Preoperative Parathyroid Localization by Superimposed Iodine-131 Toluidine Blue and Technetium-99m Pertechnetate Imaging

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A new parathyroid scintigraphic localization study by a dual radioisotope technique using radioiodinated toluidine blue (RTB) for the parathyroids and ^{99m}Tc for thyroid imaging is presented. A simple RTB labeling procedure achieving 99% tagging of the ^{131}I-TB was used. The RTB was found to be a highly specific parathyroid radiotracer, consequently enabling superimposition of the delineated thyroid gland over the RTB avid parathyroid foci without a need for subtraction of the thyroid or vascular background. Forty-six patients with primary hyperparathyroidism underwent scintigraphic study prior to cervical (41 patients) or mediastinal (5 patients) exploration and 67 pathological parathyroid glands (34 adenomas and 33 hyperplasias) were excised. On follow-up, serum calcium level returned to normal in all patients. Correlation of the scintigraphic results with the surgical findings disclosed a sensitivity of 93%, with a specificity of 80% and an overall accuracy of 87%. This new simplified and specific RTB scintigraphic method justifies its use as a routine procedure for preoperative parathyroid scintigraphic localization in primary hyperparathyroidism.

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Variable location of the parathyroid glands may be the cause for incomplete removal or negative exploration during surgery for hyperparathyroidism, resulting in persistent hypercalcemia (*1,2*). Re-exploration, occurring in 10% of patients having parathyroid surgery, is less successful and more complicated, involving sternotomies in 15% of patients, and may even be fatal (*3*).

An accurate technique for preoperative localization of the parathyroid glands is therefore needed. Various imaging methods are available, such as angiography (*4,5*), venous catheterization with PTH-RIA sampling (*6,7*), thermography (*8*), ultrasonography (*9,10*), computed tomography (CT) (*11*), and recently nuclear magnetic resonance (NMR) (*12*), but all have limitations and some questionable reliability.

Scintigraphic demonstration of the hyperactive parathyroid gland may serve two purposes: functional and morphological, by pointing to the hyperactive gland and pinpointing its exact location. The initial enthusiasm following the introduction of [^{75}Se]selenomethionine in 1964 as a parathyroid radiotracer (*13,14*) was not justified by later investigations (*15,16*). Various other radiotracers were used, such as cesium-137 (*17*), gallium-67 (*18,19*), and technetium-99m (*20*). Recently thallium-201 has been investigated (*21–23*); however, the expected results were not fully obtained.

Toluidine blue (TB), an inorganic histologic dye that specifically stains the parathyroid glands (*28,29*), has been used since 1966 for intraoperative macroscopic visualization of parathyroid glands (*30,31*). Methylene blue (MB) reacts similarly (*32*). Toluidine blue was radioiodinated (*33*) and investigated in animals (*34,35*) and humans (*36,37*). In 1970 a simple labeling method was introduced (*38*) and radioactive toluidine blue (RTB) became readily available. It was then used extensively in hepatobiliary (*39,40*) and pancreatic studies (41).

We employed RTB for preoperative localization of parathyroid pathology using a ^{99m}Tc superimposition method and reported our preliminary results in 1981 (*42*). Since then, the technique has been improved and a larger group of 46 patients was studied.

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MATERIALS AND METHODS

From 1980 to 1985, 95 patients underwent parathyroid scintigraphy with RTB for hyperparathyroidism. Forty-six consecutive patients (24 men, 22 women, age range 13–82 yr, mean age 48 yr) with clinical and laboratory diagnosis of primary hyperparathyroidism were treated surgically, and these patients form the present study. The patients' clinical presentations included renal diseases (28 cases), skeletal disorders (5 cases), gastrointestinal diseases (7 cases), cardiovascular diseases (12 cases), and neuromuscular deficiencies (28 cases); many patients had more than one disorder. Four patients had previous negative surgical exploration with persistent symptomatic hypercalcemia and one patient had asymptomatic hypercalcemia. Eleven patients had associated diffuse or nodular goiter. All patients had abnormally elevated serum calcium levels (range 10.8–15.2 mg%, mean 11.4 mg%, normal 8.5–10.5 mg%) and varying phosphorus levels (range 1.8–5.8 mg%, mean 2.9 mg%, normal 2.5–4.5 mg%). Serum PTH-RIA (a measure of the carboxy terminal region) was elevated in 42 patients (range 850–4000 ng/ml, mean 2100 ng/ml) and normal in four patients (range 500–800 ng/ml, mean 700 ng/ml, normal up to 800 ng/ml). All 46 patients underwent combined sequential RTB and [^{99m}Tc]pertechnetate parathyroid–thyroid scintigraphy for preoperative localization of parathyroid pathology. In some patients, ultrasonography and computed tomographic studies were also performed.

