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INVITED REVIEW

Selective venous sampling for primary hyperparathyroidism: how to perform an examination and interpret the results with reference to thyroid vein anatomy

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Abstract Primary hyperparathyroidism (pHPT) causes hypercalcemia. The treatment for pHPT is surgical dissection of the hyperfunctioning parathyroid gland. Lower rates of hypocalcemia and recurrent laryngeal nerve injury imply that minimally invasive parathyroidectomy (MIP) is safer than bilateral neck resection. Current trends in MIP use can be inferred only by reference to preoperative localization studies. Noninvasive imaging studies (typically preoperative localization studies) show good detection rates of hyperfunctioning glands; however, there have also been cases of nonlocalization or discordant results. Selective venous sampling (SVS) is an invasive localization method for detecting elevated intact parathyroid hormone in the thyroid and/or internal jugular and brachiocephalic veins. SVS was developed mainly for postoperative patients with persistent or recurrent pHPT; however, SVS could also be useful before initial operations due to its high sensitivity to pHPT. Currently, SVS is generally indicated for recurrent HPT, and for cases with negative imaging study results for HPT or discordant results. Multi-detector row helical CT is useful for imaging the anatomy of the jugular and thyroid veins. Knowledge of the thyroid vein anatomy enables the creation of sampling points in the internal jugular and brachiocephalic veins for catheterization of the thyroid veins and venous anastomoses.

Keywords Primary hyperparathyroidism · Localization · Thyroid vein · Venous sampling

Introduction

Primary hyperparathyroidism (pHPT) is a common endocrine disease. Most patients have one adenoma, but double adenomas have been reported in up to 15% of cases [1]. Approximately 10–15% of patients have multiglandular disease [1]. The treatment for pHPT is surgical dissection of the hyperfunctioning parathyroid gland. Bilateral neck exploration (BNE) is the conventional approach, although minimally invasive parathyroidectomy (MIP) has been preferred recently. MIP is defined as any focused surgical approach that aims to achieve preoperative identification and removal of a single enlarged parathyroid gland [2]. Both BNE and MIP are effective surgical techniques for the treatment of pHPT, as reflected in their cure rates; however, the safety of MIP appears to be superior to that of BNE, as shown by lower rates of hypocalcemia and recurrent laryngeal nerve injury [3].

Current trends in MIP use can be inferred only by reference to preoperative localization studies [2]. The role of preoperative localization studies is to assist the surgeon in identifying the precise anatomic location of a hyperfunctioning parathyroid gland and its relationship to adjacent structures. A variety of noninvasive and invasive imaging modalities are available for this: noninvasive studies include ultrasound (US), computed tomography (CT), magnetic resonance imaging, and ^{99m}Tc sestamibi (MIBI). Venous sampling, which is an invasive method, is among the types of localization study available.

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This article reviews preoperative localization studies, focusing on selective venous sampling (SVS), and illustrates how to perform a SVS examination and interpret the results.

Physiology of primary hyperthyroidism and indications for treatment

Parathyroid hormone (PTH) acts on bone; chronically elevated PTH, as seen in HPT, induces osteoclast-mediated bone resorption. PTH also directly affects the kidneys and indirectly affects the intestine via its effects on the synthesis of 1,25$(OH)_2$D (calcitriol). Furthermore, PTH augments calcium resorption at the distal tubule and stimulates the release of renal 25(OH)D-1α-hydroxydase, which results in increased absorption of calcium from the small intestine. Therefore, pHPT causes hypercalcemia. At least 50% of patients with pHPT are asymptomatic. Clinical symptoms of pHPT include impaired renal function, renal stones, decreased bone density, and elevated fracture risk. The treatment for pHPT is surgical dissection of the hyperfunctioning parathyroid gland. Surgery is recommended for patients who are showing symptoms, as well as for asymptomatic patients aged under 50 years and who have moderately elevated blood calcium levels, impaired renal function, low bone density, or vertebral fracture [4]. Age less than 50 years continues to be a guideline for surgery [4–6] because there is a greater risk of complications of pHPT in these individuals over time than in those who are older than 50 [5]. However, surgery is also recommended for peri- or postmenopausal women and men aged 50 years and older who have a *T* score of −2.5 or less (which means osteoporosis) at the lumbar spine, femoral neck, total hip, or distal one-third radius [6].

