Short Note

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Short Note

Clinical Importance and Evolving Applications of Parathyroid Scintigraphy

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Abstract

Parathyroid scintigraphy, primarily using 99mTc-sestamibi, is a cornerstone imaging modality for localizing hyperfunctioning parathyroid glands in primary, secondary, and tertiary hyperparathyroidism. Accurate preoperative localization facilitates minimally invasive parathyroidectomy and reduces surgical morbidity. Advances such as SPECT/CT integration, dual-tracer subtraction techniques, and artificial intelligence-assisted interpretation have significantly improved diagnostic accuracy, especially in complex or equivocal cases. Scintigraphy offers unique advantages in detecting ectopic glands and guiding re-operative surgery, although sensitivity declines in multigland disease or small adenomas. Complementary modalities, including high-resolution ultrasound, 4D-CT, and emerging PET tracers like 18F-fluorocholine, can enhance localization in challenging scenarios. Future developments—ranging from novel tracers to hybrid imaging and intraoperative guidance tools—are expected to further refine diagnostic pathways. Despite the growing role of alternative modalities, 99mTc-sestamibi scintigraphy remains the gold standard, valued for its functional mapping capabilities and enduring clinical utility in tailored surgical planning.

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Introduction

Parathyroid scintigraphy has become an indispensable tool for the management of hyperparathyroidism. In primary hyperparathyroidism (PHPT), and even in secondary or tertiary hyperparathyroidism, nuclear medicine imaging with *99m*Tc-sestamibi is highly sensitive for localizing hyperfunctioning parathyroid tissues, including ectopic glands. This is crucial for surgical planning; accurate preoperative localization of adenomas or hyperplastic glands enables minimally invasive parathyroidectomy (focused exploration) and reduces the need for extensive bilateral neck exploration [1]. In fact, at many centers, a dual-modality approach is used, combining sestamibi scintigraphy with high-resolution neck ultrasound as the first-line localization. When both scans concur, the localization is very reliable, and reports show a positive predictive value of up to ~97% for correctly lateralizing a parathyroid adenoma with concordant ultrasound and scintigraphy [2]. Thus, parathyroid scintigraphy plays a central role in the work-up of primary, secondary, and tertiary hyperparathyroidism, guiding surgeons by identifying the culprit gland(s) prior to incision.

Current Advances: Several technical advances and new applications are continuously improving the efficacy of parathyroid scintigraphy. The integration of SPECT/CT is one such advance that has markedly enhanced localization accuracy. Adding SPECT/CT to planar 99mTc-sestamibi imaging provides 3D anatomical correlation and boosts sensitivity (pooled sensitivity ~86% vs. ~70% with planar imaging alone). The hybrid SPECT/CT technique not only increases lesion detectability but also helps avoid false localization by differentiating parathyroid uptake from adjacent structures such as thyroid nodules or lymph nodes on fused images [3]. Another refinement is the use of dual-tracer protocols (e.g., 99mTc-sestamibi combined with 123I or 99mTc-pertechnetate). By acquiring a thyroid-specific scan and digitally subtracting it from the sestamibi image, the thyroid gland activity can be effectively canceled. This subtraction technique improves specificity and can unmask parathyroid adenomas that are otherwise obscured by nodular thyroid uptake. These innovations in imaging protocols have improved the overall accuracy of scintigraphic localization in challenging scenarios, such as in patients with coexisting thyroid disease.

In addition, emerging computer-assisted approaches have been poised to augment the interpretation of parathyroid scintigraphy. Artificial intelligence (AI) and machine learning algorithms have been applied to identify abnormal parathyroid tracer uptake, especially in equivocal cases. For instance, a recent convolutional neural network model (nicknamed "ParaNet") that simultaneously analyzes early and delayed sestamibi scans alongside thyroid scans was able to distinguish abnormal parathyroid scan results with approximately 96% accuracy (sensitivity, 96%; specificity, 97%) [4]. Such AI-assisted analysis could prove valuable for flagging subtle lesions or multi-gland diseases that might be overlooked by visual reads, thereby improving diagnostic confidence in difficult studies. Preliminary work has also shown that machine learning can predict multi-gland involvement in PHPT based on imaging and clinical parameters, [5]. which might inform surgical strategies. These developments indicate that in the near future, AI tools may become an adjunct to expert readers, enhancing the quantitative and objective assessment of parathyroid scintigrams.