Preparation of the Iodine-131 Toluidine Blue

We used commercial toluidine blue (TB)[*] (toluidine chloride); bluten chloride, 3-amino-7-dimethyl-amino-2 methylphenazathionium chloride; dimethyltoluthionine chloride, Schulz-1041, Cl-925, tolazul) (Fig. 1).

Radioiodination of the dye was accomplished by an exchange of H with ^{131}I according to the following procedure developed in our laboratory (*38*): 20 mg of TB was dissolved in 1 ml distilled water and 0.5 ml of potassium iodide/iodate solution (465 mg KI + 307 mg KIO_3 in 100 ml distilled water) were then added. Next, 10 mCi of ^{131}I of high specific activity (10 mCi/l μg I) without a reducing agent[†] and one drop of concentrated HCl for acidification were added.

The mixture was incubated for 15–20 hr at room temperature. The labeled RTB was separated from the free ^{131}I by passing the mixture through a 15-cm-high column with an anion exchange Dowex 1-X8, 50-100 mesh. The final yield of RTB was 50%–80%. The compound was stable, with a shelf life of over 40 days. After preparation the RTB was sterilized by passage through a Millipore filter and was checked first for sterility (by bacteriological culture), then for dosimetry (the established dose for adult patients was 13–15 μCi RTB/kg body weight, which is ~1 mCi RTB), and for toxicity (a1-mCi dose of RTB contained <1 mg of TB). The toxic dose of TB is 10 mg/kg body weight, or 700 mg/adult (*30*). Most of the RTB was used within the first week after preparation; therefore, the injected amount of TB did not exceed 1–2 mg/adult patient dose. Radiochemical purity was checked by radiochromatography using a solvent n-butanol:glacial acetic acid:water (60:15:25), and Whatman paper No. 1. The Rf of RTB = 0.75 and of ^{131}I = 0.32. The results obtained indicated 94%–95% RTB, 0.5%–1.0% free ^{131}I, and 1%–5% isomers in the intermediate and near-final radiochromatographic regions, having similar tracer kinetics as RTB.

Parathyroid–Thyroid Visualization (RTB-^{99m}Tc Superposition Technique)

The scintigraphic study was performed in three steps using a gamma camera equipped with a 6-mm pinhole collimator interfaced to a computer.

Parathyroid scintigraphy. The patient was positioned supine and immobilized with extended neck, 7–8 cm below the pinhole collimator. The camera was set on 364 keV with 20% window. The field of view included the neck and upper mediastinum (6–8 cm below the sternal notch). One minute after i.v. injection of RTB, sequential scintigraphic recording of the parathyroids was started and continued in 5-min frames for 30 min (Fig. 2A). The tissue concentrations of the RTB (hot foci) started ~1 min after injection and increased in concentration during the next 5 min, reaching a maximum at 5–15 min, gradually decreasing and disappearing by 30 min. During the data acquisition, a total of 180,000 counts was accumulated. The images were acquired using 128 × 128 matrix and stored on a disk for further analysis. During the last few seconds of the acquisition, two ^{57}Co point sources[‡] were used to mark the thyroid cartilage and sternal notch.

Thyroid scintigraphy. Without changing the position of the patient or the camera, 5 mCi of ^{99m}Tc was injected i.v. and scintigraphy was performed 15 min later using 140 keV, 20% window, accumulating a total of 200,000 counts. Topographic marking with the ^{57}Co point sources of the sternal notch, thyroid cartilage, and palpated neck masses was added in the thyroid image, which was computer acquired. The image was stored on the same disc.

Computer processing of the RTB and ^{99m}Tc images was performed in four steps (Figs. 2A–2D). The RTB images were displayed on the screen and abnormal RTB foci were noted (Fig. 2A). A summation of the frames was obtained and stored (Fig. 2B). The ^{99m}Tc thyroid image was displayed, and the thyroid borders, including the anatomic landmarks and palpated masses, were manually outlined as regions of interest (ROIs) (Fig. 2C). A superposition of the ROIs from image C on RTB image B resulted in a composite image D (Fig. 2D).

This final figure showed the topography of the RTB concentrations and their relation to the outlined thyroid gland and the other ROIs. The topographic marker foci from the RTB study were also superimposed in the final image (D) to

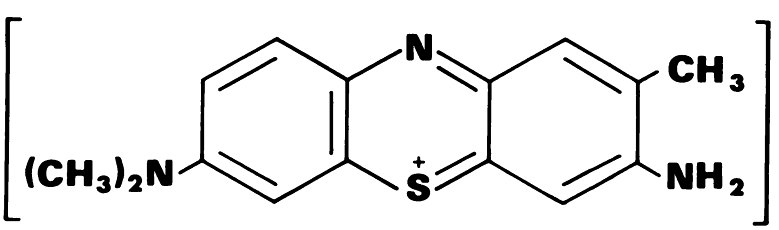

FIGURE 1
Proposed structural formula of toluidine blue; molecular weight, 436 (*38*).

