancer survivors and general population subjects did not exhibit significantly different multivariate-adjusted mean scores and clinically meaningful worse scores as 10-point than the general population in most of the functioning and symptoms except for dyspnea and financial problems on the subscales of the EORTC QLQ-C30 and dyspnea, coughing, and pain in chest wall on subscales of the EORTC QLQ-LC13.

HRQOL by Survival Times After Diagnosis in Lung Cancer Survivors

Most of the HRQOL scores based on survival time did not significantly differ in the function or symptom subscales of EORTC QLQ-C30 or QLQ-LC13 except for pain and especially chest pain. Moreover, there was no clinically significant difference between groups in terms of survival time (Table 3).

HRQOL by Types of Treatment in Lung Cancer Survivors

Most HRQOL scores by treatment type did not significantly differ in any of the functioning or symptom subscales of EORTC QLQ-C30 or QLQ-LC13, except for physical, role and social functioning, financial problems, and dyspnea. Compared with survivors receiving only lung resection, survivors receiving both lung resection and radiotherapy were clinically meaningfully worse and had worse financial problems. Cancer survivors receiving lung resection, radiotherapy, and chemotherapy showed clinically meaningful worse score in terms of dyspnea than survivors receiving only lung resection (Table 4).

TABLE 3. Item Statistics of the EORTC QLQ-C30 and QLQ-LC13 by the Time After Surgery

	Less Than 5 Years (n = 611)		5 Years or More (n = 219)		
	LSMEAN*	SE	LSMEAN*	SE	P
Functioning scales					
Global health status/QOL	55.8	1.4	57.6	1.8	0.268
Physical functioning	69.5	1.3	72.6	1.7	0.047
Role functioning	73.5	1.7	77.0	2.2	0.074
Emotional functioning	78.7	1.4	81.9	1.8	0.049
Cognitive functioning	76.9	1.4	79.5	1.8	0.106
Social functioning	78.3	1.7	81.8	2.1	0.072
Symptom scales					
Fatigue	35.2	1.7	31.9	2.2	0.088
Nausea/vomiting	7.8	1.1	7.5	1.4	0.840
Pain	22.3	1.6	16.3	2.1	0.001
Dyspnea	40.2	2.2	36.2	2.8	0.118
Insomnia	21.6	2.0	19.1	2.6	0.266
Appetite loss	20.1	1.9	15.9	2.4	0.047
Constipation	13.6	1.6	9.8	2.1	0.046
Diarrhea	8.9	1.3	6.6	1.7	0.148
Financial problems	26.4	2.1	24.4	2.7	0.410
Lung cancer symptom scales					
Dyspnea	31.9	1.6	29.3	2.0	0.153
Coughing	20.4	1.7	19.2	2.2	0.533
Hemoptysis	1.5	0.6	2.4	0.8	0.189
Sore Mouth	9.6	1.2	9.7	1.6	0.938
Dysphagia	7.0	1.2	6.3	1.5	0.599
Peripheral neuropathy	17.8	1.7	16.1	2.3	0.398
Alopecia	14.4	1.6	13.2	2.0	0.527
Pain in chest	20.8	1.8	15.4	2.3	0.009
Pain in arm or shoulder	26.3	1.9	22.4	2.5	0.079
Pain in other parts	14.9	1.7	13.5	2.2	0.469

*Adjusted for age, sex, treatment type, and comorbidity type.
High scores for the EORTC QLQ-C30 and QLQ-LC13 mean better functioning or worse symptoms. LSMEAN indicates linear square mean; SE, standard error.