Preoperative localization of a hyperfunctioning parathyroid gland

Noninvasive imaging study

US and ^{99m}Tc MIBI are standard noninvasive imaging modalities. In a meta-analysis, US had a pooled sensitivity for pHPT of 76.1% [95% confidence interval (CI) 70.4–81.4%] and a positive predictive value (PPV) of 93.2% [7]. Gland size is a factor used to detect the "culprit" (i.e., hyperfunctioning) parathyroid gland [8]. The sensitivity of ^{99m}Tc MIBI decreases by 15–39% when thyroid nodules are present [9–11].

In the same meta-analysis as mentioned above, ^{99m}Tc MIBI single-photon emission computed tomography (^{99m}Tc-MIBI-SPECT) had a pooled sensitivity for pHPT of 78.9% (95% CI 64–90.6%) and a PPV of 90.7% [7]. However, the sensitivity of ^{99m}Tc-MIBI-SPECT ranged from 39 to 90% in another systematic review article [12]. Several factors appear to influence the sensitivity of ^{99m}Tc MIBI, including the preoperative PTH level, calcium channel blockers, presence of oxyphil cells within parathyroid adenomas, *P*-glycoprotein level, presence of double adenoma/multiglandular disease, position of the adenoma, and presence of multinodular goiters [13]. Gland size is another factor affecting detection of the culprit gland [8]. The utility of ^{99m}Tc-MIBI-SPECT is significantly limited in cases with multiglandular disease; in such cases, the sensitivity of ^{99m}Tc-MIBI-SPECT was reported to be 38 and 76%, as compared to 83 and 96% for single-gland disease [14, 15]. The presence of multinodular goiters also negatively impacts the adenoma detection rate [9–11].

The sensitivity of CT scans when attempting to detect pHPT has improved due to recent developments in scanning equipment. A sensitivity of 87% was reported for cases in which US and ^{99m}Tc MIBI findings were unavailable or indeterminate [16]. Dynamic contrast-enhanced CT, also known as four-dimensional (4D)-CT, has been used to detect parathyroid adenomas [17–24], which show contrast enhancement in the early phase and washout in the delayed phase. In one study, 4D-CT showed improved sensitivity versus US and ^{99m}Tc MIBI and also appeared to be useful for detecting multiglandular disease [24]. In another study, 55% of radiologists had adopted 4D-CT as the first- or second-line modality for detecting pHPT [25].

The noninvasive imaging modalities described above have good pHPT detection rates and are typically performed as preoperative localization studies; however, in some patients, there is nonlocalization or discordant results.

Selective venous sampling

Sensitivity and role

SVS is an invasive localization modality that was reported in 1979 [26]. It measures elevated intact PTH (iPTH) in the thyroid vein and/or internal jugular and brachiocephalic veins. Table 1 lists studies that have mentioned SVS, which was developed mainly for postoperative patients with persistent or recurrent pHPT [1, 27–34]. Several studies have shown the feasibility of SVS. High sensitivity values for detecting pHPT, ranging from 78 to 94.7%, have been reported. In addition, one study demonstrated the ability of SVS to localize the culprit gland before the initial operation with a high sensitivity of 87% [35]. The reason why SVS achieves such high sensitivity is probably that SVS can measure the significant increase in iPTH in the thyroid vein when selective catheterization is performed. SVS can

