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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].

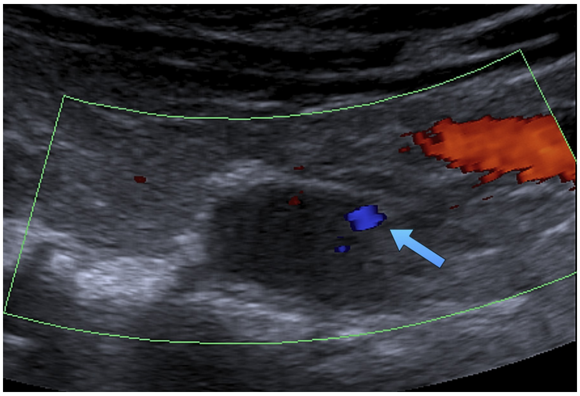

Figure 1. Neck ultrasound shows a 1.6 × 2.0 cm hypoechoic, homogenous nodule with a polar feeding vessel (arrow) located posterior to the lower pole of the left lobe of the thyroid, consistent with a parathyroid adenoma.

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].

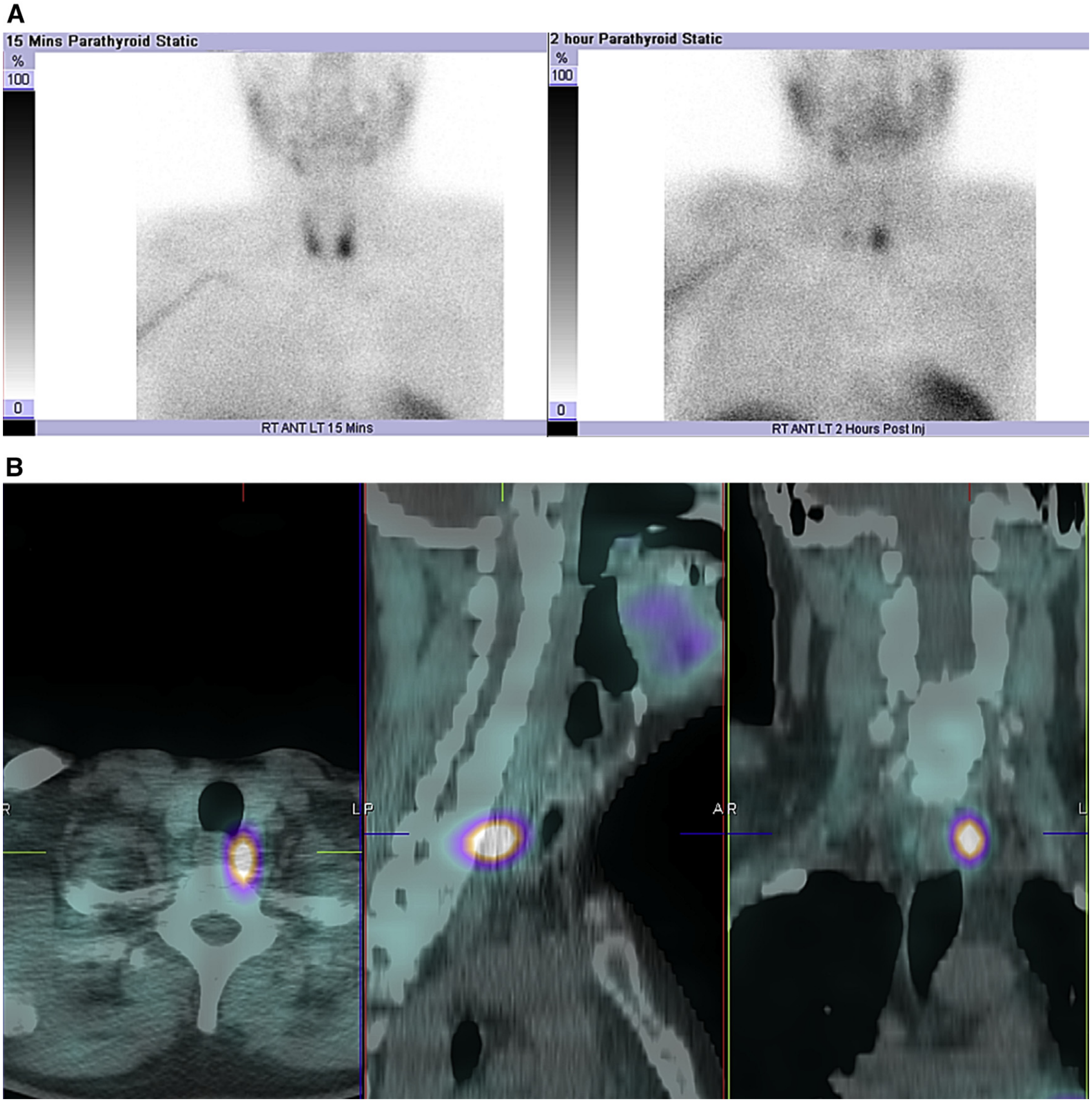

Figure 2. ^{99m}Tc sestamibi scintigraphy in a 49-year-old man with primary hyperparathyroidism and multiple endocrine neoplasia type 1. (A) Planar imaging demonstrates a focus of tracer retention in the left lower neck. (B) Single-photon emission computed tomography/computed tomography confirms a focus of intense tracer retention correlating with a 9 mm nodule located posterior and inferior to the left lobe of the thyroid, consistent with a parathyroid adenoma.

The use of single-photon emission computed tomography (SPECT) has the advantage of 3 dimensions, aiding in the identification of pathological tissue within deep body structures or behind the thyroid where it may be obscured on planar imaging. Several studies have demonstrated an improved sensitivity and accuracy of SPECT compared to planar imaging, with a sensitivity of approximately 85% [23–25]. More recently, SPECT has been fused with conventional, x-ray–based CT (Figure 3). These