ORIGINAL

The role of colour Doppler ultrasonography in the preoperative localization of parathyroid adenomas

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Abstract. The aim of the present study was to evaluate the diagnostic accuracy and imaging patterns of colour Doppler ultrasonography (US) and compare it with grayscale US, 99m-Tc methoxyisobutylisonitrile (MIBI) scans, and combined US and MIBI scans in the preoperative diagnosis of parathyroid adenomas in patients with primary hyperparathyroidism (pHPT). From June 2007 to June 2011, 36 consecutive patients (seven men and 29 women) with pHPT underwent grayscale US, colour Doppler ultrasonography (CDUS), and 99m-Tc MIBI scans prior to parathyroidectomy with traditional unilateral neck dissection. All 36 patients with pHPT underwent parathyroidectomy at our university hospital. According to histopathology results, the sensitivity, specificity, and accuracy of MIBI and US scan were 88%, 94%, and 91%, and 70%, 100%, and 85%, respectively. The overall sensitivity and specificity of combined US and MIBI was 97% and 100% respectively. The overall sensitivity, specificity, and accuracy of CDUS in the correct diagnosis of parathyroid adenoma were 97%, 100%, and 98.6%, respectively. The sensitivity and specificity of US in the detection of parathyroid adenoma and differentiating it from other cervical masses reached up to 97% and 100%, respectively, by combining CDUS with grayscale evaluations of parathyroid adenoma.

Key words: Ultrasonography, Parathyroid, Adenoma

HYPERPARATHYROIDISM is the leading cause of hypercalcemic states and is due to overproduction of the parathyroid hormone by the parathyroid glands (PTGs) [1]. Primary hyperparathyroidism (pHPT) is the third most common endocrine disease after diabetes mellitus and thyroid disease [1, 2]. pHPT is more common in postmenopausal women when compared to the general population (0.3% in the general population and 1%-3% in postmenopausal women) [2, 3]. Over 80% of patients with pHPT have a single parathyroid adenoma, and the remaining 10-20% have multiple adenomas, parathyroid hyperplasia, and, rarely, parathyroid carcinoma [1]. Surgical resection of parathyroid adenoma is the only standard treatment for patients with pHPT [3]. Focused unilateral neck exploration- i.e., minimally invasive parathyroidectomy (MIP)- and other minimally invasive approaches, including video-assisted parathyroidectomy and endoscopic parathyroidectomy, are attractive alternatives to total parathyroidectomy [4, 5]. In all of these focused approaches, the accurate preoperative localization of a parathyroid adenoma is critical prior to performing a surgical resection.

Ultrasonography (US) and 99m-Tc methoxyisobutylisonitrile (MIBI) scans are the routine, standard imaging modalities in the preoperative evaluation of PTG pathology, but both techniques have low specificity in the diagnosis of parathyroid adenomas [6]. The aim of the present study was to evaluate the diagnostic accuracy and imaging patterns of colour Doppler ultrasonography (CDUS) in comparison to grayscale US, MIBI scans, and combined US and MIBI scans in the preoperative diagnosis of parathyroid adenomas in patients with pHPT. The novelty of the present study is that it discusses the new Doppler appearance of parathyroid adenomas rather than just explaining the feeding artery. We also believe that we can help surgeons to more specifically diagnosis parathyroid adenomas when compared to using grayscale US alone.

Material and Methods

From June 2007 to June 2011, 36 consecutive patients (seven men and 29 women) with pHPT underwent grayscale US, CDUS, and 99m-Tc MIBI scans prior to parathyroidectomy with traditional unilateral neck dissection.

We prospectively evaluated the imaging data of these patients and compared them to postoperative histopathology results and at least a 50% reduction in intraoperative parathyroid hormone (PTH) as the gold-standard method for determining the diagnostic accuracy of these imaging modalities in the diagnosis of parathyroid adenoma. The patients' sex, age, and serum intact parathyroid hormone (iPTH) were collected from their records. The university review board approved the study.

We routinely perform CDUS in evaluation of all cervical masses in our department for the determination of the vascularity of cervical masses and their relation to major cervical vessels. We described the vascularity of cervical lesions as having either central, peripheral, combined, uniform, or no vascularity.

