



## <sup>18</sup>F-Fluorocholine PET/CT as a second line nuclear imaging technique before surgery for primary hyperparathyroidism

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Primary hyperparathyroidism (PHPT) is a common endocrine disorder for which parathyroid surgery is the only curative treatment [1]. It is most commonly seen after the age of 50 years, with three to four times more women than men. PHPT has evolved in its clinical presentation over the past 40 years and is now usually diagnosed at an asymptomatic stage. Guidelines for surgical decision making in asymptomatic patients have been established [1].

Parathyroid surgery requires expertise as the surgeon faces three difficulties. First, multiglandular disease (MGD), either double adenoma or parathyroid hyperplasia, is present in about 15% to 20% of patients with apparently sporadic PHPT (and is the rule in patients with a hereditary syndrome) [2]. Second, parathyroid lesions are ectopic in about 16% of patients [3], including those with major ectopy (e.g. low mediastinal, retroesophageal, submandibular/undescended, inside carotid sheath, strictly intrathyroidal). Third, parathyroid lesions can be very small, and there is a trend towards decreasing weight in recent years due to earlier surgical decision making, with a reported median weight for solitary adenomas of 0.5 g [4].

Without preoperative imaging, bilateral neck exploration by an experienced surgeon is curative in about 92% to 95% of patients with low morbidity [5]. Preoperative imaging offers several advantages. First, it reduces the risk of failure linked to ectopic parathyroid glands [3, 6, 7]. Radionuclide imaging should cover the whole area from the angle of the jaws to the upper part of the myocardium [8]. Second, it allows targeted surgery in patients with an apparently single parathyroid lesion on imaging, and therefore reduces the durations of surgery and anaesthesia and hospital time, and further reduces the small risk of complications (e.g. haematoma, infection, recurrent laryngeal nerve injury, permanent hypoparathyroidism) [8–10].

Besides <sup>99m</sup>Tc-sestamibi imaging, some PET tracers can be helpful for parathyroid imaging, such as <sup>11</sup>C-methionine, <sup>11</sup>C-choline and <sup>18</sup>F-fluorocholine [11, 12]. There is increasing interest in the use of <sup>18</sup>F-fluorocholine due to the <sup>18</sup>F labelling. The main issue, however, is to determine the indications for the use of <sup>18</sup>F-fluorocholine PET rather than the more widely available, approved, and less expensive parathyroid imaging techniques.

The prospective study reported in this issue of the *EJNMMI* by Quak et al. investigated the sensitivity of <sup>18</sup>F-fluorocholine PET/CT in patients with PHPT and negative or inconclusive neck ultrasonography and sestamibi imaging [13]. This application is interesting as sestamibi negativity presents a dilemma. Some recent studies have shown significant differences in surgical cure rates between patients with a negative sestamibi scan receiving bilateral neck exploration and those with a positive sestamibi scan (e.g. 89% vs. 97%,  $P = 0.008$  [14]; and 90.4% vs. 97.5%,  $P < 0.001$  [15]). It has also been found that patients with a negative sestamibi scan are less likely to be referred to the surgeon [16].

The prospective study performed by Quak et al. included 25 patients. Sestamibi imaging was negative in 88% and inconclusive in 12%. Following <sup>18</sup>F-fluorocholine PET/CT examination, 24 patients received surgery. Analysis per lesion showed that <sup>18</sup>F-fluorocholine had a sensitivity of 91.3% and

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a positive predictive value of 87.5% [13]. The mean size of positive parathyroid lesions on  $^{18}\text{F}$ -fluorocholine PET/CT was 13.1 mm (maximum transverse diameter on CT); the weight of resected glands is not available. There is no doubt that the results obtained in this series are interesting [13]. However, more detailed consideration of the study raises some questions:

1. Would  $^{18}\text{F}$ -fluorocholine PET/CT have been as rewarding if it had been performed after more sensitive first-line sestamibi imaging?

Negativity of MIBI scanning was based on dual-phase  $^{99\text{m}}\text{Tc}$ -sestamibi scintigraphy with early and delayed planar pinhole neck images and delayed neck and thorax SPECT/CT. As previously reported by the authors, their sestamibi protocol yields positive findings in 63% of patients with PHPT [17]. Several studies have shown that a dual-tracer parathyroid protocol consisting of simultaneous acquisition of  $^{99\text{m}}\text{Tc}$ -sestamibi and  $^{123}\text{I}$  images followed by image subtraction offers higher sensitivity and accuracy than the commonly used single-tracer, dual-phase protocol [18–21]. In a recent prospective study from Denmark including 91 patients (97 parathyroid lesions) in which dual-tracer subtraction scintigraphy and dual-phase scintigraphy were directly compared, and pinhole neck imaging was used for both techniques, the sensitivities of the two techniques were 93% and 65%, respectively ( $P < 0.001$ ) [18]. SPECT/CT can be performed as a complement to single-tracer imaging [17], or to dual-tracer imaging, with visual comparison of three-dimensional  $^{99\text{m}}\text{Tc}$ -sestamibi and  $^{123}\text{I}$  images and/or subtraction of SPECT data [11, 22, 23]. Complementary SPECT/CT has somewhat lower overall sensitivity than pinhole imaging and only rarely discovers additional foci (e.g. in the case of superposition of two foci on planar images). However, it does provide useful anatomical information [24]. Some surgeons suggest repeating imaging with dual-tracer  $^{99\text{m}}\text{Tc}$ -sestamibi and  $^{123}\text{I}$  scan when single-tracer imaging is negative [25].

