1. On radionuclide venography, the presence of jugular venous reflux may serve as an early sign of SVC syndrome, provided other causes of the reflux are ruled out.
2. Prolonged transit time (TT) from subclavian veins to the right atrium is proposed as a useful indicator of slow passage of blood through the central veins.
3. Increased values of time of half-peak count (TH) indicate sluggish blood flow through central veins.
4. The peak count ratio (PC ratio) may be considered a valuable indicator of hemodynamic disturbance in the SVC syndrome.
5. These indices are helpful in detecting hemodynamic changes in patients, irrespective of the presence or absence of clinically manifest edema of the upper half of the body.
6. These indices are potentially useful parameters in follow-up studies of the same patient.

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Iodine-123-MIBG Imaging of Neuroblastoma: Utility of SPECT and Delayed Imaging

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Possible incremental diagnostic benefits of SPECT and delayed planar imaging with [^{123}I]MIBG in neuroblastoma have not yet been fully established. **Methods:** Whole-body delayed planar [^{123}I]MIBG imaging at 48 hr and SPECT imaging of the chest-abdomen or other suspected sites obtained at 24 hr were compared with routine planar imaging at 24 hr in 83 studies of 29 children with neuroblastoma. The sensitivity for each of the [^{123}I]MIBG imaging methods was calculated on a study-by-study and on a lesion-by-lesion basis. **Results:** Fifty-one planar imaging studies were performed in 20 patients with evidence of disease which was detected in 48 studies by 24-hr imaging (94.1% sensitivity) and in 44 studies by 48-hr imaging (86.3% sensitivity). On a lesion-by-lesion basis, sensitivity was 88.8% for the 24-hr scan, 86.7% for the 48-hr scan and 92.2% for a combination of the two (p = ns). Forty-three SPECT studies were performed in 20 patients with evidence of disease in the field of view of the SPECT camera. Disease was detected in 40 SPECT studies (93% sensitivity), in 38 planar scans at 24 hr (84.4% sensitivity) and in 37 planar scans at 48 hr (86.0% sensitivity). On a lesion-by-lesion basis, sensitivity was 83.6% for the 24-hr planar scan, 86.1% for the 48-hr planar scan, 88.2% for a combination of the two planar scans and 97.9% for SPECT ($p < 0.001$ compared with planar). The anatomic locations of tumors were clearer on SPECT in 15 studies. **Conclusion:** Delayed 48-hr planar scanning may occasionally depict more lesions than 24-hr imaging, but it may also miss lesions with rapid washout. SPECT imaging significantly increases the number of lesions detected and better defines anatomic location of tumors.

Key Words: iodine-123-MIBG; neuroblastoma; planar imaging; delayed imaging; SPECT

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Metaiodobenzylguanidine (MIBG) labeled with either ^{131}I or ^{123}I has been used for nearly 15 yr in the scintigraphic evaluation of neuroendocrine tumors, particularly pheochromocytomas and neuroblastomas (*1–3*). In patients with neuroblastoma, a sensitivity of 77%–96% and a high specificity (approximately 100%) has been reported for both radiopharmaceuticals (*3–6*). Due to its physical properties (159 keV photon energy, 13-hr half-life and paucity of particulate emission of ^{123}I) and the high activity that can be administered, MIBG labeled with ^{123}I has superior imaging characteristics. These characteristics of [^{123}I]MIBG, and its favorable dosimetry, even in higher administered doses, make its use preferable in children (*7–8*).

Iodine-123-MIBG imaging is most commonly performed at 24 hr after tracer administration. However, the optimal timing for scintigraphy has not been definitively established; a recent report by Paltiel et al. (*9*) points out the improvement of thoraco-abdominal lesion visualization in 48-hr images.

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Another theoretical advantage of [^{123}I]MIBG is the feasibility of its use in high quality SPECT imaging. SPECT offers potential advantages in comparison to planar scanning: better anatomic localization of the lesions by three-dimensional reconstruction of tomographic images and better lesion definition by improved lesion contrast.