TABLE 4. Item Statistics of the EORTC QLQ-C30 and QLQ-LC13 by the Treatment Type

	OP (n = 491)		OP + RT (n = 51)		OP + CT (n = 226)		OP + RT + CT (n = 56)		
	LSMEAN*	SE	LSMEAN*	SE	LSMEAN*	SE	LSMEAN*	SE	*P*
Functioning scales									
Global health status/QOL	60.5	1.2	55.3	2.9	58.4	1.7	52.6	2.8	0.016
Physical functioning	75.1	1.2	72.0	2.8	71.0	1.6	66.2	2.7	0.002
Role functioning	80.4	1.4	72.9	3.5	77.0	2.1	70.6	3.4	0.006
Emotional functioning	81.6	1.2	81.7	2.9	80.6	1.7	77.3	2.8	0.470
Cognitive functioning	79.6	1.2	80.1	2.9	78.2	1.7	75.0	2.8	0.366
Social functioning	85.0	1.4	77.6	3.5	80.8	2.0	76.8	3.3	0.008
Symptom scales									
Fatigue	32.2	1.4	31.3	3.5	33.7	2.0	36.8	3.4	0.511
Nausea/vomiting	7.9	0.9	5.9	2.3	8.0	1.3	8.9	2.2	0.781
Pain	18.6	1.4	19.4	3.3	18.6	2.0	20.6	3.2	0.930
Dyspnea	33.0	1.9	38.3	4.6	36.6	2.7	45.0	4.4	0.032
Insomnia	22.1	1.7	14.1	4.2	22.1	2.4	23.2	4.0	0.266
Appetite loss	17.1	1.6	15.9	3.9	18.2	2.3	20.8	3.8	0.729
Constipation	12.6	1.4	10.9	3.4	12.1	2.0	11.2	3.3	0.935
Diarrhea	8.9	1.2	6.4	2.8	8.3	1.6	7.4	2.7	0.795
Financial problems	18.0	1.8	29.1	4.3	26.8	2.5	27.6	4.2	<0.001
Lung cancer symptom scales									
Dyspnea	26.1	1.4	29.3	3.3	28.9	1.9	38.2	3.2	0.002
Coughing	15.5	1.5	23.3	3.5	19.2	2.1	21.2	3.4	0.037
Hemoptysis	1.6	0.5	3.3	1.3	1.6	0.7	1.2	1.2	0.576
Sore Mouth	7.6	1.1	7.5	2.6	11.1	1.5	12.3	2.5	0.044
Dysphagia	5.8	1.0	4.8	2.5	6.2	1.4	10.0	2.4	0.311
Peripheral neuropathy	17.6	1.5	11.4	3.7	22.2	2.1	16.6	3.5	0.021
Alopecia	12.5	1.4	13.5	3.3	13.7	1.9	15.4	3.2	0.773
Pain in chest	18.9	1.5	15.0	3.8	18.8	2.2	19.7	3.6	0.757
Pain in arm or shoulder	22.4	1.7	20.1	4.1	25.4	2.4	29.5	3.9	0.163
Pain in other parts	14.2	1.4	16.0	3.5	15.1	2.0	11.6	3.4	0.753

*Adjusted for age, sex, time after surgery, and comorbidity type.

High scores for the EORTC QLQ-C30 and QLQ-LC13 mean better functioning or worse symptom. OP indicates operation; RT, radiotherapy; CT, chemotherapy; LSMEAN, linear square mean; SE, standard error.

Influence of Comorbidities on Survivor QOL

When compared by least mean square analysis of covariance, the lung cancer survivors with comorbidities reported significantly lower functioning and higher level of symptoms than survivors without any comorbidity except for nausea/vomiting, insomnia, appetite loss, constipation, and diarrhea on the EORTC QLQ-C30 symptom subscales and hemoptysis, sore mouth, dysphagia, and pain in chest on the EORTC QLQ-L13 subscales. When a clinically meaningful difference was defined as more than 10 points, however, cancer survivors with a respiratory or cardiologic comorbidity had a clinically lower level of social functioning, along with clinically higher level of symptoms such as fatigue, dyspnea, and financial problems on the EORTC QLQ-C30 subscales (Table 5).