A single radiologist with six years' experience performed all of the US examinations with an ultrasound device (Toshiba Nemio 30; Toshiba CO. Ltd, Tokyo, Japan), using a high-frequency (11 MHz) linear array transducer. The patients' hyperextended necks were examined in a supine position from the level of the mandibular angle to the sternal notch. All of the US examinations were performed before the results of the 99m-Tc MIBI scan.

In grayscale sonography, enlarged parathyroid glands appear as round or oval-shaped homogenous hypo-echoic nodules in the posterior part of the thyroid lobes, and are clearly separated from the thyroid lobes by an echogenic ring composed of capsules of adenoma and surrounding fatty tissue (Fig. 1). The nodules with this sonographic appearance were considered to be parathyroid adenomas.

The parathyroid gland size and volume were measured and the location of parathyroid adenomas defined according to US findings. Images were obtained in both transverse and sagittal views. US results were defined as true or false positive and negative according to surgical pathology results. Postoperative histopathology was considered the gold standard for the study.

CDUS and power Doppler ultrasonography (PDUS) were performed by setting the Doppler parameter

to detect the vascularity of parathyroid adenoma. In CDUS and PDUS, we evaluate the vascularity of parathyroid gland lesions using the knowledge of an adenoma's blood supply from a separate branch of the inferior thyroid artery.

Colour Doppler findings of each parathyroid lesion were defined as positive or negative on the basis of detection of hypervascularity in the parathyroid gland lesion, subjectively. We classified the lesions at the sites of PTGs according to CDUS and PDUS findings as having no detectable flow (Fig. 2), central hypervascularity (Fig. 3), peripheral hypervascularity (or a ring) (Fig. 4), uniform hypervascularity (what we called a "spot of fire") (Fig. 5), or combined central or peripheral hypervascularity (Fig. 6). The nodules in the parathyroid locations with all of these CDUS or PDUS appearances in the subjective evaluation of parathyroid lesions were considered to be true positive scans. For an objective evaluation we measured the Resistive index of the arterial supply to the adenoma by spectral Doppler sonography (Fig. 7)

In 99m-Tc MIBI scintigraphy, the thyroid images were acquired from an antero-posterior view of the neck and upper part of the thorax over five minutes, using a gamma camera 20 minutes after the intravenous administration of 99m-Tc pertechnetate (20mCi). The images were obtained with patients in a supine position.

The parathyroid scan was acquired 15 minutes (thyroid phase) and 120 minutes (parathyroid phase) after intravenous administration of 15-20 mCi of 99m-Tc
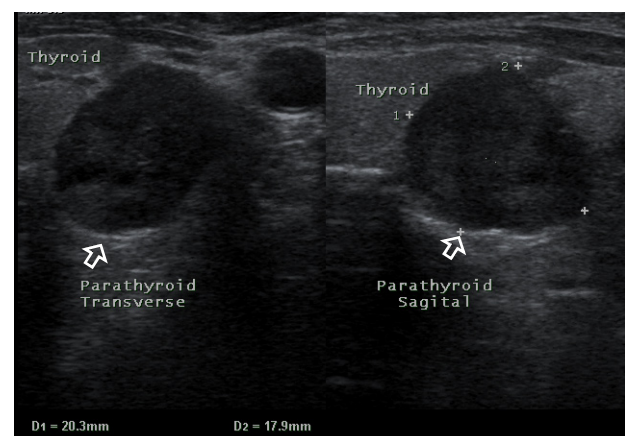

