Quality of Life and Healthcare Use in a Randomized Controlled Lung Cancer Screening Study

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Abstract

Rationale: Understanding the quality of life of lung cancer screening program participants, and the impact of program participation on quality of life and healthcare use, will help in the assessment of the value of screening.

Objectives: Determine the quality of life of participants in a lung cancer screening study and assess the effect of an abnormal screening finding on quality of life and healthcare use.

Methods: Quality-of-life measures and data on the use of healthcare services were collected prospectively during a randomized controlled lung cancer screening trial using chest radiography with computer-aided detection. Comparisons of baseline measures were made with U.S. population norms for the EuroQol 5-Dimension index. The impact of receiving a message of the presence of a lung nodule was assessed for all measures.

Measurements and Main Results: A total of 1,424 subjects participated. Twenty-five actionable nodules were reported. Baseline EuroQol 5-Dimension index scores were higher than U.S. population norms ($P < 0.0001$). The EuroQol 5-Dimension index score and St. George's Respiratory Questionnaire symptom score showed a significant change toward poorer quality of life after notification of the presence of a lung nodule (0.940 vs. 0.877, $P = 0.022$, and 25.7 vs. 34.0, $P = 0.005$, respectively). Chest imaging within 6 months of the screening examination occurred more frequently in those notified of a lung nodule (25.5 vs. 9.3%, $P = 0.002$).

Conclusions: Those who choose to enter a lung cancer screening program have a high baseline quality of life. The report of an abnormal screening finding can lower the quality of life and lead to increased chest imaging.

Clinical trial registered with www.clinicaltrials.gov (NCT01663155).

Keywords: computer-aided detection; lung nodules; EuroQol 5-Dimension

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Lung cancer screening with low-dose chest computed tomography (CT) has been shown to reduce lung cancer mortality by 20% in a well-defined high-risk population (1). When determining the impact of screening on our patients, the quality of life of those being screened and the effect of screening, testing, and treatment on their quality of life must be considered. The cost-

effectiveness of a lung cancer screening program will also be influenced by these factors, as well as the quality of life, costs of testing, and treatment within the cohort if screening did not occur.

Current recommendations suggest screening for lung cancer in the cohort of people who participated in the National Lung Screening Trial (NLST)—aged 55 to

74 years with 30 pack-years of smoking who have smoked within the past 15 years (2). By nature of these risk factors, the screening cohort is likely to have comorbid illness that influences their quality of life. A CT screening program may influence quality-of-life measures in a variety of ways. CT screening will frequently identify indeterminate lung nodules. Although most

of these are benign, receipt of a message that the screening test is abnormal could lead to anxiety and/or affect risk behaviors that influence the quality of life over time. Finding a cancer in an early stage may prevent a decline in quality of life related to the development of more advanced cancer.

To date, there is only a small literature base to provide us with quality-of-life data relevant to lung cancer screening. We performed a randomized, controlled trial of lung cancer screening using chest radiography with computer-aided detection (CAD) of lung nodules as the screening test. As part of the study, quality-of-life metrics were collected at baseline and through the program, as were measures of healthcare use. Here we describe the results of these measures, taken at baseline and at subsequent intervals, and after being informed about an indeterminate screening finding.

Methods

The screening study was a prospective, randomized, controlled trial. Study subjects were aged 40 to 75 years with 10 or more pack-years of smoking and/or an additional risk for developing lung cancer. Subjects were randomized to receive a posteroanterior view chest radiograph or placebo control. Images were reviewed first without, then with, the assistance of CAD. Actionable nodules were reported, and additional evaluation was tracked. This was a single-center study with four locations where imaging occurred through the Cleveland Clinic Health System. Subjects were enrolled from August 2008 through April 2011. Recruitment occurred through mailings to relevant populations identified from the electronic medical record, newspaper and radio advertising, as well as advertising within Cleveland Clinic Health system primary care offices, local unions, and church groups. The study was approved by the Cleveland Clinic institutional review board. All study participants signed an informed consent document (*see* online supplement for complete listing of inclusion and exclusion criteria). The primary objective of the study was to determine if lung cancer screening with CAD chest radiography could reduce the incidence of symptomatic advanced-stage lung cancer. The study was terminated early due to the results of the NLST. The

results suggested that additional evaluation of CAD chest radiography was necessary to determine if it had a role in the CT lung cancer screening era. Please see the publication for additional details (3). Note that the results presented here do not overlap with the results that have been published.