DISCUSSION

To our knowledge, this is the first large study to compare the HRQOL of lung cancer survivors with the general population. As demonstrated by these findings, lung cancer survivors have not only the general problems of cancer survivors but also certain specific problems with different HRQOL and potentially different rehabilitation needs.[11] The findings show that lung cancer HRQOL is comparable to the HRQOL (ie, clinically not different) on all of the HRQOL subscales except a few. We found that, compared with general population, lung cancer survivors had no clinically meaningful difference across all dimensions of functioning compared to the general population. Earlier studies report that HRQOL is impaired by lung cancer surgery but quickly returns to preoperative level within 6 to 12 months[8,9,25–28] and 2 years after surgery displays little difference.[8,11] Our results provide additional support for the recovery of well-being. However, we found that, compared with general population, cancer survivors had more severe respiratory problems such as dyspnea, chest pain, cough and financial problems even after recovery from treatment. The findings that lung cancer survivors, compared with the general population, had clinically meaningful differences in subscale scores for financial problems, cough, dyspnea, and chronic chest pain have important implications for planning for their care. Financial difficulties have also been reported in stomach cancer survivors,[29] and lung cancer survivors have more difficulty working and report more disruptions in day-to-day activity than survivors of other cancers,[30] which might lead to reduced income and financial difficulties. Common complaints of thoracotomy patients are respiratory symptoms with dyspnea and cough[15] and the chronic pain seen after lung cancer treatment,[2,8] a pain that persists in about 1 of 3 lung cancer survivors.[2,31,32] The survivors' perception of pain and dyspnea was important to the perceived HRQOL, implying a need for monitoring respiratory symptoms and chronic pain.[2,8] In this study, however, we found only small and not clinically meaningful differences in those symptoms between short- and long-term survivors. Those problems, though, can provide useful information for clinicians as they prepare patients for lung cancer surgery in the areas of informed decision-making, planning, and referral to the appropriate services, all of which require a full understanding of the impairment and its difficulties.[8]

TABLE 5. Item Statistics of the EORTC QLQ-C30 and QLQ-LC13 by Comorbidity Type

	None (n = 375)		Other* (n = 388)		Cardiac or pulmonary† (n = 64)		
	LSMEAN‡	SE	LSMEAN‡	SE	LSMEAN‡	SE	*P*
Functioning scales							
Global health status/QOL	60.5	1.4	56.5	1.5	53.2	2.6	0.004
Physical functioning	76.1	1.4	70.4	1.4	66.7	2.6	<0.001
Role functioning	79.8	1.7	74.4	1.8	71.6	3.2	0.002
Emotional functioning	84.8	1.5	80.0	1.5	76.1	2.7	<0.001
Cognitive functioning	82.5	1.5	76.8	1.5	75.4	2.7	<0.001
Social functioning	85.1	1.7	80.0	1.7	75.0	3.1	<0.001
Symptom scales							
Fatigue	26.6	1.7	35.0	1.7	38.9	3.2	<0.001
Nausea/vomiting	5.7	1.1	7.2	1.1	10.1	2.0	0.080
Pain	15.1	1.7	20.0	1.7	22.8	3.0	0.003
Dyspnea	31.8	2.3	39.0	2.3	43.8	4.1	0.001
Insomnia	16.8	2.1	22.2	2.1	22.2	3.8	0.028
Appetite loss	15.0	1.9	17.4	2.0	21.6	3.5	0.142
Constipation	11.1	1.7	12.7	1.7	11.3	3.1	0.613
Diarrhea	6.0	1.4	10.1	1.4	7.1	2.6	0.015
Financial problems	20.0	2.2	25.3	2.2	30.7	3.9	0.006
Lung cancer symptom scales							
Dyspnea	26.7	1.6	31.9	1.7	33.2	3.0	0.004
Coughing	16.7	1.8	22.6	1.8	20.1	3.2	0.004
Hemoptysis	3.1	0.6	1.3	0.6	1.4	1.1	0.016
Sore Mouth	8.2	1.3	9.4	1.3	11.3	2.3	0.351
Dysphagia	5.3	1.2	6.4	1.2	8.4	2.2	0.325
Peripheral neuropathy	11.4	1.8	18.1	1.8	21.3	3.3	<0.001
Alopecia	10.8	1.6	16.2	1.7	14.4	3.0	0.006
Pain in chest	14.6	1.9	18.1	1.9	21.6	3.4	0.053
Pain in arm or shoulder	18.5	2.0	26.6	2.0	27.9	3.7	<0.001
Pain in other parts	7.5	1.7	18.4	1.7	16.7	3.2	<0.001