Clinical Performance and Comparative Imaging: Parathyroid scintigraphy continues to demonstrate particular strengths in certain clinical scenarios. Its wide field of view allows exploration of the entire neck and mediastinum, enabling the detection of ectopic parathyroid glands that elude routine ultrasound [3]. This is a significant advantage in cases in which an adenoma is located in the mediastinum, carotid sheath, or other atypical locations. Scintigraphy also remains useful in re-operative parathyroid surgery: even though scar tissue and distorted anatomy can make localization challenging, a positive sestamibi SPECT/CT scan can direct the surgeon to a remnant or missed gland, potentially avoiding blind re-exploration. However, it should be noted that the sensitivity of 99mTc-sestamibi scans is highly variable and can decline in multigland disease. Multi-nodular hyperplasia or double adenomas often yield negative or only faintly positive scans, and one series reported SPECT/CT sensitivity of approximately 78% for single-gland disease but only ~31% for multi-gland cases [6]. Likewise, very small adenomas (<0.8 g) or adenomas in patients with only mild biochemical abnormalities may not sufficiently retain sestamibi, leading to false negatives [7]. In such situations, adjunct imaging modalities may complement scintigraphy. High-resolution ultrasonography is an excellent complementary test; it has no radiation and can readily identify superficial parathyroid tumors, but it is operator-dependent and often fails to visualize glands that are deep, retroesophageal, or intrathoracic. Ultrasound also struggles in the setting of reoperative necks or concomitant thyroid goiter. In contrast, Sestamibi scintigraphy is less limited by neck anatomy and can survey ectopic areas; however, it may produce false-positive results from thyroid nodules, lymph nodes, or inflammatory thyroid tissues [3]. Thus, these two tests are often used together to balance each other's limitations. Indeed, combining ultrasound with scintigraphy yields higher detection rates than either method alone, as noted above.

In recent years, four-dimensional CT (4D-CT) has emerged as a potent alternative or adjunct to nuclear scintigraphy. 4D-CT entails multiphase contrast-enhanced CT imaging of the neck (e.g., non-contrast, arterial, and venous phases), exploiting the hypervascular nature of parathyroid lesions. This technique provides excellent anatomic detail and dynamic enhancement characteristics that can differentiate parathyroid lesions from those of the thyroid or lymph nodes. Evidence suggests that 4D-CT can achieve localization accuracy on par with sestamibi scans, and in some studies, even exceed it. For example, a 2019 prospective study found that 4D-CT offered superior preoperative localization compared to sestamibi SPECT/CT in both single- and multi-gland diseases. The addition of sestamibi did not significantly improve localization beyond that provided by 4D-CT alone [8]. Similarly, in patients whose conventional scintigraphy is negative, 4D-CT has shown high success

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rates in identifying lesions: a recent report documented that 4D-CT correctly detected parathyroid adenomas in the majority of cases with negative sestamibi scans, substantially improving surgical guidance [2]. However, trade-offs include a higher radiation dose (particularly to the thyroid gland) and the need for iodinated contrast. Notably, thyroid radiation exposure from 4D-CT can be dozens of times higher than that from a sestamibi scan, which is an important consideration for younger patients. In addition, 4D-CT requires specialized expertise in interpretation and may not be universally available. In practice, many centers employ ultrasound and scintigraphy first, reserving 4D-CT for problematic cases, such as non-localizing PHPT or re-operative necks. This selective use helps to minimize unnecessary radiation while capitalizing on 4D-CT's strengths when needed. Scintigraphy continues to hold ground as a first-line, low-risk, functional imaging modality, especially in institutions with strong nuclear medicine capabilities [9]. At the same time, the complementary role of 4D-CT is well recognized when anatomical problem-solving is required.