Data Collection

On the baseline form, data collected included age, race, sex, education level, work status, income range, previous and existing medical conditions, family history of medical conditions, and occupational exposures. Every 6 months all subjects completed a follow-up form and a medical use form to capture data on physician visits in the previous 6 months. If any study subject reported that they had been diagnosed with lung cancer, their medical records were obtained.

Quality-of-Life Metrics

The EuroQol-5 dimension (EQ-5D) (4, 5), University of California San Diego (UCSD) shortness of breath questionnaire (SOBQ) (6), and the St. George's Respiratory Questionnaire (SGRQ) (7) were completed by all study subjects every 6 months. The Paper Standard Gamble (PSG) (8, 9) questionnaire was administered by trained research personnel at baseline and yearly thereafter for the subset of patients whose primary physician practiced within the Cleveland Clinic Health System (*see* online supplement for descriptions of these indices). All data were entered through a validated web-enabled user interface and electronically captured and stored in a central Oracle database (Table 1).

Statistical Methods

The statistical analysis included a comparison between the baseline quality-of-life measures and population standards where available, a comparison between quality-of-life measures performed before and after the receipt of notice that an actionable lung nodule was found, a comparison between the quality-of-life measures and healthcare use of the cases and control subjects, a description of smoking cessation, and a comparison of healthcare use between those who did and did not have an actionable lung nodule. These comparisons were performed for the study population as a whole and for those who would have met NLST entry criteria. For each of the outcome measures, the null hypothesis is that there is no difference between the groups being compared; the alternative hypothesis is that there is a difference (two-tailed alternative). All analyses were performed at the 0.05 significance level unless otherwise indicated.

The EQ-5D scores were strongly skewed to the left, with more than 50% of subjects scoring a value of 1.0 ("no problem"). Thus, as described in the EQ-5D User Guide (version 1.0, April 2011), in addition to comparing means and medians, the EQ-5D scores were dichotomized as "no problem" for all five dimensions versus the rest (at least "some problem" for one dimension). Logistic regression analysis was used to test for differences in the frequency of reported problems for control subjects and screened subjects. The independent variables in the model were treatment arm, month of visit, and the interaction of treatment and visit. Generalized estimating equations (GEEs), with an exchangeable working correlation structure, were used to account for the

Table 1. Study quality-of-life questionnaires

Study Form	Baseline	Every 6 Mo	Annual Visits
		± 2 wk	± 1 mo
Medical use form		X	X
UCSD SOBQ	X	X	X
SGRQ	X	X	X
EQ-5D	X	X	X
PSG	X		X

Definition of abbreviations: EQ-5D = EuroQol 5 Dimensions; PSG = Paper Standard Gamble; SGRQ = St. George's Respiratory Questionnaire; UCSD SOBQ = University of California San Diego Shortness of Breath Questionnaire.

multiple and unbalanced number of observations per patient.

The PSG utilities were also skewed to the left, whereas the SOBQ and SGRQ scores were right-skewed; a monotonic transformation of the scores to normality was not found. Thus, a Wilcoxon Mann-Whitney two-sample test was performed at each follow-up visit. To control the family-wise error rate, Holm's adjusted *P*-values were reported.