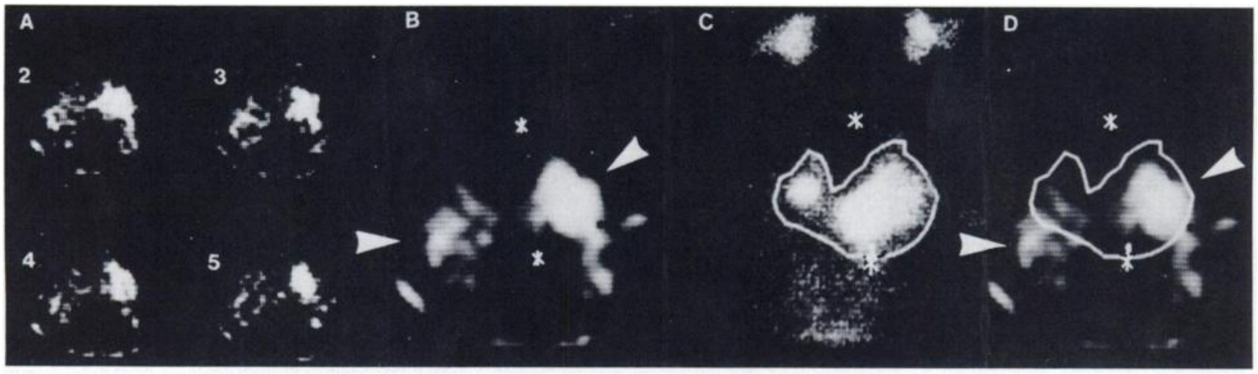

FIGURE 2
Presentation of our RTB + ^{99m}Tc superimposition technique for preoperative localization of the parathyroids, performed in four sequential stages (A–D) in a 35-yr-old hyperparathyroid patient. A: Four 5-min consecutive RTB images (frames 2–5). The maximal RTB concentration appears during the second and third frames or 5–15 min after i.v. administration and decreases in the following frames. Two RTB foci are apparent. B: Summation of the sequential images in (A) with ^{57}Co markers on two topographic sites denoted by two white asterisks located at the thyroid cartilage and sternal notch. The two RTB foci are indicated by arrows. C: ^{99m}Tc pertechnetate thyroid scan of the same patient 15 min after i.v. administration with outline drawing of the thyroid border and the ^{57}Co topographic points (ROIs), denoted by the two asterisks (see [B]). D: Superimposition of the ROIs in image (C) over the final RTB image in (B). A final composite RTB ^{99m}Tc image (D) is obtained. The two RTB foci are indicated by arrows and appear to be localized in the neck in left upper and right lower regions of the thyroid scan. During surgery, two hyperplastic parathyroids weighing 800 and 300 mg respectively as correctly localized by RTB scintigraphy were removed.

assure immobilization of the [^{99m}Tc]RTB images during the sequential imaging procedure. Visualization of images B, C, and D allowed us to diagnose separately RTB foci and ^{99m}Tc concentrations related to parathyroid and thyroid tissues. Image interpretation was performed by two physicians. There was observer agreement in 43 of 46 studies. In the remaining three studies a consensus was agreed on.

Scintigraphic Evaluation

A positive RTB focus was defined as a localized radiodye concentration appearing within 1–2 min after injection and persisting for 10–20 min. The localization of these abnormal foci was related to the thyroid gland and topographic landmarks. The scintigraphic results were reported preoperatively to the surgeons.

Surgical Procedure

During surgical exploration all parathyroid glands were identified and the following were removed: (1) RTB-positive, pathologic parathyroid glands, (2) other RTB-positive masses (e.g., thyroid nodules, lymph nodes, normal parathyroids), and (3) RTB-negative masses suspected by the surgeon of harboring parathyroid pathology. A subtotal parathyroidectomy (removal of all but 30–100 mg of parathyroid tissue) was performed in cases of parathyroid hyperplasia. The exact position of the parathyroid glands (normal and abnormal) and of other resected masses was noted in relation to the thyroid gland and sternal notch. Each specimen removed was weighed and examined histologically.

In each patient the surgical and histologic findings were correlated with the preoperative scintigraphic RTB localization and final results were defined as correct when the scintigraphic, surgical, and pathological findings coincided (Figs. 2–4), or when in addition to correct RTB foci, a false positive diagnosis of a cervical mass was made (Fig. 5). (These false-positive results were included in the calculations of the sensitivity and specificity.) Final results were defined as incorrect when no correlation was made between RTB foci and the surgical–histologic findings. Figures 2–5 present four representative case reports.

