Health-related quality of life after curative-intent treatment of non-small cell lung cancer: can exercise lessen the burden?

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Lung cancer poses a major health-care challenge. It is common, presents late, has a high mortality and is associated with many co-morbidities. It kills more people every year than breast, colon and prostate cancer combined. A minority who are candidates for curative-intent treatment experience significant challenges as their respiratory capacity is reduced by either resection (lobectomy or pneumonectomy), radiation-induced fibrosis or long-term sequelae of cytotoxic chemotherapy. The role of manageable, non-disease modifying interventions to improve clinical outcomes, overall survival and health-related quality of life (HRQL) is thus of interest. One such intervention is exercise, and evidence in lung cancer suggests that exercise programs can improve HRQL (1). In their cross-sectional study, Ha *et al.* investigate the association between exercise capacity (EC) and cancer-specific HRQL in lung cancer patients. The authors postulate that interventions to improve EC will in turn enhance the HRQL in these patients. In this editorial, we will review existing work on the benefits of exercise across the cancer care continuum in people living with and beyond non-small cell lung cancer (NSCLC, which accounts for >80% of new cases of lung cancer), with specific considerations regarding the implementation of exercise programming to improve HRQL in the context of recent practice-changing data.

Although the landscape of NSCLC treatment in the metastatic setting has undergone a number of advancements in the past decade, including the use of targeted agents and immunotherapy (2), there have been fewer advances in the management of earlier stages. In the ~50% of new NSCLC cases that are diagnosed at stage I–III, the gold standard treatment remains surgical resection. The treatment plan is based not only on the resectability of the cancer, but also risk stratification for surgery, including pre-operative evaluation of cardiac risk factors, tests of pulmonary function and cardiopulmonary exercise tests (3). The adoption of adjuvant chemotherapy post resection was the last major change in practice for early-stage NSCLC, but the recently announced results of the PACIFIC trial show that the immune-modulating drug durvalumab can significantly improve survival in stage III NSCLC (4). Other trials of immunotherapy in the post-surgical setting are likely to show additional survival benefit, and incremental improvements attributable to progress in surgical techniques and perioperative management suggest that there will be continued increase in survival for early-stage NSCLC (5). Improved outcomes necessitate a focus on issues of survivorship. Those living with NSCLC experience many negative functional, physiological and psychosocial consequences as a result of the malignancy, common comorbidities such as chronic obstructive pulmonary disease (COPD), and treatment-related side effects. These may cause significant morbidity well beyond the perioperative/acute chemoradiation treatment period.

Several clinical outcomes are used to assess the effects of treatment for NSCLC, but there is an increasing emphasis on the patient's perspective [i.e., patient-reported outcomes

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(PROs)]. One of the most common PROs is HRQL, a multidimensional construct that includes assessment of disease and treatment-related symptoms [including pain, fatigue dyspnea and coughing in lung cancer (6)], physical, emotional and social functioning. Ha and colleagues explore HRQL in 62 people who had completed curative treatment of stage I–IIIA NSCLC ≤1 month previously, using the six-minute walk test (6MWT) as a measure of functional EC (7). While exercise tests are commonly used to risk-stratify patients for resection, here functional EC was examined as an independent predictor of HRQL. The physiological impact of surgical resection, along with the potential impact of pre-existing co-morbidities and/or chemoradiation, can result in exercise impairments that arise via multiple mechanisms. This study highlights the prevalence of exercise limitations even after the acute recovery period, and the associated impact on HRQL. A substantial proportion of patients (57%) had impaired functional EC after curative treatment, identified as a 6MWT (total meters walked) below the lower limit of normal, as calculated from reference equations (8). It is possible that at least some of the 43% who were not identified as impaired by these methods still experienced a clinically meaningful decrease in 6MWT from a pre-surgical baseline. Furthermore, it should be noted that the impairment in the capacity to walk as far as possible in 6 minutes may be less than the impairment in peak oxygen uptake ($\dot{V}O_{2peak}$) after curative treatment of NSCLC (9).

