

RADIONUCLIDE TECHNIQUES IN THE DIAGNOSIS OF PRIMARY HYPERPARATHYROIDISM THE ROLE OF TECHNETIUM 99M-THALLIUM 20 SUBTRACTION SCANNING

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Qaisar Hussain Siraj, Asma Inam-ur-Rahman, Syed Azhar Ahmed (Nuclear Medical Centre, Armed Forces Institute of Pathology, Rawalpindi.)

Mahmoodul Hasan, Arshad Mirza (Combined Military Hospital, Rawalpindi.)

Abstract

The role of various radionuclide investigations, including parathyroid scintigraphy, bone scintigraphy and serum parathormone estimations in the diagnosis of primary hyperparathyroidism is reviewed briefly. The initial experience with the dual isotope (Tl-201; Tc-99m) subtraction scintigraphy for the preoperative localization of parathyroid adenomas is presented (JPMA 37 : 237, 1987).

INTRODUCTION

Various techniques are helpful in the investigation of primary hyperparathyroidism. Biochemical tests such as the estimations of serum levels of calcium, phosphates, alkaline phosphatase etc, are useful but are rather nonspecific. In the presence of metabolic bone disease skeletal radio-graphs are very helpful. Adenoma exceeds all other etiologies as the principal cause of primary hyperparathyroidism, occurring in approximately 85% of all cases¹. Various techniques have been useful in the preoperative localization of parathyroid adenomata. These include cineoesophagography², thermography³, high resolution real time ultrasonography^{4,5} computed tomography^{6,7}, arterio. graphy^{8,9}, and selective venous sampling for differential parathyroid hormone analysis⁹.

A combination of parathyroid arteriography and venous sampling with parathyroid hormone assay is probably the most accurate method available⁹. These techniques are time consuming, costly, require high expertise and are not without associated morbidity. Their replacement by noninvasive methods is desirable¹⁰.

Attempts at detecting parathyroid adenomas with Se-75 selenomethionine¹¹ and Cs-131 cesium chloride¹² have been unsatisfactory. Tl-201 has better imaging characteristics and in 1983, Young et al have demonstrated a high success rate with parathyroid scintigraphy using the dual isotope Tl-201 & Tc-99m subtraction scanning¹³. Since then others¹⁴ have reported favourable results with this new technique.

Here we briefly review the role of the various nuclear medicine investigations in the J.P.M.A. September, 1987 diagnosis of primary hyperparathyroidism and the initial experience with the dual isotope scanning for the detection of parathyroid adenomas in Paldstan.

CASE REPORT

A 23 years old woman presented with persistent skeletal pains and a history of intermittent albuminuria for the past 5 years. Albuminuria was discovered on hospitalization for typhoid fever 5 years previously and subsequently recurred on several occasions, without any other positive findings relating to the

urinary tract.

Skeletal pain of moderate to severe intensity initially appeared around the knees and shins, and later in the pelvis and legs, with no signs of joint or muscular involvement and it was not relieved by conventional analgesics. She also developed muscle weakness, easy fatigability and paraesthesias. An element of depression was also present.

The patient was a thinly built with a pulse rate of 74 beats/min and a BP of 120/80 mm Hg.

Haemoglobin was 13.6 g/dl, total leucocyte count $10.2 \times 10^{12}/l$ and erythrocyte sedimentation rate 16 mm in the first hour.

Because of a positive family history of joint pains, the possibility of functional element was considered. She however did not respond to conventional treatment and remained refractory.

Biochemical examination on several occasions, showed normal levels of serum calcium (9.2 ± 1.2 mg/dl) and 24 hrs urinary calcium (165 mg/24hrs), but urinary Sulkowitch test was positive. Serum inorganic phosphate levels were low (1.0 mg/dl) on one occasion, normal (3.4 mg/dl) on another.

Serum alkaline phosphatase was slightly raised (52 U/i).