RESULTS

Operative Findings

All 46 patients underwent cervical exploration, five of whom also underwent mediastinal exploration. A total of 111 cervical and mediastinal masses were removed (range 1–5, mean 2.7 per patient) (Table 1). The patients and scintigraphic and histopathological results are summarized in Tables 2 and 3: there were 34 adenomas (weight range 200–7400 mg, mean 1090 mg) with 26 glands weighing <1 g, and 33 hyperplastic glands (weight range 30–4000 mg, mean 850 mg) with 26 glands weighing <1 g. Twenty-seven normal cervical parathyroid glands were also removed from the adenoma group. In addition, 17 other tissue masses suspected of harboring parathyroid pathology (lymph nodes, thyroid nodules, and retrosternal thymic tissue) were also removed from both adenoma and hyperplasic groups.

Correlation with the Scintigraphic Findings

A total of 71 RTB-positive and 40 RTB-negative masses was removed (Tables 3 and 4).

RTB-positive parathyroid masses. Sixty-seven cervical and mediastinal glands were removed, corresponding with: a) 62 pathological parathyroid glands (true

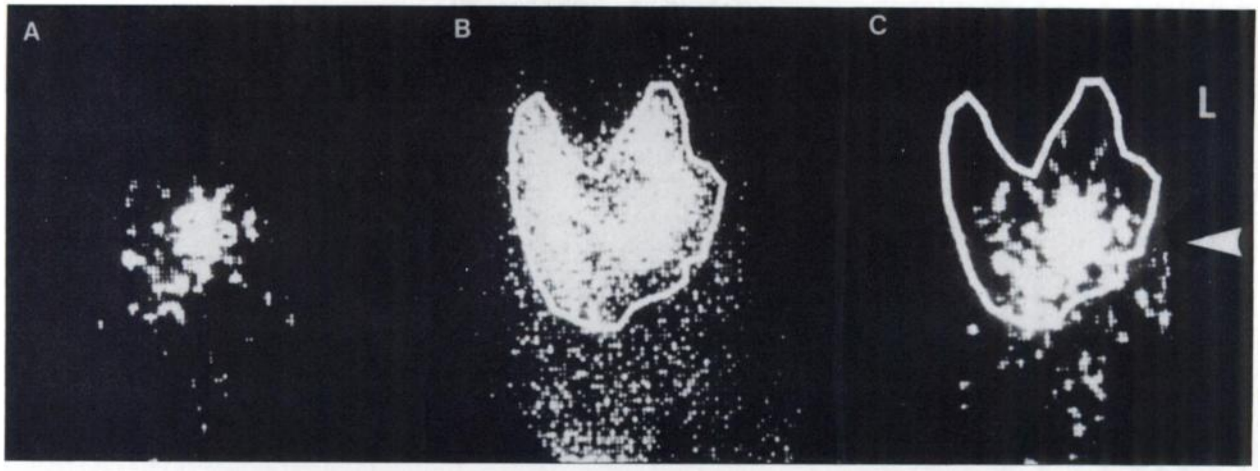

FIGURE 3
A preoperative RTB + ^{99m}Tc study of a 39-yr-old patient suffering from primary hyperparathyroidism showing a localized RTB focus in the inferior region of the left thyroid lobe (arrow). During surgery, a chief cell type parathyroid adenoma, 1.5 × 3 × 1.5 cm (4.9 g), was removed from the left lower position as correctly identified by RTB scintigraphy.

positive), of which 46 (74%) weighed less than 1 g; b) five normal large parathyroid glands (weight range 150–250 mg) (false positive).

RTB-negative parathyroid masses. Five pathological parathyroid glands (four adenomas, one hyperplastic gland; weight range 200–700 mg, mean 450 mg), which were not demonstrated on RTB scintigraphy (false negative), including two mediastinal adenomas, which were cut off in the camera's field of view were removed. Twenty-two normal parathyroid glands (weight range 10–120 mg, mean 55 mg) were also removed during surgery (true negative) (Tables 3, 4).

Nonparathyroid masses. From 17 patients, 4 RTB-positive nonparathyroid tissues (one normal lymph node adjacent to an RTB positive adenoma) and three small thyroid nodules (false positive) were removed. The other 13 masses removed were RTB-negative (Tables 3, 4).

