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Dear Editor,

We read with great interest the paper by Chander *et al*., published in *The Journal of Clinical Endocrinology & Metabolism*, on the outcomes of patients following parathyroid surgery for primary hyperparathyroidism (pHPT) (1). Taking into account the value of preoperative imaging, the authors have distinguished three different scenarios: 1) those with concordance between parathyroid ultrasonography (US) and sestamibi scan for a single gland abnormality, 2) those with discordant findings between US and sestamibi scan and 3) those with both imaging studies negative, a condition recently reported as being associated with an increased risk of persistent disease following parathyroidectomy (2). The authors should be congratulated for achieving a 96% cure rate in this population, as we have done (3). They have also stated that surgery should be considered regardless of the pre-operative imaging findings, as recommended by the NICE guidelines (4). We would like to emphasize that, in this specific population, some critical information needs to be addressed to better understand both results and recommendations.

Persistent disease is defined as persistent pHPT in the six months following surgery (5); we thus consider that the criteria for "cure" used by the authors (i.e., normalization of calcium levels at two weeks post-operatively) is suboptimal and may underestimate persistent disease rate (5).

Negative imaging in pHPT is also associated with a higher prevalence of multiglandular disease (3), potentially indicative of multiple endocrine neoplasia type 1 (MEN1) or familial hypocalciuric hypercalcemia (FHH) (6). Recently, we have shown that FHH patients often show negative parathyroid imaging (6,7). As recommended, the authors used a calcium:creatinine clearance ratio (CCCR) > 0.01 to rule out FHH. However, taken alone, CCCR is of limited clinical value due to its reduced diagnostic sensitivity with up to 50% of

FHH patients with a CCCR > 0.01 (6,8). Therefore, we suggest further investigations for pHPT patients with negative imaging or in favor of multiglandular disease. For FHH, due to the high disease penetrance (> 90%), calcemia measurements in the first-degree relatives can document FHH and, ultimately, guide genetic testing (8). In this contextual knowledge, thorough informations regarding kindreds, the surgical strategy, number of resected glands, gross aspect of the resected glands, gland weight and, eventually, pathological results, are crucial to properly characterize the patient and offer the best management. Indeed, our experience teached us that FHH patients can have calcemia exceeding 2.8 mmol/l, and that familial forms of multiglandular disease like FHH, could be diagnosed in patients older than seventy years old (7).

Thus, with great respect, we recommend these adjustments to the therapeutic strategies for pHPT patients with negative imaging, who represent a specific population that needs to be referred to a tertiary care center to ensure the most adapted diagnosis and management.

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