

Parathyroid Imaging

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I do not remember who first said (but wish it was I) that new medical techniques lose their potency as soon as they are compared to the next one. This cynical view could be taken about parathyroid scintigraphy with dual-isotope (thallium-201/technetium-99m), which was announced with high sensitivities and high specificities, but hardly had time to flourish before the onslaught of high-resolution computed tomography, high-resolution ultrasonography, and finally nuclear magnetic resonance imaging.

It cannot be denied that widely varying results have been reported, at least as far as the sensitivity is concerned. We reviewed a number of papers, more or less at random, and tabulated the results in Table 1 (1-16). While the specificity was uniformly good, the sensitivity was found to vary from 0.94 to 0.26.

First, how can results of a single (and simple) technique vary as widely as we show in Table 1? There are two working hypotheses. In the first, one assumes that putative authors who test a technique are discouraged or never heard of again if the early results are not good. The published results of methodology papers are the consequence of random series, with a selection bias in favor of lucky streaks. A correction is (later) introduced when other investigators, without making a claim of introducing a new technique, merely check the clinical efficacy.

This hypothesis remains unattested by its very nature, but is supported by the fact that the technical papers uniformly had the best results. This does not explain, however, why such a variation in the results does indeed exist. The second hypothesis is verifiable, at least in principle: series do differ because they contain different populations.

The concentration of thallium in the lesions is due to the combination of cellularity and blood flow. Highly perfused lesions are provided with large amounts of the tracer, cellular lesions are able to accumulate and retain the intracellular tracer. Cellularity and perfusion may vary (independently), and therefore one can expect a wide range

of concentrations. For any given concentration, a minimal size is needed for detection. *Pari passu*, larger lesions are more easily detected. In a separate paper, Gimlette found that the lower limit of detectability lies between 0.006% and 0.0149% of the injected dose, and between 250 and 800 mg (17).

Unfortunately, few authors give sufficient information to confirm the hypothesis. From the same references shown in Table 1, we culled size or weight information where we could, and tabulated the results in Table 2. As expected, size does play a role, but not in a uniform manner. This is no great surprise, since the contrast in the image also depends on the concentration in the lesion and in the surrounding tissues. In those few cases where individual sizes are noted, we found on the aggregate a detection rate of 0.41 below 500 mg, 0.43 between 500 and 1000 mg, 0.61 between 1000 and 2000 mg, 0.61 between 2000 and 3000 mg, and 0.66 for lesions larger than 3000 mg.

If the size of the lesion is sufficient to explain the variation between published series, we have to accept that the sensitivity of dual-isotope scintigraphy lies somewhere around 0.62. This is no cause for joy, certainly not if one considers that larger lesions, which are better detected scintigraphically, are probably easily found by palpation, and make the imaging technique superfluous.

There is, however, a saving grace: specificity is uniformly high, in the range of 0.95 (3,5,9,11-12,14,16,18,19). And there lies the potential application.

It has been proposed that the use of parathyroid imaging is not the diagnosis of parathyroid adenoma or hyperplasia, a diagnosis which is better made on biochemical criteria, but the location of the lesion(s) to facilitate (and shorten) surgery. What is required is therefore a high positive predictive value for location. In a given patient there are generally four possible juxtathyroidal sites and one potential ectopic site. The prevalence at any juxtathyroidal site is thus of the order of 0.25. From Bayes' theorem, we can deduce that the positive predictive value is therefore $0.25 \times 0.62 / (0.25 \times 0.62 + 0.75 \times 0.05)$ or at least (because juxtathyroidal locations are more frequent) 0.80. In fact, if we are allowed the indiscretion of quoting our own experience, the positive predictive value for adenomas was 0.80 with a sensitivity of 0.53 and a specificity of 0.96.

It is a feature of the present times that economic considerations have to be included. Note that if 100 studies are

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TABLE 1
Sensitivities

Scint.	CT	HRCT	US	HRUS	NMR	
0.66 (21)	—	—	—	0.59 (17)	0.75 (24)	1
0.72 (22)	—	—	—	—	—	2
0.67 (67)	—	—	—	0.72	—	3
0.76 (26)	—	—	—	—	—	4
0.81 (22)	0.73 (23)	—	0.81 (22)	—	0.74 (23)	5
0.88 (17)	0.82 (17)	—	0.76 (17)	—	—	6
—	—	0.08 (10)	—	—	—	7
0.37 (95)	—	—	—	—	—	8
0.26 (34)	0.47 (51)	—	0.26 (50)	—	0.50 (16)	9
0.72 (22)	—	—	—	—	—	10
0.94 (18)	—	—	—	—	—	11
0.90 (10)	—	—	—	—	—	12
0.91 (12)	—	—	—	—	0.93 (14)	13
—	0.45 (42)	0.76 (46)	—	0.65 (88)	—	14
0.53 (143)	0.54 (143)	—	—	0.43 (143)	—	15
0.88 (53)	—	—	—	0.75 (24)	—	16
0.62	0.55	0.77	0.49	0.57	0.72	
(562)	(276)	(56)	(89)	(339)	(77)	

In this table, published sensitivities from references 1-16 are tabulated. The numbers in parentheses are the total number of lesions. The modalities are: dual-tracer scintigraphy (Scint.), computed tomography (CT) and high-resolution CT (HRCT), ultrasonography (US) and high-resolution ultrasonography (HRUS), and nuclear magnetic resonance imaging (NMR).

performed, only 62 will be correctly positive, and an additional 15 will be misleading. If one puts no price on the misleading information, the actual cost of a successful imaging procedure is still 1.61 times the cost of the procedure itself.