Future perspectives: The role of parathyroid scintigraphy is evolving alongside innovations in both imaging technology and surgical practice. The shift toward minimally invasive parathyroid surgery is a prime example of the widespread adoption of preoperative localization (largely via sestamibi scanning), which has enabled focused parathyroidectomy to become the standard treatment for most PHPT patients [3]. This trend will likely continue, with scintigraphy remaining integral to patient selection and operative planning for targeted outpatient parathyroidectomies. In the operating room, nuclear medicine techniques are also aiding surgeons: radioguided parathyroidectomy using intraoperative gamma probes can facilitate the identification of the radiotracer-avid gland, serving as a "homing signal" after an appropriate pre-op tracer dose. Additionally, novel optical methods such as near-infrared autofluorescence (which exploits the intrinsic fluorescence of parathyroid tissue) are being explored to further improve intraoperative gland detection [10]. These tools, used in conjunction with preoperative scintigraphy, could increase surgical precision and reduce failure rates in the future. Positron emission tomography (PET) tracers have garnered attention in difficult cases. Radiolabeled choline analogs, in particular, have shown outstanding performance in localizing parathyroid adenomas that 99mTc-sestamibi scans miss. For example, 18F-fluorocholine PET/CT can detect hyperfunctioning glands in patients with negative or inconclusive sestamibi studies, with a reported per-patient sensitivity of approximately 95%, which is markedly higher than that of conventional imaging in that setting. In addition to its higher sensitivity, fluorocholine offers shorter scan times and lower radiation dose than SPECT/CT [3]. While costs and limited availability currently restrict the routine use of parathyroid PET, ongoing studies (and recent regulatory approvals in some regions) suggest that these advanced tracers will soon become more widely adopted, especially for reoperative or atypical cases. Other tracers (e.g. 11C-methionine, or even 18F-FDG in parathyroid carcinoma) have niche applications, but none has yet supplanted sestamibi, which remains the workhorse agent. Future developments may include hybrid imaging approaches, such as PET/MRI, combining the sensitivity of PET with the excellent soft-tissue contrast of MRI, which has already been piloted for simultaneous dynamic contrast and fluorocholine imaging. Moreover, the quest continues for a parathyroid-specific radiopharmaceutical (targeting a unique receptor or protein) that can increase specificity [9].

In moving forward, an individualized and evidence-based approach is paramount. No single modality suits all situations; an optimal localization plan should be tailored to each patient's clinical profile, considering the possibility of multiglandular disease, prior neck operations, concomitant thyroid pathology, resource availability, and radiation concerns. The current literature underscores this point – despite many advances, there is still no universal consensus on a one-size-fits-all imaging algorithm [3].. Therefore, we echo the call for more prospective, multicenter studies to refine parathyroid imaging protocols and identify the best practices for various clinical scenarios. Rigorous comparative studies (e.g., ultrasound + SPECT/CT vs. 4D-CT vs. PET in different patient subsets) would help clarify the most efficient pathways for accurate localization. Such research, along with continued technological development, will ensure that parathyroid scintigraphy remains at the cutting-edge.

Closing remarks: Even as new techniques emerge, 99mTc-sestamibi parathyroid scintigraphy retains its status as the gold standard imaging modality for hyperparathyroidism. Decades of clinical use have proven its utility in guiding curative surgery, and recent innovations have strengthened its performance. In our view, parathyroid scintigraphy will continue to be the cornerstone of preoperative localization, enhanced by SPECT/CT, augmented by adjunct modalities, and increasingly aided by computer intelligence. Its enduring role is assured by its unique ability to provide functional mapping of parathyroid disease, which remains fundamentally important for personalized surgical planning. We look forward to ongoing advancements and collaborative studies that will further improve the accuracy and applications of this time-tested, yet ever-evolving imaging modality.

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