Although the biochemical tests proved equivocal, skeletal radiography revealed typical appearances of hyperparathyroidism such as mild sub-periosteal resorption of the proximal phalanges plus mild erosion of terminal phalangeal tufts, oval cystic lesions in the distal ends of the left ulna and radius, mild granular decalcification of the vault of the skull with areas of increased density, sclerosis of the vertebral margins and rarefaction of the centre of acetabulum.

Based on the above findings a diagnosis of primary hyperparathyroidism was made and surgical exploration of neck was performed on 16.7.84 but without positive results.

The skeletal pains persisted and the patient repeatedly returned for medical advice.

RADIONUCLIDE INVESTIGATIONS

In Dec. 1985 the patient was referred to the Nuclear Medical Centre, Armed Forces Institute of Pathology, Rawalpindi, for investigations where whole body bone scintigraphy, estimation of levels of serum parathormone by means of radioimmunoassay, and parathyroid scanning were performed.

MATERIAL AND METHODS

PARATHORMONE RIA

Serum was collected in the morning after an overnight fast and the serum parathormone estimation was performed using Mallinckrodt Diagnostica RIA-mat PTH kit for the radioimmunological determination of C-terminal parathyroid hormone in human serum. According to the manufacturers' specifications this kit had an intra-assay variance range of 3-10% and an inter-assay variance range of 7-15%. The non-specific binding was quoted to be less than 5%.

BONE SCAN

The patient was given a dose of 555 MBq Tc-99m methylene diphosphonic acid intravenously and whole body skeletal imaging was performed 3 hrs later. Images were acquired using a Scintrex Gamma Camera with a general purpose parallel hole collimator linked with an on-line Data General Nova 4C computer.

PARATHYROID SCINTIGRAPHY

The above mentioned equipment was also used for parathyroid imaging. After carefully explaining the test procedure to the patient, she was positioned under the camera head and instructed to avoid moving during the course of the study. Head and neck region was immobilized. Using computer programmes the region between the chin and sternum was zoomed in and the window was set for Tl-201 energy. An injection of 75 MBq Tl-201 thallos chloride was given intravenously and after a 5 min delay a 10 min image was acquired and stored on the computer. Next an intravenous injection of 37 MBq of Tc-99m sodium pertechnetate was given and after a 10 minute delay another image was acquired for the same

time duration as the previous one but with the window now set for Tc-99m energy. The data was stored in the computer for subsequent processing. As the ^{111}In localizes in the thyroid as well as parathyroid glands and the Tc-99m localizes only in the thyroid gland the Technetium image was subtracted from the Thallium image.

RESULTS

The serum parathyroid hormone levels were consistently raised i.e. greater than 5.0 ng/dl. the normal range being 0.15-0.60 ng/dl.

Radionuclide bone scan confirmed the markedly increased skeletal metabolic rate and revealed a 'Super Scan' appearance with markedly increased tracer uptake specially in the skull, mandible, costochondral junctions and long bones of the distal extremities with individual resolution of the radius-ulna and tibia-fibula (Figure 1).



Figure 1 (a)