Table 1 Previous studies on venous sampling for primary hyperparathyroidism

Author	Year	Cases (*n*)	Sensitivity (%)	Indication
Jones [29]	2002	64	75	Persistent and recurrent
Estella [28]	2003	13	88.8	Persistent and recurrent
Udelsman [34]	2003	7	83	Persistent
Seehofer [33]	2004	21	90	Persistent and recurrent
Liew [31]	2004	9	78	Persistent and recurrent
Chaffanjon [27]	2004	23	94.7	Persistent and recurrent
Eloy [35]	2006	8	87.5	Primary
Reidel [32]	2006	51	83.3	Persistent and recurrent
Gimm [1]	2012	5	80	Persistent
Labastchi [30]	2015	31	89	Persistent

also detect an intrathyroid parathyroid adenoma. Four of six cases with intrathyroid adenomas were detected in two studies [27, 30]; however, its ability in this respect should be evaluated further. At present, SVS is generally indicated for recurrent or persistent HPT and for cases with negative imaging studies or discordant results. SVS can be used as a third-line localization modality, after US and MIBI (first-line modalities) and CT and magnetic resonance imaging (MRI) (second-line modalities) [36]. The invasive SVS procedure has become more important in the era of MIP because the precise localization information provided by SVS can assist the surgeon during initial surgery.

Most parathyroid adenomas are functional, and nonfunctioning parathyroid adenomas are rare, unlike adrenocortical adenoma. Nonfunctioning parathyroid adenomas have been recognized in only a couple of case reports [37, 38]. Therefore, the coexistence of nonfunctioning adenoma identified on imaging studies and functioning adenoma not identified