Scores for PROs including items from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) (5) and the EORTC-QLQ-Lung Cancer Module 13 (10), were identified as abnormal if the score was lower than published reference values (11). In this sense, nearly half of the participants had 'abnormally low' scores for physical function, and up to 40% of people had scores below reference values for other domains of HRQL. However, it is unclear which reference data were used for this comparison e.g., scores based on 'all cancer patients', 'lung cancer', or specifically 'NSCLC: all stages' (10). Combined with the large standard deviations in the reference data (10), the comparison to mean scores should be interpreted with caution. Although in Ha *et al.*,'s cross-sectional study it is not possible to determine if the HRQL scores anteceded surgery, a previous cohort study of 66 lung cancer patients reported that EORTC QLQ-C30 scores decreased from before to 3 months after surgical resection, with the largest effects in physical, social and role functioning, and the dyspnea symptom score (12). Ha and colleagues reported that 6MWT was an independent predictor of HRQL, accounting for 20% of the variance in the composite EORTC QLQ-C30 summary score. As discussed by the authors, their findings present an opportunity for exercise-based interventions to improve EC and HRQL in survivors of lung cancer.

Exercise may play a role not only as a therapeutic strategy in the recovery from cancer treatment, but also during the time between diagnosis and the beginning of treatment. Cancer prehabilitation is a growing area of research in oncology [see (13) for a review], particularly in lung cancer (14). Prehabilitation involves baseline assessment and targeted interventions and aims to prevent or reduce the severity of treatment-related impairments, and/or to reduce the risk of peri or postoperative complications. The first feasibility study involving preoperative exercise training was published over a decade ago (15), providing early evidence that $\dot{V}O_{2peak}$ and the 6MWT could be improved prior to pulmonary resection. More recently, meta-analyses suggest that preoperative exercise training for NSCLC patients scheduled for lung resection may confer a number of benefits, including a reduced risk of postoperative pulmonary complications and length of hospital stay (14,16). Although the optimal preoperative exercise prescription remains unknown (14), exercise training can also improve preoperative EC and some measures of lung function (e.g., forced vital capacity) (14,16). Such improvements may be related to enhanced HRQL (1). To facilitate translation of this evidence into practice (and routine implementation), evidence-based guidelines on how to deliver pre-operative exercise training have been developed (17). The key recommendations include using a combination of aerobic, resistance and inspiratory muscle training, tailoring the exercise prescription to each patient based on their initial health status, and evaluating the program by assessing functional capacity, HRQL and the patient experience (17).

The timing of exercise interventions after treatment may also be influential. Immediately following lung resection, early mobilization is predictive of reduced length of hospital stay (18). Most patients are able to walk the day after surgery, and one study reported a progression in walking such that patients accumulated over 10,000 steps by postoperative day 5 (19). These patients were also invited to perform two bouts of 15-min stationary cycling from the day after surgery under supervision of a physiotherapist, and it was suggested that this may have influenced their confidence for walking. For those offered adjuvant post-

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surgical chemotherapy, patient preference was to begin an exercise program during therapy, as opposed to 3–6 months later after chemotherapy was finished (20). Although the side-effects of chemotherapy may limit participation for some, exercise initiated early in the treatment trajectory may be beneficial from a patient perspective (21), and a supervised 12-week walking program delivered during treatment resulted in superior functional EC (*vs.* usual care) from 1–6 months after surgery (22). One study that incorporated individualized exercise training (including resistance training and progressive resistance training at 5–7 weeks after surgery) found the physical and mental domains of HRQL were significantly higher *vs.* a no-exercise control group, and coincided with improvements in $\dot{V}O_{2peak}$ and muscle strength. However, a 2017 meta-analysis concluded that there is currently insufficient evidence to support the efficacy of exercise training after surgical resection for NSCLC (23), reflecting a lack of data overall, and heterogeneity in the existing data.

