European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-024-06707-9

EDITORIAL

How nuclear imaging changed parathyroid surgical strategies through time

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Introduction

In 1986, John Doppman made the statement that "the only localization study indicated in a patient with untreated hyperparathyroidism (HPT) is the localization of an experienced parathyroid surgeon" [1]. Nowadays, preoperative localization with several available imaging techniques aids the surgeon in identifying an adenoma preoperatively. Recently, to identify the best second-line imaging, Noltes et al. published the first prospective study in which [^{11}C]-methionine PET/CT, [^{11}C]-choline PET/CT, and 4D-CT were compared in the same patient with primary hyperparathyroidism (pHPT) [2]. This study showed that [^{11}C]-choline PET/CT had a sensitivity of 85% for localizing parathyroid adenomas as second-line imaging technique. Considering that in this study only patients with upfront negative or discordant first-line imaging were included, the diagnostic performance of [^{11}C]-choline PET/CT is impressive. A growing number of endocrine departments are now implementing choline PET imaging in their clinic in a first-line fashion [3, 4].

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Primary hyperparathyroidism

The parathyroid glands are usually four delicate structures in close anatomical relation with the thyroid gland that secrete parathyroid hormone (PTH) which is responsible for regulating calcium homeostasis in the blood [5]. They were first discovered in 1850 by Sir Richard Owen while dissecting an Indian rhinoceros in the London Zoo. He described a "small compact yellow glandular body" but did not perform microscopic examination or further research. For this reason, Ivar Sandström, an anatomist from Uppsala, Sweden, who did give a microscopic description for the parathyroid gland structure, has also widely been recognized for the discovery of the glands [6]. Later on, these glands were connected to diseases such as pHPT.

pHPT is characterized by elevated levels of parathyroid hormone (PTH) secretion by one ore multiple parathyroid glands which causes a rise in plasma calcium concentrations to inappropriate levels [7]. Some patients develop HPT due to lithium or radiotherapy exposure, leading to multiglandular disease, but in most cases, an underlying or genetic cause of this condition is not identified [8, 9]. Furthermore, it can result from the rare parathyroid carcinoma. However, it is still predominantly caused by a solitary parathyroid adenoma in one of the four parathyroid glands (85–90%). Surgery stands as the sole curative treatment for the condition [10].

In 1891, Von Recklinghausen was the first to describe HPT but called it "osteitis fibrosa cystica" which was characterized by loss of bone mass. In autopsy reports of such patients, he described that he found a "redish brown lymph node" in the thyroid region but did not suspect a connection between the two [11]. In 1925, Mandl was the first to cure a symptomatic patient by removing a parathyroid adenoma. All symptoms resolved, and the patient remained cured for almost 31 years, resulting in surgical treatment becoming the golden standard [12]. At the same time, the disease was further characterized and described as the

Published online: 23 April 2024

disease of stones, bones, moans, and groans because of symptoms of nephrolithiasis, skeletal disease, abdominal groans (nausea, vomiting, and constipation), and mental moans (psychosis, lethargy, depression, and coma) [13, 14]. Radiographically, the disease was recognized by subperiosteal bone resorption and "salt-and-pepper" erosions of the skull [7].

When, around the 1970s, serum calcium analysis was more routinely used in clinical practice, the disease was recognized more often in an early stage resulting in a four to five-fold increase of pHPT incidence [15, 16]. Nowadays, most patients are asymptomatic, when diagnosed during routine blood tests, and radiographically diagnosed bone disease is rare [17].

Parathyroid adenomas appear in many different anatomic locations that are related to the embryology of the parathyroid gland. In most cases, the four parathyroid glands are located posteriorly to the thyroid gland, but their embryologic migration route opts for plenty of ectopic locations such as the superior mediastinum, the thyroid (intrathyroidal), the carotid sheet, and the thymus [18–20].

The original surgical approach to remove the parathyroid adenomas responsible for the disease was a bilateral neck exploration [21]. If performed by experienced endocrine surgeons, this approach cures HPT in 95% or more of cases. But since the disease is mostly caused by one parathyroid adenoma (85–90%), a focused approach via a minimally invasive parathyroidectomy (MIP) seems more justifiable [22]. However, in order to perform a MIP, accurate preoperative localization of the parathyroid adenoma is essential. The importance of preoperative localization regardless of the surgical approach was illustrated by the "Captain Martell case," a patient who underwent six unsuccessful explorative parathyroid surgeries due to the lack of preoperative localization. Eventually, during the seventh operation, a culprit gland was found in the mediastinum. Unfortunately, a few weeks after the successful surgery, Martell died due to complications related to urolithiasis [23–25].

