

Impact of surgery for stage IA non-small-cell lung cancer on patient quality of life

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Background There is a paucity of literature comparing quality of life (QoL) before and after surgery in stage IA lung cancer, where surgical resection is the recommended curative treatment.

Objective To assess the impact of surgery on physical and mental health-related QoL in patients with stage IA lung cancer treated with surgical resection.

Methods Participants in the I-ELCAP cohort who were diagnosed with their first primary pathologic stage IA non-small-cell lung cancer, underwent surgery, and provided follow-up information on QoL 1 year later were included in the present analysis (N = 107). QoL information was collected using the SF-12 (12-item Short Form Health Survey), which generates 2 component scores related to mental health and physical health.

Results Statistical analyses indicated that physical health QoL was significantly worsened from before surgery to after surgery, whereas mental health QoL marginally improved from before to after surgery. Physical health QoL worsened for women from baseline to follow-up, but not for men. Only lobectomy (not limited resection) had an impact on QoL from before to after surgery.

Limitations Results are considered preliminary given the small sample size and multiple comparisons.

Conclusions The current study findings have implications for lung cancer health care professionals in regard to how they can most effectively present the possible impact of surgery on quality of life to this subset of patients in which disease has not yet significantly progressed.

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There is a growing body of literature that highlights the importance of health-related quality of life (HRQoL) when evaluating the efficacy of cancer treatments and cancer outcomes.¹⁻³ Although there are a number of definitions for HRQoL, there is broad agreement that it is the effect on a patient's well-being of a medical condition and/or of the therapy administered to treat that condition.³⁻⁵ Consequently, HRQoL is a subjective, multidimensional construct that encompasses physical, social, cognitive, psychological, and somatosensory domains.^{2,6-8}

Compared with other cancers, patients with lung cancer experience especially high symptom burdens, multiple comorbidities, and numerous emotional concerns.⁹⁻¹⁵ Although surgery is the primary course of treatment for early stage non-small-cell lung cancer (NSCLC),¹⁶ there has been limited research examining HRQoL in oncology and thoracic sur-

gery.^{17,18} Given the high burden of disease and lack of research, evaluations of HRQoL after treatment for lung cancer are needed.

The literature is mixed regarding the impact of surgery for lung cancer on physical and mental HRQoL. Some study findings suggest that a low baseline HRQoL is predictive of poorer survival in lung cancer patients,^{1,2,17,19-26} and HRQoL is reported to be low in lung cancer survivors compared with the general population and populations at risk for lung cancer.^{27,28} However, other studies contradict those findings, reporting that baseline HRQoL scores have no significant effect on overall survival or recurrence-free survival.^{29,30} Numerous studies have found a decrease in post-operative HRQoL, compared with pre-operative levels.^{27,31-36} Several of these studies indicate that the decrease in QoL is a short-term event, and the scores return to pre-operative levels within 3 to 9 months after

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surgery;^{37,38} one study found that physical QoL surpassed baseline levels 1 year after surgery.³¹ However, others report that HRQoL deficits persist in the long-term,^{2,32-36} with some reporting stable deficits that last throughout survivorship.^{2,35,36} These permanent impairments to physical and mental HRQoL include effects on sleeping, normal daily activities, sexual activity, mental function, depression, distress, and vitality, while the most severe impairments to physical HRQoL are impaired mobility and breathing.^{28,35}

Changes in HRQoL among lung patients who undergo surgery is also dependent on the extent of surgery, with less invasive approaches being associated with better post-surgery physical QoL scores,^{30,39,36} and fastest return to pre-surgical values,³⁰ although a recent study suggested that QoL did not differ between bilobectomy and lobectomy patients.³⁹ Furthermore, patients who receive post-surgical rehabilitation and supportive care services have been found to have improved HRQoL after surgery.^{40,41}