*Have been diagnosed with cerebrovascular disease (ex: stroke), diabetes mellitus, liver disease (ex: chronic hepatitis, cirrhosis), hypertension, infectious diseases (ex: tuberculosis), digestive diseases (ex: chronic gastritis, stomach ulcers, duodenal ulcer), musculoskeletal disorders (ex: osteoarthritis, rheumatoid arthritis), kidney disease, etc.

†Have been diagnosed with pulmonary (ex: chronic bronchitis, asthma) or cardiac diseases (ex: chronic heart failure).

‡Adjusted for sex, age, treatment type, and time after surgery.

High scores for the EORTC QLQ-C30 and QLQ-LC13 mean better functioning or worse symptom. LSMEAN indicates linear square mean; SE, standard error.

Our study suggested that while the combination of chemotherapy and radiotherapy after thoracotomy did not show clinically meaningful differences in many symptoms of EORTC QLQ-C30 and its lung cancer module, it might result in clinically meaningful changes in dyspnea symptoms. Following lung resection, dyspnea is a common sequela of radiation therapy and many chemotherapeutic agents.[2,33–35] The recent wider application of multimodality treatment options thus may influence the clinical significance of dyspnea.

In this study, more than half of the survivors had at least 1 comorbid condition, which is comparable with earlier findings.[11] The presence of cardiac or pulmonary disease was clinically negatively related to HRQOL in terms of social functioning and symptoms (fatigue, dyspnea, and financial difficulties). In particular, the comorbid condition of cardiac disease might have a significant negative impact on the HRQOL outcomes in cancer survivors.[2,36–38]

The interesting findings from this study suggest that after the initial diagnosis, and tailored interventions together with risk assessment such as multimodality treatment, continued smoking, and comorbidities should be provided for respiratory symptoms, pain, financial problems.[8,11,39] In addition, long-term intervention strategies for ameliorating respiratory symptoms and easing socioeconomic difficulties, and continued surveillance of lung cancer survivors with recurrence, need to be included in survivorship care planning.[2]

There are important limitations to consider in interpreting the results of this study. One of the threats to validity is the low response rate (44.2%), which restricted the generalizability of our findings to similar groups of lung cancer survivors. More severely impaired survivors may have elected not to participate. However, we minimized that potential bias by using a response propensity-weighted analysis. Second, another limitation was selection bias, which restricted the generalizability of these findings to similar groups of lung cancer survivors. Our study sample may not be representative of the general population of lung cancer survivors, because it was accrued from 2 selected academic centers. Third, because we did not match treatment and control subjects by age and sociodemographic characteristics, there may have been a selection bias. However, the propensity-based weighting method allows for much better control than prior studies of cancer survivors who were matched on only a few characteristics, such as age and education.[40] In addition to the biases we adjusted for, there might also be a bias following from the lung cancer survivors' being older than the general population and having had chemo-/radiation therapy, which the adjustment for propensity scores would not have overcome. Fourth, in this cross-sectional study, we were not able to assess HRQOL changes before and after treatment, thus it was not possible to determine how the HRQOL before lung cancer treatment influenced the HRQOL after treatment. Fifth, though it would be reasonable to compare the lung cancer patients' HRQOL with the HRQOL of the patients who underwent a thoracotomy for other purposes, this study did not include them. For greater understanding of lung cancer patients' HRQOL, further studies need to be done with those patients included.