hybrid SPECT/CT images not only provide additional anatomic information of use to the surgeon, but are also more sensitive and accurate [26–29]. A 2015 meta-analysis comparing SPECT/CT, SPECT, and planar imaging concluded that SPECT/CT was superior to SPECT with an overall pooled sensitivity and PPV of 84% and 95%, respectively, compared with 66% and 82% for SPECT [30]. More recently, Treglia et al [31] pooled data from 1,236 patients and reported a detection rate for SPECT/CT of 88% for both a per-patient and a per-lesion analysis.

One of the most notable advantages of MIBI over US is its ability to detect ectopic lesions. In 1 study of 202 patients with ectopic parathyroid lesions, planar MIBI had a sensitivity of 89%, performing particularly well in cases of thymic, mediastinal, and retroesophageal adenomas [32]. In contrast, US had a sensitivity of only 59% for detecting ectopic glands; and although it performed well in cases of undescended and intrathyroidal glands, it was particularly poor at detecting glands within the thymus or in the retroesophageal areas, and failed to detect any glands located within the mediastinum or carotid sheath. In a further study of 88 patients, Koberstein et al [29] found that SPECT/CT was an accurate and reliable means of localizing both retrothyroid and ectopic adenomas with a sensitivity and specificity of 81.5% and 100%, respectively, for ectopic lesions.

