Precision Clinical Medicine, 2(1), 2019, 8–12

doi: 10.1093/pcmedi/pbz001
Advance Access Publication Date: 11 March 2019
Short Communication

SHORT COMMUNICATION

Maximizing quality of life remains an ultimate goal in the era of precision medicine: exemplified by lung cancer

Ping Yang*

Mayo Clinic College of Medicine and Science, Mayo Clinic Arizona, 13400 E. Shea Boulevard, Scottsdale, AZ 85259, USA

*Correspondence: Ping Yang, yang.ping@mayo.edu

Abstract

An ultimate goal of precision medicine in lung cancer treatment is to restore patient health with maximized quality of life (QOL). Results from Mayo Clinic studies show that a significant improvement in fatigue, dyspnea, and pain scales could lead to better overall QOL. Although treatments and guidelines for clinical implementation to alleviate these key symptoms are available, few cancer patients receive adequate therapy, mostly because of limitations in current care delivery systems and unclear clinicians' roles. For optimal care of lung cancer survivors in different subpopulations, three barriers must be overcome: physicians' lack of knowledge, unwarranted practice variation, and uncertainty regarding care provider roles. Appropriate culturally adapted, tested and validated tools for QOL measures must be developed, rather than directly translating existing tools between different languages and across cultures or diverse subpopulations. Finally, lack of sensitive, adequate, and relevant tools in measuring health-related QOL (HRQOL) has long been an issue for effective data collection, demanding a global consensus on a set of core components that reflect the needs of all critical parties for the best cure and care, supporting patients to achieve optimal HRQOL.

Key words: lung cancer; survivorship; health-related quality of life

Precision medicine is an emerging disease treatment and prevention approach accounting for variability in genes, environment, and lifestyle for individuals,[1] aiming at achieving optimal response and survival length. The premise of precision medicine is the ability to classify individuals into subpopulations in which preventive or therapeutic interventions can be focused on those who will benefit, sparing cost and adverse effects for those who will not.[2] Non-small cell lung cancer (NSCLC) therapy is one of the best showcases in precision medicine, with a rapidly increasing number of drugs directed against a growing number of specific tumor targets, e.g., tyrosine kinase inhibitors targeting epidermal growth factor receptor or anaplastic lymphoma kinase, even though the clinical benefit is limited by virtually universal resistance in the end, and repeatedly after subsequent generation target drug.[3–5]

Received: 21 January 2019; **Accepted:** 22 January 2019

In parallel to the primary goal to *cure* the disease, an ultimate goal of precision medicine is to *restore* patient health with maximized quality of life (QOL). Six decades ago the World Health Organization defined QOL as "the state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."[6] Twenty years ago, the United States Center for Disease Control and Prevention defined health-related quality of life (HRQOL) as "an individual's or group's perceived physical and mental health over time."[7] HRQOL, focusing on the impact of health status or disease and its treatment, is a multidimensional concept including domains related to subjective physical, mental, emotional, spiritual, and social functioning.[8–10] In lung cancer, however, attention to HRQOL among survivors has only been given, gradually and slowly, over the past two decades.[11–13]

Thirty years ago when developing effective antineoplastic therapies to save the lives of cancer patients, lung cancer included, tolerability and adverse effects of pharmacologic compounds were the primary concerns; consequently, performance status surrounding the treatment and drug-related toxicities within 6-24 months have been the surrogate measures for QOL.[14,15] An early successful case was proactive treatment after brain metastasis, i.e., brain tumor resection or whole brain radiation therapy, and chemotherapy, showing significantly longer survival and also improving patients' QOL.[16] Additionally, palliative care, e.g., for pleural effusion and bone metastasis, has been established to reduce suffering and improving quality of life.[17–19] However, more often than not the drug-safety monitoring, designed to prevent patients from irreversible adverse effects in the long term, has been overlooked in routine clinical practice.[11,17]

Knowledge and gaps in long-term lung cancer survivors: Mayo Clinic experience

Despite having survived the original diagnosis and treatment ordeals, lung cancer survivors do not return to functioning and QOL levels comparable to pre-diagnosis, as can be the case in age-matched adult survivors of other cancers.[12,20–22] Most lung cancer survivors experience poorer physical function, more severe symptoms, and more symptom-related distress than those with comparable stages of other cancers.[23–33] Results from limited studies on long-term (≥5 years post diagnosis) lung cancer (LTLC) survivors report that this group of survivors' excessively low performance status persists regardless of having active disease or treatment.[34–37] Selected key findings are discussed in more detail below.