Despite the body of literature on the impact of surgery on HRQoL in patients with lung cancer who undergo various treatment options, and the few studies^{28,39} that analyzed QoL exclusively after surgery in early-stage lung cancer, there is a paucity of literature comparing QoL before and after surgery in stage IA lung cancer, for which surgical resection is the recommended curative treatment.⁴² One study involving patients with stage I lung cancer who were randomized to either sublobar resection or sublobar resection with brachytherapy, found that there was no significant difference between the 2 treatment groups in the percentage of change (pre-post surgery) in QoL score.³⁰ This research did find, however, that greater improvement in physical health QoL was more likely among patients who underwent VATS (video-assisted thoracic surgery) compared with those who had thoracotomy.²⁹ The study did not analyze the impact of surgery on mental compared with physical health QoL. Ostroff and colleagues found that early-stage lung cancer survivors who had undergone surgery 1-6 years prior had lower physical health QoL scores compared with a screening sample, but there was no difference between the 2 samples on mental health QoL scores.²⁷ When compared with healthy controls, however, mental and physical HRQoL has been shown to be significantly worse among post-lobectomy lung cancer patients.⁴³

It is imperative that the effects of surgery and of the type of surgical approach (lobectomy versus limited resection) on HRQoL are understood in surgically treated stage I lung cancer in order to guide the treatment decision-making process. The current study assesses for the first time the impact of surgery on physical and mental health-related quality of life in patients with stage IA lung cancer diagnosed by computerized-tomography (CT) screening and treated with surgical resection, and attempts to understand

whether there is differential impact on HRQoL based on type of surgery (limited resection vs lobectomy). Further, in lung cancer specifically, studies have noted differences between men and women in terms of HRQoL outcomes and overall survival, with women usually faring worse than men on all outcomes,^{29,44-47} although one study found that men fared worse on physical health QoL than did women,⁴⁷ and another found no differences in QoL based on gender.⁴⁸ As such, the current study also aims to delineate any differences in outcomes by sex, and it is hypothesized that women will likely have worse HRQoL outcomes after surgery than do men.

Methods

This report draws from the database of the diagnosed cases of NSCLC identified as a result of CT screening in the International Early Lung Cancer Action Program (I-ELCAP) cohort. The screenings were performed under an IRB-approved, HIPAA-compliant common protocol at each of the participating institutions from 2001 (when the SF-12 [12-item Short Form Health Survey] HRQoL measure started to be collected) to 2014 on smokers, never-smokers, and participants with occupational exposure to airborne carcinogens or exposure to secondhand smoke who were 40 years or older.⁴⁹ Consent was obtained from all of the participants at the time of enrollment. They were interviewed to obtain information on relevant demographics, occupational history, smoking habits, and comorbidities. For the purposes of this study, only participants diagnosed with their first primary pathologic stage IA NSCLC who underwent surgery and provided follow-up SF-12 HRQoL information 1 year later (range, 7-18 months) were included in the present analysis. This time interval corresponds to the I-ELCAP screening clinical regimen for repeat CT scans. Staging classification for lung cancer was made centrally based on the American Joint Committee on Cancer Staging Manual (6th ed), with 1 exception. Cases of multiple adenocarcinomas (<30 mm in diameter) without lymph node metastases were classified as synchronous primaries and considered to be stage IA.^{6,7}

QoL information was collected using a standard SF-12 form, a shorter version of the SF-36 questionnaire.⁵⁰ The SF-12 has been widely used and validated with samples of surgical patients.^{51,52} It assesses 8 domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. The SF-12 was used to calculate 2 component scores, the Physical Component Summary Score (PCS) and the Mental Component Summary Score (MCS). Scores for MCS and PCS range from 0-100 (worst to best HRQoL). The PCS is a combination of SF-12 items that focus on participants' perceptions of their

general health, mobility, limitations due to physical problems, and limitations in work/productivity due to physical problems and pain. Similarly, the MCS focuses on participants' experiences of symptoms of depression and anxiety, difficulties with social activity, and amount accomplished due to emotional difficulties. The SF-12 had good reliability in the present sample yielding a Cronbach's alpha of 0.85 at baseline and 0.90 at follow-up.

Statistical analysis

Continuous variables are presented as means and standard deviations, categorical variables as percentages. Univariate and multivariate analyses were performed to examine the difference in physical (PCS) and mental (MCS) health component scores of the SF-12 before and after surgery using the paired *t* test and analysis of variance tests. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC). Covariates included age, education, ethnicity, gender, current smoking status and presence of comorbid conditions (eg, liver disease, asthma, diabetes) as these are often associated with lung cancer QoL outcomes in the literature.^{48,53}

Results

There were 107 participants (54 women, 53 men) who matched the inclusion criteria and had an SF-12 questionnaire completed at baseline CT screening and at 1-year follow-up after surgery for pathologic stage IA non-small-cell lung cancer (Table 1). Their mean age was 63 years (SD, 8.1; range, 45-83); 83 patients had lobectomy and 24 had sublobar resection. Average time of follow-up was 11 months after surgery (SD, 2.3 months; range, 7-18 months after surgery).