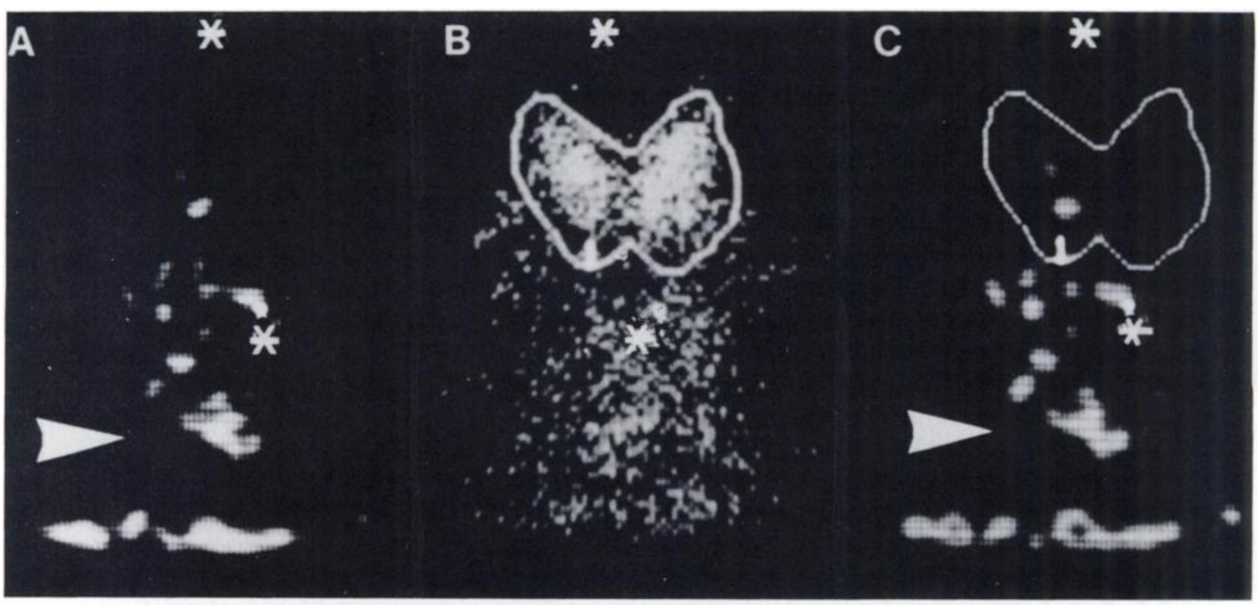

FIGURE 4
A preoperative RTB + TcO_4 study of a 63-yr-old man who, 3 yr prior to this study, underwent parathyroid surgery, where three parathyroid glands were removed. Clinical hyperparathyroidism persisted. This study disclosed a large retrosternal RTB focus (arrow) 6 cm below the sternal notch (denoted by a white asterisk) (A–C). Some insignificant background activity in the mediastinum above appears as well. A 6 g mediastinal chief cell parathyroid adenoma was resected through a median sternotomy in the indicated scintigraphic site.

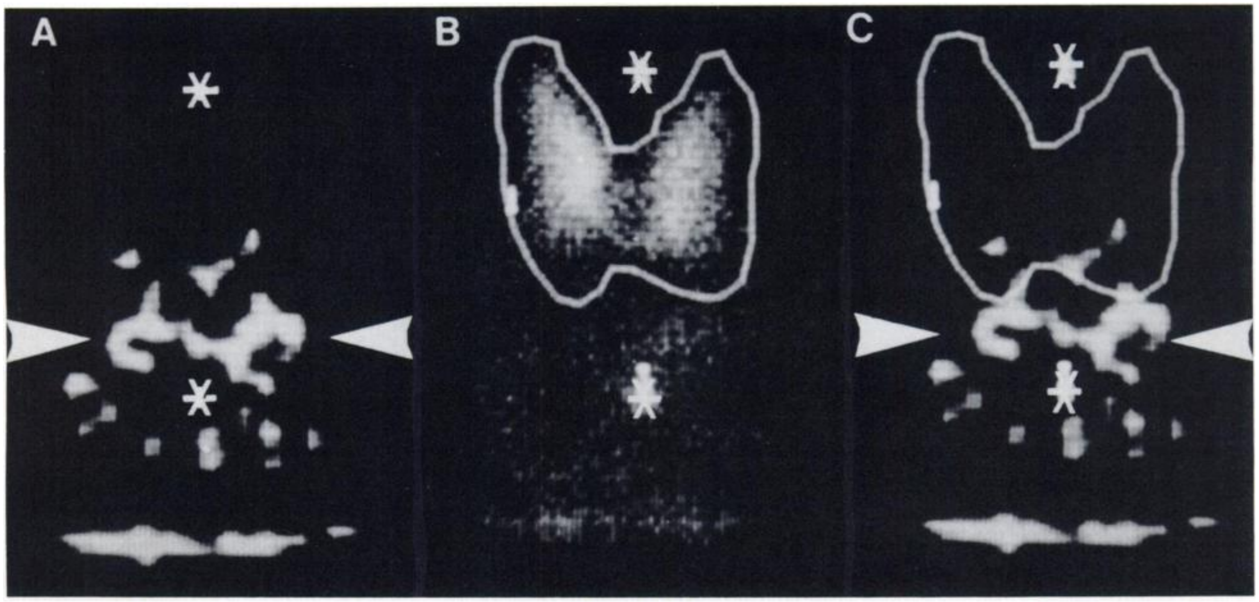

FIGURE 5
A preoperative RTB + TcO_4 study of a 65-yr-old woman with primary hyperparathyroidism revealed two RTB foci (A–C) situated adjacent to the inferior poles of the thyroid lobes in right lower and left lower infrathyroidal neck positions (arrows). Sternal notch and thyroid cartilage are denoted by white asterisks. During surgery the two masses were resected. The histology of the left mass (0.8 × 1.3 × 0.5 cm, 280 mg) showed parathyroid adenoma and of the right mass (0.8 × 0.6 × 0.6 cm, 200 mg), an enlarged normal parathyroid. We classify this result as correct in localizing the parathyroid pathology with an additional false-positive RTB finding.