Fig. 1 Ultrasound image showing typical hypoechoic adenoma (arrows) deep in relation to the lower pole of the thyroid in transverse sonogram (A: sagittal and B: transverse views).
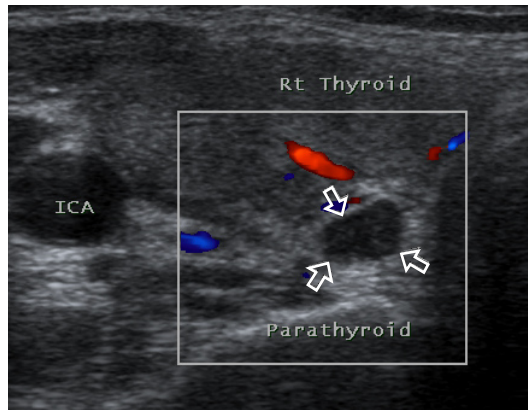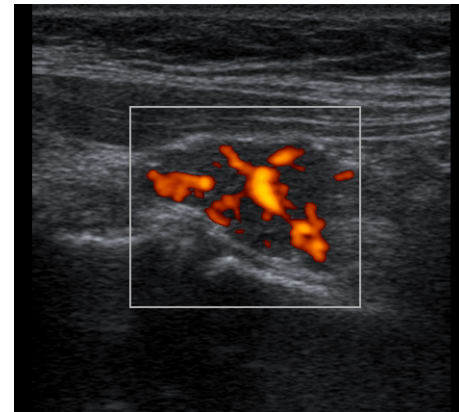
Fig. 2 Colour Doppler sonogram shows typical hypoechoic adenoma deep in relation to the lower pole of the thyroid without a detectable flow in a colour Doppler sonogram.
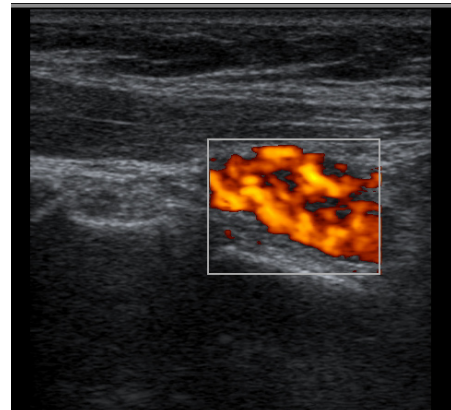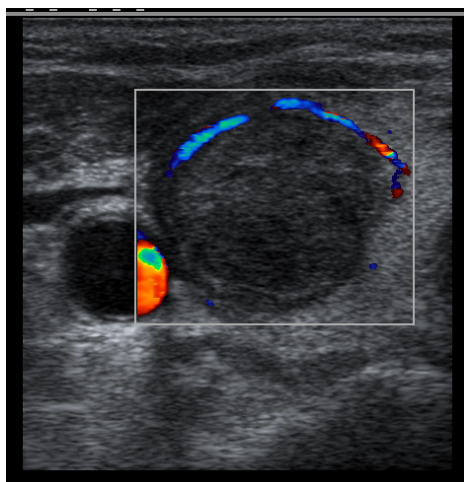

Fig. 5 Colour Doppler sonogram shows a typical spot of fire pattern vascularity in a power Doppler sonogram.
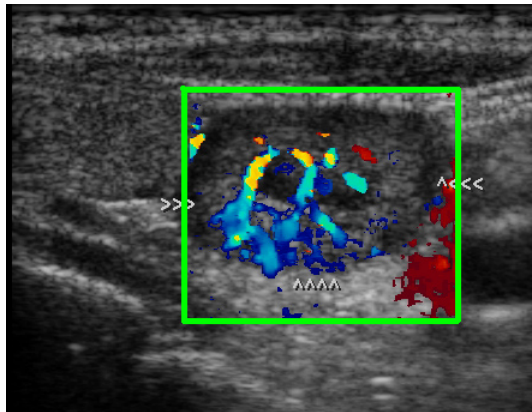
Fig. 3 Colour Doppler sonogram shows a typical hypoechoic adenoma deep in relation to the lower pole of the thyroid with central vascularity in a colour Doppler sonogram.

Fig. 6 Doppler sonogram shows a round hypoechoic intrathyroidal adenoma, deep with a combined central and peripheral vascularity in a colour Doppler sonogram.
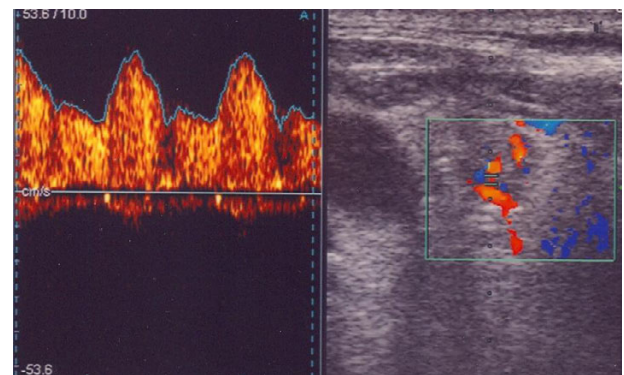

Fig. 4 Colour Doppler sonogram shows a typical hypoechoic adenoma deep in relation to the lower pole of the thyroid, with ring-pattern vascularity in a colour Doppler sonogram.