Parathyroid imaging

Preoperative molecular parathyroid imaging was first tried in the 1970s by the aid of [^{75}Se]Se-methionine [26]. Due to suboptimal results, dual tracer subtraction methods, where a second tracer ([^{123}I]-iodide, [^{131}I]-iodide, or [^{99m}Tc]-pertechnetate) is administered and subtracted to separate thyroid and parathyroid tissue, were introduced [27, 28]. In the 1980s, [^{201}TI]-chloride with [^{99m}Tc]-pertechnetate, for subtraction, became the standard procedure but due to unfavorable characteristics of ^{201}TI (high radiation dose and low contrast resolution), this was not for long [29]. Eventually, the surge for better tracers led to the development of [^{99m}Tc]Tc-sestamibi, which was approved for cardiac imaging in 1990 [30]. It is postulated that [^{99m}Tc]Tc-sestamibi accumulates in parathyroid adenomas due to the abundance of mitochondria rich oxyphil cells [31].

[^{99m}Tc]Tc-sestamibi also showed uptake in the thyroid gland, but it had a slower washout from the parathyroid gland compared to the thyroid gland in most cases [32, 33]. Eventually, this led to "single tracer dual phase imaging" where parathyroid lesions were identified based on this difference in washout time. In 1992, the utilization of [^{99m}Tc]Tc-sestamibi for identifying parathyroid adenomas based on this discrepancy was prospectively validated. However, it was not considered optimal as the delayed washout was not consistently observed in every patient [34].

Soon thereafter, it was discovered that dual tracer dual phase imaging with for example [^{99m}Tc]Tc-sestamibi and ^{123}I provided a better resolution for detecting parathyroid adenomas by addressing the problem of thyroid nodules that also show delayed washout of [^{99m}Tc]Tc-sestamibi [35, 36]. Today, dual tracer multi-phase imaging with [^{99m}Tc]Tc-sestamibi and ^{99m}Tc-pertechnetate, which is cheaper and more readily available compared to ^{123}I, combined with Single Photon Emission Computed Tomography/Computed Tomography (SPECT/CT), and ultrasound is often the first method of choice [37, 38]. Ultrasound is considered a helpful imaging method but is rarely used as the sole imaging technique even though some studies report sensitivities varying from 72 to 85% in large series [39–41]. It is however very useful as a perioperative guide for the surgical approach and also serves as a useful differentiating diagnostic tool for thyroid-related co-morbidities (nodules) [42, 43].

In 2006, 4-dimension computed tomography (4D-CT) was first implemented. This technique uses four phases (pre-contrast, arterial, venous, and delayed) to emphasize differences between the adenoma, lymph nodes, and the thyroid gland [42, 44]. The great benefit is the short imaging time, high spatial resolution, and low costs; however, it has a 57 times higher radiation burden compared to [^{99m}Tc]Tc-sestamibi SPECT/CT [45].

In recent years, positron emission tomography (PET) imaging has emerged as a preferred technique, given its superior sensitivity and spatial resolution in comparison to SPECT/CT [46]. Several PET tracers such as [^{11}C]-methionine, [^{11}C]-choline, and [^{18}F]F-fluorocholine have been used for parathyroid imaging. All have been reported useful with different benefits and disadvantages [47]. For example, carbon-11 tracers, in contrast to fluorine-18 tracers, require an onsite cyclotron (due to short half-life), and [^{11}C]-choline has high sensitivity but could lack specificity since it also accumulates in cells with a high turnover rate [48].