In this study, we retrospectively reviewed the images of all patients with neuroblastoma studied from May 1991 to December 1994 at the University of Michigan Medical Center with planar imaging at 24 and 48 hr and SPECT imaging at 24 hr. The study was undertaken to compare the diagnostic sensitivity of: (a) planar imaging at 24 hr versus delayed planar imaging at 48 hr and (b) SPECT imaging at 24 hr versus planar imaging at 24 and 48 hr.

MATERIALS AND METHODS

Patients

Images of all patients with previously known or subsequently proven neuroblastoma studied at the University of Michigan Medical Center from May 1991 to December 1994 were reviewed. Only those studies that included both planar images at 24 hr and 48 hr as well as 24-hr SPECT images were included in this analysis. A total of 83 studies performed in 29 children (19 boys and 10 girls, age range at diagnosis: 2 mo–12 yr, mean age 31.3 mo) were reviewed. One to eight scans had been obtained in each patient (mean 2.8 scans/patient). At diagnosis, 5 patients were in Stage II, 4 in Stage III, 19 in Stage IV and 1 in Stage IVS, according to the Evans criteria (*10*). The studies were performed in different clinical phases: 8 at diagnosis, 6 after initial surgery, 31 after therapy (various combinations of surgery, radiotherapies and chemotherapy), 34 during follow-up of patients off therapy and 4 at relapse.

MIBG Scintigraphy

Iodine-123-MIBG was synthesized at the University of Michigan by the method of Mangner, Wu and Wieland (*11*). After intravenous administration of 10 mCi (370 MBq) [^{123}I]MIBG/1.7 m^2 body surface area (range 1.6–9 mCi, mean 4.2 mCi), both planar and tomographic images were obtained. Thyroidal uptake of free ^{123}I was blocked with iodides in doses adjusted according to the patient's age. When necessary, children were sedated by oral, intravenous or inhalational agents in accordance with local guidelines. The scintigraphic study was performed with informed parental consent.

Planar Imaging. Anterior views of the entire body and posterior views of the chest and abdomen were obtained at 24 hr. Anterior views from the head to the knees and posterior views of the chest and abdomen were acquired at 48 hr. Each image was acquired for 10 min at 24 hr and 15 min at 48 hr using a large field of view gamma camera with a low-energy, general-purpose collimator interfaced to a computer.

SPECT. Tomography was performed at 24 hr using a single-head or a triple-head gamma camera with low-energy, high-resolution collimation. SPECT studies were acquired in a 64 × 64 matrix; the camera was rotated through 360° in 64 steps of 20 seconds. Data were reconstructed using filtered backprojection, a Butterworth filter and a cutoff frequency of 0.2–0.5 cycles/cm. Transaxial, sagittal and coronal sections as well as the three-dimensional projection images were displayed. The SPECT camera's field of view was 40 cm over the chest-abdomen or over other sites where disease was strongly suspected from other clinical or radiographic evidence: head and neck = 4 studies; neck and thorax = 7 studies; thorax and abdomen = 48 studies; abdomen = 9 studies; abdomen and pelvis = 15 studies.

Data Analysis

Areas of pathological uptake within the field of view of the SPECT camera were taken separately for the planar 24-hr, planar 48-hr and SPECT studies. For the planar 24- and 48-hr studies, the areas of pathological uptake not in the SPECT camera's field of view also were noted.

The total number of tumor sites for each patient was tabulated, taking into account the results obtained by MIBG scintigraphy and all other available diagnostic modalities (e.g., CT, MR, US, bone scan, bone marrow biopsy) performed not more than 2 mo before or after the scintigraphic study. Attention was also directed to those aspects of normal [^{123}I]MIBG biodistribution that pose diagnostic difficulties (e.g., gut and liver uptake).

The sensitivity of planar 24-hr, planar 48-hr and 24-hr SPECT images was calculated on a study-by-study as well as on a lesion-by-lesion basis.

Chi square methodology was used to assess statistical differences in the diagnostic sensitivity of each [^{123}I]MIBG technique.