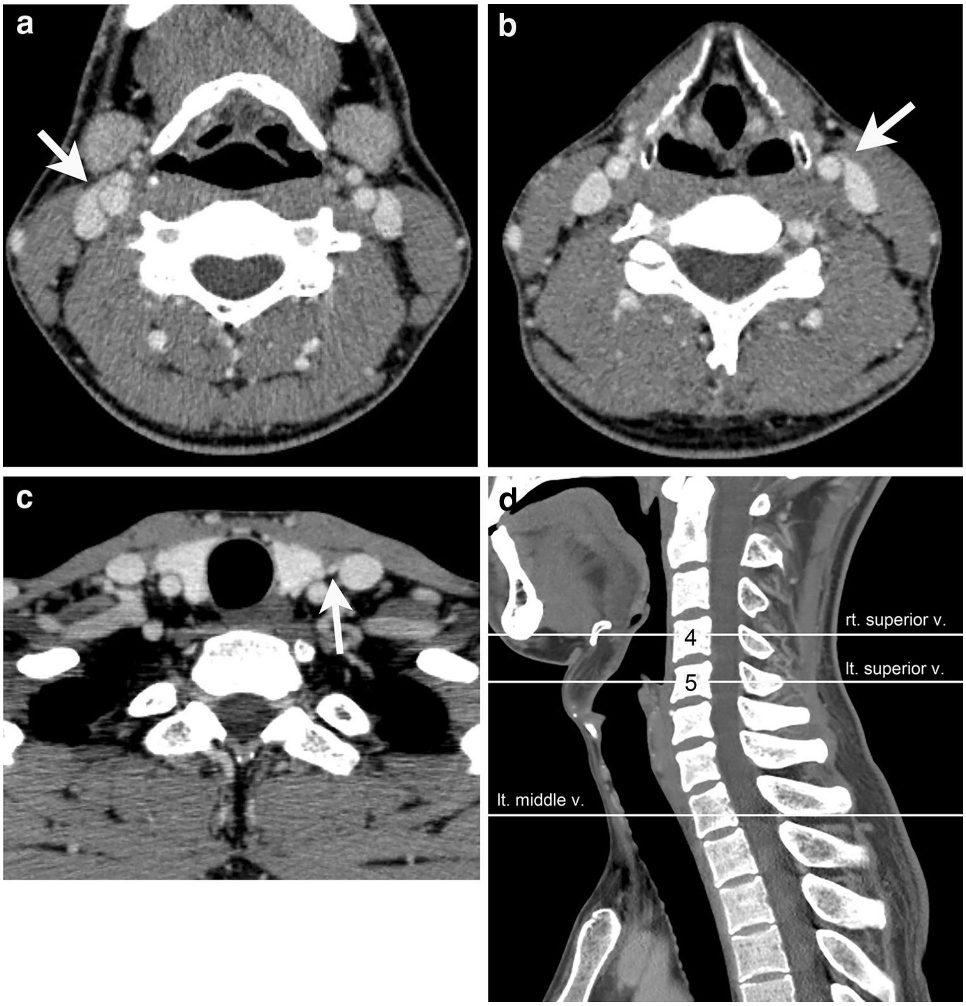

Fig. 1 A 35-year-old male with primary hyperparathyroidism (pHPT). Axial computed tomography (CT) images and sagittal multi-planar reconstruction (MPR) images derived from multi-detector row CT (MDCT). **a–c** The right superior (*arrow*), left superior (*arrow*), and left inferior (*arrow*) thyroid veins can be seen. The right middle thyroid vein is not apparent. **d** The *horizontal lines* on the sagittal MPR image correspond to the axial CT images in **a–c**. They are correlated with the level of the vertebral body, which provides a landmark for the site of entry of the thyroid veins into the internal jugular vein

Fig. 2 Coronal MPR images derived from MDCT. The right inferior (❼) and left inferior (❽) thyroid veins form a common trunk (❼, ❽) that joins the internal jugular vein at the left brachiocephalic vein (⑮, *arrowhead*). The left superior (⓳) and left middle (❽) thyroid veins are noted. The right superior thyroid vein was apparent in another image (not shown). An accessory right inferior vein is apparent (*)

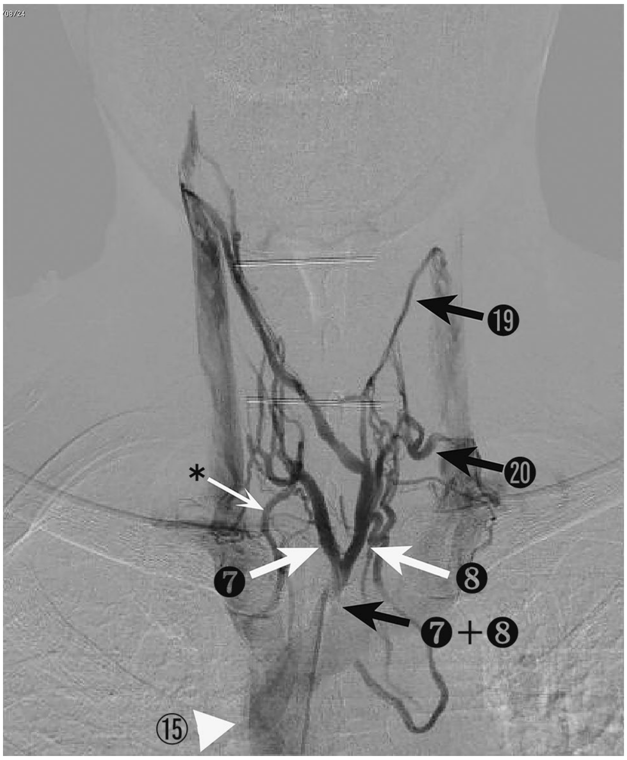

Fig. 3 Selective venous angiogram. Venous angiogram of the common trunk (❼, ❽) shows the inferior (❼, ❽), left middle (⓴), and superior (⓳) thyroid veins. An accessory right inferior vein (*) is also apparent

on them is considered extremely rare. To our knowledge, such cases have not been reported in the literature.

Anatomical variation in thyroid veins and their appearance on multi-detector row CT

Anatomical information is necessary for SVS to determine the optimal blood sampling points in the internal jugular and brachiocephalic veins, to in turn detect the increase in iPTH due to joining thyroid veins, and for accurate catheter insertion into the thyroid veins.

