The impact of surgeon-based ultrasonography for parathyroid disease on a British endocrine surgical practice

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ABSTRACT

INTRODUCTION Surgeon-based ultrasonography (SUS) for parathyroid disease has not been widely adopted by British endocrine surgeons despite reports worldwide of accuracy in parathyroid localisation equivalent or superior to radiology-based ultrasonography (RUS). The aim of this study was to determine whether SUS might benefit parathyroid surgical practice in a British endocrine unit.

METHODS Following an audit to establish the accuracy of RUS and technetium sestamibi (MIBI) in 54 patients, the accuracy of parathyroid localisation by SUS and RUS was compared prospectively with operative findings in 65 patients undergoing surgery for primary hyperparathyroidism (pHPT).

RESULTS The sensitivity of RUS (40%) was below and MIBI (57%) was within the range of published results in the audit phase. The sensitivity (64%), negative predictive value (86%) and accuracy (86%) of SUS were significantly greater than RUS (37%, 77% and 78% respectively). SUS significantly increased the concordance of parathyroid localisation with MIBI (58% versus 32% with RUS).

CONCLUSIONS SUS improves parathyroid localisation in a British endocrine surgical practice. It is a useful adjunct to parathyroid practice, particularly in centres without a dedicated parathyroid radiologist, and enables more patients with pHPT to benefit from minimally invasive surgery.

KEYWORDS

Parathyroidectomy – Ultrasonography – Parathyroid glands – Surgical procedures, minimally invasive – Technetium Tc 99m Sestamibi

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Minimally invasive parathyroidectomy (MIP) for primary hyperparathyroidism (pHPT) has several advantages over bilateral neck exploration (BNE) including fewer postoperative complications, shorter hospital stay and cheaper cost without compromising biochemical cure.¹ Consequently, MIP has now been widely adopted when preoperative localisation studies have confirmed single-gland disease (SGD).² However, the success of MIP is highly dependent on preoperative localisation of parathyroid disease, the accuracy of which has therefore come under scrutiny.

The preoperative localisation studies recommended in patients with pHPT are technetium sestamibi (MIBI) and neck ultrasonography.³ Neck ultrasonography is traditionally performed in radiology departments where the outcome has been shown to be dependent on the skill and experience of the operator.^{4,5} The outcomes of surgeon-based ultrasonography (SUS) in parathyroid disease have been reported from North America and Australasia though not

from the UK.^{6–15} The sensitivity of SUS of 60–89% reported in these studies is equivalent or superior to radiology-based ultrasonography (RUS) and SUS has now become a useful adjunct to parathyroid surgery in these countries.

In comparison, SUS has not been widely adopted by endocrine surgeons in the UK and the benefit of SUS to British endocrine surgical practice has not been established. The aim of this study was therefore to examine the impact of SUS on parathyroid surgical practice in a British endocrine unit and discuss its potential applications.

Methods

The study comprised two parts. An audit was undertaken to establish the accuracy of RUS in patients referred for parathyroid surgery. Case notes of all patients referred to one of three endocrine surgeons (TWJL, RB and SRA) over a twelve-month period from January 2009 from seven nearby

Table 1 Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of radiology-based ultrasonography (RUS) in the audit study

	RUS	Literature ^{4,10,15–21}
Sensitivity	40%	42–96%
Specificity	89%	63–98%
Positive predictive value	62%	90–98%
Negative predictive value	78%	
Accuracy	75%	71–90%

Table 2 Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of technetium-labelled sestamibi (MIBI) in the audit study

	MIBI	Literature ^{3,7,11–13,15,17,21,22}
Sensitivity	57%	44–98%
Specificity	88%	80–99%
Positive predictive value	65%	78–99%
Negative predictive value	83%	87–92%
Accuracy	79%	92%

Table 3 Sensitivity, specificity, positive predictive value, negative predictive value, accuracy and concordance of surgeon-based ultrasonography (SUS) and radiology-based ultrasonography (RUS) with technetium-labelled sestamibi (MIBI)

	SUS	RUS	p-value (Fisher's exact test)
Sensitivity	64%	37%	0.0009
Specificity	96%	97%	>0.05
Positive predictive value	88%	85%	>0.05
Negative predictive value	86%	77%	0.03
Accuracy	86%	78%	0.03
Concordance with MIBI	58%	32%	0.005

NHS trusts were reviewed. This reflected the ‘real world’ variation in ultrasonography practice around the region with some experienced and less experienced scanners of varying skill baselines. Those included were patients undergoing MIP, unilateral neck exploration or BNE for pHPT in whom all details of preoperative ultrasonography, MIBI and operative findings were available. Exclusion criteria included secondary or tertiary hyperparathyroidism, re-do surgery or when details of localisation or operative findings were incomplete.