To compare smoking status and healthcare use rates of the two treatment groups, a Chi-square test was performed at each time point. For the subset of patients currently smoking at baseline, logistic regression with GEEs was used to compare smoking cessation rates between the two treatment groups. The dependent variable in the model was whether or not the patient was currently smoking, and the independent variables were treatment group, visit (12 months, 18 months, or 24 months), and the interaction between treatment group and visit. Similarly, healthcare use rates were modeled using logistic regression with GEEs, where the dependent variable in the model was whether or not the patient had used the specific healthcare service, and the independent variables were treatment group, visit (12 months, 18 months, or 24 months), and the interaction between treatment group and visit.

For comparing patient-reported outcomes before versus after notification of an actionable nodule, an actionable nodule was defined as a nodule triggering notification to the patient and their primary care physician that a nodule had been detected at screening. Subjects' survey results from the study visits before the letter was sent versus after the letter was sent were compared. For each subject at each time point, the mean patient-reported outcome score was computed. A Wilcoxon signed rank test was used to compare patients' scores before versus after notification.

Results

From September 2008 through March 31, 2011, 1,424 subjects were enrolled and completed their baseline screen. Study participant characteristics are described in Table 2. A total of 29 actionable nodules were noted in 29 patients at baseline, 18 of which led to a notification letter. Seven

additional nodules leading to notification letters were identified during incidence rounds of screening. Fourteen of these 25 actionable nodules were identified in subjects meeting the NLST criteria.

Study subjects had been enrolled in the study from 1 to 31 months. A total of 80.8% of subjects had follow-up data at 6 months, 66.5% at 12 months, 38.5% at 18 months, and 1.8% at 2 years or beyond, for a total of 1,331.5 subject follow-up years. Six hundred twenty-eight of the subjects met the NLST eligibility criteria (320 control subjects and 308 screened subjects).

Table 3 summarizes the baseline scores of all quality-of-life measures. As shown in Figure 1, the EQ-5D scores for the screening group are higher than those for U.S. population-based control subjects ($P < 0.0001$) (10). None of the quality-of-life measures changes significantly over time, and none differed between the screened and control groups (*see* online supplement for details).

Figure 2 illustrates the change in EQ-5D scores for patients with an actionable nodule before notification of the nodule versus after notification. For the 25 patients with an actionable nodule, the

mean EQ-5D was significantly higher before the letter was sent compared with after notification: 0.940 (SD = 0.096) versus 0.877 (SD = 0.158) ($P = 0.022$). The differences before and after notification were not statistically significant for the PSG (mean scores before vs. after: 0.898 vs. 0.909, $P = 0.556$), SOBQ (10.5 vs. 12.3, $P = 0.504$), SGRQ overall score (17.5 vs. 20.3, $P = 0.197$), SGRQ activity score (29.1 vs. 28.4, $P = 0.907$), or SGRQ impact score (7.9 vs. 11.0, $P = 0.347$). The SGRQ symptom score, however, was statistically significantly increased after notification of an actionable nodule (25.7 vs. 34.0, $P = 0.005$).

For the 14 NLST-eligible patients, the mean EQ-5D was significantly higher before the letter was sent compared with after notification: 0.954 (SD = 0.085) versus 0.890 (SD = 0.141) ($P = 0.047$). The differences before and after notification were not statistically significant for the PSG (0.934 vs. 0.905, $P = 1.0$), SOBQ (14.1 vs. 16.3, $P = 0.787$), SGRQ overall score (21.7 vs. 25.3, $P = 0.424$), SGRQ activity score (33.8 vs. 35.1, $P = 0.970$), SGRQ impact score (12.1 vs. 14.9, $P = 0.970$), or SGRQ symptom score (28.5 vs. 39.6, $P = 0.064$).