Overall QOL predicting overall survival

Patients' self-reported conditions have been known to bear an impact on lung cancer outcome. A study of 2442 lung cancer patients validated the overall QOL score, being a strong and independent prognostic factor (Fig. 1). The association with overall survival was adjusted for age, treatment, sex, disease stage, Eastern Cooperative Oncology Group performance score, disease recurrence/progression, having any other cancer, and time since cancer diagnosis.[38,39]

Major disabling symptom burden

A longitudinal study assessed multiple QOL domains at <3 years and >5 years post diagnosis, in which 35% of LTLC survivors reported a clinically significant decline in overall QOL, and > 50% indicated significantly worsening fatigue and dyspnea.[40] Among those with degraded overall QOL, most symptom-specific scales exceeded a 15% decline (fatigue, dyspnea, pain, cough, and appetite). Furthermore, the deficits often appeared concurrently in symptom clusters[41,42]; and patients with fatigue, dyspnea, and pain had a significantly higher death rate than patients free of these symptoms.[43,44]

Type of lung surgery and pulmonary comorbidity

Choice of surgical resection of operable lung cancer is made bearing in mind both curative goal and minimal normal tissue damage or loss. Comparing the clinical outcomes and changes in pulmonary function after segmentectomy versus lobectomy for NSCLC did not reveal any significant differences[45]; neither were any significant differences seen on morbidity, overall survival, or disease-free survival, and overall QOL between patients treated with bilobectomy and lobectomy.[46] When chest wall resection is inevitable, overall QOL and pulmonary function of patients who underwent pulmonary resection with chest wall removal were comparable to those of patients who underwent pulmonary resection without chest wall invasion.[47] Moreover, when early-stage lung cancer is complicated with emphysema, a regional emphysema score, derived from the emphysematous region (mild, moderate, or severe), is predictive of post-treatment QOL related to dyspnea and changes in lung function.[48]

Pharmacological therapy and adverse events

A research team studied 950 primary lung cancer patients, who received platinum or platinum-combination drug chemotherapy, and found that 279 (29.4%) developed chemotherapy-induced peripheral neuropathy; these findings provide strong evidence that taxane, not platinum drugs was the culprit.[49] However, another study found that platinum-based chemotherapy may lead to loss of menses in premenopausal women who survived lung cancer, with the potential to result in infertility and early menopause.[50]

Emotional and spiritual functioning

Researchers examined how emotional problems relate to QOL and symptom burden in > 2200 lung cancer survivors, reporting that emotional problems were associated with younger age, female gender, current cigarette smoking, current employment, advanced lung cancer disease, surgical or chemotherapy treatment, and a lower

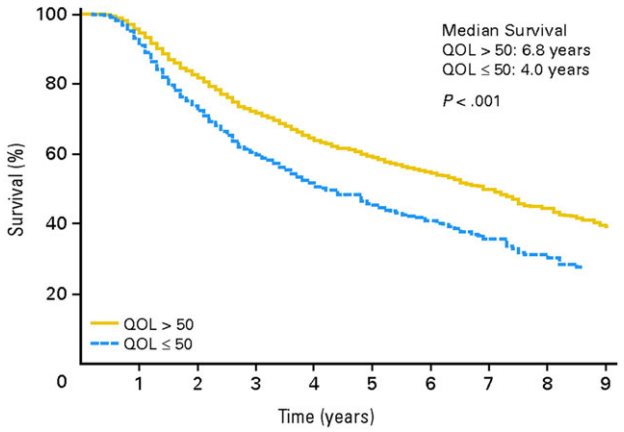

Figure 1. Survival curves by quality-of-life (QOL) assessment adjusted for known prognostic factors.[38]

performance score.[51,52] Strong associations were found between greater severity of emotional problems, lower QOL, and greater symptom burden[51]; besides, a pessimistic explanatory style is prognostic for poor survival.[52] They also analyzed the spiritual well-being data, finding the mean scores to be stable over time and strongly associated with overall QOL, as well as having a potential relationship to physical activity level.[53,54]

Cigarette smoking

In a study of the relationship between cigarette smoking and QOL after lung cancer diagnosis among > 1500 lung cancer survivors,[55,56] 30% of current smokers at diagnosis continued to smoke at the time of follow-up assessment (i.e. persistent smokers). Seven QOL scales (appetite, fatigue, cough, shortness of breath, lung cancer symptoms, illness affecting normal activities, and overall QOL) were clinically and statistically better in never, than in persistent, smokers. Furthermore, continued cigarette smoking after small cell lung cancer diagnosis decreased QOL profile and survival.[57,58] Offering strategies of smoking cessation to continuing smokers and maintaining tobacco abstinence in former smokers call for action.