A prospective study was then carried out to compare the accuracy of SUS with RUS and examine the impact of SUS performed by a single committed surgeon (SRA) on the rate of minimally invasive surgery. SUS was performed on patients with pHPT in the operating theatre (not in the out-patients department) using an S-Nerve™ ultrasound system (SonoSite Inc, Bothell, WA, US) and a 6–13 MHz probe in an anaesthetised patient positioned with neck extended immediately prior to surgery. The results of preoperative RUS and MIBI were available and had been reviewed by the surgeon prior to performing SUS. The surgeon was therefore not blinded to the outcome of previous studies. The presence and site (right upper, right lower, left upper, left lower quadrant) of an enlarged parathyroid were recorded prior to surgery. Parathyroidectomy was performed under general anaesthesia. The operative strategy was to excise pathologically enlarged parathyroid glands and leave normal glands in situ. Following surgery, operative findings were recorded and compared with SUS findings.

Results

In the audit phase of the study (January to December 2009), 78 parathyroidectomies were performed. Of these cases, 24 were excluded: 2 had re-do procedures, 4 had secondary hyperparathyroidism and in 18 patients details of localisation and operative findings were incomplete. Fifty-nine pathological glands were excised from the remaining fifty-four patients.

RUS identified 26 enlarged glands correctly but failed to identify 33 (false negative). Twelve parathyroid glands were thought incorrectly to be enlarged on RUS (false positive). MIBI localised 35 parathyroid glands correctly but failed to identify 24 (false negative) and reported eighteen hyperfunctioning glands incorrectly (false positive).

Forty-seven patients (87%) were found to have SGD at operation whereas only nineteen (35%) had concordant localisation and so were suitable for MIP. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of RUS and MIBI are shown in Tables 1 and 2. As BNE was not undertaken in every patient, two assumptions were made in the audit and prospective parts of the study in order to calculate the specificity. These were that four parathyroid glands were present in each patient and that the parathyroid glands that were left in situ were not pathologically enlarged or hyperfunctioning.

In the prospective study, 65 consecutive patients undergoing surgery for pHPT were included, from which 81 parathyroid glands were excised. Fifty patients (77%) had SGD and fifteen (23%) had multi-gland disease (MGD). Forty

Figure 1 Weight of pathological parathyroid glands identified correctly and incorrectly by surgeon-based ultrasonography

Figure 2 Volume of pathological parathyroid glands correctly and incorrectly identified by SUS

patients underwent BNE and twenty-five had a focused approach, ie either MIP or unilateral neck exploration. SUS correctly identified 52 of the 81 pathological parathyroid glands that were excised at operation. Seven parathyroid glands were incorrectly thought to be enlarged on SUS (false positive). Twenty-nine enlarged parathyroid glands were not identified by SUS (false negative).

The weight of the pathological parathyroid glands identified correctly and incorrectly by SUS are shown in Figure 1. The weight of pathological glands identified correctly had a range of 90–6,940mg (median: 600mg, interquartile range [IQR]: 290–1,400mg) whereas the weight of the pathological glands that were missed had a range of 100–900mg (median: 200mg, IQR: 100–560mg). The difference in weight between the pathological glands identified correctly by SUS and those that were not was statistically significant (Mann–Whitney U test, $p<0.0001$).

Figure 3 Influence of multi-gland disease on the accuracy of SUS

Figure 2 shows the volume of the pathological parathyroid glands identified correctly and incorrectly by SUS. The volume of the glands identified correctly had a range of 0.1–16cm³ (median: 1.05cm³, IQR: 0.48–2.25cm³) whereas the volume of the glands that were missed had a range of 0.02–2.1cm³ (median: 0.25cm³, IQR: 0.12–0.75cm³). The difference in volume between the pathological glands identified correctly by SUS and those that were not was also statistically significant (Mann–Whitney U test, $p<0.0001$).