Head-to-head comparison

The significant rise in research utilizing PET and CT scans for preoperative parathyroid adenoma localization underscored the necessity for a comparative analysis of these techniques. [^{11}C]-choline PET/CT, [^{11}C]-methionine PET/CT, [^{18}F]F-fluorocholine PET/CT, and 4D-CT are globally commonly utilized in patients with pHPT [49–52]. Noltes et al. investigated which imaging modality ([^{11}C]-choline PET/CT, [^{11}C]-methionine PET/CT, or 4D-CT) is superior and should be conducted as second-line scan after negative first-line imaging [2]. In this study, which was executed by multiple authors of this editorial, the majority of patients were referred for the study since initial imaging (cUS, [^{99m}Tc]Tc-sestamibi SPECT/CT, and/or [^{18}F]F-fluorocholine PET/CT) could not localize the parathyroid adenoma. Therefore, this study had a highly selected group of patients with initial negative imaging. [^{11}C]-choline PET/CT showed to be superior to [^{11}C]-methionine PET/CT and 4D-CT in localizing parathyroid adenomas. Existing literature already showed this for [^{18}F]F-fluorocholine PET/CT [53].

Even in this negatively selected patient population, [^{11}C]-choline PET/CT achieved a sensitivity of 85%. It is important to note that Noltes et al. studied the use of [^{11}C]-choline PET/CT as a second-line scan. The logical next step would be to explore if [^{11}C]-choline PET/CT could also be effective and cost-beneficial as a first-line scan in a similar setting.

In 2022, Yap et al. were the first to study the potential cost-effectiveness of [^{18}F]F-fluorocholine PET/CT as a primary localization technique for pHPT. They found that 4D-CT was the least costly and provided more health utility compared to neck ultrasound and sestamibi-SPECT, which are dominated strategies. [^{18}F]F-fluorocholine PET/CT was however not dominated by 4D-CT [54]. [^{18}F]F-fluorocholine PET/CT was the most expensive modality but also provided the most health utility gained because of its high diagnostic ability. However, the margin for its cost-effectiveness was narrow and subject to variations of practice and resource constraints [54]. They showed, for example, that adjusting the sensitivity of [^{18}F]F-fluorocholine PET/CT from 100 to 90% demonstrated a significant impact on its classification of cost-effectiveness, highlighting the sensitivity threshold's pivotal role in determining its economic viability.

Although the study of Yap et al. provides positive insights into the cost-effectiveness of [^{18}F]F-fluorocholine PET/CT for a first-line imaging technique, additional studies are needed to confirm these findings in other parts of the world such as Europe. These studies should also include multimodal imaging techniques either in tandem or sequel as a comparative arm, given that this is common practice.

It should be noted that [^{11}C]-choline and [^{18}F]F-fluorocholine are two different tracers. The most remarkable difference is the difference in their half-lives: only 20 min for [^{11}C]-choline PET/CT compared to 110 min for ^{18}F-fluorocholine PET/CT. Thereby, the use of [^{11}C]-choline is restricted to centers with their own cyclotron to produce the tracer on site. In the study of Noltes et al., [^{11}C]-choline PET/CT was able to localize a lesion suspicious of a hyperfunctioning parathyroid gland when externally performed [^{18}F]F-fluorocholine PET/CT could not in 12/14 patients. The researchers postulated that the disparity in detection rates between the two tracers primarily comes from divergent scan protocols employed across different centers. Given the unlikelihood of conducting direct comparative studies in patients, elucidation of this phenomenon requires ex vivo experiments integrating both choline tracers.

Changes in surgical strategies

With the development of high-quality diagnostic nuclear imaging such as choline PET/CT for preoperative localization, surgeons may or already have changed strategies for parathyroid surgery. Parathyroid surgery is evolving to resemble a strategic chess game. The combination of good surgical skills combined with reliable information based on pre- and per-operative imaging defines the success rate. Experienced parathyroid surgeons, nuclear medicine physicians, radiologists, and pathologist are essential in this process. Continuous engagement with imaging studies and receiving feedback on surgery and pathology not only refines clinical expertise but also fosters proficiency in pattern recognition and interpretation, ultimately enhancing diagnostic accuracy and patient outcomes. Because of the improving potential of imaging, surgeons moved from a four-gland exploration to a focused MIP. Next to the high sensitivity of choline PET/CT, the negative predictive value of the scan is also worth investigating. In other words, choline PET/CT may also play a role in excluding the presence of a single adenoma (when no focal activity is noted) in the neck or in identifying patients with multiglandular disease (MD). This knowledge influences the surgical strategy and may affect several clinical scenarios (Fig. 1).