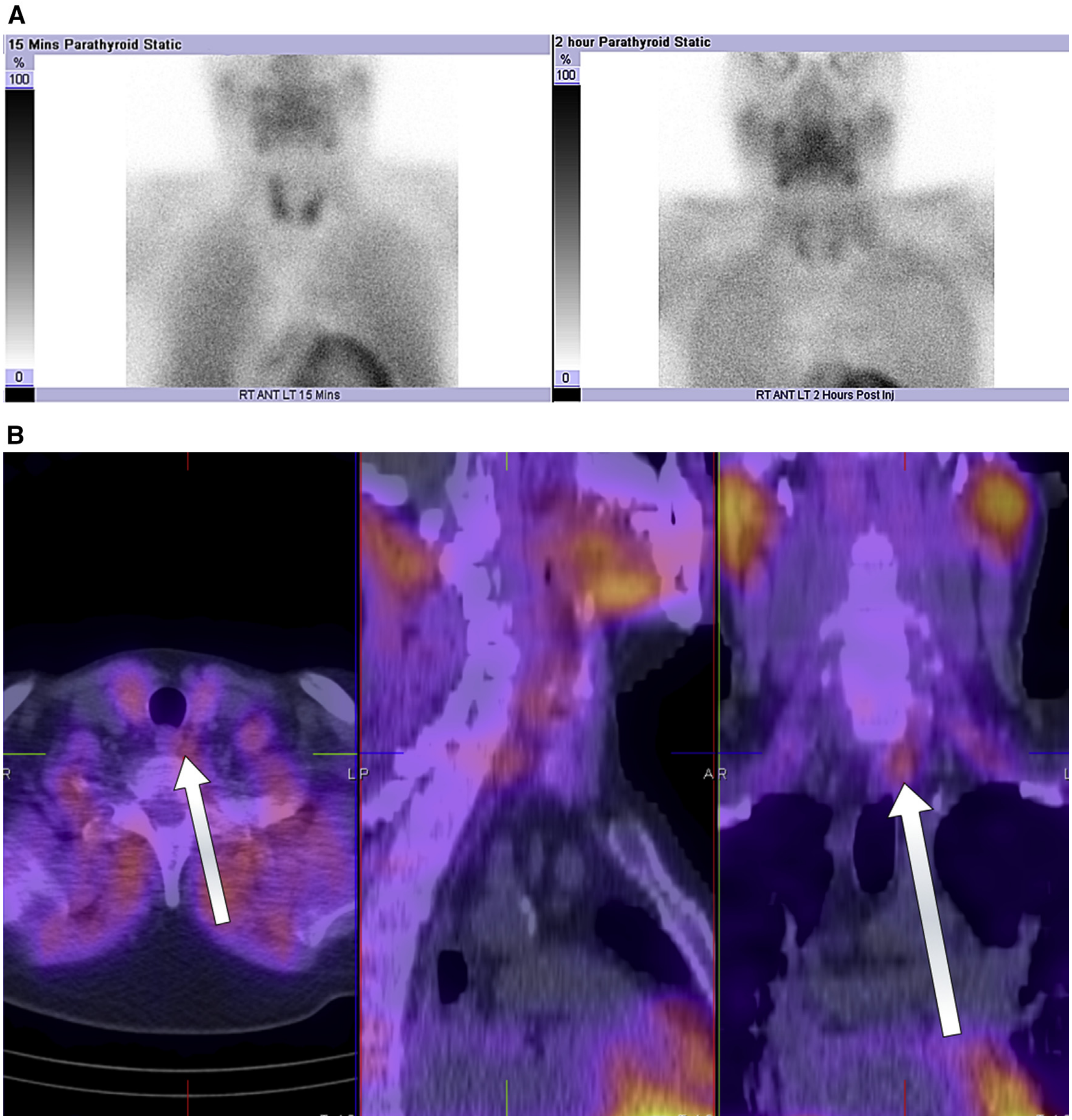

Figure 3. ^{99m}Tc sestamibi scintigraphy in a 52-year-old man with primary hyperparathyroidism. (A) Planar imaging shows diffuse tracer uptake within both lobes of the thyroid but no focus of tracer retention suggestive of parathyroid adenoma. (B) Single-photon emission computed tomography/computed tomography reveals a 1 cm soft tissue nodule (white arrow) immediately lateral to the esophagus and posterior to the left lower pole of the thyroid. The nodule shows low-grade tracer uptake illustrating the improved sensitivity of Single-photon emission computed tomography/computed tomography over planar imaging. A parathyroid adenoma was removed at surgery.