Table 2. Baseline characteristics of the screening trial cohort

	Control Group	Screened Group	<i>P</i> Value*
No. of participants	713 (100)	711 (100)	
Age, mean (range)	60.2 (41.5–77.7)	59.9 (42.5–77.8)	0.45
Women	387 (54.3)	385 (54.2)	0.96
Active smokers	361 (50.6)	366 (51.5)	0.85
Never smokers	11 (1.5)	13 (1.8)	
Former smokers	341 (47.8)	332 (46.7)	
No. of pack-years:			0.17
<20	118 (16.8)	125 (17.9)	
20–40	323 (46.0)	276 (39.5)	
40–60	172 (24.5)	193 (27.7)	
60–80	62 (8.8)	69 (9.9)	
80+	27 (3.8)	35 (5.0)	
Diabetes	58 (8.1)	61 (8.6)	0.76
Hypertension	238 (33.4)	217 (30.5)	0.25
CAD	139 (19.5)	144 (20.3)	0.72
CHF	4 (0.6)	14 (2.0)	0.017
CVA	12 (1.7)	20 (2.8)	0.15
COPD	95 (13.3)	122 (17.2)	0.04
Pulmonary fibrosis	1 (0.1)	3 (0.4)	0.32
Asthma	65 (9.1)	64 (9.0)	0.94
Kidney disease	9 (1.3)	9 (1.3)	1.0
Family history lung cancer	182 (25.5)	183 (25.7)	0.93
Cough/shortness of breath	251 (35.2)	252 (35.4)	0.92

Definition of abbreviations: CAD = computer-aided detection; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident. Data are presented as No. (%) unless otherwise noted.

**P* value for null hypothesis that there is no difference in the control and screened groups.

Table 3. Summary of quality-of-life scores at baseline for all subjects and National Lung Screening Trial–eligible subjects

	All Subjects		NLST-Eligible Subjects	
	Mean	Median	Mean	Median
EQ-5D	0.905	1.0	0.904	1.0
PSG	0.904	0.995	0.887	0.990
UCSD SOBQ	12.3	8	13.9	9.0
SGRQ	16.8	12.7	18.5	15.2

EQ-5D = EuroQol 5 Dimensions; NLST = National Lung Screening Trial; PSG = Paper Standard Gamble; SGRQ = St. George's Respiratory Questionnaire; UCSD SOBQ = University of California San Diego Shortness of Breath Questionnaire.

At baseline, 51.0% of all study subjects were currently smoking. At the 1- and 2-year visits, 15.1% (95% confidence interval [CI], 12.1–18.1%) and 19.6% (95% CI, 15.2–24.0%), respectively, of those smoking at baseline were no longer smoking (see Figure E1 in the online supplement). Similarly, at baseline, 51.1% of NLST-eligible study subjects were currently smoking (50.5% of control subjects and 51.8% of screened subjects). At the 1- and 2-year visits, 18.0% (95% CI, 13.3–22.7%) and 22.8% (95% CI, 16.1–29.5%), respectively, of those smoking at baseline were no longer smoking.

Among the 25 patients with an actionable nodule found, 15 were active smokers at baseline. One smoker quit before receiving the notification letter, one quit after receiving the letter, and 13 did not quit. Similarly, among the 14 NLST-eligible patients, 8 were active smokers at baseline. One subject quit before receiving the letter, one quit after receiving the letter, and six did not quit.

Table 4 compares the healthcare use rates of control and screened patients over time. There were no differences at each time point (unadjusted P values > 0.05). Similarly, the logistic regression models showed no treatment effect or treatment/time interaction ($P = 0.694$ for X-ray or CT scan, $P = 0.230$ for hospitalization, $P = 0.135$ for doctor visit, and $P = 0.627$ for laboratory test). For the NLST-eligible patients, there was a significantly lower rate of X-ray/CT procedures in the screened group compared with the control group at 24 months (adjusted P value = 0.038). Similarly, the logistic regression model for X-ray/CT scan use showed a statistically significant treatment/time interaction ($P = 0.043$). The other differences did not reach statistical significance (from logistic regression model: $P = 0.748$ for hospitalization, $P = 0.773$ for doctor visit, and $P = 0.529$ for laboratory test).

