IMAGING OF THE PARATHYROID GLANDS IN PRIMARY HYPERPARATHYROIDISM

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Primary hyperparathyroidism is one of the most frequent endocrine diseases worldwide. Surgery is the only potentially curable option for patients with this disorder, even though in asymptomatic patients 50 years of age or older without end organ complications, a conservative treatment may be a possible alternative. Bilateral neck exploration under general anaesthesia has been the standard for the definitive treatment; however, significant improvements in preoperative imaging, together with the implementation of rapid parathyroid hormone determination, have determined an increased implementation of focused, minimally invasive surgical approach. Surgeons prefer to have a localization study before operation (both in the classical scenario and in the minimally invasive procedure); they are not satisfied by having been referred a patients with just a biochemical diagnosis of PHPT. Imaging studies mustn’t be utilized to make the diagnosis of primary hyperparathyroidism; they should be obtained to both assist in determining disease etiology and to guide operative procedures together with the nuclear medicine doctor and, most importantly, with the surgeon. On the contrary, apart from minimally invasive procedures in which localization procedures are an obligate choice, some surgeons believe that literature on parathyroidectomy over the past two decades reveals a bias towards localisation. Therefore, surgical expertise is more important that the search for abnormal parathyroid glands.
Introduction

Primary hyperparathyroidism (PHPT) is one of the most frequent endocrine diseases worldwide. Surgery is the only potentially curable option for patients with this disorder, even though in asymptomatic patients 50 years of age or older without end organ complications, a conservative treatment may be a possible alternative, according to recent guidelines (1,2). Bilateral neck exploration (BNE) under general anaesthesia has been the standard for the definitive treatment; however, significant improvements in preoperative imaging, together with the implementation of rapid parathyroid hormone (PTH) determination, have determined an increased adoption of focused, minimally invasive surgical approach (3).

Theoretically, preoperative imaging studies should not be used when planning traditional “open” parathyroid surgery. On the contrary, the minimally invasive procedure assumes accurate preoperative localization of abnormal parathyroid gland(s) (4). Before discussing for or against preoperative localization procedures, we believe it is important to briefly summarize the most commonly techniques utilized.

High-resolution ultrasound (US) represents, together with nuclear medicine imaging, a reliable first-line modality for preoperative localization of a parathyroid lesion. Neck US is currently performed with a high-frequency (7.5-15 MHz) transducer to enhance spatial resolution, thus allowing detection of glands larger than 5 mm (5). Colour Doppler assessment is a useful integration for the distinction of parathyroid lesions from other cervical masses, thus reducing false positive findings (6). These can also occur in cases of thyroid nodules or concomitant Hashimoto’s thyroiditis. The sensitivity of US technique is strongly dependent on operator’s experience, being about 84% when performed by an experienced doctor (7). Advantages of US technique include low cost, widely availability, absence of ionizing radiation exposure, together with the possibility of evaluating concomitant thyroid disease (8). Nonetheless, US does not allow detection of small lesions; furthermore, ectopic glands and the presence of concomitant large thyroid goiter may cause false negative findings (9).
Technetium (\textsuperscript{99m}Tc)-sestamibi (methoxyisobutyl isonitrile, MIBI), is the agent of choice for the identification of abnormal parathyroid glands by scintigraphy; it is a lipophilic cation entering the over-activated mitochondria rich oxyphil cells. The differential washout rate of this tracer from the thyroid relative to the parathyroid gland allows parathyroid scintigraphy to be performed with this single tracer according the so-called dual phase procedure. Combining sestamibi with a tracer exclusively taken up by the thyroid tissue (double-tracer technique) permits the subtraction of thyroid imaging, thus avoiding false positive results deriving from the concentrations of sestamibi by solid thyroid nodules. The two techniques have a similar diagnostic performance for localization of single parathyroid adenoma, with a 88-90% sensitivity. The specificity is over 90% when using the double tracer technique. Sensitivity and specificity is reported to be even better with the use of early \textsuperscript{99m}Tc sestamibi-single-photon emission computerized tomography (SPECT) and SPECT/computed tomography (CT), allowing a 3-D visualization (10). These last procedures should be considered in patients with ectopic parathyroid adenomas or in those who had undergone previous surgery (11,12).