Fig. 7 Spectral Doppler sonogram revealed the low resistance blood flow to the parathyroid adenoma (RI=0.56)

MIBI. The images were obtained with a single-head gamma camera (ADAK, Epic, Netherlands) over 10 minutes, using a pinhole collimator. The MIBI scan was considered to be positive for parathyroid lesions when an increase in uptake was detected in the thyroid phase.

The 99m-Tc MIBI single-photon emission computed tomography (SPECT) was performed 20-30 minutes after IV injection, and reconstructed to produce three-dimensional projections. The SPECT was performed in a full anterior (180-degree) view as 32 frames, at 30 seconds per frame. Focal increased uptake in the parathyroid site was considered positive. Our nuclear physician specialist was blinded to the results of ultrasound examination.

Statistical analysis was performed using *SPSS* statistical analysis software (version 16, Chicago, IL, USA). Continuous variables were reported as means ± SD, and categorical variables as frequencies. Since the distribution of PTH and volume was not normal, a nonparametric spearman's test was used for analysis. One-way ANOVA, a chi-square test, and a multivariate linear model were used for the evaluation of variables.

Results

All 36 patients (female-to-male ratio of 4:1) with pHPT underwent parathyroidectomy at our university hospital. The mean age was 52.2±12.6 years.

Skeletal involvement, especially bone pain, was the most common presenting symptom of our patients (70%). The bone pain and limb claudication due to a giant brown tumour in the iliac wing were the first presenting symptoms in two patients. Renal calculi, including nephrocalcinosis, were present in (44%) patients. Proximal muscle weakness was seen in 48% of our patients. Parathyroid adenoma was palpable on careful examination in three patients. None of our patients had psychiatric symptoms or obvious neurological problems. Gastrointestinal symptoms such as nausea, vomiting, and constipation were seen in three patients, and intractable vomiting was the major presenting sign in one male patient.

The mean preoperative serum calcium was elevated (12.64±1.33 mg/dL, ranging from 10.7-17mg/dL), and the patients had low inorganic phosphorus levels (2.11±0.56 mg/dL). The mean postoperative serum calcium was 8.9±1.02 mg/dL. The mean preoperative serum iPTH level was 584±510 pg/mL
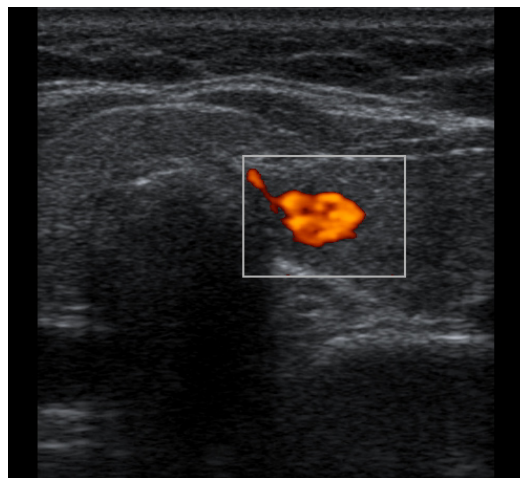
Fig. 8 Colour Doppler sonogram shows a hypervascular intrathyroidal adenoma with a spot-of-fire appearance.

(ranging from 80-2000 pg/mL), and the mean postoperative serum iPTH level was 52±5.3 pg/mL (ranging from 39-68 pg/mL). The mean intraoperative serum iPTH was129±61pg/mL that revealed 78% decrease in serum iPTH 20 minutes after adenoma excision. The mean volume of parathyroid adenomas was 2.18±2.03 cc (ranging from 0.2-7.5 cc).

Three patients with pHPT had intra-thyroidal parathyroid adenomas; all were identified *via* MIBI scans. US were negative in all three patients due concomitant multinodular goitres. All three intrathyroidal nodules had significant hypervascularity in CDUS (Fig. 8). Histopathology revealed that one US-confirmed parathyroid lesion was a lymph node that had not hypervascularity in CDUS, and one lesion was an exophytic thyroid nodule mimicking a parathyroid adenoma on grayscale sonography but it had hypervascularity in CDUS compatible with parathyroid adenoma.