The X-ray and CT scan use rates did differ for patients without an actionable nodule versus patients who had received

notification of an actionable nodule. Among patients without an actionable nodule, 9.3% reported undergoing an X-ray or CT scan in the last 6 months versus 25.5% among patients notified of an actionable nodule ($P = 0.002$). There were no other significant differences in healthcare use: hospital emergency room visits (13.6 vs. 13.7, $P = 0.869$), doctor's visits (71.9 vs. 82.4%, $P = 0.253$), and laboratory tests (57.5 vs. 72.5%, $P = 0.143$). Similarly, among NLST-eligible patients, 11.0% of patients without an actionable nodule reported undergoing an X-ray or CT scan in the last 6 months versus 32.1% among patients notified of an actionable nodule ($P = 0.004$). There were no other significant differences in healthcare use, although the sample size is small: hospital emergency room visits (14.5 vs. 25.0%, $P = 0.324$), doctor's visits (76.7 vs. 85.7%, $P = 0.103$), and laboratory tests (62.2 vs. 75.0%, $P = 0.167$).

Discussion

Lung cancer screening with low-dose CT scan in a well-defined high-risk population is currently recommended by many organizations (2). The impact of screening on our patients requires an understanding of the quality of life of those likely to enter a screening program and the impact of the screening program on their quality of life. The impact of the screening program must take into account the effect of the test and its results on both those with and those without a finding of lung cancer. In this study, where subjects on average were slightly younger and smoked less than those in the NLST, we found that the quality of life of those entering our screening program on the whole, and in the subgroup who would meet current guidelines for screening, was quite high compared with those of similar age in the general population. We also found that the report of a lung nodule on imaging leads to a reduction in quality-of-life measures and an increase in subsequent chest imaging. Smoking cessation rates and other aspects of healthcare use for this population are reported, but the relatively small number of lung nodules limited our ability to identify a connection between these outcomes and nodule identification.

The quality of life of those entering a lung cancer screening program can

Figure 1. Baseline EQ-5D results compared with the general population.

Figure 2. Effect of notification of actionable nodule on EQ-5D. NLST = National Lung Screening Trial.

influence the net benefit of the program. The benefit of mortality reduction would be minimized in those with a very low quality of life at baseline, whereas the impact of complications would be greater in those with a very high quality of life at baseline. Two studies have assessed the potential make-up of the screening population. The first found that smokers were significantly more likely than never smokers to report poor health status and less likely to be willing to consider CT screening for lung cancer (11). The second study found that self-selected screening participants were younger, more frequently current smokers, had more pack-years of smoking, and had a higher rate of a family history of lung cancer and of occupational lung cancer risk relative to nonparticipants (12). Our study showed that the quality of life of those who chose to enroll was quite high compared with the general population as well as with

prior reports of similar quality-of-life measures in individuals with moderate to severe COPD (13) and those undergoing surgery for lung cancer (14). This suggests a high potential benefit from mortality reduction and highlights the importance of minimizing the complications of screening in this relatively healthy population.

The screening process may impact the quality of life of those being screened. Two reports from the NELSON screening trial have been published. The first reported increased lung cancer-specific anxiety in those found to have an indeterminate lung nodule (15). In the second, participants were reported to have discomfort related to having to wait for the results of the CT scan and dreading those results (16). Our results support those of the NELSON trial. Despite a relatively small number of actionable lung nodules leading to study subject notification, those who received notification had a decrease in their general

quality of life (a lower mean EQ-5D) and a heightened impact of their respiratory symptoms (a higher SGRQ symptom score). This highlights the need for screening programs to report results in a timely fashion and educate patients about the meaning of those results.

