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Preoperative Imaging in Primary Hyperparathyroidism: Literature Review and Recommendations

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Primary hyperparathyroidism is the third most common endocrine disorder after diabetes mellitus and hypothyroidism, and affects an estimated 0.3% of the general population [1,2]. Approximately 90% of such patients are subsequently found to have a single parathyroid adenoma, 10% are found to have multigland hyperplasia or multiple adenomas, and the rare patient is found to have parathyroid carcinoma [3].

Surgical removal of the hyperfunctioning parathyroid tissue is the only definitive cure and is warranted in symptomatic patients or in those who develop complications, as well as in all patients under 50 years of age [4]. Traditionally, this was done by way of a bilateral neck exploration with direct visualization of all 4 glands, with preoperative imaging studies rarely required. In 1986, interventional radiologist John L. Doppman remarked that ‘‘the only localising study indicated in untreated primary hyperparathyroidism is to localise an experienced parathyroid surgeon’’ [5].

Over the last 30 years improvements in imaging techniques have enabled radiologists to identify parathyroid adenomas with greater confidence and accuracy, allowing surgeons to perform unilateral or targeted parathyroidectomies. More recently, concerns regarding higher rates of recurrent or persistent disease have prompted some surgeons to abandon unilateral parathyroidectomy and return to the traditional bilateral neck exploration [6].

Nonetheless, targeted parathyroidectomy remains the preferred operative technique for many surgeons and is associated with a shorter operative duration, a lower risk of postoperative complications and greater patient satisfaction [7,8]. This approach is dependent on precise localization of the abnormal gland(s) and is therefore predicated on accurate preoperative imaging.

In approximately 16% of cases of primary hyperparathyroidism, 1 or more hyperfunctioning gland(s) is found in an ectopic location [9]. The location of ectopic glands depends on their embryological origin. The superior glands, which are derived from the fourth branchial pouch, can occasionally be found within the thyroid gland, as the parafollicular cells of the thyroid also derive from the fourth branchial pouch. The inferior glands, which are derived from the third branchial pouch, descend with the thymus and undergo a much lengthier migration compared to the superior glands. Hence, they experience more variation in their final location. It is useful to note that this descent occurs in a narrow coronal plane anterior to the recurrent laryngeal nerves and extending from the angle of the mandible to the pericardium, explaining why they can occasionally be found in the thyrothymic tract or the superior mediastinum.

Ultrasonography (US) and ^{99m}Tc sestamibi scintigraphy (MIBI) are widely used first-line investigations and are commonly used in combination. If both tests are in agreement, the patient is considered a candidate for a targeted parathyroidectomy. However, parathyroid lesions can prove elusive and first-line imaging studies are often indeterminate, particularly if the lesion is small, has an unusual anatomic location, or if there is coexistent thyroid disease. Furthermore, both US and planar MIBI experience a significant reduction in sensitivity in cases of multigland disease [10,11]. Dynamic, contrast-enhanced computed tomography (CT) has emerged as a popular second-line investigation in ambiguous or problematic cases. Recent advances in magnetic resonance imaging (MRI) and development of several novel positron emission

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tomography (PET) radiotracers have shown promise in early studies and may lead to an expanded role for these modalities.

Ultrasound

Parathyroid US was first described in 1975 and has since become widely used in the preoperative localization of abnormal parathyroid glands [12]. Parathyroid imaging is an excellent application of US as the superficial location permits the use of high-frequency transducers, usually 5-15 MHz, with their increased spatial resolution.

Parathyroid adenomas tend to be homogenous, round to ovoid in shape, and appear hypoechoic compared with thyroid tissue. The application of Doppler can assist in distinguishing parathyroid lesions from other surrounding structures. A typical adenoma has a peripheral rim of vascularity and asymmetrically increased blood flow compared with the adjacent thyroid tissue. Furthermore, the identification of a prominent extrathyroidal feeding artery entering at 1 pole, known as polar artery, can further help in discriminating between an adenoma and a cervical lymph node, which usually has a hilar blood supply (Figure 1) [13]. Positioning the transducer in the transverse plane and rotating the patient's head to the opposite side can often aid in detecting an inconspicuous gland.