Computed tomography (and magnetic resonance imaging) is considered a second-line technique useful in cases of ectopic glands or when there is persistence or recurrence of the disease after initial operation. A new 4-D CT technique, combining anatomic and functional information has been recently developed; taking advantage of the evaluation of enhancement patterns of abnormal parathyroid glands reaches a sensitivity of 85.7% (13). The use of magnetic resonance imaging (MR) allows the evaluation of parathyroid anatomy, detection of ectopic glands, in the absence of patient’s radiation exposure; reported sensitivity is 80% with the 1.5 Tesla magnets (14). Better visualization has been recently obtained with the use of 3.0 Tesla MRI magnet being a valid method for parathyroid lesions identification, particularly in PHPT patients with negative first-line imaging (15,16).
Section 1: Discussion in favour of

The argument for routine parathyroid localisation for primary hyperparathyroidism.

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About 30 years ago, when we started to be interested in primary hyperparathyroidism (17), the only clinical task was to make the diagnosis. Imaging of the parathyroid glands was an almost unexplored field and patients were immediately referred to the surgeon with expertise in neck operation.

During the last three decades there has been a flourishing of imaging modalities to visualize abnormal parathyroid glands; these are sometimes difficult to compare each other because of the different settings in which they are employed (i.e. sensitivity of a particular technique is different in the setting of a large parathyroid adenoma vs small adenoma or multiple gland disease, MGD). This surge of techniques has been mainly fuelled by the need of a precise localization of the abnormal gland(s) in order to perform a minimally invasive parathyroidectomy. The last could result, among other things, in saving of money, due to shorter time of operation.

In the next section we will argument for a routine preoperative parathyroid localization based on four main arguments.

Surgical expertise

A number of studies have demonstrated that successful parathyroidectomy (PTx) is predominantly dependent on surgeon’s experience rather than the technique employed (3,18). Indeed, both traditional and focused approaches showed excellent outcomes in terms of cure and complications rate depending on experience of both the surgeon and the center (18). Data on long-term follow-up in patients who had undergone parathyroid surgery showed curative rates of 95-98% (18,19,20). These last data apply to centres with high quality surgery teams and large series, reflecting high expertise in the field (18).
Less data are available from centres with lower parathyroid surgical experience, but collectively suggest that the absence of specific expertise represents the actual challenge (18). In this context, few studies evaluated the impact of surgical expertise on parathyroid surgery in terms of number of patients referred to surgery, i.e. surgical volume (21,22,23). This parameter has been found to influence curative rate, operative failure and complications. Historical data from Scandinavia illustrated that 76% of patients who had undergone parathyroidectomy in general survey parathyroid surgery were normocalcemic after an average follow-up of 4.4 years, compared with 90% in specialized surgery centres (21). Additionally, less experienced centres reported higher incidence of persistent PHPT (15%) and permanent hypoparathyroidism (14%) (21). Studies in the United States reported persistent PHPT being more common at the low volume centers (87%) vs the high volume centers (43%) (22). Mitchell et al. reported higher rates of avoidable parathyroid re-operations in low-volume (78%) vs high-volume centres (22%) (23). These data are of note, particularly considering that re-operative surgery is associated with higher complications rate (22).

The overall data substantially confirm what generally is also observed in clinical practice, i.e. the need for experienced and trained surgery teams as the key point for ensuring successful parathyroidectomy. Primary hyperparathyroidism represents a curable disease; however, the availability of experienced parathyroid surgeon is currently the greatest challenge in PHPT management and in predicting patient’s outcome (3).

Based on these premises and on the real world evidence of the existence of few centres with very qualified surgical teams, we favour the use of preoperative imaging studies. This is especially important if the operation is carried out by surgeon with low volume procedures. The availability of pre-surgical localization renders the surgeon more confident and reduces procedure’s length and costs.