Alcohol drinking and anorexia

Poor appetite and any weight loss are predictors of poor outcomes in advanced lung cancer; non-cancer literature suggests that drinking alcohol can increase appetite and weight. In > 400 consecutive survivors, we found 49% non-users of alcohol, 14% "moderate" users (<7 drinks/week), and 12% "heavier" (≥7 drinks/week) users, measured within 6 months of diagnosis. Heavier users had a lower likelihood of anorexia and weight loss compared to those who consumed no alcohol, but neither moderate nor heavier consumption was associated with better or worse survival. These results suggest a need for further study of the possible benefits versus harms of using alcohol as a palliative agent for cancer-associated loss of appetite and weight.[59,60]

Physical activity exercise

A study examined motivational readiness for physical activity (stage of change for physical activity level) and QOL in 272 LTLC survivors, and 37% of respondents reported that they currently engaged in regular physical activity (a total of ≥30 min/day, at least 5 days/week). Those who were engaging in regular physical activity reported a better overall QOL, better QOL on all five functioning domains (mental, physical, social, emotional, and spiritual), and fewer symptoms compared to those with a sedentary lifestyle.[61] A follow-up study examined 1937 survivors and confirmed these results. Decreased physical activity was associated with decreased overall, mental, physical, emotional, social, and spiritual QOL, and decreased symptom control for pain, coughing, dyspnea, and fatigue. In contrast, increased physical activity was associated with improved QOL and improved symptom control (e.g. bodily pain).[62]

Summary: lessons learned from the past and moving forward to the future

Long-term NSCLC survivors (those > 5 years from their diagnosis) are underrepresented in survivorship research efforts, because the historic long-term survival rate in this disease is low and QOL research has typically focused on patients with advanced disease.[11,17,63] The lack of long-term therapeutic response data (> 5 years) remains an unsolved dilemma.[9,13] Results from Mayo Clinic studies show that the two most significant debilitating symptoms that diminish both overall quality and quantity of life of lung cancer survivors are fatigue and dyspnea.[40–42] It is clear that improvement in key symptoms could lead to better overall QOL; specifically, a significant improvement in fatigue, dyspnea, and pain scales.[23,40] Although treatments and guidelines for clinical implementation to alleviate fatigue, dyspnea, and pain are available, few cancer patients receive adequate therapy for these symptoms.[64] The major reasons are limitations in current care delivery systems and unclear clinicians' roles.[65]

The United States National Cancer Institute's Survivorship Research Office conducted the National Survey of Physician Attitudes Regarding the Care of Cancer Survivors, which identified the following three barriers to optimal care of cancer survivors: physicians' lack of knowledge, unwarranted practice variation, and uncertainty regarding care provider roles.[65] Appropriate culturally adapted, tested and validated tools are required for QOL measures, rather than directly translating existing tools between different languages and across cultures or diverse subpopulations.[56,66] Finally, lack of sensitive, adequate, and relevant tools in measuring HRQOL has long been an issue in effective data collection, demanding a global consensus on a set of core components that reflect the needs of all critical parties for the best cure and care, supporting patients to achieve optimal HRQOL.[67]

Acknowledgements

The work is partially supported by the Mayo Foundation.