Multi-detector row CT (MDCT) helps us to identify the superior and middle thyroid veins, and the sites at which they join with the internal jugular veins (by referring to the level of the vertebral body) (Fig. 1). A previous study reported good thyroid vein detection rates using MDCT. The superior thyroid veins were always recognized on CT scans (100%) [39] but middle thyroid veins were not frequently recognized (36–49%) [35]. Another study using cadavers reported that a medial vein (the middle vein in this article) existed in only 43% of the cadavers [40]. MDCT also helps us evaluate the number and course of inferior thyroid veins, and the locations at which they join with the brachiocephalic vein (Fig. 2). The inferior thyroid veins show variety in terms of number, course, and location at which they join with brachiocephalic veins. Five joining patterns were demonstrated previously [39]: in the most common pattern, inferior thyroid veins on each side joined the ipsilateral brachiocephalic vein separately (41% of cases). In the second most common pattern, the inferior thyroid veins first formed a common trunk before joining the left brachiocephalic vein (35% of cases).

Correlation between MDCT and venous angiography: anatomy of the thyroid veins

MDCT depicts the thyroid veins outside of the thyroid gland and the results correlate well with those from venous angiograms (Figs. 2, 3). However, MDCT is of little use for showing venous anastomoses of the gland. Selective venous angiograms are crucial to identifying venous anastomoses. When obtaining angiograms of venous anastomoses, selective venous angiography with a relatively protracted infusion of contrast medium is recommended after selectively placing a catheter into one of

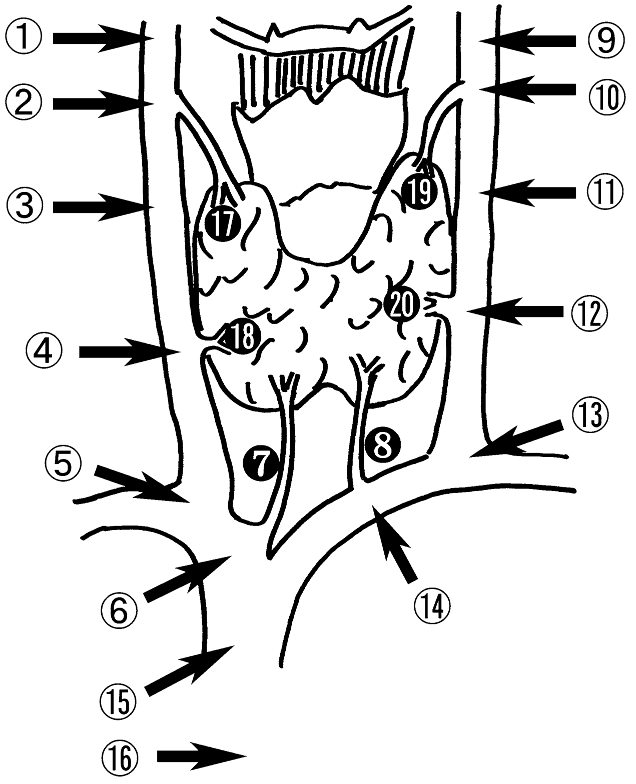

Fig. 4 Sampling points for the internal jugular, brachiocephalic, and thyroid veins: ①, ⑨ at the upper superior thyroid vein; ②, ⑩ at the join of the superior thyroid vein; ③, ⑪ between the superior and middle thyroid veins ④, ⑫ at the join of the middle thyroid vein; ⑤, ⑬ at the join of the internal jugular and subclavian veins; ⑥ at the right brachiocephalic vein; ❼ at the right inferior thyroid vein; ❽ at the left inferior thyroid vein; ⑭ at the left brachiocephalic vein; ⑮ at the superior vena cava; ⑯ at the inferior vena cava; ⓱ at the right superior thyroid vein; ⓲ at the right middle thyroid vein; ⓳ at the left superior thyroid vein; and ⓴ at the left middle thyroid vein

the thyroid veins. The good point to insert the catheter tip to obtain comprehensive retrograde venography of the thyroid venous system would be the most prominent of the thyroid veins. An inferior thyroid vein, especially the common trunk of both inferior veins, is frequently appropriate (Fig. 3). The contrast medium passes through the venous anastomoses of the thyroid gland and the other thyroid veins are frequently opacified via the anastomoses (Fig. 3). However, the depiction of other thyroid veins through venous anastomoses is affected by the venous flow against the retrograde flow of contrast medium; when this is dominant, the retrograde opacification of other thyroid veins is not satisfactory.