Many people affected by NSCLC may limit activity to avoid worsening symptoms such as dyspnea, but there is increasing recognition that exercise is safe and has potential clinical benefit in terms of EC and HRQL [see (24) for a full review]. HRQL typically diminishes substantially after surgery for NSCLC, followed by an improvement between hospital discharge and the next 4 months (25). However, ~50% of people who had not experienced recurrence 2 years after surgery still had lower levels of physical and role functioning, and increased dyspnea and fatigue (25). In long term survivors of lung cancer (up to 12 years post diagnosis), higher levels of physical activity are associated with better HRQL and symptom control (26).

Although there are guidelines for exercise in cancer survivors [e.g., (27)], and recent calls for exercise to be embedded as part of standard practice in cancer care [e.g., (28)], the importance of identifying the facilitators and barriers to implementation [i.e., pragmatic concerns (29)] cannot be overstated. To support the implementation of exercise guidelines as standard practice, Santa Mina and colleagues recently presented a patient ‘pathway’ from an oncology-directed clinical setting to exercise programming (30). The pathway is described as a systematic and directed approach to bridging the gap between inactivity [where survivors of NCSCL spend on average 9.8 h per day in sedentary pursuits (31)] and exercise as an adjuvant cancer therapy. It is noted that further individualization of the pathway is required, but it serves as a useful foundation for the future delivery of exercise services for people treated for NSCLC. The pathway emphasizes the role of the healthcare professional (a clinician responsible for managing health care throughout, or at any point after diagnosis) as a starting point for access to resources (access to exercise programming where available, and/or to physical activity promotion materials). Risk stratification and medical clearance by a healthcare professional as early as possible may expedite the initiation of exercise (e.g., via referral to a qualified exercise professional) (30). For an individual diagnosed with stage I–IIIA NSCLC, the first step may be referral to a medically-supervised prehabilitation program (based on risk-stratification for surgery, but also based on potential benefits for those classed as low risk prior to scheduled surgery) and later a medically-supervised program to support acute recovery from surgery. The role of the physiatrist and the rehabilitation team in the cancer setting is essential in supporting medically-supervised programs, as some may be offered as in-hospital programs. In this context, for patients who are classed as ‘high risk’, tools are being shared to facilitate safe and accessible exercise programming. Specifically, a ‘safety reference guide’ was recently put forward by Santa Mina *et al.* (30). The guide is currently used in a Canadian exercise program to provide evidence-based directives for common exercise contraindications, and to assist with the prescription of exercise across heterogeneous patients. This is particularly applicable to stage IIIA NSCLC (a particularly heterogenous patient population), where the need for complex decision-making regarding exercise safety could otherwise restrict participation. Alongside the current exercise guidelines [e.g., (27)], this safety guide could be adapted for specific considerations in lung cancer, to assist exercise practitioners in a medically-supervised setting. Following this, a person treated for NSCLC could then be medically cleared and referred to a supervised community-based cancer exercise program [for example, Alberta Cancer Exercise (ACE), see (30) for more information]. ACE is an ongoing hybrid implementation-effectiveness study that is building the processes, and required evidence, to embed exercise into standard cancer care.

An in-depth understanding of the current landscape of NSCLC is necessary when considering the potential impact of exercise. There are several recent influential developments that should be considered. First, the recently-updated analysis of the phase 3 PACIFIC trial demonstrated increased overall survival in stage III non-resectable NSCLC patients treated with durvalumab therapy *vs.* placebo (4). The increased survivorship due to the adoption

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of long-term immunotherapy in these patients following chemoradiation (as well as in patients treated with surgery and stereotactic radiation) poses a major opportunity for implementing exercise-based interventions in this setting. Second, the adoption of screening programs for asymptomatic individuals at high risk of developing lung cancer (current and former smokers) seems poised to change the stage profile of NSCLC at diagnosis. The results of the NELSON trial demonstrate a substantial reduction in lung-cancer mortality in screened *vs.* unscreened patients (32), because the shift in stage (in particular from stage III/IV to stage I/II at diagnosis) provided curative-intent treatment options for many more individuals. A natural development based on the demonstrated benefits of screening programs is chemoprevention strategies for high-risk individuals [see (33) for a review]. A core pillar of this would be tobacco cessation, but the role of exercise in both primary and secondary prevention deserves further attention (33). Last, there is growing appreciation of the age- and sex-specific differences in the incidence of lung cancer, in particular the higher incidence among young, biomarker-positive women, that is not explained by differences in smoking behaviours (34). In the study by Ha and colleagues, the sample included only 3 females (6%) and consequently, like many other studies, does not reflect the gender split in the lung-cancer population. This sub-population of young women, many of whom are 'never smokers', could benefit from investment in exercise-based research.