According to CDUS and PDUS, 35 adenomas were detected correctly. Seventeen had ring vascularity with a mean volume of 2.12±1.88 cc, two had central vascularity with a mean volume of 2.2±1.83 cc, and nine had a combined pattern with a mean volume of 3.84±2.06 cc. The remaining adenomas (7 of 35) had uniform hypervascularity in CDUS and PDUS, what we called a "spot of fire," with a mean volume of 0.47±0.3 cc. Only one parathyroid adenoma, with a volume of 0.2 cc, had no flow on CDUS.

According to histopathology results, Table 1 summarizes the diagnostic usefulness of each modality in the diagnosis of parathyroid adenoma. Our study

Table 1

Modality	US	MIBI	Combined US/MIBI	CDUS
Sensitivity	88%	70%	97%	97%
Specificity	94%	100%	100%	100%
Accuracy	91%	85%	98.6%	98.6%

Table 2

Variable	MIBI Positive	MIBI Negative	P-value
iPTH (pg/mL)	666±554	222±146	P<0.025
Volume (cc)	2.42±2.09	1.6±1.94cc	P = 0.3

showed that there is a significant difference between serum iPTH levels and positive MIBI scans, but the mean volume of parathyroid lesions did not show significant differences between MIBI-positive and MIBI-negative patients. Table 2 summarizes the relationship between MIBI and parathyroid adenoma volumes and serum iPTH levels.

We found that there is a positive correlation between the volume of parathyroid adenomas and serum iPTH levels (r=0.35, *P*<0.035). The mean RI of parathyroid adenoma blood flows was 0.55±0.06, which revealed a low-resistance blood flow.

Discussion

Most of the healthy adult members of the population have four PTGs, less than 5% have fewer than four, and 3% have more than four [7, 8]. The average PTG dimension is $5 \times 3 \times 1$ mm, and the average weight is 30-40 mg [7, 8].

Recently, we encountered an increase in the prevalence of pHPT. The prevalence of pHPT reached 0.67% in 2006, compared to a previous report of 0.18% in 1997. It is more-frequently diagnosed in females than in males, the incidence increases with age, and mostly occurs between the ages of 40 and 60 [9, 10]. Yu *et al.* [11] showed that patients with pHPT have an increased risk of all-cause mortality and cardiovascular mortality even with mild untreated PHPT.

Currently, focused unilateral cervical parathyroidectomy and other MIPs, such as video-assisted parathyroidectomy and endoscopic parathyroidectomy, have made the accurate preoperative localization of parathyroid disease essential to a satisfactory surgical

outcome [4]. Today, US and 99mTc-sestamibi scintigraphy are the routine modalities for preoperative localization of parathyroid adenomas, especially when both techniques are used together preoperatively [12, 13]. However, in ectopic parathyroid adenomas in mediastinal locations, hybrid techniques like single-photon emission computed tomography/computed tomography are the most accurate approaches to use [14].

Hyperparathyroidism is commonly accompanied by thyroid disease, and reactive lymph nodes may be particularly prominent in these patients. Therefore, reactive lymph nodes can be mistaken for parathyroid adenomas or hyperplasia [8].

In our study, the prevalence of parathyroid adenomas was more frequent in females than in males. The mean age of our patients was 52.2±12.6 years, which agrees with previous data [16, 20].

According to our last search, the mean parathyroid adenoma gland size and serum iPTH level in pHPT cases in our study agreed with the study in Europe, the United States, Asia, and South America [19, 21-24]. Despite the mean gland size, there were eight parathyroid adenomas with a volume under 0.6 *cc* in our study that was still correctly diagnosed by colour Doppler sonography. Although our study is mainly subjective, it showed that parathyroid adenomas have a very low-resistance blood flow, which can be an objective confirming measurements in the diagnosis of parathyroid adenomas. In our study, the diagnostic accuracy of a combination of US and MIBI scans was higher than each alone, making our results in agreement with previous studies [25-27].

There was a significant difference in serum iPTH levels in patients with MIBI-positive results compared to the MIBI-negative group (*p*=0.039). Previous articles showed many controversies about the relationship between serum iPTH levels and MIBI scans. Some previous investigations have demonstrated a relationship between serum iPTH levels and MIBI results [28-30], while others have not shown such a correlation [31]. Sukan *et al.* [19] showed that there was a significant difference in intact PTH levels between MIBI-positive and -negative patients.