Availability of rapid PTH assay

Rapid PTH measurement has developed in the last decades as a valuable tool in the surgical management of patients undergoing neck exploration for PHPT (24,25).
Numerous studies have shown that the intra-operative evaluation of serum PTH (ioPTH) has high accuracy in predicting surgical cure and can function as a guide for surgeon’s judgment (25). The short half-life of the hormone in patients with normal renal function enables the use of serum PTH drop after parathyroid resection as an appropriate index of surgical cure (3,26). The absence of serum PTH reduction after surgical removal of the parathyroid gland conversely represents an indication for surgeons to perform additional neck exploration (3). Several cutoff criteria and mathematical model have developed over time to predict the percent change of surgical cure showing positive results, particularly in multiple gland disease (25,27). Intra-operative PTH measurement is therefore considered essential, in association with pre-operative imaging studies, for the adoption of minimally invasive techniques (3). Hence, the availability of rapid PTH assay is a key point in any surgery center aimed to perform minimally invasive parathyroidectomy. In this context, it must be recognized that the use of rapid PTH assays assumes additional costs, related to the need for trained staff, instrumentation and collaboration with local laboratory (25). This point arises some considerations about the need of including experienced laboratories in specialized parathyroid centers performing minimally invasive procedures. As a fact, rapid PTH assay is not available to many surgery centers around the world (3). Statistical data from 2002 have reported that the majority of rapid PTH tests were performed by central laboratories, 23% by on-site laboratories (i.e. located in the operating room) and 6% by satellite laboratories (28). The 2014 guidelines for surgical management of PHPT recommended the use of focused procedures in centers able to perform rapid intra-operative PTH measurement as part of the operative protocol (3).

This point again emphasizes that in the real world not all surgical theaters are able to provide “on site” measurement of ioPTH; being this a pre-requisite for focused surgery, most surgeons are forced to open cervical explorations. Once more, previous considerations of usefulness of pre-operative imaging for surgeons are therefore valid.

Localization is an obligate choice in patients with persistent or recurrent primary hyperparathyroidism.
The goal of localization through imaging techniques in patients with persistent or recurrent PHPT after unsuccessful operation, is to obtain an adequate road map to guide the surgeon, thus achieving a definitive cure and reducing complications. Indeed, reoperation is associated with a potential three-fold increase in morbidity and a risk of low curative rate; this is mainly due to distortion and scarring of surgical planes caused by the initial surgery (29).

However at the present time, the routine use of well-established preoperative localization techniques in high-volume centers, resulted in cure rates of a second parathyroidectomy that are almost the same as those reported in primary operations for PHPT (30). Among the conventional non-invasive techniques usually employed to identify parathyroids glands, those performed after a previous neck surgery have different sensitivity compared with the same techniques performed before surgery; more than a single technique is usually performed in the same patient (11). The preferred sequence of imaging continues to evolve and significant institutional variation exists.

As initially described, the first imaging study is usually US, together with nuclear medicine imaging. However, in patients with persistent PHPT, the 99mTc-MIBI sensitivity has been shown to decline from 80%, before initial surgery, to 50% (12,31). If localization is not obtained with US and 99mTc-MIBI scan, additional imaging studies should be performed. For example, a recent study has shown that sestamibi-negative patients who had undergone 4D-CT had also a high rate of surgical concordance with imaging results (p<0.0001)(32). 4D-CT has also the advantage of better identifying ectopic parathyroid glands that are commonly found in conditions of recurrent or persistent PHPT disease. Magnetic resonance has been reported to have a sensitivity of 67% in patients re-operated (33). If mediastinal parathyroid adenoma is suspected, at least one of these two last imaging techniques is mandatory to assist in the transthoracic operative approach (i.e. median sternotomy or thoracoscopic).

When non-invasive investigations are negative or equivocal, invasive studies such selective venous sampling and parathyroid arteriography are warranted. In addition, selective venous sampling significantly improves 4D-CT localization of parathyroid
adenomas in those patients with negative 99mTc-MIBI and US, increasing the sensitivity from 50% to 95% (p = 0.004) (34).

Therefore, judicious use of localization studies in patients unsuccessfully operated for primary hyperparathyroidism, allows the same success rate of initial operations, with a minimized risk of recurrent laryngeal nerve palsy and with a decreased prevalence of permanent hypoparathyroidism. Moreover, other complications such as wound infection, postoperative bleeding, and pneumonia were shown to be significantly lower in a group that underwent repeated PTx between 1998-2008 when more sophisticated diagnostic tools were available compared to a group that underwent re-operation between 1987-1997 (p<0.001) (30).

These data strongly indicate that, localization studies in PHPT patients with persistent or recurrent disease are an obligate choice before performing a second operation.

