the immunologic basis of these paraneoplastic syndromes remains an enigma.

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Commentary: Toward a better understanding of the natural history of surgically treated thymoma associated with paraneoplastic syndromes

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Thymoma is a rare disorder, with an incidence of 0.15 cases per 100,000 person-years.¹ Surgery is the mainstay treatment for resectable tumors, with chemotherapy and radiotherapy offered in the neoadjuvant and adjuvant settings under certain circumstances.² Thymoma is associated with a host of autoimmune and nonautoimmune paraneoplastic syndromes (PNSs), the clinical implications of which have been studied mostly in the context of myasthenia gravis (MG). Notably, a randomized trial of surgical resection versus medical management alone for nonthymomatous MG demonstrated improved symptomatology and quality of life for complete thymectomy over medical management alone.³

In this issue of the *Journal*, Zhao and colleagues⁴ report the results of a systematic review of 407 published studies on paraneoplastic disorders in patients treated with surgery

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CENTRAL MESSAGE

Zhao et al provide an authoritative cataloging of paraneoplastic syndromes associated with surgically treated thymomas. Questions on long-term outcomes for syndromes other than myasthenia remain.

for thymoma between 1960 and 2019. They identified 507 patients, with a total of 123 distinct PNSs, which were present in 80% of patients before resection. Surgical resection led to remission or improvement of symptoms in 76% of patients. New onset of PNS was observed in 20% of previously asymptomatic patients, whereas recurrence of PNS occurred in 34% of patients, one third of whom had concurrent PNS and thymoma recurrence. A key finding was that complete resolution of PNS symptoms was associated with improved long-term survival.

This study is a noteworthy contribution to the literature. Compared with a recent study of PNSs in patients with thymoma from the International Thymic

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Malignancy Interest Group database, in which MG accounted for 97% of PNS disorders,⁵ the study from Zhao and colleagues separated outcomes of patients with MG and patients with non-MG PNSs as well as those of patients with multiple concurrent PNSs and found no statistically significant differences in survival across the 3 groups. Interestingly, no association between Masaoka stage and PNS status was observed, contrary to previous publications.^{5,6} Unfortunately, given the underlying rarity of thymoma and the infrequency of PNSs, a more detailed evaluation of the long-term outcomes of some of the more common individual PNSs other than MG, such as red cell aplasia or Good syndrome, was still not feasible. Are different PNSs associated with specific histologic subtypes? How often does surgical resection lead to remission of these non-MG PNSs? Does stage or resection status correlate with chance of complete remission? Aside from achieving a better understanding of the pathophysiology of PNS and thymoma biology, future studies should pool outcomes with respect to individual PNSs to better guide clinical care.

Ultimately, the authors should be congratulated for the tremendous amount of work they completed, which collates almost 60 years of surgical experience. This systematic overview of the literature goes beyond MG to provide an

authoritative cataloging of all PNSs associated with surgically treated thymomas. It provides information on incidence and prognosis, as well as adjunctive medical treatments for these patients. Importantly, for those taking care of this patient population, it underscores the need for prolonged multidisciplinary follow-up, as delayed recurrence of either the tumor or the PNS can occur long after treatment.

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