We found a correlation between serum iPTH levels and ultrasonographic estimations of parathyroid adenoma volumes. Our results contrast those of another study, which did not show a correlation between serum iPTH and the weight of the parathyroid glands [19, 20]; however, they are in agreement with another

study that did show a correlation between serum iPTH and the weight of parathyroid glands [28]. Kakuta *et al.* showed that the volume of PTGs given by US is a good indicator of their weight: larger PTGs secrete more whole iPTH per gland [28].

We did not find a relationship between ultrasonographic PTG volumes and MIBI results (*p*=0.3). This agrees with the findings of a study by Kasai *et al.*, which reported that a negative correlation between gland weight and MIBI uptake were not significant [29]. They reported that the overall sensitivity of MIBI and US scans was 84% and 72.5%, respectively [29].

A study by Kebapci *et al.* showed that, in patients without concomitant thyroid disease, US alone should be used as a first step for preoperative localization, and the combination of US and MIBI scintigraphy is a reliable localization technique in patients with concomitant thyroid disease [30]. Wolf *et al.* reported that 63% of parathyroid adenomas had a vascular arc in CDUS (90 to 270 degrees), and that the identification of a vascular arc improves the diagnostic specificity of parathyroid adenomas [31].

Rickes *et al.* [32] and Lane *et al.* [33] reported that the detection of feeding vessels by CDUS is an important indication of a parathyroid lesion, and that these vessels can serve as "road maps" to abnormal parathyroid glands. We found that, although in some cases feeding may not be detectable, there are some other patterns that could be helpful.

Kamaya *et al.* [34] found that an enlarged feeding artery and peripheral arc of vascularity seen on CDUS and PDUS are the typical imaging characteristics of parathyroid adenoma in sonographic evaluation. Reeder *et al.* [35] found that a combination of CDUS and PDUS with grayscale imaging was required for the sonographic localization and identification of small parathyroid adenomas.

If a parathyroid adenoma is not located in the upper or lower gland locations (ectopic), the correct preoperative localization of parathyroid adenomas with routine imaging modalities will be challenging. It was recently revealed that the single-photon emission computed tomography/computed tomography (SPECT/CT) fusion technique offers the advantage of combining function and anatomy for the exact localization of ectopic parathyroid adenomas. SPECT/CT permitted the highest reader confidence in the localization of the carotid sheath, anterior mediastinum, retropharynx, or intrathyroidal ectopic parathyroid adenomas [36].

Another diagnostic difficulty in the preoperative localization of parathyroid adenomas is concomitant thyroid nodules; a previous study [30] showed that, in patients without thyroid disease, the sensitivity of these techniques was 90% and 75%, respectively. In patients with thyroid disease, the sensitivity was 78% and 70%, respectively. Localization of typical blood supply patterns on colour Doppler imaging and the diagnosis of feeding arteries derived from the inferior thyroidal artery can be helpful in differentiating PTGs from thyroid nodules.

There is two major differential diagnosis for parathyroid adenoma that may be mistake in grayscale sonograghy, lymph node and thyroid nodule. Ying *et al.* showed that only high resistive central vascularity was found in cervical nodes that are more prominent in submental region [37]. Shimamoto *et al.* showed the perinodular flow in 10 patients from 13 patients [38]. According to our experience revealed that prominent hypervascularity in comparison with other cervical structure can aid in differentiation of parathyroid adenoma from lymph nodes and thyroid nodules.

Conclusion

Parathyroid adenomas demonstrate different imaging patterns in CDUS. These patterns include central, ring (most common), combined, and uniform (spots of fire) patterns; they are highly specific for parathyroid adenoma and can differentiate it from other cervical masses. Parathyroid adenoma is usually more vascular than other cervical soft tissue components.

Our study revealed that the sensitivity and specificity of US in the detection and differentiation of parathyroid adenoma from other cervical masses reaches up to 97% and 100% by combining CDUS with the grayscale sonographic evaluation of parathyroid adenoma. Since US is cheap, non-invasive, and easy to perform, we recommend using US as a first modality, and suggest that it should always be combined with CDUS to increase the diagnostic value; the use of US should be followed by a MIBI scan in case it is not diagnostic.

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