Costs

Another important point to favor the utilization of imaging studies, before surgical procedures for primary hyperparathyroidism, is the potential to save money. There are few detailed data on this topic. However, an exhaustive study carried out by Pata and co-workers showed, for example, that the utilization of SPECT/CT ensures better focus for the surgical exploration, shortens surgical times and eventually cut costs when used for localization of parathyroid surgery (35).

Conclusions

We believe that in 2015, the majority of surgeons prefer to have a localization study before operation and are not satisfied by having been referred a patients with just a biochemical diagnosis of PHPT. This might also have some legal implications in case of surgery failure. The crucial point is that imaging studies must by no means utilized to make the diagnosis of primary hyperparathyroidism; they should be obtained to both assist in determining disease etiology and to direct operative procedures. As such they
should be ordered and discussed in conjunction with the nuclear medicine doctor and most importantly with the surgeon. Finally, more complex cases, that is, patients with multiple gland disease, negative preoperative imaging studies, persistent and recurrent disease should be managed in experienced tertiary centers with a volume of at least 50 parathyroidectomy a year. (22).

The time has come for optimally combining the best that technology has to offer in this scenario with the best surgical expertise, for best benefit to the patients. We therefore propose the algorithm illustrated in Figure 1, as a wise approach balancing the needs and expectations of surgeons and taking into account a pragmatic real world situation.
Section 2: Discussion opposing

The argument against routine parathyroid localisation for primary hyperparathyroidism.

David SCOTT-COOMBES

The traditional approach for parathyroidectomy in patients with primary hyperparathyroidism is a bilateral neck exploration and the desired outcomes are:

1. to achieve lasting normocalcaemia
2. with minimum morbidity
3. a short length of stay
4. and with minimal pain and minimal scarring

BNE had a 95% normocalcaemia rate in the best units (36) but undoubtedly there is a publication bias. BNE can be undertaken with minimum morbidity, minimal discomfort and an excellent cosmetic outcome in a 23h:59m admission. The commonest reasons why surgeons fail (i.e. less than 100% normocalcaemia rate) are ectopia (53%) and MGD (37%) (37). However most ‘ectopic’ glands were in well-recognised locations including the paraoesophageal space and thymus. In a recent series of remedial parathyroid surgery for first-time failures, 38% of glands were ectopic, of which most (68%) were in ‘typical’ locations (38). These outcomes highlight the importance of surgeon experience. There is strong evidence that better outcomes are achieved in Units who undertake more than fifty cases per year (22).

Minimal invasive parathyroidectomy (MIP) has replaced BNE as the procedure of choice when a solitary adenoma can be localised pre-operatively (19). The benefits of MIP include shorter operating time, less pain, less scarring, shorter length-of-stay and less cost. MIP is successful in expert centres. When failures occur, MGD accounts for the majority because ectopia would be predicted by pre-operative localisation. For example in a series
of 1000 MIPs in Sydney, failures (1.7%) were due to missed double adenoma (59%) and missed 4-gland hyperplasia (18%) (39).

But MIP is only feasible when localisation is successful. So how successful is localisation? The sensitivity for ultrasound ranges between 60-75% (40,41) and is very operator dependant. The sensitivity is higher for MIBI scintigraphy. A wide variety of sensitivities are reported (54-96%) (4), with an overall sensitivity around 85% (41). Sensitivity can be ameliorated by the use of dual tracer subtraction method (12). 4D-CT technique has reports of a sensitivity around 90% (42).

What is clear is that no localisation technique is 100% reliable. This unreliability deserves further consideration. Localisation fails for two important reasons.

Localisation is unreliable in patients with multiple gland disease.

Whilst a meta-analysis of over 20 000 studies reports an overall sensitivity of 88% for detection of a single adenoma (43), this sensitivity collapses to 45% in patients with 4-gland hyperplasia and 30% for double adenoma. Ultrasound fares even worse: 35% for 4-gland hyperplasia and a mere 16% for double adenoma.

Localisation is unreliable for small parathyroid tumours

Several papers have demonstrated that localisation is less successful for smaller tumours (9,44,45). Gland weight below 600mg is associated with false negative results (9,46).

Logically identification of a smaller adenoma is going to be more difficult for the surgeon compared with finding a larger gland (eutopic or ectopic). Remembering that the commonest reasons to fail are failure to identify a tumour and failure to recognise MGD, it is disconcerting that the reliability of pre-operative localisation falls away when tumours are smaller and multiple. In other words, when localisation is most needed, it is least reliable!