Ultrasound or Scintigraphy?

US and MIBI are the 2 most commonly employed first-line investigations, with many institutions using the 2 in combination. Other authors have compared the performance of US with planar MIBI and SPECT and have largely concluded that they are of similar efficacy in the detection of parathyroid adenomas [14,33]. A 2009 review found level III evidence in support of using either US or MIBI as the initial investigation [33]. However, most of the studies included in that review evaluated planar scintigraphy, whereas SPECT/CT has become more widely used in recent years. A direct comparison between US and tomographic scintigraphy is made difficult by the myriad techniques and protocols in current use.

Guerin et al [34] compared US with dual-tracer SPECT among 127 patients and concluded that SPECT was more sensitive (93%) and more accurate (83%) than US in cases of uniglandular disease. Kluijfhout et al [35] examined US, SPECT/CT and PET in 63 patients and found a higher sensitivity (80%) and PPV (93%) with SPECT/CT compared with US and suggested that SPECT/CT should be performed first, with US reserved for confirming positive SPECT/CT findings and preoperative marking. Berner et al [36] compared dual-tracer SPECT/CT with US and found that SPECT/CT had a superior sensitivity (71% vs 60%) and specificity (94% vs 72%). In particular, SPECT/CT outperformed US in cases of multigland disease and nodular thyroid disease with sensitivity of 64% and 84%, respectively, compared with 36%

and 68% for US [36]. It should be noted that the overall sensitivity reported in this series of 71% for SPECT/CT is lower than has been reported in meta-analysis, likely due to the low rate of 20 mAs. In contrast, Butt et al [37] described their experience of using US alone and noted that is correctly identified the parathyroid adenoma in 98% of cases suitable for targeted parathyroidectomy.

There are a large number of published series, many of which summarize their results with differing conclusions and opposing recommendations. However, the overriding impression is that SPECT/CT has a higher sensitivity and specificity compared to US, and is far superior in cases of ectopic and multigland disease.

Computed Tomography

Historically, conventional CT has performed poorly in comparison with other imaging modalities in imaging parathyroid adenomas, with a sensitivity of approximately 40%-70% [38,39]. The advent of high-resolution CT and progressively thinner sections allowed radiologists to interpret images with greater confidence than before. However, it still failed to adequately distinguish between parathyroid adenomas and cervical lymph nodes, which can closely resemble adenomas in size and shape. Dynamic, contrast-enhanced CT, also referred to as 4-dimensional CT, was first described in 2006 and aims to address this problem by incorporating 2 contrast-enhanced phases in addition to the standard, non contrast phase (Figure 4) [40]. The typical parathyroid adenoma is of low attenuation on the noncontrast phase, demonstrates peak enhancement on the arterial phase, followed by a washout of contrast on the delayed phase images [41,42]. Lymph nodes, however, will continue to demonstrate progressive enhancement for approximately 90 seconds, corresponding to the delayed phase.

Similar to SPECT/CT, dynamic CT provides excellent anatomic detail for adenoma localization while also detecting ectopic lesions. In addition, it appears to be of superior sensitivity to planar scintigraphy and ultrasound. Rodgers evaluated dynamic CT as an initial investigation in 75 patients with primary hyperparathyroidism and recorded an improved sensitivity (85%) compared with both SPECT/CT (65%) and US (57%) when localizing the lesion to 1 side of the neck [40]. Starker et al [43] also examined dynamic CT as an initial localising study and found that dynamic CT localized the lesion to the correct quadrant in 86% of cases compared with 40% for SPECT and 48% for US. Brown et al [44] looked at dynamic CT in 100 consecutive cases and reported an overall sensitivity of 92% compared with 70% for SPECT/CT.