In spite of its limitations, this study did indicate that disease-free survivors of lung cancer had good HRQOL, but many lung cancer survivors had cough, dyspnea, and pain, as well as associated financial problems, compared with the general population. These findings comprise useful information for clinicians preparing patients for lung cancer treatment by providing them with an understanding of the potential outcomes (HRQOL).[8] They also can serve as the basis for potential intervention for rehabilitation and supportive care needs among lung cancer survivors after cancer treatment.[11] Further study is needed to explore potential interventions to support lung cancer patients afflicted with pulmonary symptoms, pain, and other cardiopulmonary diseases.

REFERENCES

1. Visbal AL, Williams BA, Nichols FC, III, 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.
2. Sugimura H, Yang P. Long-term survivorship in lung cancer: a review. *Chest.* 2006;129:1088–1097.
3. American Cancer Society. *Cancer Facts and Figures 2005*. Atlanta, GA: American Cancer Society, Inc; 2005.
4. Hoffmann H. Resected non-small-cell lung cancer stage I/II: indication for adjuvant/neoadjuvant therapy? *Lung Cancer.* 2004;45(suppl 2):S91–S97.
5. Manser R, Wright G, Hart D, et al. Surgery for early stage non-small cell lung cancer. *Cochrane Database Syst Rev.* 2005;(1):CD004699.
6. National Cancer Center. *Cancer Facts and Figures 2010*. Plainview, NY: National Cancer Center; 2010.
7. Smith SK, Zimmerman S, Williams CS, et al. Health status and quality of life among non-Hodgkin lymphoma survivors. *Cancer.* 2009;115:3312–3323.
8. Kenny PM, King MT, Viney RC, et al. Quality of life and survival in the 2 years after surgery for non small-cell lung cancer. *J Clin Oncol.* 2008;26:233–241.
9. Win T, Sharples L, Wells FC, et al. Effect of lung cancer surgery on quality of life. *Thorax.* 2005;60:234–238.
10. Osoba D, Bezjak A, Brundage M, et al. Analysis and interpretation of health-related quality-of-life data from clinical trials: basic approach of The National Cancer Institute of Canada Clinical Trials Group. *Eur J Cancer.* 2005;41:280–287.
11. Sarna L, Padilla G, Holmes C, et al. Quality of life of long-term survivors of non-small-cell lung cancer. *J Clin Oncol.* 2002;20:2920–2929.
12. Rocco G, Vaughan R. Outcome of lung surgery: what patients don't like. *Chest.* 2000;117:1531–1532.
13. Cooley ME, Short TH, Moriarty HJ. Patterns of symptom distress in adults receiving treatment for lung cancer. *J Palliat Care.* 2002;18:150–159.
14. Tanaka K, Akechi T, Okuyama T, et al. Impact of dyspnea, pain, and fatigue on daily life activities in ambulatory patients with advanced lung cancer. *J Pain Symptom Manage.* 2002;23:417–423.
15. Sarna L, Evangelista L, Tashkin D, et al. Impact of respiratory symptoms and pulmonary function on quality of life of long-term survivors of non-small cell lung cancer. *Chest.* 2004;125:439–445.
16. Arndt V, Merx H, Stegmaier C, et al. Quality of life in patients with colorectal cancer 1 year after diagnosis compared with the general population: a population-based study. *J Clin Oncol.* 2004;22:4829–4836.
17. Rauch P, Miny J, Conroy T, et al. Quality of life among disease-free survivors of rectal cancer. *J Clin Oncol.* 2004;22:354–360.
18. Rossen PB, Pedersen AF, Zachariae R, et al. Health-related quality of life in long-term survivors of testicular cancer. *J Clin Oncol.* 2009;27:5993–5999.