Where is the venous blood in the internal jugular and thyroid veins sampled from?

Figure 4 illustrates the sampling points in the internal jugular and thyroid veins in this study. Conventional 4 Fr catheters such as Berenstein, multipurpose, and headhunter catheters are generally used in the internal jugular and brachiocephalic veins, and to catheterize the thyroid veins. A 2.2 Fr microcatheter with a side hole (Gold Crest; Hi-Lex, Hyogo, Japan) is used coaxially for super-selective blood sampling in the distal portions of thyroid veins in our clinical practice. If a particular thyroid vein is not detected by CT scans or venous angiography, the selective catheterization step can be skipped. For example, if the right middle thyroid vein cannot be identified on imaging studies, no sample is obtained at the middle thyroid vein (point ⓲ in Fig. 4). Point ④ then occupies a position between points ③ and ⑤.

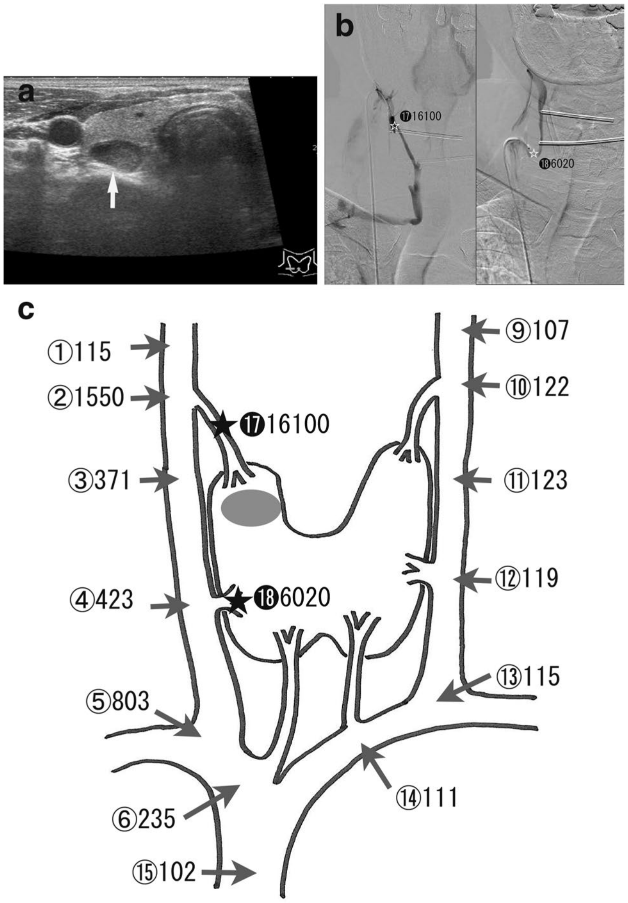

Fig. 5 A 63-year-old male with inconsistent imaging findings. **a** Ultrasound (US) shows a discrete nodule located dorsally in the right thyroid gland (*arrow*). ^{99m}Tc-sestamibi (MIBI) scintigram does not demonstrate a suspicious accumulation pattern (not shown). **b**, **c** Intact parathyroid (iPTH) values are very high in the right superior thyroid vein (⓰) and high in the right middle thyroid vein (⓱). Values in the right internal jugular vein are also increased (②–⑤). A suspicious lesion is predicted in the right superior quadrant of the right lobe. A pathological parathyroid adenoma can be seen (*gray ellipse*)

We sometimes collect blood samples from the distal portion of the thyroid vein or venous anastomoses