RESULTS

Planar Imaging

In 35 studies performed in 20 patients at 24 hr, no abnormal foci of uptake were detected; all of these studies were normal at 48 hr. Of these scans, 32 were performed in patients free of disease by all criteria (true-negative results). In three studies, both planar 24- and 48-hr scans failed to detect neuroblastoma lesions: one large partially calcified primary neuroblastoma and two small residual tumors after chemotherapy, each less than 2 cm in diameter by CT.

Fifty-one studies were performed in 20 patients with evidence of disease. Abnormal foci of uptake were identified in 48 studies performed in 17 patients at 24 hr; of these abnormal studies 4 were not identified at 48 hr. In these four studies, the lesions not detected at 48 hr were six bone lesions in three patients and a primary neuroblastoma in the left adrenal in a fourth patient. Figure 1 shows rapid washout of [^{123}I]MIBG between 24 and 48 hr in a 3-yr-old boy with a left Stage III adrenal neuroblastoma studied at diagnosis.

Among a total of 473 lesions seen by all combined radiographic modalities, 420 abnormal foci were seen at 24 hr and 410 at 48 hr, with a sensitivity of 88.8% and 86.7%, respectively (p = not significant). The combination of planar 24 hr and 48 hr images allowed 436 lesions to be detected with a combined sensitivity of 92.2% (p = not significant) (Table 1).

In 27 of the 48 abnormal images (56.4%), the number of lesions detected was equal for the 24-hr and the 48-hr scans. In 14 studies (29.0%), 25 additional abnormal foci were evident at 24 hr; in 7 studies (14.6%) 15 more abnormal foci were seen at 48 hr (Table 2).

SPECT Imaging. In the SPECT camera's field of view, normal uptake was noted in 43 SPECT examinations (performed in 23 patients), all of whom had normal planar 24-hr and 48-hr images; three of these studies were false-negative in the same three patients discussed in the previous section.

Forty-three studies were performed in 20 patients with evidence of disease in the SPECT camera's field of view. Abnormal uptake was observed in 40 SPECT examinations (performed in 17 patients); of these studies, 38 had abnormal planar images at 24 hr, 37 at 48 hr and 39 when the 24 hr and the 48 hr scans were combined. Although in one patient SPECT revealed two bone lesions which were negative on planar scans, staging was not altered because of bone lesions at sites not in the SPECT camera's field of view which were detected on planar images.

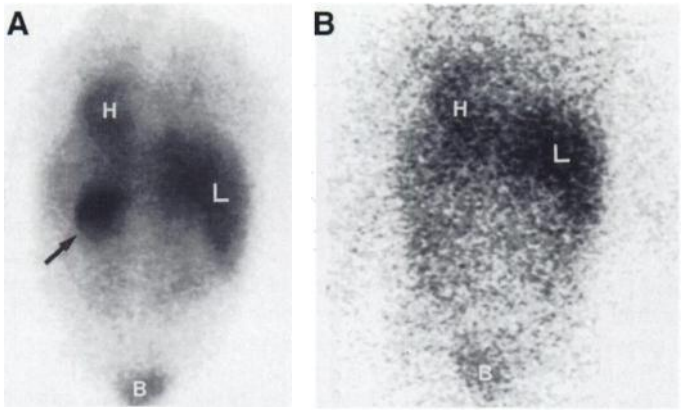

FIGURE 1. Posterior planar 24-hr scan shows [^{123}I]MIBG uptake in the left adrenal mass (arrow) (A), which is no longer evident in the 48-hr scan (B). H = heart, L = liver, B = bladder.

In all, 282 abnormal sites were seen on SPECT, 241 on planar 24-hr scans, 248 on planar 48-hr scans and 254 with the combination of the two. When analyzing the specific lesions, the improved visualization with SPECT applied to both bone and soft-tissue metastases (liver, lymph nodes), while the detection of primary/residual tumor was not affected by the addition of SPECT (Table 3).

Table 1 also depicts the diagnostic sensitivity of planar and SPECT studies. On statistical analysis, when sensitivity was calculated on a study-by-study basis, there was no significant difference between SPECT and planar imaging, while on a lesion-by-lesion basis, the improved visualization with SPECT was highly significant ($p < .001$).