19. Cella D, Zagari MJ, Vandoros C, et al. Epoetin alfa treatment results in clinically significant improvements in quality of life in anemic cancer patients when referenced to the general population. *J Clin Oncol.* 2003;21:366–373.
20. Levy PS, Lemeshow S. *Sampling of Populations: Methods and Applications*. New York, NY: John Wiley; 1991.
21. Yun YH, Kim SH, Lee KM, et al. Age, sex, and comorbidities were considered in comparing reference data for health-related quality of life in the general and cancer populations. *J Clin Epidemiol*. 2007;60:1164–1175.
22. Fayers PM, Aaronson N, Bjordal K. *The EORTC QLQ C-30 Scoring Manual*. 3rd ed. Brussels, Belgium: European Organisation for Research and Treatment of Cancer; 2001.
23. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology*. 2000;11:550–560.
24. Fayers PM. Interpreting quality of life data: population-based reference data for the EORTC QLQ-C30. *Eur J Cancer*. 2001;37:1331–1334.
25. Dales RE, Belanger R, Shamji FM, et al. Quality-of-life following thoracotomy for lung cancer. *J Clin Epidemiol*. 1994;47:1443–1449.
26. Zieren HU, Muller JM, Hamberger U, et al. Quality of life after surgical therapy of bronchogenic carcinoma. *Eur J Cardiothorac Surg*. 1996;10:233–237.
27. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85:365–376.
28. Li WW, Lee TW, Lam SS, et al. Quality of life following lung cancer resection: video-assisted thoracic surgery vs thoracotomy. *Chest*. 2002;122:584–589.
29. Bae JM, Kim S, Kim YW, et al. Health-related quality of life among disease-free stomach cancer survivors in Korea. *Qual Life Res*. 2006;15:1587–1596.
30. Schag CA, Ganz PA, Wing DS, et al. Quality of life in adult survivors of lung, colon and prostate cancer. *Qual Life Res*. 1994;3:127–141.
31. Karmakar MK, Ho AM. Postthoracotomy pain syndrome. *Thorac Surg Clin*. 2004;14:345–352.
32. Rogers ML, Duffy JP. Surgical aspects of chronic post-thoracotomy pain. *Eur J Cardiothorac Surg*. 2000;18:711–716.
33. Roberts JR, Eustis C, Devore R, et al. Induction chemotherapy increases perioperative complications in patients undergoing resection for non-small cell lung cancer. *Ann Thorac Surg*. 2001;72:885–888.
34. Martin J, Ginsberg RJ, Abolhoda A, et al. Morbidity and mortality after neoadjuvant therapy for lung cancer: the risks of right pneumonectomy. *Ann Thorac Surg*. 2001;72:1149–1154.
35. Leo F, Solli P, Spaggiari L, et al. Respiratory function changes after chemotherapy: an additional risk for postoperative respiratory complications? *Ann Thorac Surg*. 2004;77:260–265; discussion 265.
36. Ko CY, Maggard M, Livingston EH. Evaluating health utility in patients with melanoma, breast cancer, colon cancer, and lung cancer: a nationwide, population-based assessment. *J Surg Res*. 2003;114:1–5.
37. Bonner JA, Tincher SA, Fiveash JB. Balancing the possible effectiveness of postoperative radiotherapy for non-small-cell lung cancer against the possible detriment of radiation-induced toxicity. *J Clin Oncol*. 2001;19:3905–3907.
38. Shin DW, Nam JH, Kwon YC, et al. Comorbidity in disease-free survivors of cervical cancer compared with the general female population. *Oncology*. 2008;74:207–215.
39. Clark MM, Novotny PJ, Patten CA, et al. Motivational readiness for physical activity and quality of life in long-term lung cancer survivors. *Lung Cancer*. 2008;61:117–122.
40. Park SY, Bae DS, Nam JH, et al. Quality of life and sexual problems in disease-free survivors of cervical cancer compared with the general population. *Cancer*. 2007;110:2716–2725.