The influence of MGD on the accuracy of SUS is shown in Figure 3. SUS was significantly better at identifying enlarged parathyroid glands in patients with SGD than in those with MGD (Fisher’s exact test, $p<0.0001$). SUS identified 42 enlarged parathyroid glands correctly in patients with SGD and 10 in patients with MGD. Nineteen enlarged parathyroid glands in patients with MGD and ten in patients with SGD were not identified by SUS.

Parathyroid gland position also affected the accuracy of SUS though not significantly (Fisher’s exact test, $p=0.08$). There was a trend towards inferiorly placed glands being easier to identify. SUS identified 39 enlarged inferior parathyroid glands correctly and missed 16 (Fig 4). In comparison, SUS found 15 enlarged superior parathyroid glands but also missed 13.

In the presence of thyroid pathology (solitary nodule or multi-nodular goitre), 32 enlarged parathyroid glands were identified by SUS and 22 were missed whereas 20 enlarged parathyroid glands were found and 7 were missed in patients with no thyroid pathology (Fig 5). There was a trend towards less accurate parathyroid localisation in the presence of thyroid pathology although this failed to reach statistical significance in this study (Fisher’s exact test, $p=0.22$).

The negative predictive value, sensitivity and accuracy of SUS were significantly greater than for RUS (Table 3). In addition, SUS significantly increased the rate of concord-

ance with technetium-labelled sestamibi from 32% with RUS to 58% (Fisher's exact test, $p=0.005$), thereby increasing the number of patients suitable for minimally invasive surgery.

Discussion

The reliance of MIP on preoperative localisation has focused attention on the accuracy of these investigations. Ultrasonography is an inexpensive, non-invasive imaging modality that does not expose the patient to ionising radiation. It is effective in identifying parathyroid disease although its reported sensitivity varies widely from 42% to 96%.^{4,10,15-21} Ultrasonography is well recognised as being 'operator dependent' and the accuracy of parathyroid ultrasonography has been shown to be affected by operator experience.^{4,5,17} A dedicated, experienced parathyroid ultrasonographer optimises preoperative parathyroid localisation whereas multiple ultrasonographers of varying experience performing less parathyroid ultrasonography may compromise parathyroid localisation.

The sensitivities of RUS in both parts of this study of 40% and 44% are similar to those reported by Van Husen and Kim from Arkansas, US.¹⁵ Their study is similar to ours in that it was not possible to enable all parathyroid scans to be performed by a single dedicated radiologist within the radiology department. Putting ultrasonography in the hands of the surgeon may circumvent this problem.

Although the surgeon's experience with ultrasonography is limited, there are benefits of SUS in managing parathyroid disease. The surgeon has a detailed knowledge of cervical anatomy as well as parathyroid embryology. Perioperative ultrasonography enables the surgeon to immediately correlate the ultrasonography findings with operative

findings and so the surgeon ultrasonographer has a steep learning curve.²⁵ The volume of parathyroid operations performed by the surgeon enables experience to be accumulated quickly, particularly in high volume endocrine surgical units. Ultrasonography findings define the parathyroid in relation to the thyroid and vascular structures, facilitating incision placement and anatomical dissection as well as reducing operating time.^{8,10} The availability of portable ultrasonography equipment also allows the surgeon to perform ultrasonography in the outpatient department, thereby potentially avoiding multiple hospital visits for the patient with consequent cost savings.²⁵

Several studies from the US and Australia have demonstrated that SUS is an effective tool in parathyroid disease. The reported sensitivities of SUS in these studies of 60–89%^{7,9-15,15} are equivalent or superior to that of RUS. The sensitivity of SUS reported in our study (63%) was significantly greater than that achieved by RUS (34%; $p=0.0002$) and is comparable to the above studies. In turn, this significantly increased the concordance of ultrasonography with MIBI from 32% to 58% ($p=0.005$), suggesting that SUS is a useful adjunct to endocrine surgical practice in the UK in centres without a dedicated parathyroid ultrasonographer.