References

1. United States National Library of Medicine, https://ghr.nlm.nih.gov/primer/precisionmedicine/definition, 2015.
2. Wikipedia, Precision Medicine, updated on December 05, 2018. https://en.wikipedia.org/wiki/Precision_medicine.
3. Liu X, Wang P, Zhang C, *et al*. Epidermal growth factor receptor (EGFR): A rising star in the era of precision medicine of lung cancer. *Oncotarget* 2017;**8**:50209–20. PMCID: PMC5564844.
4. Lin JJ, Riely GJ, Shaw AT. Targeting ALK: Precision Medicine Takes on Drug Resistance. *Cancer Discov* 2017;**7**:137–55. PMC5296241.
5. Bahce I, Yaqub M, Smit EF, *et al*. Personalizing NSCLC therapy by characterizing tumors using TKI-PET and immuno-PET. *Lung Cancer* 2017;**107**:1–13. PMID: 27319335.
6. World Health Organization [WHO], 1948. https://www.who.int/mental_health/publications/whoqol/en/.
7. The WHOQOL Group. The World Health Organization Quality of Life Assessment (WHOQOL). Development and psychometric properties. *Soc Sci Med* 1998;**46**:1569–85.
8. Office of Disease Prevention and Health Promotion, Health-Related Quality of Life and Well-Being. The U.S. Department of Health and Human Services, as of January 10, 2019. https://www.cdc.gov/hrqol/concept.htm.
9. 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**:2920–9. PubMed: 12089220.
10. Cella DF. Measuring quality of life in palliative care. *Semin Oncol* 1995;**22**:73–81. PubMed: 7537908.
11. Montazeri A, Gillis CR, McEwen J. Quality of life in patients with lung cancer: a review of literature from 1970 to 1995. *Chest* 1998;**113**:467–81. PubMed: 9498968.
12. Sugimura H, Yang P. Long-term survivorship in lung cancer: a review. *Chest* 2006;**129**:1088–97. Review. PubMed PMID: 16608961.
13. Yang P. Epidemiology of lung cancer prognosis: quantity and quality of life. *Methods Mol Biol* 2009;**471**:469–86. PMC2941142.
14. Sekine I, Saijo N. Novel combination chemotherapy in the treatment of non-small cell lung cancer. *Expert Opin Pharmacother* 2000;**1**:1131–61.
15. Vijayvergia N, Shah PC, Denlinger CS. Survivorship in Non-Small Cell Lung Cancer: Challenges Faced and Steps Forward. *J Natl Compr Canc Netw* 2015;**13**:1151–61. Review. PMID: 26358799; PMC5450910.
16. Chang DB, Yang PC, Luh KT, *et al*. Late survival of non-small cell lung cancer patients with brain metastases. Influence of treatment. *Chest* 1992;**101**:1293–7. PubMed PMID: 1316262.
17. Ennezat PV, Cosgrove S, Bouvaist H, *et al*. From evidence-based medicine to personalized medicine, with particular emphasis on drug-safety monitoring. *Arch Cardiovasc Dis* 2017;**110**:413–9. PMID: 28552224.
18. DeCamp MM Jr, Mentzer SJ, Swanson SJ, *et al*. Malignant effusive disease of the pleura and pericardium. *Chest* 1997; **112**:291S–5S.
19. Baldini EH. Palliative radiation therapy for non-small cell lung cancer. *Hematol Oncol Clin North Am* 1997;**11**:303–19.
20. 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.
21. Schag CAC, Ganz PA, Wing DS, *et al*. Quality of life in adult survivors of lung, colon, and prostate cancer. *Qual Life Res* 1994;**3**:127–41.
22. Given B, Given C, Azzouz F, *et al*. Physical functioning of elderly cancer patients prior to diagnosis and following initial treatment. *Nurs Res* 2001;**50**:222–32.
23. Degner L, Sloan J. Symptom distress in newly diagosed ambulatory cancer patients and as a predictor of survival in lung cancer patients. *J Pain Symptom Manage* 1995;**10**:423–31.
24. Cooley ME. Symptoms in adults with lung cancer. A systematic research review. *J Pain Symptom Manage* 2000;**19**:137–53.
25. Sarna L, Brecht ML. Dimensions of symptom distress in women with advanced lung cancer: a factor analysis. *Heart Lung* 1997;**26**:23–30.
26. Cooley ME, Short TH, Moriarty HJ. Patterns of symptom distress in adults receiving treatment for lung cancer. *J Palliat Care* 2002;**18**:150–9.
27. Cooley ME, Short TH, Moriarty HJ. Symptom prevalence, distress, and change over time in adults receiving treatment for lung cancer. *Psychoonocology* 2003;**12**:694–708.
28. Weisman A, Worden J Coping and vulnerability in cancer patients. In: Report;1R01A CA-14104: National Cancer Institute. 1997.
29. Given CW, Given B, Azzouz F, *et al*. Predictors of pain and fatigue in the year following diagnosis among elderly cancer patients. *J Pain Symptom Manage* 2001;**21**:456–66.
30. Doorenbos AZ, Given CW, Given B, *et al*. Symptom experience in the last year of life among individuals with cancer. *J Pain Symptom Manage* 2006;**32**:403–12. PMC1894855
31. Gift AG, Jablonski A, Stommel M, *et al*. Symptom clusters in elderly patients with lung cancer. *Oncol Nurs Forum* 2004;**31**: 202–12.
32. Gift AG, Stommel M, Jablonski A, *et al*. A cluster of symptoms over time in patients with lung cancer. *Nurs Res* 2003; **52**:393–400.
33. Lilenbaum RC, Cashy J, Hensing TA, *et al*. Prevalence of poor performance status in lung cancer patients: implications for research. *J Thorac Oncol* 2008;**3**:125–9.
34. Buccheri G, Ferrigno D, Tamburini M. Karnofsky and ECOG performance status scoring in lung cancer: a prospective, longitudinal study of 536 patients from a single institution. *Eur J Cancer* 1996;**32**:1135–41.
35. Sarna L. Fluctuations in physical function: adults with non-small cell lung cancer. *J Adv Nurs* 1993;**18**:714–24.
36. Sarna L. Women with lung cancer: impact on quality of life. *Qual Life Res* 1993;**2**(1):13–22.
37. Radzikowska E, Glaz P, Roszkowski K. Lung cancer in women: age, smoking, histology, performance status, stage, initial treatment and survival. Population-based study of 20 561 cases. *Ann Oncol* 2002;**13**:1087–93.
38. Sloan JA, Zhao X, Novotny PJ, *et al*. Relationship between deficits in overall quality of life and non-small-cell lung cancer survival. *J Clin Oncol* 2012;**30**:1498–504. PMID: 22454418; PMCID: PMC3383120.
39. Schild SE, Tan AD, Wampfler JA, *et al*. A new scoring system for predicting survival in patients with non-small cell lung cancer. *Cancer Med* 2015;**4**:1334–43. PMID: 26108458; PMCID: PMC4567018.

