Editorial

The process to overcome lung cancer sarcopenia

Yo Kawaguchi

Division of General Thoracic Surgery, Department of Surgery, Shiga University of Medical Science, Shiga, Japan

Correspondence to: Dr. Yo Kawaguchi. Tsukinowacho, Seta, Otsu, Shiga, 502-2192, Japan. Email: kawaguchi1228@yahoo.co.jp.

Comment on: Wakefield CJ, Lund N, Coughlin J, *et al.* The association between thoracic sarcopenia and survival is gender specific in early-stage lung cancer. J Thorac Dis 2022;14:4256-65.

Keywords: Sarcopenia; lung cancer; prognosis

Submitted Jan 10, 2023. Accepted for publication Mar 01, 2023. Published online Mar 27, 2023.
doi: 10.21037/jtd-2023-01
View this article at: https://dx.doi.org/10.21037/jtd-2023-01

Lung cancer sarcopenia has several problems to overcome, including identification of diagnostic tools, investigation of molecular biological mechanisms, and identification of therapeutic approaches. To date, many reports have demonstrated that sarcopenia increases postoperative complications and leads to poor prognosis using clinical data sets (1,2). Furthermore, we demonstrated that the results were reproducible by a meta-analysis (3). In the future, researchers should address these problems.

Identifying diagnostic tool

As diagnostic tools for lung cancer sarcopenia, many researchers used a sum of skeletal muscles at L3 level normalized for height (L3MI, cm^2/m^2) or the psoas muscle area at L3 level normalized for height (PMI, cm^2/m^2) (3). Recently, Connor *et al.* showed that a low T5MI predicted poor prognosis only in male patients. They also investigated the association of T12MI and L3MI with prognosis in the same cohort. Low T12MI and L3MI showed a poor prognosis in all patients, regardless of sex (4). These results indicate that the muscle area at L3 and T12 is optimal for diagnosing sarcopenia and predicting prognosis. Clinicians need a brief and predictable tool for diagnosing sarcopenia. Considering the predictability of prognosis, sufficient evidence, and ease of assessment, PMI at the L3 level may be feasible.

Investigation of molecular-biological mechanisms

Despite accumulating evidence on the association between sarcopenia and prognosis, investigation of molecular biological mechanisms is insufficient. We propose "lung cancer-skeletal muscle cycle" which functions as negative loop for prognosis (*Figure 1*). Myostatin (5) and activin A (6) are expressed in lung cancer. These cytokines inhibit protein synthesis and enhance ubiquitin-proteasome pathway-mediated protein degradation in the skeletal muscle. Lung cancer cells may produce these cytokines, secrete them into the serum, reach skeletal muscle, and cause muscle atrophy. In contrast, muscles have a potential tumor-inhibitory effect through the secretion of myokines. Myokines suppress the growth of cancer cells and are involved in immune cell regulation. For example, muscle-derived myokines, such as Oncostatin M, Irisin, SPARC, IL-6, inhibit the growth of cancer cells *in vitro* (7,8). When skeletal muscle is reduced by myostatin or activin A myokines decrease, and the tumor inhibitory effect may also decrease. When this lung cancer-skeletal muscle cycle works as a negative loop, sarcopenia develops and the tumor progresses, resulting in poor prognosis.

Finding out for therapeutic approach

From the perspective of the lung cancer-skeletal muscle

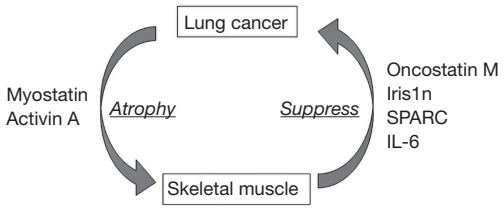

Figure 1 Lung cancer-skeletal muscle cycle.

cycle, there are two therapeutic approaches for lung cancer sarcopenia. First, inhibition of myostatin or activin A may improve muscle loss. Administration of a myostatin/activin A receptor inhibitor to mice with lung cancer resulted in an improvement in body muscle weight and agility. Furthermore, tumor volume in treated mice was decreased compared with control mice (9). Myostatin gene inactivation prevents skeletal muscle loss in engrafted mouse lung cancer (10). Second, exercise may improve the loss of skeletal muscle, leading to increased myokines and the prevention of tumor growth. Chen *et al.* demonstrated that patients who engaged in regular exercise during the first 6 months after diagnosis had significantly higher overall survival and Disease free survival than those who did not exercise (11).

In conclusion, PMI at the L3 level may be useful for defining lung cancer sarcopenia in predicting prognosis. Sarcopenia may be induced by myostatin or activin A secreted by lung cancer, which reduces skeletal muscle mass. The inhibition of myostatin/activin A or exercise has the potential to prevent skeletal muscle loss and cancer growth. With these therapeutic strategies, the negative loop of the cancer-skeletal muscle cycle may be suppressed. In the future, the molecular biological mechanisms should be clarified.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Thoracic Disease*. The article did not undergo external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-2023-01/coif). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Kawaguchi Y, Hanaoka J, Ohshio Y, et al. Sarcopenia predicts poor postoperative outcome in elderly patients with lung cancer. Gen Thorac Cardiovasc Surg 2019;67:949-54.
2. Kawaguchi Y, Hanaoka J, Ohshio Y, et al. Sarcopenia increases the risk of post-operative recurrence in patients with non-small cell lung cancer. PLoS One 2021;16:e0257594.
3. Kawaguchi Y, Hanaoka J, Ohshio Y, et al. Does sarcopenia affect postoperative short- and long-term outcomes in patients with lung cancer?-a systematic review and meta-analysis. J Thorac Dis 2021;13:1358-69.
4. Wakefield CJ, Lund N, Coughlin J, et al. The association between thoracic sarcopenia and survival is gender specific in early-stage lung cancer. J Thorac Dis 2022;14:4256-65.
5. Sharma M, McFarlane C, Kambadur R, et al. Myostatin: expanding horizons. IUBMB Life 2015;67:589-600.
6. Loumaye A, de Barsy M, Nachit M, et al. Role of Activin A and myostatin in human cancer cachexia. J Clin Endocrinol Metab 2015;100:2030-8.
7. Hojman P, Dethlefsen C, Brandt C, et al. Exercise-induced muscle-derived cytokines inhibit mammary cancer cell growth. Am J Physiol Endocrinol Metab 2011;301:E504-10.
8. Aoi W, Naito Y, Takagi T, et al. A novel myokine, secreted protein acidic and rich in cysteine (SPARC), suppresses colon tumorigenesis via regular exercise. Gut 2013;62:882-9.
9. Busquets S, Toledo M, Orpí M, et al. Myostatin blockage using actRIIB antagonism in mice bearing the Lewis lung

carcinoma results in the improvement of muscle wasting and physical performance. J Cachexia Sarcopenia Muscle 2012;3:37-43.
10. Gallot YS, Durieux AC, Castells J, et al. Myostatin gene inactivation prevents skeletal muscle wasting in cancer. Cancer Res 2014;74:7344-56.
11. Chen X, Lu W, Zheng W, et al. Exercise after diagnosis of breast cancer in association with survival. Cancer Prev Res (Phila) 2011;4:1409-18.

Cite this article as: Kawaguchi Y. The process to overcome lung cancer sarcopenia. J Thorac Dis 2023;15(4):1530-1532. doi: 10.21037/jtd-2023-01