The primary concern with dynamic CT is the high dose of radiation, ranging between 10 and 27 mSv [43,45]. Many institutions have now adapted the originally described protocol by either omitting the initial, noncontrast phase or by removing 1 of the subsequent, contrast-enhanced phases. However the radiation dose still remains high. Mahajan et al [46] analysed the radiation dose of dynamic CT and SPECT and calculated that the patient effective doses were similar (10.4 vs 7.8 mSv) but that the dose to the thyroid was 57 times higher for dynamic CT. In a prototypic 20-year-old woman this translates into a lifetime risk of thyroid cancer of approximately 0.1%. More recently, a 2-phase, low-dose protocol with a similar radiation dose to SPECT/CT has been described and appears to have a similar sensitivity to standard protocols [47]. Nonetheless, concerns about the radiation dose persist, leading many centres to reserve dynamic CT for use as a confirmatory study or as a second-line study in problematic cases.

MRI

Although less commonly used than ultrasound or scintigraphy, MRI is generally considered to have a similar accuracy to other modalities in the detection of parathyroid lesions with a reported sensitivity of 63%-91% [48−53]. Similar to dynamic CT, MRI is predominantly used as a second-line investigation. In 1 study of 44 patients with

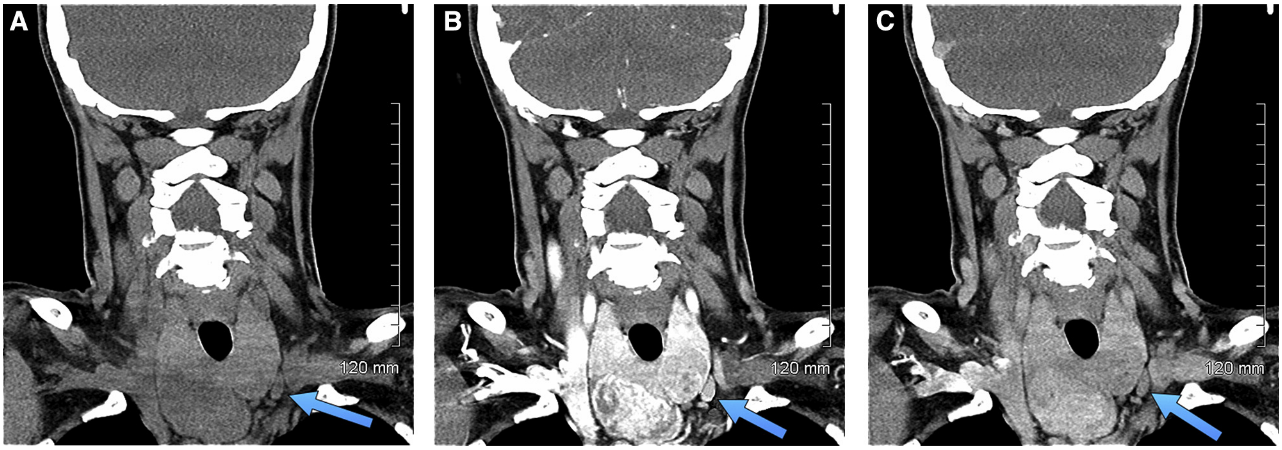

Figure 4. Dynamic computed tomography in a 68-year-old female with primary hyperparathyroidism and a multinodular goiter demonstrating the typical imaging features of a parathyroid adenoma (arrow). Coronal noncontrast imaging (A) shows a low attenuation, ovoid lesion lateral to the left lobe of the thyroid. This lesion enhances avidly on arterial phase imaging (B) and demonstrated washout of contrast on delayed phase imaging (C).

persistent hyperparathyroidism undergoing reoperation, MRI correctly identified 74% of abnormal parathyroid glands, with a comparable detection rate for adenomas and hyperplastic glands [54].