40. Yang P, Cheville AL, Wampfler JA, *et al*. Quality of life and symptom burden among long-term lung cancer survivors. *J Thorac Oncol* 2012;**7**:64–70. PMID: 22134070; PMCID: PMC3241852.
41. Cheville AL, Novotny PJ, Sloan JA, *et al*. Fatigue, dyspnea, and cough comprise a persistent symptom cluster up to five years after diagnosis with lung cancer. *J Pain Symptom Manage* 2011;**42**:202–12. PMID: 21398090; PMCID: PMC3381986.
42. Cheville AL, Novotny PJ, Sloan JA, *et al*. The value of a symptom cluster of fatigue, dyspnea, and cough in predicting clinical outcomes in lung cancer survivors. *J Pain Symptom Manage* 2011;**42**:213–21. PMID: 21398089; PMCID: PMC3382064.
43. Rummans TA, Clark MM, Sloan JA, *et al*. Impacting quality of life for patients with advanced cancer with a structured multidisciplinary intervention: A randomized controlled trial. *J Clin Oncol* 2006;**24**(4):635–42.
44. Lapid MI, Rummans TA, Brown PD, *et al*. Improving the quality of life of geriatric cancer patients with a structured multidisciplinary intervention: a randomized controlled trial. *Palliat Support Care* 2007;**5**:107–14.
45. Deng B, Cassivi SD, de Andrade M, *et al*. Clinical outcomes and changes in lung function after segmentectomy versus lobectomy for lung cancer cases. *J Thorac Cardiovasc Surg* 2014;**148**:1186–1192.e3. PMID: 24746994; PMCID: PMC4169754.
46. Xie D, Deschamps C, Shen RK, *et al*. Bilobectomy Versus Lobectomy for Non-Small Cell Lung Cancer: A Comparative Study of Outcomes, Long-Term Survival, and Quality of Life. *Ann Thorac Surg* 2015;**100**:242–50 PMID: 26007206.
47. Liu M, Wampfler JA, Dai J, *et al*. Chest wall resection for non-small cell lung cancer: A case-matched study of postoperative pulmonary function and quality of life. *Lung Cancer* 2017;**106**:37–41. doi:10.1016/j.lungcan.2017.01.014. Epub 2017 Jan 29. PubMed PMID:28285692.
48. Dai J, Liu M, Swensen SJ, *et al*. Regional Emphysema Score Predicting Overall Survival, Quality of Life, and Pulmonary Function Recovery in Early-Stage Lung Cancer Patients. *J Thorac Oncol* 2017;**12**:824–32. doi:10.1016/j.jtho.2017.01.016. Epub 2017 Jan 23. PubMed PMID: 28126539; PubMed Central PMCID: PMC5403545.
49. Johnson C, Pankratz VS, Velazquez AI, *et al*. Candidate pathway-based genetic association study of platinum and platinum-taxane related toxicity in a cohort of primary lung cancer patients. *J Neurol Sci* 2015;**349**:124–8. PMID: 25586538; PMCID: PMC4334320.
50. Cathcart-Rake EJ, Ruddy KJ, Gupta R, *et al*. Amenorrhea after lung cancer treatment. *Menopause* 2018. doi:10.1097/GME.0000000000001199. [Epub ahead of print] Aug 27. PMID: 30153217.
51. Morrison EJ, Novotny PJ, Sloan JA, *et al*. Emotional Problems, Quality of Life, and Symptom Burden in Patients With Lung Cancer. *Clin Lung Cancer* 2017;**18**:497–503. PMID: 28412094.
52. Novotny P, Colligan RC, Szydlo DW, *et al*. A pessimistic explanatory style is prognostic for poor lung cancer survival. *J Thorac Oncol* 2010;**5**:326–32. PMID: 20139778; PMCID: PMC2854019.