Changes in quality of life after surgery

On baseline screening CT, average PCS and MCS scores were 49.0 (SD, 6.9) and 52.2 (SD, 9.4), respectively. Mean post-surgery PCS was 46.8 (SD, 9.0) and MCS was 54.0 (SD, 1.8). There was a statistically significant decrease in PCS from baseline to post-surgery follow-up (-2.2; 95% confidence interval [CI], -3.64 and -0.78); whereas MCS did not change significantly from baseline to post-surgery follow-up.

Effect of type of surgery on PCS

There was no statistically significant difference in post-surgical PCS among patients who underwent limited resection (Table 2), but there was a significant decrease in PCS score among those who underwent lobectomy (-3.1; 95% CI, -4.69 and -1.42). At multivariate analysis, adjusting for sex, age, ethnicity, education, current smoking status and presence of comorbid conditions, the mean PCS at baseline and follow-up did not vary by type of surgery. The difference between baseline and follow-up was statistically

TABLE 1 Description of patient characteristics (N = 107)

Variable	n (%)	Mean (SD)
Age, y	—	62.8 (8.1)
Sex		
Women	54 (50)	—
Men	53 (50)	—
White	95 (89)	—
College education	50 (47)	—
Smoking status (baseline)		—
Never-smoker	1 (1)	—
Former smoker	55 (51)	—
Current smoker	51 (48)	—
Pack-years (among smokers)	—	50.1 (24.4)
Lesion size before resection, mm	—	14.2 (6.0)
Tumor pathology size, mm		
1-10	37 (35)	—
11-20	56 (52)	—
21-30	14 (13)	—
Lesion location		
LLL	13 (12)	—
LUL	27 (25)	—
RLL	19 (18)	—
RML	2 (2)	—
RUL	46 (43)	—
Type of surgery		
Wedge resection	13 (12)	—
Segmentectomy	11 (10)	—
Lobectomy	79 (74)	—
Bilobectomy	4 (4)	—
Type of resection		
Limited	24 (22)	—
Lobectomy	83 (78)	—
Baseline SF-12		
Mental health component	—	52.2 (9.4)
Physical health component	—	49.0 (6.9)
Length of follow-up, mo.	—	11.3 (2.3)
Smoking status (follow-up)		
Former smoker	92 (86)	—
Current smoker	15 (14)	—
At least 1 comorbid condition		
Yes	77 (72)	—
No	30 (28)	—

LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; SF-12, 12-item Short Form Health Survey

TABLE 2 SF-12 quality-of-life scores before and after surgery, by type of surgery (N = 107)

Score	Limited resection, mean (SD) [95% CI for mean]	Lobectomy, mean (SD) [95% CI for mean]	Limited vs lobectomy, parameter estimates (95% CI) [Limited = 1]	
			Unadjusted ^a	Adjusted ^b
PCS				
Baseline	49.0 (7.4)	49.0 (6.8)	0.00 (-3.19, 3.19)	0.42 (-2.89, 3.73)
Follow-up	49.7 (7.7)	46.0 (9.2)	3.78 (-0.32, 7.88)	4.28 (0.21, 8.36)
Difference (follow-up baseline)	0.7 (6.6) [-2.07, 3.50]	-3.1 (7.5) [-4.69, -1.42]	3.77 (0.42, 7.13)	3.86 (0.48, 7.24)
MCS				
Baseline	51.3 (12.8)	52.5 (8.2)	-1.16 (-5.49, 3.17)	-0.73 (-5.09, 3.62)
Follow-up	52.2 (10.0)	54.5 (9.2)	-2.27 (-6.57, 2.04)	-2.26 (-6.63, 2.11)
Difference (follow-up baseline)	0.9 (11.7) [-4.01, 5.85]	2.0 (8.8) [0.10, 3.95]	-1.10 (-5.48, 3.27)	-1.52 (-5.98, 2.89)

CI, confidence interval; MCS, Mental Health Component Score; PCS, Physical Health Component Score; SF-12, the 12-item Short Form Health Survey

^aRegression analysis comparing QoL score between limited resection and lobectomy. ^bMultivariate regression analysis comparing QoL score between limited resection and lobectomy after controlling for sex, age, ethnicity, education, current smoking status, and presence of comorbid conditions.