Focal thyroidal RTB uptake. The RTB did not accumulate in normal thyroid tissue and the thyroid glands were not visualized (Figs. 2–5). Focal RTB accumulation was demonstrated in three of the 11 patients with nodular and diffuse thyroid goiters, corresponding to two follicular papillary adenomas and one Hashimoto thyroiditis nodule (false-positive results). The other eight thyroid nodules excised consisted of adenomatous thyroid nodules (true negative results) (Table 3).

Correlation between RTB scintigraphy and surgical findings. Correct results were obtained in 90% of patients (88% in patients with adenomas (including the two mediastinal adenoma cases where the mediastinum was cut off on scintigraphy), and 92% in patients with hyperplasia) (Table 2) giving 93% sensitivity, 80% specificity, and 87% accuracy for all the 111 masses removed (Table 4). No clear correlation was found between the histologic cellular types (*43*) of the adenomas or hyperplastic glands and RTB avidity.

Radiolabeled Toluidine Blue Scintigraphy in Selected Cases

Reoperation for persistent hypercalcemia. Four patients underwent previously unsuccessful operation for hyperparathyroidism. Prior to reoperation, the RTB-TcO_4 study demonstrated mediastinal RTB foci in two patients and the corresponding adenomas were removed. One of these cases is presented in Figure 4. One of these patients underwent a CT study with identical

Table 1
Summary of the 111 Surgically Removed Masses in 46 Patients

46 Patients	34 Patients with adenoma	Adenomas	34 (5)*
		Normal parathyroids	27
		Other tissues	9
	12 Patients with hyperplasia	Hyperplasia	33
		Other tissues	8

*Mediastinal adenomas.

TABLE 2
Summary of Preoperative Parathyroid Imaging and Surgical Findings in 46 Patients

Final histologic diagnosis	Number of patients	Scintigraphic results	
		Correct	Incorrect
Adenoma	34	30 (88%)	4 (12%)
Hyperplasia	12	11 (92%)	1 (8%)
Total	46	41 (90%)	5 (10%)

mediastinal results, and the other patient underwent selective venography with PTH sampling, which incorrectly demonstrated a left upper neck mass.

In the other two reoperated patients, two (Fig. 2) and three RTB foci were demonstrated in each patient and the corresponding cervical hyperplastic glands were resected. Ultrasound examination performed in one of these patients detected only one of his three hyperplastic glands.

Mediastinal adenomas. Five of our cases had mediastinal parathyroid adenomas. The RTB study correctly localized the adenomas in two patients (see above). In two others, the mediastinal area was not included in the scintigraphic field of view, due to a technical error.

In the fifth patient a cervical RTB focus that corresponded to a large normal parathyroid gland (200 mg) was demonstrated, while a 600 mg mediastinal adenoma had insignificant RTB uptake. Thus, two out of three imaged mediastinal adenomas were correctly localized.

TABLE 3
Summary of Histopathological and Scintigraphic Findings in 111 Removed Suspicious Masses in 46 Patients

Histologic diagnosis	Number of patients*	Number of surgically removed masses		
		RTB-positive	RTB-negative	Total
Parathyroid tissue				
Adenoma				
cervical	29	28	1	29
mediastinal	5	2	3†	5
Hyperplasia	12	32	1	33
Normal parathyroid	22	5	22	27
Other tissues				
Thymus	3	—	3	3
Lymph nodes	3	1	2	3
Focal thyroid masses	11	3	8	11
Total	46	71	40	111

*Many patients had more than one mass removed (111 masses/46 patients).

† Including two adenomas that were cut off the scintigraphic field of view.

Patient Follow-up

During the patient follow-up examination period (between 3 mo and 5 yr), all had normal calcium levels and 36 patients showed regression of their clinical symptomatology.

DISCUSSION

Experimental and surgical in vivo studies have demonstrated that TB is concentrated selectively in the parathyroids as opposed to the thyroid (*28–31*) and that RTB behaves identically (*33–35*). This histologic radiodye, which is a basic anion, combines electrostatically with acidic components of tissue such as nucleic acids (*35*).

The complexity of RTB labeling has limited its use, and only a few small clinical parathyroid studies were reported between 1970 and 1976 using RTB alone (*36,37*) or in combination with ^{99m}Tc and ^{133m}In radionuclides (*44,45*). Following the introduction of a simple labeling method (*38*), experimental and clinical studies of RTB pharmacokinetics and imaging were performed (*39*). In the present study and in previous studies (*28–35*), the radiodye reached a maximal concentration in the parathyroids at 5–15 min after i.v. injection with a ratio of at least 10:1 of parathyroid to vascular, thyroid, and other neck tissue background activity. This parathyroid concentration remained steady for up to 20–25 min, gradually clearing into the circulation thereafter.