Although we have directed readers to some examples of existing research regarding HRQL and exercise in people living with and beyond NSCLC, we agree with the overall conclusions of Ha and colleagues (7). That is, given the prevalence of functional exercise limitations and the relationship with multiple domains of HRQL, exercise is likely to have multiple benefits across the cancer care continuum in NSCLC. There is a need for randomized, prospective, multi-centre clinical trials to verify the role of exercise in NSCLC. Future work should also include the development of complex pragmatic behavioral trials in order to maximize the efficacy of exercise interventions (e.g., optimize the frequency, intensity and type of exercise), and include methods adapted from pharmacological trials in regards to the conduct and reporting of exercise adherence and tolerability, as recently outlined by Nilsen *et al.* (35). The impact of the curative treatment of NSCLC is wide-ranging and cannot be measured via disease-specific symptom severity or functional EC alone. Alongside maintaining independence and being able to perform normal activities, HRQL has been ranked as the most important concern for people affected by lung cancer (36). Thus, exercise interventions designed to impact the HRQL of those with lung cancer must be a priority for research and program development.

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Footnote

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References

1. Granger CL, McDonald CF, Berney S, et al. Exercise intervention to improve exercise capacity and health related quality of life for patients with non-small cell lung cancer: a systematic review. Lung Cancer 2011;72:139-53.
2. Pabani A, Butts CA. Current landscape of immunotherapy for the treatment of metastatic non-small-cell lung cancer. Curr Oncol 2018;25:S94-102.
3. Salati M, Brunelli A. Risk stratification in lung resection. Curr Surg Rep 2016;4:37.
4. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with Durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med 2018. [Epub ahead of print].
5. Xia W, Yu X, Mao Q, et al. Improvement of survival for non-small cell lung cancer over time. Onco Targets Ther 2017;10:4295-303.
6. Poghosyan H, Sheldon LK, Leveille SG, et al. Health-related quality of life after surgical treatment in patients with non-small cell lung cancer: a systematic review. Lung Cancer 2013;81:11-26.
7. Ha D, Ries AL, Mazzone PJ, et al. Exercise capacity and cancer-specific quality of life following curative intent treatment of stage I-IIIA lung cancer. Support Care Cancer 2018;26:2459-69.
8. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. Am J Respir Crit Care Med 1998;158:1384-7.
9. Cavalheri V, Jenkins S, Cecins N, et al. Comparison of the six-minute walk test with a cycle-based cardiopulmonary