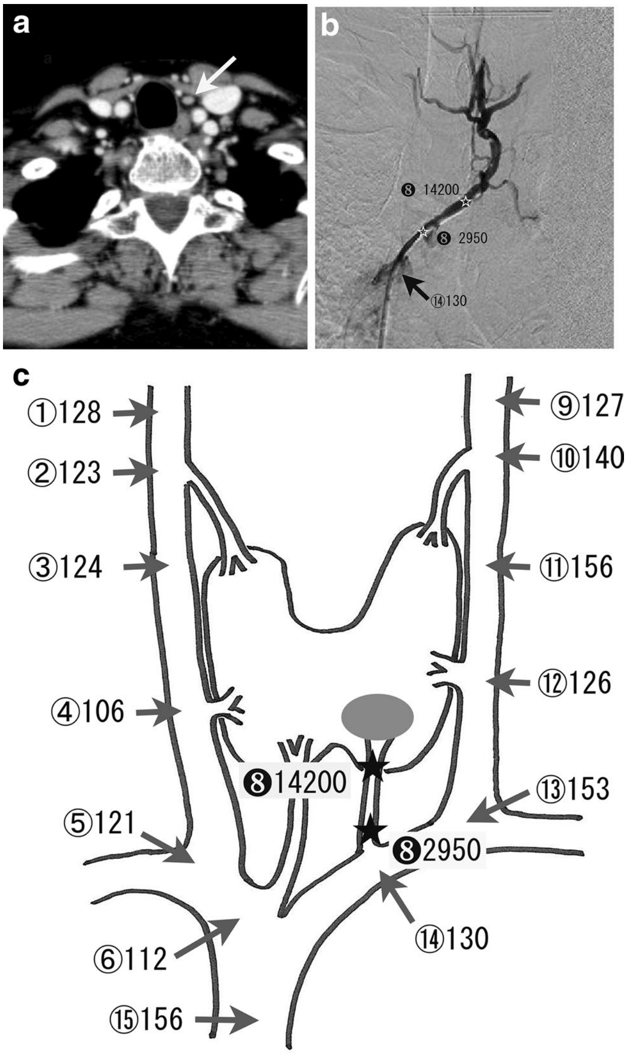

Fig. 6 A 67-year-old female with indeterminate image findings. **a** A small nodule (*arrow*) is apparent inferior to the left lobe, which is indeterminate for parathyroid lesion. No suspicious lesion was detected on neither US nor ^{99m}Tc-MIBI scintigram (not shown). **b**, c The iPTH value is very high in the distal left inferior vein (❽; 14,200 pg/ml) and then shows a steep decline (❽; 2950 pg/ml). The iPTH value is not elevated in the left brachiocephalic vein (⑭ 130 pg/ml). A suspicious lesion is predicted in the left inferior quadrant of the left lobe. A pathological parathyroid adenoma can be seen (*gray ellipse*)