Our study has shown that RTB is not visualized in the normal thyroid, thymus, or lymph nodes; thus it is possible to monitor the hyperactive parathyroid glands during the first 20 min of RTB accumulation. Subtraction of the vascular background or thyroid uptake was not necessary, although it was needed in previous work (*44,45*).

Our data (Tables 2–5) demonstrated a high sensitivity for detection of a small hyperplastic parathyroid gland (30 mg) located in the thyroidal region as well as ectopic pathological parathyroids with a wide range of weights. High specificity (80%) was obtained with only exceptionally large "normal" parathyroids demonstrating RTB accumulation (5 of 27). Focal thyroidal abnormalities and lymph nodes accounted for four of 14 of the false positive results in these tissues. These results are significantly better than those of previous clinical studies using RTB (*36,37,44,45*), and can be attributed mainly to the greater efficiency of our RTB-^{99m}Tc superposition method, and the use of high-resolution scintigraphic images with recently developed computer enhanced visualization techniques.

When comparing our results with other radionuclide studies, several difficulties arise due to differences in

TABLE 4
Summary of Nosological Probabilities for RTB-Tc Preoperative Parathyroid Scintigraphy

Parameter rate	Number of histologic confirmed masses	Percentage
Sensitivity (true positive)	62/62 + 5 = 62/67	93.0
Specificity (true negative)	35/9 + 35 = 35/44	80.0
False positive	9/44	20.0
False negative	5/67	7.0
Accuracy*	62 + 35/62 + 5 + 9 + 35 = 97/111	87.0

* True positive plus true negative/total.

the surgical protocols and the variable correlations made with the surgical–pathological findings. Thus, in many studies the true negative and/or false positive scintigraphic results were scarcely mentioned, causing difficulties in comparing specificities and overall accuracies by various methods. Nosological comparisons with other series were undertaken whenever gland data were sufficiently detailed for analysis. As summarized in Table 5, it appears that since 1969 the overall sensitivity of the parathyroid studies has increased from 47% with ^{75}Se (*46*) to 93% in the present study. The ^{75}Se that has been used since 1964 in large series of patients (*13,16,46,47*) has proven to be of a very limited value and a recent study concluded that preoperative ^{75}Se parathyroid scintigraphy should be abandoned (*48*).

Regarding the specificity of the radionuclides used: ^{201}Tl-chloride, the currently used radionuclide, was found to perfuse and accumulate in both normal and abnormal thyroid tissues and carcinomatous metastases (*24–27*), as well as in normal parathyroids (*49*). This low specificity for abnormal parathyroid glands limits the detectability of the parathyroids, which are in close proximity and behind the thyroid (about 60% of the parathyroids), and renders their detection almost impossible even by thyroid (^{99m}Tc), parathyroid (^{201}Tl) subtraction techniques (*50*). This limitation affects the detection of the hyperplastic glands, which are commonly located juxtaposed to the thyroid. Thus ^{201}Tl is valid more for parathyroids that are ectopic and not adjacent to the thyroid, and also in a very select group of patients having had thyroidectomy in whom up to 100% parathyroidal detectability can be achieved (*25*).

The above mentioned limitations were not encountered in our RTB method. None of the thyroid glands visibly accumulated RTB, and we used the ^{99m}Tc thyroid image mainly for topographic superposition for optimal localization of the RTB foci within the neck region. Only three of 11 (27%) of the focal small nonpalpable thyroid lesions that were not visualized on the ^{99m}Tc thyroid scan showed RTB accumulation. These findings, however, did not influence the final results in our patients. Visualization of mediastinal parathyroid adenomas with ^{201}Tl is difficult due to cardiac and large vessel mediastinal uptake (*24*), but such difficulties were not encountered in our series (Figure 4).

In our opinion, the best imaging results are achieved when specifically avid parathyroid and thyroid tracers are used in combination for each of the tissues. Optimal localization of the glands can thus be achieved by a simple superimposition of the thyroid ROI over the parathyroid concentrations as shown here. The use of a specific tracer facilitates the detection of a small