US is inexpensive and widely available, and has sufficient sensitivity to permit its use as a first-line investigation. It also allows for the concurrent assessment of the thyroid and facilitates percutaneous biopsy if necessary. Due to its widespread availability and regular advances in technology over the last 20 years, US has been extensively evaluated. In 2012 Cheung et al [14] carried out a meta-analysis of preoperative imaging in primary hyperparathyroidism and found US to have an overall pooled sensitivity of 76.1% and positive predictive value (PPV) of 93.2%. More recently, Smith et al [15] examined the performance of US in 220 patients with primary hyperparathyroidism and noted that the localization by US was accurate in 82% of cases.

Both multigland disease and multinodular thyroid disease can impact on the performance of ultrasound. A 2005 systematic review of 20,225 cases of primary hyperparathyroidism found that the sensitivity of ultrasound dropped from 78.5% to 34.9% in cases of multigland hyperplasia, and fell further to 16.2% where double adenomata were concerned [3]. A further 2006 study of 123 patients with primary hyperparathyroidism reported a reduction in sensitivity of high frequency ultrasound from 89% to 84% in cases of concomitant thyroid nodules [16].

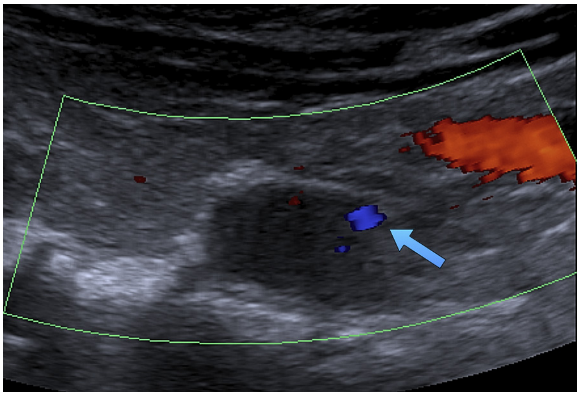

Figure 1. Neck ultrasound shows a 1.6 × 2.0 cm hypoechoic, homogenous nodule with a polar feeding vessel (arrow) located posterior to the lower pole of the left lobe of the thyroid, consistent with a parathyroid adenoma.

As with any application of US, it can be limited in patients with an elevated body mass index and is highly dependent on an experienced sonographer performing the study. Visualization of low inferior glands can be particularly difficult in patients who are unable to adequately extend their neck. In addition, US has poor penetration of air filled or bony structures, limiting its ability to detect ectopic glands, particularly those located in the mediastinum. For these reasons, US is usually employed in conjunction with another imaging modality, most commonly ^{99m}Tc MIBI.

^{99m}Tc SestaMIBI Scintigraphy

Radioisotope scintigraphy of the parathyroid glands was described in 1983 with thallium as the initial radionuclide of choice [17]. ^{99m}Tc MIBI was later introduced in 1989 and greatly increased the sensitivity of nuclear imaging [18]. MIBI is a lipophilic cation that accumulates in the mitochondria rich oxyphil cells of abnormal parathyroid tissue. There are several protocols in use for parathyroid scintigraphy, most of which are based on 2 techniques: single-tracer double phase and dual-tracer single phase.

In the single-tracer double-phase technique ^{99m}Tc MIBI is administered and a first set of images acquired after 10-15 minutes. A second acquisition is then taken 1.5-3 hours later. The radiotracer washes out more rapidly from the surrounding tissues than from the parathyroids, allowing for the identification of abnormal gland(s) on interval imaging (Figure 2). In the dual-tracer single-phase technique, also known as subtraction scintigraphy, a second radiotracer (usually ^{123}I or $^{99m}TcO_4^{-}$) is administered and is then taken up more avidly by the thyroid. This thyroid scintigram can then be digitally subtracted from or can be viewed alongside the ^{99m}Tc MIBI images, allowing the viewer to distinguish abnormal parathyroid glands from thyroid tissue.

MIBI's wide field of view enables detection of ectopic lesions, particularly those in the mediastinum. In addition, there is less interobserver variation compared with neck US. Pitfalls in MIBI imaging however include the potential for both false positives and false negative studies. Thyroid nodules, thyroiditis, and enlarged cervical lymph nodes can all delay the washout of the radionuclide giving the appearance of a parathyroid adenoma. In particular, follicular and Hurthle cell neoplasms readily accumulate MIBI and can often lend themselves to such errors [19]. The sensitivity of planar MIBI in the detection on parathyroid adenomas varies widely but is usually reported in the region of 70%-85%, with dual-tracer protocols performing slightly better than single-tracer techniques [20–22].