53. Piderman KM, Sytsma TT, Frost MH, *et al*. Improving Spiritual Well-Being in Patients with Lung Cancers. *J Pastoral Care Counsel* 2015;**69**:156–62. PMID: 26463853; PMCID: PMC4800747.
54. Frost MH, Novotny PJ, Johnson ME, *et al*. Spiritual well-being in lung cancer survivors. *Support Care Cancer* 2013;**21**:1939–46. PMID: 23420557; PMCID: PMC3669652.
55. Garces YI, Yang P, Parkinson J, *et al*. The Relationship Between Cigarette Smoking and Quality of Life after Lung Cancer Diagnosis. *Chest* 2004;**126**(6):1733–41.
56. Svobodník A, Yang P, Novotny PJ, *et al*. Quality of life in 650 lung cancer survivors 6 months to 4 years after diagnosis. *Mayo Clin Proc* 2004;**79**(8):1024–30. PubMed PMID: 15301330.
57. Chen J, Qi Y, Wampfler JA, *et al*. Effect of cigarette smoking on quality of life in small cell lung cancer patients. *Eur J Cancer* 2012;**48**:1593–601. DOI: 10.1016/j.ejca.2011.1012.1002.
58. Chen J, Jiang R, Garces YI, *et al*. Prognostic factors for limited-stage small cell lung cancer: A study of 284 patients. *Lung Cancer* 2010;**67**:221–6. PMCID: PMC2815153.
59. Jatoi A, Qi Y, Wampfler JA, *et al*. The Purported Effects of Alcohol on Appetite and Weight in Lung Cancer Patients. *Nutr Cancer* 2011;**63**:1251–5. PMCID.
60. Jatoi A, Qi Y, Kendall G, *et al*. The cancer anorexia/weight loss syndrome: exploring associations with single nucleotide polymorphisms (SNPs) of inflammatory cytokines in patients with non-small cell lung cancer. *Support Care Cancer* 2010;**18**:1299–304. PMID: 20012999; PMCID: PMC2944398.
61. 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**:117–22. PMCID: PMC2944397.
62. Solberg Nes L, Liu H, Patten CA, *et al*. Physical activity level and quality of life in long term lung cancer survivors. *Lung Cancer* 2012;**77**:611–6. PMCID: PMC3882512.
63. Yang P, Mandrekar SJ, Hillman SH, *et al*. Evaluation of glutathione metabolic genes on outcomes in advanced non-small cell lung cancer patients after initial treatment with platinum-based chemotherapy: an NCCTG-97-24-51 based study. *J Thorac Oncol* 2009;**4**:479–85. PMCID: PMC2998042.
64. Mock V, Atkinson A, Barsevick AM, *et al*. Cancer-related fatigue. Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2007;**5**:1054–78.
65. Potosky AL, Han PK, Rowland J, *et al*. Differences between primary care physicians' and oncologists' knowledge, attitudes and practices regarding the care of cancer survivors. *J Gen Intern Med* 2011;**26**:1403–10. PMC3235622.
66. Chie WC, Yang CH, Hsu C, *et al*. Quality of life of lung cancer patients: validation of the Taiwan Chinese version of the EORTC QLQ-C30 and QLQ-LC13. *Qual Life Res* 2004;**13**:257–62. PubMed PMID: 15058806.
67. Basu Roy U, King-Kallimanis BL, Kluetz PG, *et al*. Learning from Patients: Reflections on Use of Patient-Reported Outcomes in Lung Cancer Trials. *J Thorac Oncol* 2018;**13**:1815–7. PMID: 30337169.