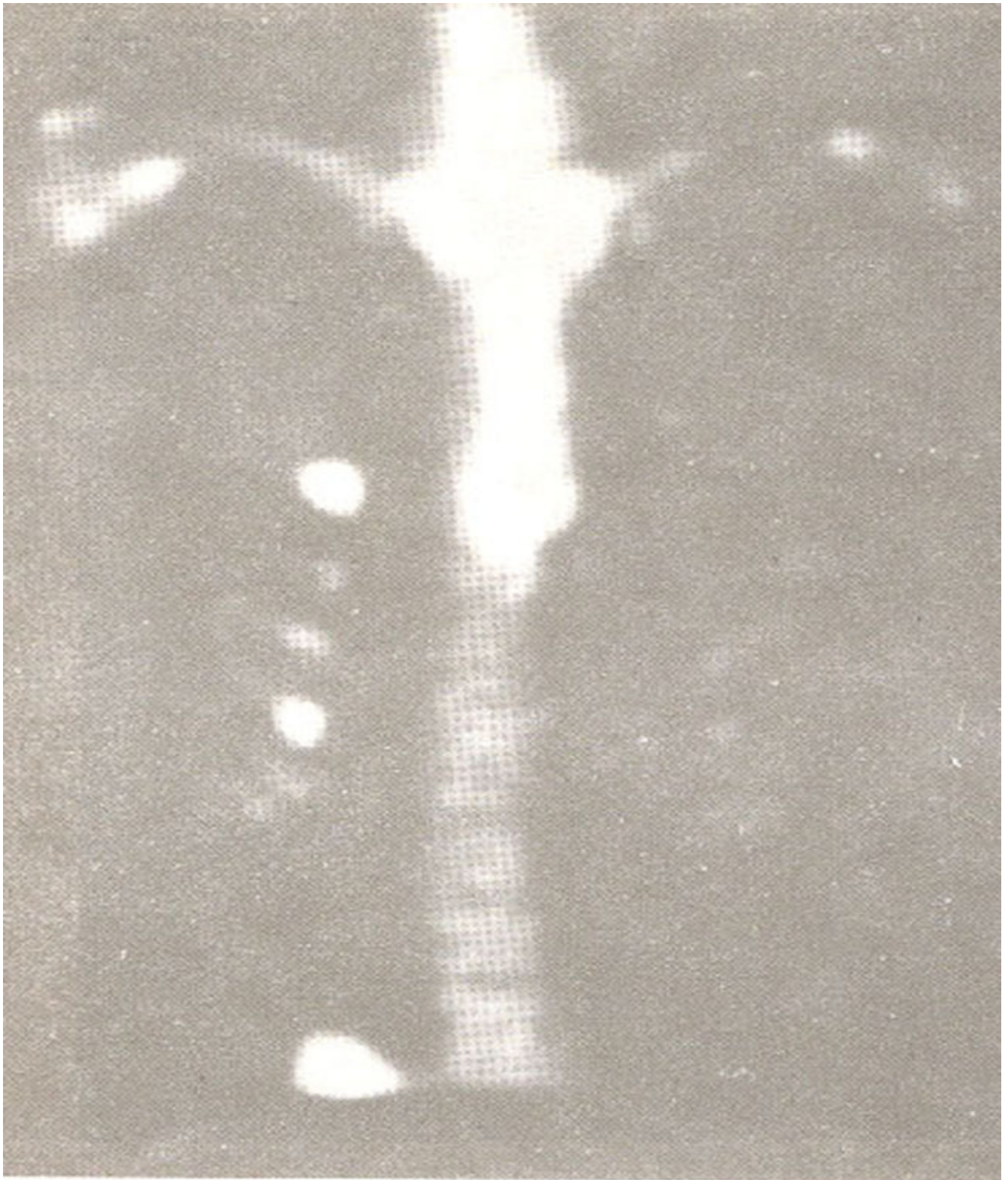


Figure 1 (b)



Figure 1 (c)

Fig.1. Bone scan of the patient showing "Super Scan" appearance. Note (a) increased activity in the skull and mandible, (b) prominent costochondral junctions, and (c) individual resolution of the radius-ulna.

Parathyroid scanning revealed a focus of increased activity in the region of the left upper pole of the thyroid gland (Figure 2)



Figure 2 (a)