TABLE 5
Comparative Data for Preoperative Radionuclide Parathyroid Imaging

Radionuclides (reference)	Number of patients	Parathyroid glands: Adenoma Range*	Adenoma <1 g† No. (%)	Hyperplasia Range*	Hyperplasia <1 g† No. (%)	Evaluation (%): Sensitivity	Specificity	Accuracy
^{75}Se (*46*)	33	0.04–8.3	3 (21)	—	—	47	50	47
^{75}Se + ^{99m}Tc (*47*)	12	0.2–24.0	3 (33)	0.74–0.76	2 (67)	82	75	73
^{201}T1 + ^{99}Tc(^{123}I) (*22*)	26	0.09–80.0	6 (26)	0.15	1 (33)	92	—	—
^{201}Tl + ^{99m}Tc (*50*)	25	0.4–10.0	—	—	—	92	75	79
RTB + ^{99m}Tc + ^{133m}In (*45*)	21	0.6–7.8	6 (50)	0.05–1.7	4 (80)	80	—	—
RTB + ^{99m}Tc (present study)	46	0.2–7.4	26 (78)	0.03–4.0	26 (70)	93	80	87

* Weight in grams.
† Less than 1 g.

hyperactive parathyroid gland underneath or in close proximity to the thyroid gland, and avoids the difficulties that are encountered with thallium and other nonspecific parathyroid radionuclides.

Third, imaging efficiency is also evaluated by considering the weight and the functional state of the detected glands in each method used. A comparison of these parameters in various radionuclides used is made in Table 5: the minimal detected adenoma was 90 mg (*21*), and the minimal detected hyperplastic gland was 30 mg (present study). The highest percentage of detected adenomas weighing <1 g was 78%, and 70% for hyperplasias in the present study.

Regarding the influence of the functional state of the glands versus their measurement, there are differences in opinions. The opinion that size is the only determining factor in detectability was verified by DiGuilio and Beierwaltes, using ^{75}Se with 11 of 14 glands over 2 g detected, but only 4 of 35 below 2 g detected (*13*). Ferlin et al. (*21*) and MacFarlane et al. (*25*) showed that 92% of the glands over 1 cm were detected and 50% of those smaller than 1 cm were detected. In our opinion, functional activity of the gland also influences the detectability. This is substantiated by the fact that the functional activity of the pathological parathyroid gland is not always reflected by its weight (*43*). The data summarized in Table 5 indicate the same. In addition, no clear correlation was found between the size of the RTB foci and the actual weight of the resected glands. Lastly, technical and instrumental efficiency of the method employed, as well as radiopharmaceutical tissue avidity and metabolic specificity, affect every scintigraphic detectability.

Several technical issues have to be considered with the RTB method:

1. Technical pitfalls. In the early stage of our study we experienced two technical pitfalls. The first was limitation of the field of view of the pinhole collimator, which resulted in missing two retrosternal adenomas. This was overcome by including an area of up to 8 cm below the sternal notch in the field of view. Second, topographic changes due to patients' involuntary body shifting during the dual radioisotope imaging procedure occurred in two patients. Careful monitoring of the patients' head positioning during examination was sufficient to overcome this difficulty.

2. The choice of ^{131}I for radioiodination was made mainly because of the TB labeling technique, the longer shelf life of the ^{131}I labeled material, its being readily available for routine laboratory work, and the relatively low cost of this preparation (we used one batch of RTB containing usually 6 mCi for about four patient studies during 1–2 wk).

3. The radiation exposure from an RTB examination was calculated (*36*) and found to be acceptable to both personnel and patients. With a 1 mCi dose of [^{131}I]TB the exposure delivered to the thyroid from 0.5%–1% of the free iodine found in the preparation and in the blood and urine after RTB injection was 20–40 rads, 0.09 rad to the whole body, and 0.7 rad to the genitalia. The ^{75}Se estimated doses calculated for a usual dose of 250 μCi i.v. injection are 1.5 rad to the thyroid, 2.2 rad to the whole body, and 2.8 rad to the genitalia (*51*). The ^{201}Tl estimated doses for 2 mCi injected i.v. are 2.1 rad to thyroid, 0.4 rad to the whole body, and 1.2 rad to the genitalia (*52*). The examination caused no untoward effects or discomfort to the patients and was simple to perform.

The presented [^{131}I]TB method with the superimposed ^{99m}Tc thyroid image has proven to be of high efficacy, with 93% sensitivity in preoperative localization of pathological parathyroid tissues. This result is higher than most surgical results on a first operation (*1–3*). Thus, it is our opinion, first that this result justified the use of this examination routinely for preoperative parathyroid localization, and second that this RTB compound represents an advancement as a specific scintigraphic tracer over the ^{201}Tl, which represents a nonselective parathyroid tracer.

In the future, further optimization of the RTB as a scintigraphic compound can be searched for by labeling TB with lower energies and shorter half-life radionuclides (such as ^{123}I or ^{99m}Tc) to enable the use of larger tracer doses with an increased image count rate, which is relatively low with [^{131}I]TB images, and even lower patients' absorbed dose on one hand, and/or in enhancing the RTB parathyroid tissue uptake by hypocalcemia induced parathyroid stimulation mechanisms.

NOTES

* Commercial toluidine blue No. 17854 from G.T. Gurr, Ltd., London.

† Supplied by the Nuclear Research Center, Negev, Israel.

‡ Amersham International, Buckinghamshire, United Kingdom.

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