Commentary: A journey of a thousand miles begins with a single step

Toyofumi F. Chen-Yoshikawa, MD

From the Department of Thoracic Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan.

Disclosures: Author has nothing to disclose with regard to commercial support.

Received for publication Sept 19, 2019; revisions received Sept 19, 2019; accepted for publication Sept 19, 2019; available ahead of print Oct 15, 2019.

Address for reprints: Toyofumi F. Chen-Yoshikawa, MD, Department of Thoracic Surgery, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, 466-8550, Japan (E-mail: tyoshikawa@med.nagoya-u.ac.jp).

J Thorac Cardiovasc Surg 2020;159:2092-3

0022-5223/\$36.00

Copyright © 2019 by The American Association for Thoracic Surgery

<https://doi.org/10.1016/j.jtcvs.2019.09.040>

Toyofumi F. Chen-Yoshikawa, MD

Central Message

Preoperative hypofractionated radiation might prime the immune system and potentially contribute to the benefits of multimodality treatment for malignant pleural mesothelioma.

See Article page 2082.

For treating malignant pleural mesothelioma, multimodal therapies consisting of chemotherapy, surgery, and radiation therapy are used worldwide for achieving better survival. As a surgical modality, pleurectomy or decortication has also been widely performed, along with extrapleural pneumonectomy. Furthermore, similar to the treatment of primary lung cancer, immunotherapy has recently been introduced for the treatment of malignant pleural mesothelioma. Despite these therapeutic advances, however, the prognosis of malignant pleural mesothelioma remains poor.^{1,2} In accordance with their Surgery for Mesothelioma After Radiation Therapy (SMART) protocol,³ de Perrot's group have been performing hypofractionated accelerated hemithoracic radiation followed by extrapleural pneumonectomy for patients with malignant pleural mesothelioma since 2008. The SMART protocol recommends an accelerated course of hemithoracic hypofractionated radiation between 25 Gy and 30 Gy in 5 fractions, followed by an extrapleural pneumonectomy within 1 week after radiotherapy.

Given that the novel use of immunotherapy may induce a paradigm shift in the treatment of malignant pleural mesothelioma, a better understanding of the mesothelioma tumor immune microenvironment is inevitable. In their study in this issue of the *Journal*, de Perrot and colleagues⁴ present research on the tumor microenvironment of malignant pleural mesothelioma and focused on PD-1/PDL-1 and CD8⁺ tumor-infiltrating lymphocytes (TILs) in patients treated by the SMART protocol.

Patients with nonepithelioid malignant pleural mesothelioma have poorer survival outcomes than those with epithelioid malignant pleural mesothelioma, and there is evidence that the tumor microenvironment differs profoundly between epithelioid and nonepithelioid mesotheliomas.⁵ In their current study, de Perrot and colleagues⁴ have shown the importance of identifying the histologic subtype of mesothelioma when analyzing the tumor microenvironment, such as PDL-1 positivity and its association with overall

survival. They found that CD8⁺ TILs were independent predictors of improved survival outcomes in patients with epithelioid malignant pleural mesothelioma; however, CD8⁺ TILs had no such association with survival outcomes in patients with nonepithelioid malignant pleural mesothelioma. In their current study, de Perrot and colleagues⁴ also found that CD8⁺ TILs in patients undergoing SMART were lower after preoperative radiation than after induction chemotherapy, although CD8⁺ TILs were independent predictors of better survival in patients with epithelioid malignant pleural mesothelioma. They suggest that these findings cannot be confirmed without further research to investigate the critical role of several factors, such as interferon in response to hypofractionated radiation. They also reported data concerning the effect of CD8⁺ TILs on survival in patients with epithelioid malignant pleural mesothelioma undergoing SMART, suggesting that a short course of hypofractionated hemithoracic radiation can be used as a potential platform for immunotherapy.

As of now, the optimal immunotherapeutic targets remain to be determined. Preoperative hypofractionated radiation might prime the immune system and potentially contribute to the benefits of multimodality treatment for malignant pleural mesothelioma. A new clinical trial that de Perrot's group are currently preparing may thus help determine the most appropriate preoperative radiation therapies in the multimodality treatment of malignant pleural mesothelioma in the near future.

References

1. Maio M, Scherpereel A, Calabrò L, Aerts J, Cedres Perez S, Bearz A, et al. Tremelimumab as second-line or third-line treatment in relapsed malignant mesothelioma (DETERMINE): a multicentre, international, randomised, double-blind, placebo-controlled phase 2b trial. *Lancet Oncol.* 2017;18:1261-73.
2. de Gooijer CJ, Baas P. Treat it or leave it: immuno-oncology in mesothelioma observed by the eyes of Argus. *J Thorac Oncol.* 2018;13:1619-22. Erratum in: *J Thorac Oncol.* 2019;14:314.
3. Cho BC, Feld R, Leighl N, Opitz I, Anraku M, Tsao MS, et al. A feasibility study evaluating Surgery for Mesothelioma After Radiation Therapy: the "SMART" approach for resectable malignant pleural mesothelioma. *J Thorac Oncol.* 2014;9:397-402.
4. de Perrot M, Wu L, Cabanero M, et al. Prognostic impact of tumor microenvironment after hypofractionated accelerated radiation and radical surgery for malignant pleural mesothelioma. *J Thorac Cardiovasc Surg.* 2020;159:2082-91.e1.
5. Lee HS, Jang HJ, Choi JM, Zhang J, de Rosen VL, Wheeler TM, et al. Comprehensive immunoproteogenomic analyses of malignant pleural mesothelioma. *JCI Insight.* 2018;3:e98575.