The use of ultrasonography by clinicians is established in other hospital specialties and is being used increasingly in other general surgical subspecialties. It has been referred to as 'an extension of the fingers in examination'²⁴ and is commonly used by endocrine surgeons and endocrinologists in North America and Australia. In comparison, it has not been widely adopted by British endocrine surgeons.

This study is the first to examine the impact of SUS on British endocrine surgical practice. The impetus for this study was the realisation that preoperative localisation was suboptimal, which denied some patients the benefits of MIP.

The audit part of the study identified that suboptimal ultrasound localisation of parathyroid adenomas was largely responsible for low preoperative localisation. The impact of SUS on parathyroid localisation was examined prospectively and the findings demonstrated that the use of SUS improves both preoperative localisation of parathyroid disease and concordance with MIBI, potentially enabling more patients with SGD to benefit from MIP.

Several factors may have influenced the outcome of this study and are worth consideration. The surgeon had a considerable advantage over the radiology ultrasonographer when performing ultrasonography for two reasons. Firstly, SUS was performed under general anaesthesia with the neck extended in the optimum position for scanning rather than on an awake patient in the outpatients or radiology department. Secondly, the surgeon reviewed the results of RUS and MIBI immediately prior to performing SUS and so was not blinded, resulting in an inherent bias in the design of this study in favour of SUS. This point needs stressing when interpreting the results. However, the study does reflect clinical practice as SUS, RUS and MIBI are all likely to be performed. These results also reflect a high volume multi-surgeon practice, enabling rapid acquirement of expertise, which may not necessarily be translated to all surgeons.

The influence of gland weight, volume and co-existing thyroid pathology on the accuracy of SUS was examined in this study. Our findings concur with previous reports in that the mean size/weight of the parathyroid glands identified correctly by SUS was significantly greater than of those missed;¹⁰ SUS was significantly better at identifying SGD than MGD;⁴ and there was a trend towards less accurate parathyroid localisation in the presence of multi-nodular goitre.²¹ One unexpected finding was a trend towards inferior parathyroid glands being easier to identify than superior glands, perhaps due to their more superficial location in the neck and the optimisation of neck extension under anaesthesia.

Two patients developed persistent disease in the prospective part of this study; the rate of persistent pHPT was therefore 3% (2/65). In the first of these two patients, RUS and SUS were negative. MIBI showed an area of increased activity below the thyroid. At the first operation a 225mg left superior parathyroid gland was removed that had prolapsed posteriorly to occupy an inferior position in the neck. Re-imaging following confirmation of persistent pHPT showed a left inferior adenoma in the upper mediastinum that was successfully removed at a second operation via a neck incision.

The second patient with persistent pHPT presented initially with severe hypercalcaemia requiring admission to the intensive care unit. MIBI showed an increased area of activity in the right and left lower positions relative to the thyroid. RUS identified an enlarged left lower parathyroid gland that was also seen by SUS, which also identified an enlarged right upper parathyroid gland. At the first operation, a 6.9g left lower parathyroid and 2.3g right upper parathyroid gland were identified. Subsequent re-imaging for persistent disease identified a 6.9g right lower parathyroid gland that was situated in a paraoesophageal position at the

thoracic inlet. This was successfully removed at a second operation with resolution of the pHPT. Our unit does not use intraoperative parathyroid hormone assays routinely.

The rate of MGD (15/65, 23%) apparent at operation was high. Serum vitamin D levels were not investigated. Given the limitations of parathyroid ultrasonography in MGD, it is likely that this may have contributed to the low the rate of preoperative parathyroid localisation observed in this study.

Conclusions

The advantages of MIP have been established. Our attention should now focus on ensuring that accurate preoperative localisation of parathyroid disease occurs so that more patients with pHPT due to SGD may benefit from MIP. This study raises important questions about who should be performing parathyroid ultrasonography. The results demonstrate that the experienced surgeon-ultrasonographer rapidly develops the skills to localise parathyroid disease and, although there was an inherent bias, the results of SUS were superior to RUS. The introduction of SUS in North America has been more market driven than scientific but this study suggests that SUS is a useful tool that can improve parathyroid localisation in a British endocrine practice and enables more patients to benefit from MIP. Endocrine surgeons in the UK should be encouraged to adopt this technique.

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