In the first scenario, choline PET/CT localizes one adenoma. One can argue if in this case it is necessary to also identify the second ipsilateral parathyroid to exclude an adenoma if the highly sensitive scan clearly identified a unifocal lesion. In many clinics, intraoperative PTH (io-PTH) is still used after removing an adenoma. However, it is questionable if a well-trained surgeon who operates guided by choline PET/CT and finds the typical adenoma at the predicted anatomical location has any benefit of waiting for io-PTH. As

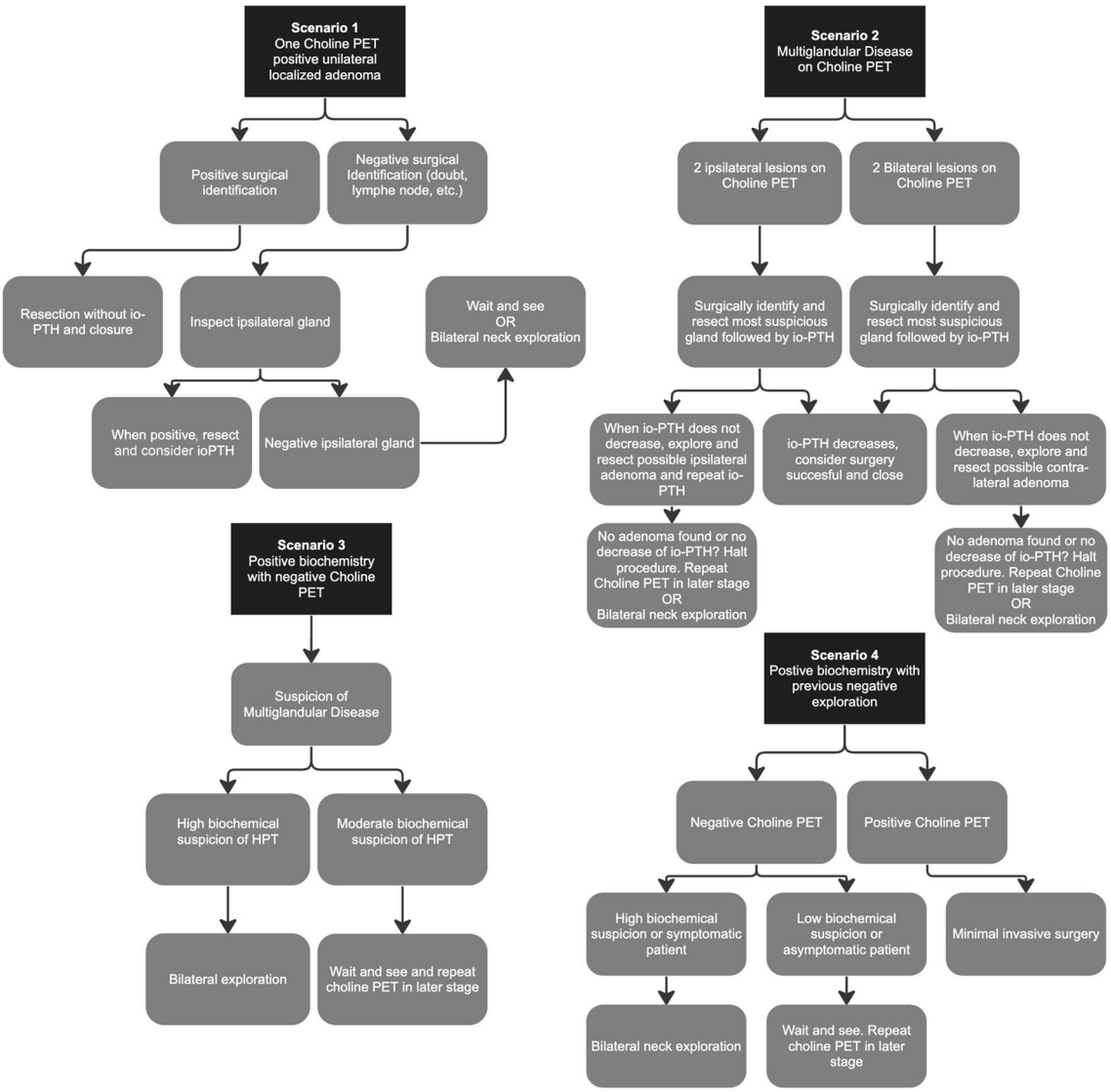

Fig. 1 Four different scenarios when utilizing choline PET/CT imaging as a diagnostic tool for localizing parathyroid adenomas: Scenario 1: One choline-positive unilateral lesion. Scenario 2: Multiglandular disease (MD) on a choline PET/CT scan. Scenario 3: Positive biochemistry with a negative choline PET/CT scan. Scenario 4: Positive biochemistry but a previous negative neck exploration