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exercise test in people following curative intent treatment for non-small cell lung cancer. Chron Respir Dis 2016;13:118-27.
10. Bergman B, Aaronson NK, Ahmedzai S, et al. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. Eur J Cancer 1994;30A:635-42.
11. Scott NW, Fayers P, Aaronson NK, et al. EORTC QLQ-C30 Reference Values Manual. 2nd ed. Brussels: EORTC Quality of Life Group; 2008.
12. Pompili C, Koller M, Velikova G, et al. EORTC QLQ-C30 summary score reliably detects changes in QoL three months after anatomic lung resection for non-small cell lung cancer (NSCLC). Lung Cancer 2018;123:149-54.
13. Silver JK, Baima J. Cancer prehabilitation: an opportunity to decrease treatment-related morbidity, increase cancer treatment options, and improve physical and psychological health outcomes. Am J Phys Med Rehabil 2013;92:715-27.
14. Cavalheri V, Granger C. Preoperative exercise training for patients with non-small cell lung cancer. Cochrane Database Syst Rev 2017;6:CD012020.
15. Jones LW, Peddle CJ, Eves ND, et al. Effects of presurgical exercise training on cardiorespiratory fitness among patients undergoing thoracic surgery for malignant lung lesions. Cancer 2007;110:590-8.
16. Sebio Garcia R, Yáñez Brage MI, et al. Functional and postoperative outcomes after preoperative exercise training in patients with lung cancer: a systematic review and meta-analysis. Interact Cardiovasc Thorac Surg 2016;23:486-97.
17. Tew GA, Ayyash R, Durrand J, et al. Clinical guideline and recommendations on pre-operative exercise training in patients awaiting major non-cardiac surgery. Anaesthesia 2018;73:750-68.
18. Rogers LJ, Bleetman D, Messenger DE, et al. The impact of enhanced recovery after surgery (ERAS) protocol compliance on morbidity from resection for primary lung cancer. J Thorac Cardiovasc Surg 2018;155:1843-52.
19. Esteban PA, Hernández N, Novoa NM, et al. Evaluating patients' walking capacity during hospitalization for lung cancer resection. Interact Cardiovasc Thorac Surg 2017;25:268-71.
20. Leach HJ, Devonish JA, Bebb DG, et al. Exercise preferences, levels and quality of life in lung cancer survivors. Support Care Cancer 2015;23:3239-47.
21. Missel M, Pedersen JH, Hendriksen C, et al. Exercise intervention for patients diagnosed with operable non-small cell lung cancer: a qualitative longitudinal feasibility study. Support Care Cancer 2015;23:2311-8.
22. Chang NW, Lin KC, Lee SC, et al. Effects of an early postoperative walking exercise programme on health status in lung cancer patients recovering from lung lobectomy. J Clin Nurs 2014;23:3391-402.
23. Li J, Guo NN, Jin HR, et al. Effects of exercise training on patients with lung cancer who underwent lung resection: a meta-analysis. World J Surg Oncol 2017;15:158.
24. Bade BC, Thomas DD, Scott JB, et al. Increasing physical activity and exercise in lung Cancer: reviewing safety, benefits, and application. J Thorac Oncol 2015;10:861-71.
25. 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;26:233-41.
26. 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.
27. Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors: Med Sci Sport Exerc 2010;42:1409-26.
28. Cormie P, Atkinson M, Bucci L, et al. Clinical Oncology Society of Australia position statement on exercise in cancer care. Med J Aust 2018;209:184-7.
29. Mina DS, Langelier D, Adams SC, et al. Exercise as part of routine cancer care. Lancet Oncol 2018;19:e433-6.
30. Mina DS, Sabiston CM, Au D, et al. Connecting people with cancer to physical activity and exercise programs: a pathway to create accessibility and engagement. Curr Oncol 2018;25:149-62.
31. D'Silva A, Gardiner PA, Boyle T, et al. Associations of objectively assessed physical activity and sedentary time with health-related quality of life among lung cancer survivors: a quantile regression approach. Lung Cancer 2018;119:78-84.
32. De Koning H, Van Der Aalst C, Ten Haaf K, et al. PL02.05 Effects of Volume CT Lung Cancer Screening: Mortality Results of the NELSON Randomised-Controlled Population Based Trial. J Thorac Oncol 2018;13:S185.
33. New M, Keith R. Early detection and chemoprevention of lung cancer. F1000Research 2018;7:61.
34. Jemal A, Miller KD, Ma J, et al. Higher lung cancer incidence in young women than young men in the United States. N Engl J Med 2018;378:1999-2009.
35. Nilsen TS, Scott JM, Michalski M, et al. Novel

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methods for reporting of exercise dose and adherence: an exploratory analysis. Med Sci Sports Exerc 2018;50:1134-41.
36. Gralla RJ, Hollen PJ, Msaouel P, et al. Evidence-based determination of issues affecting quality of life and patient-reported outcomes in lung cancer: results of a survey of 660 patients. J Thorac Oncol 2014;9:1243-8.

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