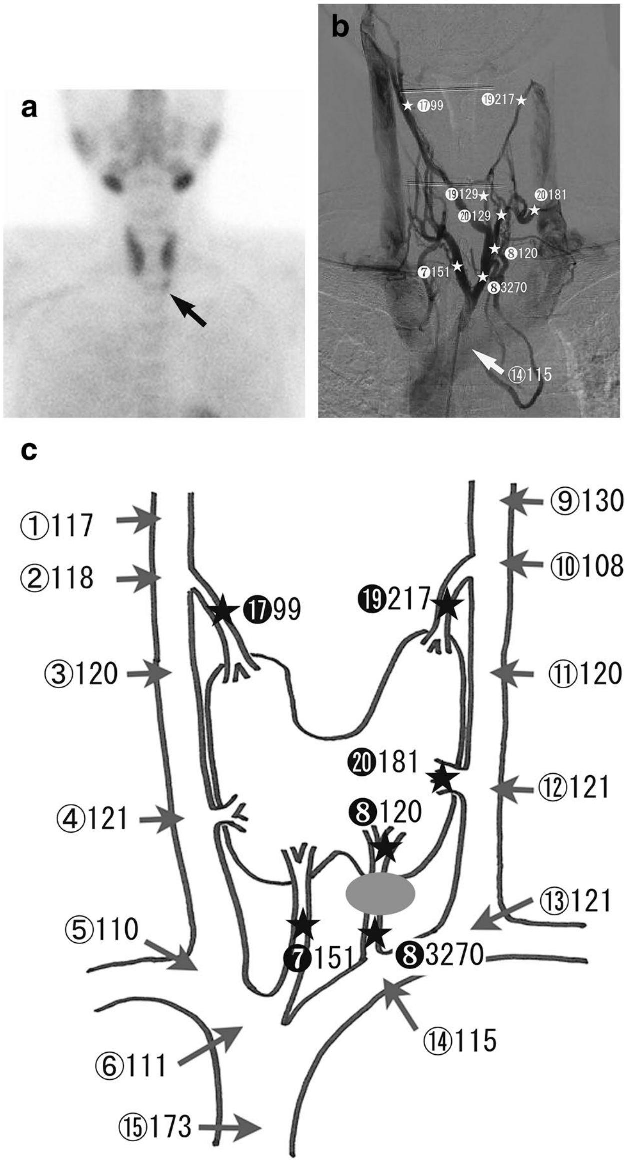

Fig. 7 A 35-year-old male with inconsistent imaging findings (same case as shown in Figs. 1, 2, 3). **A** ^{99m}Tc-MIBI scintigram demonstrates suspicious accumulation inferior to the left lobe of thyroid gland (*arrow*). US does not show a suspicious lesion (not shown). **b**, **c** The iPTH value is increased in the proximal left inferior vein (❽ 3270 pg/ml) compared with that in the distal portion (❽ 120 pg/ml). The iPTH value is not elevated in the left brachiocephalic vein (⑭ 115). A suspicious lesion in the left inferior quadrant of the left lobe, consistent with the ^{99m}Tc-MIBI findings. A pathological parathyroid adenoma can be seen (*gray ellipse*)

(Fig. 7b) via super-selective venous sampling (sSVS). A positive step-up in iPTH in the same thyroid vein can be encountered (Figs. 5, 7). In addition, the other thyroid vein may occasionally be sampled from by inserting a microcatheter into the venous anastomoses, thus saving time by forgoing selective catheterization of the other thyroid vein.

The disadvantage of this procedure is that it is time-consuming. Selective catheterization of thyroid veins depends on the degree of development of the internal jugular and thyroid veins, and on the anatomical variation among thyroid veins; this means that selective sampling from the thyroid veins is not always possible.

Interpretation of the selective venous sampling results referring to the retrograde venography

In previous studies, the location of the culprit gland was predicted in terms of laterality (right, left, or bilateral) and thyroid gland quadrant. Most studies adopted a threshold of at least a twofold increase in the value of iPTH relative to the peripheral vein to create a positive gradient [27–30, 32]. sSVS in the thyroid vein, near to the culprit lesion, results in a marked increase in the iPTH value, as described previously. Even though the iPTH value is elevated in the thyroid vein, an increase in this value in the internal jugular or brachiocephalic vein is not always seen (Figs. 6, 7). Therefore, sSVS has more utility when searching for the culprit lesion. However, one drawback may be that a high iPTH value reflects only venous flow from a different quadrant of the thyroid gland—that containing the culprit gland. A retrograde venous angiogram does not necessarily demonstrate the actual venous flow of the thyroid veins to the internal jugular or brachiocephalic veins.

Conclusion

SVS is an invasive localization modality with high sensitivity to pHPT. It has been used to detect both persistent and recurrent hyperparathyroidism; however, it is also useful in the initial operative setting, especially for cases demonstrating discordant or negative imaging findings. The knowledge of venous anatomy gained from MDCT and retrograde venous angiography is helpful for setting sampling points, and for catheterization of thyroid veins.

Compliance with ethical standards

Conflict of interest The authors declare no relevant relationships.

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