Parathryoid adenomas typically appear hypointense on T1-weighted sequences, enhance avidly postcontrast, and appear hyperintense on T2-weighted images, particularly following fat suppression; however, their imaging features can demonstrate considerable variability [55].

Recently, some investigators have sought to improve on traditional static MRI by exploring dynamic MRI [53]. This novel technique is similar in to dynamic CT in that it takes advantage of the hypervascular nature of parathyroid adenomas. However, whereas dynamic CT can only provide snapshots at 2 or 3 time points (depending on the number of acquisitions) MRI is not restricted by radiation dose and could therefore acquire images at several time points. In 1 small pilot study of 30 patients, dynamic MRI distinguished parathyroid adenomas from thyroid tissue and lymph nodes with an accuracy of 96% [56].

PET/CT

PET/CT is not widely used in primary hyperparathyroidism and is largely of academic interest at present. Nonetheless, its potential advantages make it an attractive option in the localization of parathyroid adenomas. It has greater spatial resolution than SPECT/CT as well as a shorter image acquisition time. However its high cost and limited availability have made data on its use in parathyroid imaging scarce. One study from 1996 found [18F] 2 fluorodeoxyglucose (FDG) PET to be highly sensitive and adequately specific and even suggested that it may even be preferred to ^{99m}Tc MIBI SPECT [57]. These findings however have not been widely repeated and the results up until recently were largely disappointing.

The last few years have seen the development of a number of novel PET radiotracers such as ^{18}F fluorocholine and ^{11}C methionine (Figure 5). ^{18}F fluorocholine appears to be the most promising, as it is already in regular use in prostate and hepatocellular carcinoma and is thus more easily accessible than some other radiotracers. Two pilot studies suggested that it

