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EDITORIAL

Parathyroid Imaging—Current Status and Future Prospects

The prevalence of hyperparathyroidism seems to be increasing (*1*). Some of this apparent increase is due to the earlier detection of hypercalcemia through the routine measurement of serum calcium in clinical chemistry screens. This increasing prevalence of suspected hyperparathyroidism, as indicated by an elevated serum calcium detected on a routine screen, may be no more than a lead time bias induced by the detection of a chemical abnormality in presymptomatic patients. Some presymptomatic hyperparathyroidism may not ever become clinically significant. The role of further diagnostic work-up of patients with hypercalcemia is controversial, because there have been very few studies on the implications of presymptomatic hyperparathyroidism. Further diagnostic studies, which attempt preoperative localization of abnormal parathyroid tissue in patients with suspected hyperparathyroidism, present an even greater problem in efficacy. As many as 90%–95% of individuals with symptomatic hyperparathyroidism and hypercalcemia will be readily treated by an experienced surgeon without preoperative localization of the abnormal gland (*1–3*). The question becomes: does every patient with a chemically detected hypercalcemia, who may indeed have an occult parathyroid adenoma, warrant further diagnostic studies directed toward the localization of that prospective parathyroid lesion? Some authors have questioned whether every patient with asymptomatic hyperparathyroidism even needs surgical removal of the offending gland (*4*). With this background, we need to assess the propriety and utility of alternative schemes designed to locate a parathyroid lesion preoperatively.

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There is a long history of nuclear medicine efforts to diagnose and locate abnormal parathyroid tissue. Sisson and Beierwaltes, in 1962, attempted the use of radiocyanocobolamine with only modest results (*5*). Subsequently, Potchen (1963) demonstrated prospects for ^{75}Se localization of parathyroid tissue (*6*). This too had only minimal clinical utility. The utility of selenomethionine was dependent upon tissue blood activity changes over time. The time-dependent variation in tissue activity contrast is similar to the time-dependent relative thyroid parathyroid activity with ^{99m}Tc-sestamibi reported in this issue (*7*).

In addition to these early radioisotopic approaches, other techniques had been attempted for the preoperative localization of hyperactive parathyroid adenomas. Esophageal displacement, as seen on the barium swallow, had been the standard approach in the early detection of abnormal parathyroid tissue. This technique was rarely successful in identifying lesions not detected at the time of surgery. Since then, multiple alternative diagnostic modalities have been advocated for the detection of abnormal parathyroid tissue. A group at the NIH had early experience with parathyroid angiography and venous sampling (*8*). More recently, there have been multiple studies using ultrasound, CT, magnetic resonance and nuclear medicine procedures (*1,9–11*). These techniques have a similar sensitivity and specificity depending, in part, upon the size of the lesion. The non-nuclear procedures are based on the anatomy, rather than the metabolism, of the parathyroid adenoma. Kobayashi et al. reported that hyperplasia was less easy to detect than a primary parathyroid tumor. They concluded that the CT scan was superior to the Tl-Tc subtraction image or to ultrasound for locating hyperplasia (*12*). Gooding et al., in 1986, reported on the comparison of Tl-Tc double-tracer scintigraphy with high-resolution ultrasound. They observed that neither modality was particularly sensitive to detect primary hyperplasia and that the combined techniques were more effective than the use of any single modality. They concluded that both double-tracer scintigraphy and high-resolution ultrasound should be done in patients who have had previous parathyroid surgery, inasmuch as no single technique had sufficient sensitivity to detect the abnormality in many patients. Most of the tumors which have been detected by anatomically defined means have been those tumors that may be readily detected at the time of surgery. Relatively few published series comparing the various techniques were designed to study the efficacy of preoperative localization of a difficult parathyroid adenoma in those patients with clinically significant hyperparathyroidism and in whom surgery had failed to locate the abnormal gland (*13*). A group from Hammersmith Hospital, however, reported successful preoperative localization of a 7-mm intrathyroidal parathyroidal adenoma using dual-tracer substraction scintigraphy (*14*).