Two questions come immediately to mind: Is there an alternative? Can one select cases in which one is likely to be more successful?

The selection of potentially more favorable cases by size was dispensed with in the above discussion. It has been suggested that hyperplasia is not as likely to be detected as adenomas. However, this is probably due to the smaller size of the hyperplastic glands. For adenomas, we found in the sampled papers that the average size was 1840 mg with a detection rate of 0.66 (187/281), in contrast hyper-

TABLE 2
Sensitivities as a Function of Weight (mg)

W	Scint.	CT	HRCT	US	HRUS	NMR
20	0.71 (7)	—	—	—	0.33 (6)	—
86	0.33 (9)	—	—	—	0.57 (7)	—
185	0.69 (13)	—	0.00 (1)	—	0.90 (11)	—
291	0.26 (56)	0.00 (15)	—	0.26 (15)	0.57 (7)	0.00 (5)
385	0.60 (15)	—	—	—	0.577	—
487	0.33 (78)	0.28 (67)	—	—	0.20 (73)	—
650	0.55 (9)	—	—	—	1.0 (3)	—
850	0.60 (5)	—	—	—	0.20 (5)	—
997	0.86 (15)	—	—	—	0.66 (3)	—
1200	0.76 (13)	—	—	—	0.75 (4)	—
1500	0.57 (76)	0.55 (18)	—	0.29 (17)	0.80 (5)	—
3000	0.90 (22)	0.82 (17)	—	0.76 (17)	0.33 (3)	—
3750	0.77 (76)	0.77 (76)	—	—	0.65 (76)	—
>4000	0.81 (27)	0.77 (18)	—	0.22 (18)	1.0 (2)	0.85 (7)

The data in this table were culled from references 1-16 where available. The values for weight (W) are the averages. The grouping was according to mid-range.

plasia with an average weight of 619 mg, and a detection rate of 0.60 (316/519). The difference is not significant.

Prior surgery has been believed to decrease the sensitivity, but from the available data, the hypothesis cannot be supported. We found on the aggregate that for first-look surgery the sensitivity was 36%, and for second-look surgery, 32%, in those papers where the data were given (1-5,9,13,15-16).

Finally, would the biochemical state of the patient correlate with the detection rate? In our experience, the serum calcium level did not, and the parathyroid hormone level did so only to an insignificant level.

The alternative imaging methods have high potential, since their spatial resolution may be close to an order of magnitude better. The results, however, are disappointing, at least in our brief survey (Tables 1 and 2). This is not surprising, since there is, even with a relatively low resolution, a distinctive advantage in favor of the detection of "hot" lesions.

Indeed, if the relative sensitivities of the alternative modalities are as suggested by the data in Table 1, the vexing problem of complementary arises. The problem is vexing, since the solution is the use of multiple modalities to achieve the same goal. At best, the results of the modalities are independent, that is, the probability of detection by one modality is unaffected by the failure to detect by another. We found no data to support this view (20). At the limit, size ought to have some effect on all modalities (Table 2).

However, if independence can be assumed, the detection rate by multiple modalities can be derived. We assume that the numbers in Table 1 are correct for dual-isotope scintigraphy, high-resolution computed tomography and ultrasonography, and nuclear magnetic imaging. Of 100 abnormal glands, scintigraphy would detect 62. Of the remaining 38, high-resolution computed tomography would detect 77% or 29; of the remaining 9, high-resolution ultrasonography would detect 57% or 5; and of the remaining 4, nuclear magnetic resonance would detect 72% or 3. One case only would remain undetected. If all modalities had the same unit price, the total cost to detect the 99 cases would be 100 + 38 + 9 + 4 = 151 unit prices.

The order does matter as follows. If we proceed by decreasing sensitivity, the procedure is high-resolution computed tomography (77), nuclear magnetic resonance imaging (17), scintigraphy (4), and ultrasonography (1). The cost would be 131 unit prices for the same detection rate. In addition, the cost would, however, include mislocations.

On review, we found the specificities to be better than 95%, except for nuclear magnetic imaging, where the value seems closer to 90%. In the second scenario, one would correctly localize 77 cases and mislocate 4 with high-resolution tomography. Of the 19 remaining cases, 14 would be detected by nuclear magnetic resonance, and 1 would be mislocated. Two more would be gained by

scintigraphy, perhaps with one mislocation, shared with the next step to locate the 99th lesion. Mislocations would be 5 or 6 for a total gain of 94 at the end of the sequence.

What is one to conclude? There are obvious hazards in mega-analysis of published results. In our experience, the sensitivity was 0.53 (48 cases); a recent paper reports 0.38 for 113 cases (21). Inclusion or exclusion of one paper would change the average value significantly, since the total number of reported cases is not very large (562 in Table 1).

It is probably safe to conclude the following:

1. While the values found in the literature for the sensitivity for the location of parathyroidal adenomas or hyperplastic glands vary widely, they seem to be settling around 60% or lower, and the specificity is uniformly high.
2. There are no clinical or biochemical predictors of success.
3. The alternative modalities are probably not much better (yet?).
4. If much value is placed on preoperative location of the lesion, sequential studies can be considered, preferably in a sequence according to the sensitivity, on an order modulated, however, by the relative cost.

We should hope, however, for a better alternative.

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