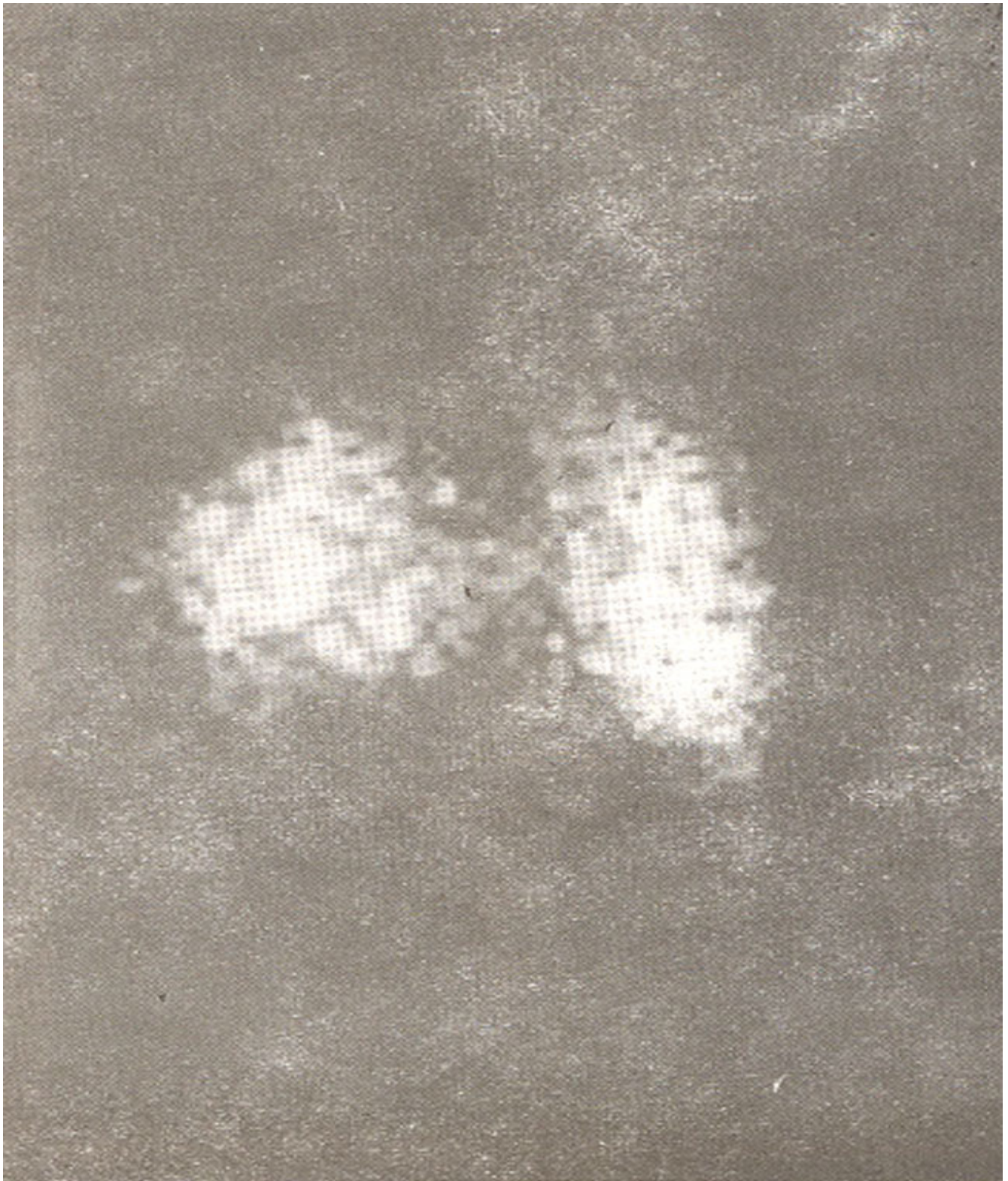


Figure 2 (b)



Figure 2 (c)

Figure 2. Dual isotope subtraction parathyroid scintigraphy. (a) Thallium-201 image of the thyroid plus parathyroid; (b) Tc-99m pertechnetate image of the thyroid; (c) Computer subtracted (a-b) image of the parathyroid adenoma.

and a diagnosis of parathyroid adenoma was made.

Following the above investigations, reexploration surgery of the neck was performed on 23.1.86 and a left upper parathyroid adenoma buried in the substance of the thyroid tissue was identified and removed. It was about 1x1.5 cms in size. The specimen was sent for frozen section and

histopathological examination proved it to be a parathyroid adenoma.

DISCUSSION

PARATHORMONE ASSAY

Parathyroid hormone is a polypeptide with 84 amino acids¹⁵ The first 34 amino acids on the N-terminal end confer biological activity to the molecule. As the intact PTH molecule is cleaved into smaller molecules soon after secretion the active 1-34 N-terminal fragment is present in the circulation along with the intact molecule and the inactive C-terminal fragment. The biologically active N-terminal fragments are rapidly cleared from the plasma and have a short half life (approx. 18-30 min), whereas the biologically inactive C-terminal fragments have a longer half life (about several days)¹⁶.