The methods of Tl-Tc subtraction scintigraphy have undergone many iterations in efforts to improve the sensitivity and specificity in locating smaller parathyroid adenomas that are not readily distinguished at the time of surgery. Brownless and Gimlette compared the various techniques in dual-subtraction scintigraphy to ascertain how small a parathyroid adenoma could be for potential detection with this technique. Their phantom studies suggest that a lesion as small as 0.3 g parathyroid could be seen in a 5-min image with a pinhole camera (*15*).

Of the published series applying the Tl-Tc subtraction techniques, none have been limited to the difficult parathyroid lesion (*16–19*). Some have had relatively poor results (*17*), whereas others have had positive experiences (*14*). Samata et al. published one of the larger series, in which 86 consecutive patients with clinical indications of hypercalcemia had subtraction parathyroid scans. Only 53 of these studies were deemed technically adequate in patients in whom the hypercalcemia may possibly be due to hyperparathyroidism. Thirty-eight percent of these patients had positive scans. Of the 13 patients who had surgery, the parathyroid adenoma was correctly located in ten. Whether these adenomas would have been readily found at surgery without a preoperative scan was not reported. These authors advocate the use of the adjusted calcium phosphate product ratio to creatinine as an index of whether or not parathyroid imaging will be useful to localize parathyroid adenomas. In their experience, the chemical measurement of Ca x P/Cr was significantly lower in the scan positive group, which also had a significantly higher mean level of PTH than did those patients who were scan-negative. These studies correlate the sensitivity of the dual-subtraction scan to the metabolic activity of the parathyroid adenoma. Thus, this nuclear medicine procedure is not necessarily dependent on the size of the adenoma, as in CT, US and MRI. The anatomy of the gland is the requirement for CT, MR or ultrasonic identification of abnormal parathyroid tissue (*16*). These nonradioisotopic procedures are severely limited when seeking to identify small parathyroid adenomas which were not found at the time of surgery.

Faced with this background, recent interest has been developed in alternative nuclear medicine approaches to locate hyperactive parathyroid glands. Researchers at Washington University in St. Louis have developed a parathyroid-specific monoclonal antibody (*21–22*). Their antibody is an effective experimental model. They have not yet reported on clinical experience using this technique.

More recently O'Doherty et al., have applied ^{99m}Tc-sestamibi for the preoperative localization of parathyroid tumors (*23*). This modality has been well recognized as a useful agent for myocardial imaging (*24*). O'Doherty et al. sought to compare the standard pertechnetate-T1 subtraction technique with ^{99m}Tc-sestamibi. They presented 40 adenomas, of which 37 were localized with the Tl subtraction technique and 39 with sestamibi. In 15 patients with hyperplastic glands, 29 glands were localized with Tl and 32 with sestamibi. The uptake per gram of parathyroid tissue with sestamibi was higher than the uptake per gram of thyroid tissue. The authors concluded that this may be true in part due to a higher target-to-background ratio and to the superior physical characteristics of ^{99m}Tc.

In this issue of the *Journal*, Taillefer et al. further developed the sestamibi approach. They report that a double-phase study, in which the time dependence of localization within the thyroid and parathyroid tissue, is used to accentuate the parathyroid image relative to the thyroid background. This is due to the fact that the tissue kinetics of the thyroid and hyperactive parathyroid have substantially different resident times for ^{99m}Tc-sestamibi. While there is a need for more accurate data on the kinetics of ^{99m}Tc-sestamibi thyroid and parathyroid uptake, it is apparent from this paper that there is a substantial prospect toward refining and improving parathyroid imaging methods. Technetium-99m-sestamibi has a number of advantages over other techniques: (1) technetium has superior physical characteristics and (2) the application of the differential metabolism of thyroid, parathyroid and hyperactive parathyroid tissue in the localization scheme. Thus, this technique has a greater potential than other methods for locating small adenomas not found at surgery.

There is now a need for a more comprehensive prospective study to document sestamibi's ability to identify small, surgically obscure parathyroid lesions. Surgically obscure parathyroid adenomas, which lead to clinically significant hyperparathyroidism, are an infrequent occurrence. It will be necessary to consider a multi-institutional prospective study using the techniques advocated by Taillefer et al. Indeed, although these clinical problems may not be common, there are a number of patients who could substantially benefit from this marginal contribution to the localization of parathyroid adenomas. Taillefer's observations from a sufficient framework upon which further prospective studies are clearly warranted.

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