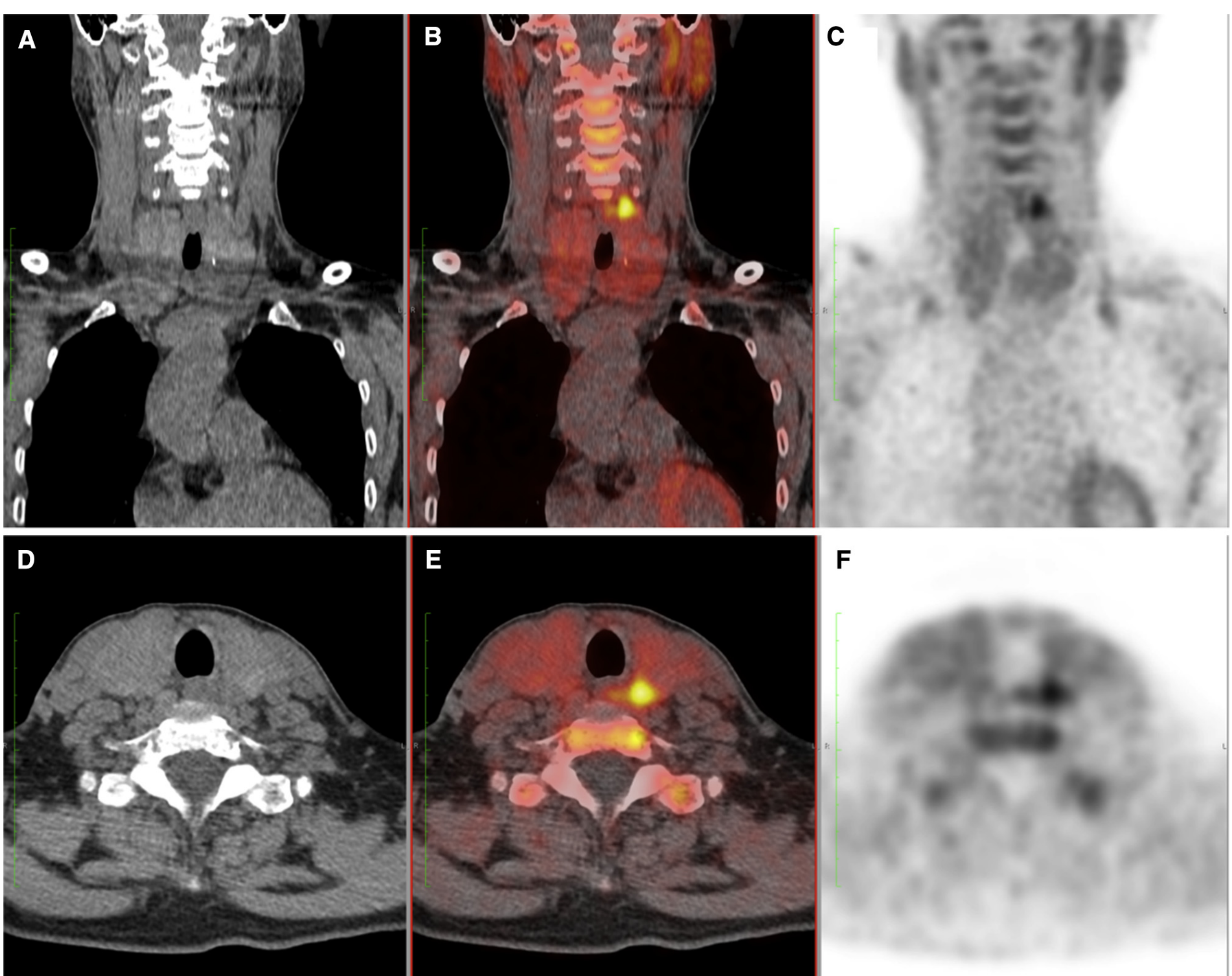

Figure 5. ^{11}C methionine positron emission tomography/computed tomography in a patient with a solitary parathyroid adenoma. Coronal and axial computed tomography (A, D), fused (B, E), and positron emission tomography (C, F) images show a focus of intense uptake posterior to the upper pole of the left lobe of thyroid.

could detect adenomatous or hyperplastic glands with good accuracy and that its diagnostic performance may even be superior to that of SPECT/CT [58,59]. A further study comparing ^{18}F fluorocholine PET/CT with US and planar MIBI in 17 patients with primary or secondary hyperparathyroidism found that PET/CT was more sensitive than US and was at least as sensitive as planar MIBI with a similar specificity [60].

^{18}F fluorocholine PET/CT is a promising new technique in preoperative parathyroid imaging. Larger studies will be necessary to confirm the above findings and clarify its role, but it is likely to be of greatest value in cases with discordant first-line imaging or in those with recurrent or persistent disease.

Selective Venous Sampling

Despite the numerous modalities and techniques at our disposal, a small subset of patients continues to have negative or inconclusive noninvasive investigations and may benefit from selective venous sampling. Selective venous sampling was first described in 1969 and has been in regular use since the mid 1990s [61]. More recently, the development of a rapid parathyroid hormone assay and its use in the interventional radiology suite have provided near real time data sampling, guiding the operator into smaller venous branches in an effort to more precisely localize the abnormal gland. This modified technique, also known as super selective venous sampling, accurately localized the affected gland in 90% (28 of 31) of cases with negative noninvasive imaging in 1 recent series [62]. However, the authors did not specify whether the patients had undergone SPECT/CT or just planar scintigraphy. Thus, the reported data may not accurately reflect current practice.

Cost Effectiveness

Several authors have attempted to compare the economic costs associated with various strategies; however, many of the calculations rely on data acquired prior to the widespread use of SPECT/CT. Hence, the available comparisons are more applicable to environments in which SPECT/CT is not routinely used.