Antibodies have been raised that recognise the intact molecule and/or the C and N fragments. While antibodies to the biologically active N-terminal fragment exist, the short half life of this part of the molecule limits their usefulness in separating normals from patients of hyperparathyroidism. Since the C-terminal fragment has a longer half life, it more closely reflects the amount of hormone secreted by the parathyroid glands, even though it has no biologic activity. Furthermore it has been shown that over 80% of the immunoreactive PTH in the serum of hyperparathyroid man consists of the C-terminal fragments¹⁷.

In patients with malignant disease and hypercalcemia, the so called 'ectopic hyperparathyroidism PTH measurement using anti-C antibodies is helpful in distinguishing it from primary hyperparathyroidism¹⁸. Assays utilizing antisera with specificity towards the C-fragment exhibit the highest clinical correlation with parathyroid gland function and dysfunction¹⁹.

BONE SCAN

The excessive PTH secretion in hyperparathyroidism may result in an increase in bone resorption and bone formation. Increased radionuclide uptake on bone scan could be expected in sites of increased bone formation; these sites would include areas of trabecular bone (spine, ends of long bones etc.) with its more rapid metabolic turnover, certain areas of cortical bone including the lamina dura of the jaw and the phalanges (subperiosteal resorption) and areas of bone cyst and bone tumor involvement²⁰ generally, the skeletal uptake of the radiotracer has been found to be variable and no pattern specific for hyperparathyroidism has been noted on bone scintigraphy²¹ While bone scan may be helpful in the delineation of sites as well as extent of bone pathology its role appears to be primarily academic in these disorders. Diagnosis and quantitation of disease severity and assessment of effects of therapy appear to be more easily elicited by the usual techniques of immunoreactive parathyroid RIA, serum calcium/phosphorus/alkaline phosphatase, X-rays etc.²²

PARATHYROID SCINTIGRAPHY

The earlier reports of successful visualisation of parathyroid adenomas by Se-75 selenomethionine¹¹ resulted in an immediate interest in this new method of investigation but though the initial results were encouraging, various workers reported only a moderate degree of success using this method^{23,24}. Digulio and Morales (1969) concluded that selenomethionine scintigraphy could usually localise tumors larger than 2 g but smaller lesions could not be seen²⁵ Computer processing with thyroid image subtraction resulted in an improvement on the earlier results²⁶. However the poor energy characteristics and the high radiation dose delivered by this isotope has caused most centres to abandon this technique. Earlier results with I-131 labelled Toluidine blue and triple subtraction technique also showed some success²⁷, but was later abandoned.

In 1983, Young et al reported a new method of parathyroid scintigraphy using dual isotope (Tc-99m, I-125) subtraction scintigraphy¹³. They reported a high success rate with this method. They showed

that solitary parathyroid adenomas larger than 5 mm in diameter could be reliably located not only in normal anatomical positions but also elsewhere in the neck, including those within the thyroid gland and in the cervical and upper mediastinal region. In addition to visualising the parathyroid adenomas they were also able to locate 20 out of 36 hyper. plastic parathyroid glands as well. Since then there has been a flurry of interest in this new method of parathyroid scintigraphy and various workers have reported similar results.

The preoperative localization of the parathyroid adenomas is advantageous for various reasons. It is particularly helpful in patients requiring second look surgery where residual abnormal parathyroids may be ectopically situated in the neck and/or mediastinum. Further prior knowledge as to the location of an abnormal parathyroid may result in a quicker and surer surgery.

Whether subtraction scanning is a more useful technique than selective venous sampling can only be confirmed by further experience. However Young et al 'obtained 3 out of 4 positive scans in patients who required re-exploration and who had unsuccessful venous sampling.

Tc-99m/Tl-201 subtraction scintigraphy is a non-invasive technique which is simple to perform and provides a reliable method of preoperative screening of patients with primary hyperparathyroidism.

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