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Real-World Application of the NAVIGATE Trial

To the Editor:

Folch et al. present the largest registry of electromagnetic navigation bronchoscopy (ENB) for the diagnosis of peripheral lung lesions,[1] reporting a robust diagnostic yield of 73%, which is significantly higher than the 39% yield previously published in a multicenter ENB prospective registry.[2] Strengths of the study are its real-world practical design, including consideration of nodules difficult to access bronchoscopically (because of small size and peripheral location) and a low complication rate. That said, the approach to the diagnosis of peripheral lung nodules is extremely complicated, and these findings need be interpreted in the proper context.

A major concern that this registry highlights is the wide variation in practice patterns when evaluating pulmonary nodules. The American College of Chest Physicians guidelines recommend surgical biopsy for nodules with a high pretest probability (>65%) of malignancy[3] if preoperative staging of the mediastinum with linear endobronchial ultrasound (EBUS) is not clinically indicated.[4] ENB with sampling of the peripheral nodule is recommended in patients who (1) may have a diagnosis equally as probable as lung cancer, (2) are at an increased surgical risk, or (3) when the patient or surgeon wishes to know whether the nodule is malignant before resection.[3] In this registry, 59% of the patients who underwent ENB were deemed to have a high pretest probability of malignancy, raising concern for guideline-discordant care in a high proportion of patients. Furthermore, the absence of a protocolized approach is highlighted by the low proportion of patients who underwent simultaneous nodal staging with EBUS during the index procedure (448 of 1157 [39%]) and the inconsistent use of rapid on-site pathologic evaluation (69%). About 46% of the patients in the study had clinical stage II to IV NSCLC after the ENB, arguing that nodal staging with EBUS and use of rapid on-site pathologic evaluation during the index procedure may have avoided additional unnecessary procedures.

The measure of diagnostic yield is heavily affected by the prevalence of disease. In fact, only 44% of cases in the study ultimately led to a diagnosis of malignancy during the index procedure. If the definition of diagnostic yield used in the AQUIRE registry[2] (diagnosis secured after index procedure, not at 12- or 24-month follow-up) is applied to the NAVIGATE registry, the yield would be 49% (562 diagnosis after bronchoscopy out of 1157 bronchoscopies). As the ultimate concern is malignancy, perhaps the best measure to assess utility is sensitivity. With a sensitivity of only 69% (and negative predictive value of 56%), one cannot be truly reassured by a negative biopsy result.

Another important issue is the definition of the term *true negative*. Folch et al.[1] appropriately included biopsy samples that were diagnostic of a nonmalignant process as negative, as well as "indeterminate" lesions that were radiographically stable at 12 months. The latter may not be accurate, however. Folch et al.[1] will be following each patient to confirm 24-month radiographic stability, and only in that setting should these indeterminate nodules be considered true negatives.

Despite some of the limitations, the study by Folch et al.[1] strongly reflects the current real-world use of ENB, and this large registry adds to the growing literature and rapidly advancing field of ENB.

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Isolated Hypogonadotropic Hypogonadism Secondary to Anti-Programmed Death Ligand 1 Inhibitor

To the Editor:

Immune checkpoint inhibitors (ICIs) targeting programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) are now routinely used in the management of patients with NSCLC. Durvalumab is a monoclonal antibody directed against PD-L1 that is approved for use in patients with unresectable stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy. We present a case of secondary hypogonadism after two cycles of durvalumab in a patient with stage III lung adenocarcinoma.

A 75-year-old man with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 and no significant medical comorbidities commenced maintenance durvalumab (10 mg/kg every 2 weeks) 6 weeks after completing definitive chemoradiotherapy for stage III lung adenocarcinoma. He received a total dose of 60 Gy in 30 treatments concurrently with weekly carboplatin and paclitaxel chemotherapy to the primary lung lesion. The first two cycles of durvalumab therapy were well tolerated; however, before cycle 3 the patient developed profound fatigue, hot and cold flushes, excessive sweating, and a decline in his ECOG PS (to 2). Concern for durvalumab-induced hypophysitis was raised and laboratory analysis of pituitary hormones showed low early morning testosterone 2.8 nmol/L (6 to 28 nmol/L), normal follicle stimulating hormone at 8 IU/L (1 to 10 IU/L) and luteinizing hormone at 6 IU/L (1 to 10 IU/L). Thyroid function tests, cortisol, and adrenocorticotropic hormone were normal. A magnetic resonance image of the brain did not show any evidence of hypophysitis. Repeat testing of pituitary hormones 2 weeks later showed a decrease in luteinizing hormone to less than 0.2 IU/L (1 to 10 IU/L) and follicle stimulating hormone to 0.4 IU/L (1 to 10 IU/L), and a persistently low testosterone reading. The patient was referred to the endocrinology unit and commenced on monthly injections of esterified testosterone replacement therapy (Sustanon 250). Within weeks of commencing treatment, the patient's symptoms resolved and his ECOG PS returned to pre-treatment levels. Following three injections, blood tests revealed serum testosterone levels normalized to 6.7 nmol/L (6 to 28 nmol/L), sex hormone binding globulin at 26 nmol/L (15 to 50 nmol/L), free testosterone at 145 pmol/L (200 to 600 pmol/L), and dehydroepiandrosterone at 1.1 μmol/L (0.9 to 5.9 μmol/L). The patient declined further treatment with durvalumab and is currently on surveillance.

Single-agent anti–PD-1 and anti–PDL-1 therapies are generally well tolerated and show comparable safety profiles.[1] The most common ICI-mediated endocrinopathies reported are hypophysitis and primary thyroid dysfunction.[2] However, the exact mechanism of how these occur remains unclear. The incidence of hypophysitis is significantly higher in patients treated with the anti–cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitor, ipilimumab, compared to PD-1 and PDL-1 inhibitors.[3] Low levels of testosterone have been reported in patients treated with checkpoint

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