TABLE 3 SF-12 quality-of-life scores before and after surgery, overall and by sex (N = 107)

Score	All, mean (SD) [95% CI for mean]	Men, mean (SD) [95% CI for mean]	Women, mean (SD) [95% CI for mean]	Men vs women, parameter estimates (95% CI)	
				Unadjusted ^a	Adjusted ^b
PCS					
Baseline	49.0 (6.9)	49.4 (6.6)	48.6 (7.2)	0.80 (-1.86, 3.46)	1.34 (-1.58, 3.85)
Follow-up	46.8 (9.0)	47.5 (8.4)	46.1 (9.6)	1.34 (-2.13, 4.81)	1.75 (-1.65, 5.16)
Difference (follow-up baseline)	-2.2 (7.5) [-3.64, -0.78]	-1.9 (7.5) [-4.01, 0.13]	-2.5 (7.5) [-4.51, -0.44]	0.54 (-2.33, 3.41)	0.62 (-2.22, 3.45)
MCS					
Baseline	52.2 (9.4)	53.8 (9.3)	50.7 (9.3)	3.14 (-0.43, 6.70)	3.16 (-0.40, 6.73)
Follow-up	54.0 (9.4)	56.5 (9.6)	52.5 (8.9)	3.03 (-0.53, 6.60)	3.55 (-0.05, 7.14)
Difference (follow-up baseline)	1.8 (9.5) [-0.04, 3.59]	1.7 (8.2) [-0.53, 3.98]	1.8 (10.7) [-1.09, 4.75]	-0.11 (-3.76, 3.55)	0.38 (-3.24, 4.00)

CI, confidence interval; MCS, Mental Health Component Score; PCS, Physical Health Component Score; SF-12, the 12-item Short Form Health Survey

^aRegression analysis comparing QoL score between men and women. ^bMultivariate regression analysis comparing QoL score between men and women after controlling for age, ethnicity, education, current smoking status, and presence of comorbid conditions.

significant (+3.86; 95% CI, 0.48 and 7.24) between the 2 types of surgery, although the confidence interval was wide.

Effect of type of surgery on MCS

MCS was statistically significantly improved after lobectomy (+2.0; 95% CI, 0.10 and 3.95), but not after limited resection (Table 2). At multivariate analysis, adjusting for sex, age, ethnicity, education, current smoking status

and presence of comorbid conditions, the mean MCS at baseline), the mean MCS at follow-up and the difference between baseline and follow-up were not significantly different according to type of surgery.

Effect of sex

A decrease in PCS was observed in both men (-1.9; 95% CI, -4.01 and 0.13) and women (-2.5; 95% CI: -4.51 and

-.44) after surgery, but the change was statistically significant only among women (Table 3). MCS did not significantly change from baseline to after surgery among men or women. After adjustment for age, ethnicity education, current smoking status, and presence of comorbid conditions, no differences between men and women were observed at baseline and after surgery for both PCS and MCS.

Sensitivity analysis

To eliminate the concerns about the use of a relatively wide follow-up interval (7-18 months), which is dictated by the clinical follow-up setting of the I-ELCAP study, the analyses were repeated using a narrower follow-up interval of 9-15 months after surgery (85 patients). Patients' characteristics and the direction of the results were consistent with results obtained with the wider 7-18 months interval.

Discussion

The current study is one of the first to examine the impact of surgery on both mental health and physical health quality of life among early-stage (1A) lung cancer survivors who underwent surgery as curative treatment. About a year after surgery physical health quality of life was significantly poorer than before surgery. This is consistent with other findings in more advanced lung cancers, which have indicated that physical QoL was significantly worsened after surgery. When sex is considered, the associations become more nuanced. Results indicated that mental health QoL was not significantly impacted by surgery, but that physical health QoL significantly worsened for women from baseline to follow-up, but this same effect was not observed in men. This seems to imply that women who have lung cancer surgery are at greater risk than are men for experiencing post-surgical difficulties with physical functioning. These findings are consistent with research involving other types of oncologic surgery in that women tend to have worse physical and mental health outcomes after surgery.^{54,55} The differences in follow-up MCS scores between men and women approached statistical significance ($P = .05$), therefore it's possible that with an appropriately larger sample size, a significant difference would have been observed in mental health QoL.