2. What was the sensitivity for MGD detection in the first-line and second-line imaging?

The main limitation of single-tracer sestamibi imaging is its low sensitivity in identifying MGD; it usually shows either a single lesion or no lesion [18, 26]. Detection of only one lesion increases the likelihood of intraoperative conversion to bilateral exploration, or of surgical failure if intraoperative PTH (iOPHT) assessment is not available [27]. Patients with a negative sestamibi scan have much higher rates of MGD at surgery than those with a positive scan [14, 15]; for example, 32% vs. 13% ( $P < 0.001$ ) in the series by Dy et al. [15]. The finding of only one patient with MGD on choline PET in the series by Quak et al. raises the question as to the sensitivity for MGD detection

[13]. Unfortunately, iOPHT was not measured and no follow-up was available so calcium levels could not be assessed at 6 months to firmly rule out persistent disease, or beyond 6 months to assess for recurrence.

3. Did  $^{18}\text{F}$ -fluorocholine PET/CT lead to better surgical outcomes?

This final question relates to the impact on surgical outcome. As mentioned above, the success of surgery consisting of bilateral neck exploration is suboptimal in patients with a negative sestamibi scan (close to 90%) [14, 15, 28]. Based on the results of  $^{18}\text{F}$ -fluorocholine PET/CT imaging in the series by Quak et al., 18 of 24 patients were able to receive targeted surgery, which is interesting. On the other hand, surgical success, as assessed by early measurement of calcium levels, pointed to surgical failure in 3 of the 24 patients [13]. The authors warn about the risk associated with considering equivocal “inconclusive” foci as positive. Surgery failed in two of the three patients who received unilateral surgery on the basis of choline results that were judged equivocal [13]. Measurement of iOPHT was not available in this series, which might have been of benefit in this difficult population [28]. Larger series are clearly necessary to assess the impact of  $^{18}\text{F}$ -fluorocholine PET/CT imaging on surgical outcomes in patients with a negative sestamibi scan.

The report by Quak et al. is of importance as prospective studies with  $^{18}\text{F}$ -fluorocholine in PHPT are still rare. Michaud et al. investigated 17 patients with primary or secondary hyperparathyroidism in whom conventional imaging results were uncertain, either due to discrepancies between ultrasonography and dual-tracer sestamibi imaging or due to equivocal images on one of these imaging modalities [29]. The sensitivity of  $^{18}\text{F}$ -fluorocholine was relatively high. However, the study also showed that thyroid lesions may induce false-positive results [13]. In a pilot study of ten patients with inconclusive ultrasonography + single-tracer sestamibi scan, Kluijfhout et al. confirmed the potential of  $^{18}\text{F}$ -fluorocholine PET/MR imaging [30].  $^{18}\text{F}$ -Fluorocholine PET/MR was positive in nine patients; however, in one of them, hyperplasia was misdiagnosed as a single adenoma [30].

Two groups have evaluated  $^{18}\text{F}$ -fluorocholine PET/CT as the first-line imaging modality in PHPT. In the study by Thanseer et al. including 54 patients (56 lesions),  $^{18}\text{F}$ -fluorocholine PET/CT detected 52 of the 56 parathyroid lesions, while single-tracer sestamibi (dual-phase planar + late SPECT) detected 42 lesions. However, there was also a higher number of false-positive studies with  $^{18}\text{F}$ -fluorocholine (four vs. one). Two patients had no parathyroid tissue identified at surgery and two others had elevated PTH levels after surgery [31]. Again, Lezaic et al. [32] and Rep et al. [33] found that  $^{18}\text{F}$ -fluorocholine PET/CT has high sensitivity exceeding that

of sestamibi imaging. In their updated series including 43 patients, surgical failure occurred in three patients [33]. We found no published study comparing  $^{18}\text{F}$ -fluorocholine PET/CT to  $^{99\text{m}}\text{Tc}$ -sestamibi and  $^{123}\text{I}$  as first-line imaging. There is as yet no proof that first-line  $^{18}\text{F}$ -fluorocholine imaging would improve surgical outcomes.

An advantage of  $^{18}\text{F}$ -fluorocholine PET/CT imaging is the higher resolution associated with PET technology and the shorter imaging time. Potential drawbacks are the higher cost, the uptake by inflammatory lymph nodes, and the absence of comparison with a specific thyroid tracer which might increase the risk of false-positives from thyroid nodules.

Choline PET tracers open new avenues for radionuclide imaging of parathyroid glands. Larger prospective studies are needed to compare  $^{18}\text{F}$ -fluorocholine PET/CT to state of the art conventional scintigraphy to clarify the role of choline imaging in specific settings (reoperation for PHPT, patients undergoing their first operation with inconclusive imaging, etc.). The role of CT contrast medium administration during choline PET/CT imaging needs to be investigated as it might further improve results, especially in patients undergoing repeat surgery. Fundamental studies are also needed to understand what drives choline uptake in parathyroid tumours, which cells are responsible for uptake (the chief cells that secrete PTH, or the oxyphil cells as is the case with MIBI), and the sources of false-negative studies. Studies of metabolomics may be of interest in this regard [34]. We also need to better identify the sources of potential false-positive studies that may be relevant for parathyroid imaging [35].

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