Lung cancer screening could benefit the quality of life of individuals determined to have lung cancer by preventing a decline in quality of life related to the cancer. Studies have reported poorer measures of quality of life related to symptoms, initial treatment with chemoradiation therapies, and higher stage, whereas measures improved with a treatment response (17–19). A metaanalysis of health utility measures for lung cancer found lung cancer stage and subtype, the upper bound label of the utility scale, and respondent identity were significant predictors of utility. A linear model was developed. The metaregression determined a collection of reference lung cancer utility values of 0.573, 0.772, and 0.823 for metastatic, mixed/not specified, and nonmetastatic NSCLC, respectively, with patient as respondent, Standard Gamble (SG) as method, and death to perfect health as bounds of the scale (20). In total, these studies demonstrate a lower quality of life for patients with lung cancer than we noted in the screening population and further decline in the quality of life with lung cancer-related symptoms, advancement of the disease, and treatments of late-stage disease. These findings support the potential for a successful screening

Table 4. Healthcare use over time

Time Point	All Subjects			NLST-Eligible Patients		
	Control (%)	Screened (%)	P Value*	Control (%)	Screened (%)	P Value*
12 mo						
X-ray or CT scan	15.3	14.6	0.734	12.0	15.6	0.234
Hospitalized	15.6	13.4	0.300	15.2	15.2	0.979
Doctor visit	75.5	70.3	0.050	77.8	74.2	0.335
Lab test	63.1	62.4	0.798	66.5	69.0	0.545
Missed work	8.4	8.0	0.872	4.4	4.8	0.878
Additional help	6.3	4.7	0.497	4.3	2.9	0.601
24 mo						
X-ray or CT scan	12.5	11.0	0.575	17.8	8.1	0.019
Hospitalized	15.4	12.9	0.382	15.0	17.7	0.543
Doctor visit	75.9	71.6	0.227	81.2	79.8	0.781
Lab test	67.1	64.2	0.447	73.4	66.1	0.189
Missed work	11.8	11.3	0.911	8.0	4.6	0.494
Additional help [†]	4.3	5.6	0.672	4.0	6.7	0.561

Definition of abbreviation: CT = computed tomography.

*P value for the comparison at each specific time point, unadjusted for multiplicity.

[†]Relates to the need for additional help needed to take care of activities of daily living.

program to mitigate the reduction in quality of life related to advanced symptomatic lung cancer presentations.

Lung cancer screening studies have reported smoking cessation rates of 5 to 23%. Participation in a screening program has not been found to consistently influence smoking behavior, for the better or for worse (2). One report suggested that finding a positive screening test led to higher quit rates and lower relapse rates (21). Another suggested the quit rate was higher than the expected spontaneous quit rate (22). The quit rate in our study was 15.1% at 1 year and 19.6% at 2 years, which is relatively high. We could not adequately assess quit rate with the report of a lung nodule due to the overall small number of nodules identified.

There have been very few publications about healthcare use in the context of lung cancer screening. Data about the tests that

follow the discovery of lung nodules are available, suggesting an overall increase in healthcare use would be expected from a screening test that identifies a large number of difficult-to-classify false-positive findings (2). In the current study, in which the screening test identified only a small number of false-positive findings, an increase in imaging tests after finding a lung nodule was noted, but no differences in other healthcare use measures were found.

The strengths of our study include the rigorous documentation of a range of quality-of-life measures relevant to our population, as well as the inclusion of a broad population of at-risk individuals, a portion of which would currently be considered for lung cancer screening. Weaknesses include the low power to detect changes related to the finding of lung nodules due to the small number of subjects

who were found to have lung nodules. It is also unclear if the results found from this voluntary lung cancer screening study could be extrapolated to a standard of care screening program where entry is influenced by the ordering physician.

In summary, patients who choose to enter a lung cancer screening program have a high baseline quality of life. The report of an abnormal screening finding can lower the quality of life and lead to increased chest imaging. Smoking cessation rates are relatively high, and screening with a test that leads to a relatively low rate of false-positives did not influence healthcare use for the cohort as a whole. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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