a matter of fact, existing literature suggests that in the case of well-localized adenomas, surgeons may not need to wait for their results [55, 56]. Io-PTH is often deemed most beneficial for patients with MD or for patients undergoing revision surgery. However, when a preoperative scan indicates a unifocal lesion, challenges may arise during surgery if the surgeon experiences uncertainties about whether the identified lesion is an adenoma, struggles to precisely locate it, or encounters a potential false positive result (such as choline PET/CT suggesting a lymph node). Should the surgeon still further explore the neck according to the classic routine? If there is no identified location on the contralateral side or in any other (ectopic) area on the choline PET/CT scan, it might be advisable to halt the procedure, leave the neck area untouched for a subsequent session, and repeat the choline scan after a certain time interval.

A second scenario is that choline PET/CT is so sensitive that we preoperatively encounter multiglandular disease (MD) more often. In the case of multiple ipsilateral lesions, the surgeon can operate and remove the most suspicious gland and perform an io-pTH, and if PTH is not convincingly decreased, inspect or remove the other ipsilateral lesion. Should the PTH hereafter still not decrease significantly, it might be questionable to cross the trachea, further explore, and look for the remaining two parathyroid glands. In this situation, there is a possibility of MD, and because of

the preoperative visualization of two adenomas on the same side, it may be strategically better to leave the contralateral side untouched for a potential future procedure and repeat the choline scan after a certain time interval. The scenario differs when the choline PET/CT reveals two or more bilateral lesions, and there is no reduction in io-PTH following the resection of the initial identified possible adenoma. In this case, a bilateral exploration should be considered.

A third scenario is one with positive biochemistry and no lesions on the choline PET/CT scan. From experience, endocrine surgeons, nuclear medicine physicians, and endocrinologists know that this scenario points into the direction of MD disease [57]. However, the question is, when a high-quality PET scan does not show target lesions, is it advisable and of benefit to patients to start an explorative four gland operation? Or does this depend on the magnitude of the biochemical suspicion (high or moderate) and/or symptoms of the patient (osteoporosis, kidney stones, etc.)? When these factors justify surgery, bilateral exploration can still be a good option.

Reoperations following a negative exploration in another center represent a distinct fourth scenario. Lower cure rates (82–98%) and elevated complication risks necessitate more stringent operation indications [58]. Choline PET/CT can significantly aid in these difficult cases where the golden rule is never to start surgery if there is no identified gland. A positive choline PET/CT scan sincerely helps the surgeon, and thus the patient, with a solution to these difficult problems.

Altogether, the surgical dogma "the only localization study indicated in a patient with untreated HPT is the localization of an experienced parathyroid surgeon" still applies today when it concerns surgical identification during the operation. However, without doubt, the availability of hypersensitive scans, such as choline PET/CT, will change our parathyroid surgical practice. Integrating functional scans with cost-effective anatomical imaging modalities such as ultrasound establishes a robust framework for precise surgical planning and execution. Due to the most recent developments, it appears that the available scans have taken a new step, from only functioning as a localizing entity, towards potentially functioning as a potential quantitative and negative predictive diagnostic module [59, 60]. For this reason, it is important to keep collecting data on the surgical management (bilateral neck exploration or wait and see) and the follow-up (including quality of life), especially from patients without positive localization on preoperative PET/CT, and develop imaging-based surgical guidelines. The current imaging evolution might prevent unnecessary surgery that has potential morbidity for patients. Of course, this means that sometimes not all biochemistry of the patient will be resolved but at least no harm will be done according to our physicians' Hippocratic oath.

Data availability Not applicable.

Declarations

Conflict of interest The authors declare no competing interests.

Informed consent Not applicable.

Ethical approval Not applicable to this Editorial.

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