Lubitz et al [63] calculated that US alone followed by dynamic CT in inconclusive cases was the most cost-effective strategy. The savings associated with this approach were largely due to the higher sensitivity of dynamic CT enabling more patients to undergo minimally-invasive parathyroidectomy. However, this analysis assumed a sensitivity of 78.9% for MIBI, a figure derived in part from studies of planar scintigraphy. This value is somewhat lower than has been reported for SPECT and SPECT/CT. Moreover, their costing analysis is based on data from Medicare national reimbursement and thus may be of limited relevance outside the United States.

Wang et al [64] also examined the cost of various imaging algorithms and concluded that the most cost effective model was SPECT and US together, followed by dynamic CT if the 2 initial studies were discordant. However, Lubitz et al's [63] suggestion of US followed by dynamic CT was not considered in Wang et al's analysis. In contrast, Solorzano and Carneiro-Pla [65] suggested 2 potential strategies: 1) US followed by dynamic CT; or 2) US followed by MIBI with or without dynamic CT.

An Optimal Imaging Strategy?

Any recommendations regarding an imaging protocol will be limited by the inherent limitations of the available data. First, over the last 30 years there has been a significant change in the profile of the patients being referred for parathyroidectomy. The introduction of automated serum calcium measurements in the 1970s, the development of national osteoporotic screening guidelines, increased disease awareness, as well as a reduction in surgical morbidity have all served to lower the threshold for surgery [66]. One series from a tertiary referral endocrine surgical unit, for example, reported that there had been a reduction in preoperative serum calcium from 342 pg/ml during 1983-1992 to 155 pg/ml during 1993-2002. A reduction in mean adenoma size from 2.04 g to 1.33 g was also observed during the same period [67]. These changing referral practices call into question the relevancy of many of the older series, whose patient populations are likely to be very different from the patients referred today.

Second, many of the published series are retrospective reviews and were not designed to make a direct comparison between one modality and another. Thirdly, patients with negative or equivocal first-line imaging are more likely to progress to second-line imaging, leading to a selection bias favoring patients with smaller adenomas or mulitgland disease. Last, several of the described techniques were performed at high-volume centres by skilled operators and experienced interpreters. Hence, not all results will be easily applicable to all institutions.

Nonetheless, due to its high sensitivity and specificity, as well as its ability to provide excellent anatomic detail for surgical planning, SPECT/CT appears to be the most suitable initial investigation. Dynamic CT has similar advantages and may be reasonably employed as a first-line study, however its higher radiation dose means that SPECT/CT should be preferred, particularly in younger patients [44,46]. Although some practitioners maintain that US is sufficient, both SPECT/CT and dynamic CT have a higher sensitivity thereby allowing more patients to undergo minimally-invasive parathyroidectomy. Hence, the role of US would now seem limited to jurisdictions in which SPECT/CT or dynamic CT are unavailable, or to those patients in whom radiation dose is of particular concern.

Although initial results are encouraging, there is currently insufficient evidence to recommend the routine use MRI or PET/CT. However, they offer viable alternatives in cases with negative or discordant imaging, particularly in those being considered for reoperation. Selective venous sampling can be considered in patients undergoing reoperation and have had negative imaging at a high volume centre.

However, due to the risk of complications it can only be recommended when all noninvasive options have been exhausted.

We now have a wide array of highly sensitive imaging modalities at our disposal. Further studies should aim to evaluate the diagnostic performance of the various modalities in specific patient groups (ie, those with inconclusive first-line imaging and those undergoing reoperation), while taking note of the cost, convenience, and radiation dose.

Conclusion

The advent of targeted parathyroidectomy has led to greater demand for highly sensitive and increasingly accurate preoperative imaging. Preferred imaging strategies vary greatly from 1 institution to the next and it remains unclear which investigations should be performed alone, in combination, or in succession. ^{99m}Tc MIBI SPECT/CT would appear to be the most appropriate initial investigation with dynamic CT offering a reasonable alternative. Currently, MRI and PET/CT are not widely used but recent advances in parathyroid MRI and the development of several novel PET/CT radiotracers may lead to an expanded role for these modalities in the future.

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