A consequence of pre-operative localisation is the emergence of the image-negative patient. This is reported to occur in 12-18% of cases (47,48) and is a portent of both smaller tumours (49) and MGD; which accounts for one-third of cases (47,48). The Scandinavian
Quality Register for Thyroid and Parathyroid Surgery (27 departments and 3,158 patients) reported image-negative patients to occur 17% of the time (50). In this series, MGD accounted for 22% of cases and the median weight of excised tissue was only 350 mg. Of concern, the rate of negative explorations in this group was 13% and the rate of persistent hyperparathyroidism was a worrisomely high 18%. This study highlights the increased complexity of the negative-image group and also raises questions about the role of centralisation to high volume centres for this group of patients.

Cost

Financial

In a European randomised trial comparing unilateral neck exploration (UNE) with BNE, there was no difference in cost (51). However most studies comparing the cost benefit between BNE and MIP largely support the value of MIP (52,53). Duration of time in theatre (at 15 min intervals) has a significant influence on the costs in USA (54). There is also an assumption that all patients undergoing MIP are not admitted, which is not always the case in UK practice (depending upon the time of day that surgery occurs).

Radiation exposure

The average annual UK dose of natural background radiation is 2.2 mSv. A chest X-ray has a typical dose of 0.02 mSv. The average radiation doses in parathyroid imaging are as follows: MIBI (3.33 mSv); dynamic CT (5.56 mSv), SPECT-MIBI (7.8 mSv) (55). However, the greatest radiation dose is 4D-CT (10.4 mSv), which is the equivalent of 520 chest-X-rays (56). Such a huge exposure of radiation to the thyroid has led to recommendations that 4D-CT should be used judiciously in young patients.

Whilst MIP is faster than BNE, the benefit is measured in minutes. Day case (outpatient) surgery is not only determined by the surgical approach but influenced by the culture of national health services and the geography of the referral base. Whilst there is an increased risk of recurrent laryngeal nerve injury in BNE, this risk is theoretical and should be close to zero when undertaken by an experienced surgeon. Whilst much is made
of the cosmetic benefit of MIP, BNE is undertaken with a 4-5cm collar incision with excellent outcomes. In other words, the benefits of MIP over BNE are marginal. But the practice of localisation has unwelcome consequences.

Localisation is most successful for larger solitary adenomas, which would rarely be a challenge to an experienced surgeon without localisation. Therefore localisation leads to ‘cherry picking’ of the easiest cases. As a consequence, BNE is less frequently undertaken and risks deskilling surgeons-in-training.

Another consequence of localisation is the emergence of the image-negative patient. MGD and smaller glands are inevitable in this group and there is already evidence that this leads to poorer surgical outcomes outside high volume centres. As PHPT is diagnosed earlier the proportion of image-negative patients is set to rise (57).

First-time parathyroidectomy for PHPT is an operation that has evolved from one that required no imaging to one that is now dependent on imaging. In 1986 the interventional radiologist John Doppman said ‘in my opinion the only localising study indicated in a patient with untreated PHPT is to localise an experienced surgeon’ (58) as a reflection of the [in]accuracy of localisation studies and the initial attitudes towards them at that time. Any review of the literature on parathyroidectomy over the past two decades reveals a bias towards localisation. The time has come for the focus to shift away from technology and back towards surgical expertise.
Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Figure 1: Initial diagnostic imaging approach in patients with primary hyperparathyroidism, without previous parathyroid surgery.
Figure 1: Initial diagnostic imaging approach in patients with primary hyperparathyroidism, without previous parathyroid surgery

↑ albumin-corrected serum calcium (or increased serum Ca++) and elevated or non-suppressed serum PTH

First line diagnostic imaging:
   a) Dual-phase scintigraphy or
   b) Dual-tracer scintigraphy or
   c) Ultrasound

Unequivocal result or side concordance
- Focused exploration

Equivocal result or side discordance
- Second line diagnostic imaging:
   a) Contrast-CT
   b) 4D-CT
   c) MRI

   Side definition
   - Focused exploration

   No conclusive results
   - Bilateral cervical exploration

*Exclude Familial Hypocaciuric Hypercalcemia