When type of surgery is considered, the study findings indicate that only lobectomy (not limited resection) had an impact on QoL from before to after surgery. In fact, there was a significant decrease in physical health QoL and an improvement in mental health QoL from pre-surgery to follow-up in the lobectomy group. The multivariate analysis confirmed that physical health QoL was lower at follow-up (compared with before surgery) among patients who underwent lobectomy, but no change in physical health QoL was observed among those who underwent limited resection. It is possible that the more invasive nature of lobectomy in comparison to sublobectomy is partially

responsible for the observed differences in QoL after surgery. Lobectomy is associated with more complications and longer hospital stay in comparison to sublobectomy.^{56,57} The modest improvement in mental health QoL that was seen in univariate analysis is difficult to explain given the greater potential for complications and longer hospital stays associated with lobectomy,^{58,59} but perhaps it reflects a sense of release or decreased anxiety associated with the removal of a more advanced tumor that required lobectomy. The mental health QoL result, however, should be interpreted with caution as the finding was no longer statistically significant in the multivariate analysis.

The study has a number of limitations. The small sample size may have made it less likely to detect significant differences. It is possible that some of the borderline significant results, such as the multivariate finding regarding the lower mental health QoL at follow-up among women compared with men would have been statistically significant had the sample size been larger. Although we limited the analysis to the main a priori hypotheses that QoL varied according to type of surgery and sex, the results must be taken as preliminary, because there is the possibility of chance findings due to multiple comparisons in a small sample of participants. Further, it is difficult to know whether the decreased physical health QoL would persist in the long term as the current study used a window of 7-18 months after surgery for inclusion in the study. This study is not consistent with some of the literature on surgery for advanced lung cancer, reporting that physical QoL goes back to baseline or even exceeds baseline levels 3-9 months after surgery. It has to be noted that these studies used different indicators of physical QoL including a pulmonary function test, and this may account for some of the differences.^{37,38} The SF-12 is a general measure of QoL, not specific to cancer or lung cancer; as a result it is inferior to other disease-oriented questionnaire in use to assess QoL in cancer survivors, and is more susceptible to floor and ceiling effects. However, the current study findings may be consistent with other studies that have found that decreased physical QoL persists in the long term.^{2,32-36} Future prospective longitudinal research will help to delineate the chronicity of these effects on QoL. Finally, the results presented in the current study are preliminary in nature and, although the physical component of QoL changed in a statistically significant manner, those results may not translate into clinical relevance. A change of 2-3 points on the SF-12 may result in only a minimal experience of improved or worsened QoL if at all. Future research with larger sample sizes and more specific QoL measurement may help to better differentiate the scores leading to greater clinical significance.

The current study findings have implications for surgeons and other lung cancer health care professionals regarding how to most effectively present the possible impacts (or non-impacts) of surgery on the quality of life to this sub-

set of patients in which disease has not yet significantly progressed. The physical health QoL negative impact has to be carefully explained, with special attention given to issues specific to women's QoL as women may be at higher risk for negative QoL consequences of surgery. The potential improvement in mental health QoL after surgery, perhaps resulting from decreased anxiety among other factors, is also something that lung cancer health care professionals can point to regarding one of the less obvious potential positive consequences of undergoing surgery at an early stage.

Given the numerous surgical options that are sometimes available when lung cancer is detected at such an early stage, it is also helpful for patients to understand the potential impacts of the various types of surgery on their overall QoL as well as their mental and physical health QoL. Perhaps particular attention should be paid to the post-surgical functioning of patients who underwent lobectomy as these patients may experience more of the negative physical health QoL impact, but ultimately seem to have a more positive mental health QoL impact compared with patients who underwent limited resection. This research adds new information to the body of literature that will assist in guiding surgeons and other lung cancer health care professionals in their discussions and their decisions regarding surgery for early-stage lung cancer patients. Although clinicians treating this group of patients may view their patients as "cured" after surgical resection, the present results highlight that there may be post-surgical quality of life issues that require ongoing attention. Future research should focus on examining these issues with larger numbers of early-stage lung cancer patients and conducting longer term follow-up (perhaps 5-10 years after surgery) assessments to determine what QoL impacts are persistent over time.

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