Overall, in 13 studies (32.5% of the abnormal studies), SPECT imaging detected a larger number of lesions and gave a more complete depiction of the extent of disease. Figures 2 and 3 are planar and SPECT studies performed after surgery in a 3-yr-old boy with Stage IV neuroblastoma which demonstrate lesions on 48-hr delayed planar imaging and 24-hr SPECT but not visualized on 24-hr planar imaging.

Compared to planar images, SPECT gave better anatomical delineation of disease sites in 15 abnormal studies (37.5%). SPECT imaging's use of three-dimensional projection images clarified intense activity seen on planar images as being due to bowel uptake in seven studies. In four patients considerable inhomogeneities of tracer uptake not corresponding to documented liver involvement by US or CT of the abdomen on clinical follow-up were observed in 11 studies.

DISCUSSION

Iodine-123 is the best radiolabel for MIBG in assessing neural crest tumors. With pheochromocytomas, [^{123}I]MIBG may visualize lesions not depicted by [^{131}I]MIBG (*12,13*). In neuroblastoma, the superior sensitivity of [^{123}I]MIBG has not been definitively demonstrated; a comparison of both radiopharmaceuticals showed no significant difference in tumor detection (*14*). Nevertheless, for neuroblastoma, there is a marked preference for [^{123}I]MIBG due to favorable dosimetry and superior image quality (*3,7,9*). Iodine-123-MIBG provides high photon flux, high resolution, and quality images, but the imaging interval is limited to 48 hr and is thus not suited to prolonged studies (e.g., dosimetry before [^{131}I]MIBG therapy). Optimal timing of [^{123}I]MIBG scintigraphy is not definitively established. Variable methodology is reported, varying from 24-hr scan alone (*15–17*) to 24 hr with 6 hr and/or 48-hr scans (*3,4,9,18–20*). Recently, Paltiel et al. (*9*) observed improved lesion visualization at 48 hr in 55% of their abnormal studies.

TABLE 1
Sensitivity of Iodine-123-MIBG Planar Imaging: Comparison of 24-hr and 48-hr Whole-Body SPECT and Planar Results

	Abnormal studies		Abnormal foci	
	No./Total	Sensitivity	No./Total	Sensitivity
Whole-body 24 hr	48/51	94.1%	420/473	88.8%
Whole-body 48 hr	44/51	86.3%*	410/473	86.7%*
Whole-body 24 hr + 48 hr	48/51	94.1%*	436/473	92.2%*

	Abnormal studies		Abnormal foci	
	No./Total	%	No./Total	%
SPECT	40/43	93.0	282/288	97.9
SPECT Field-of-View Planar 24 hr	38/43	88.4†	241/288	83.6‡
SPECT Field-of-View Planar 48 hr	37/43	86.0†	248/288	86.1‡
SPECT Field-of-View Planar 24 hr + 48 hr	39/43	90.7†	254/288	88.2‡

*p not significant vs. 24 hr, chi square.
†p not significant vs. SPECT, chi square.
‡$p < 0.001$ vs. SPECT, chi square.

This improvement applied mainly to soft-tissue thoraco-abdominal lesions and was due to better clarity of abnormal sites, not a greater number of lesions detected.

Our study attempted to assess if the 48-hr planar scan is necessary and whether it can be usefully combined with a routine 24-hr scan. The potential advantage of delayed imaging is a better tumor-to-background ratio due to longer retention in tumors than normal tissues. When evaluated on a study-by-study basis, sensitivity was not significantly increased in the 48-hr scan. More lesions were seen at 24 hr than at 48 hr (sensitivity 88.8% versus 86.7%), even though in 14.6% of abnormal studies, more lesions were detected at 48 hr. The highest sensitivity (92.2%) was achieved by combining the two scans, although this was statistically insignificant when compared to the 24-hr scan alone. Three studies were false-negative at both 24 and 48 hr. Most series report small numbers of false- negative MIBG studies (*4–6,15,21,22*). This is due to technical factors: limitations in spatial resolution (two of our three undetected lesions were less than 2 cm) or intrinsic neuroblastoma characteristics, such as low or absent specific type 1 uptake or rapid tracer washout from the storage pool (*7*). The latter phenomenon may be implicated in lesions visualized at 24 hr but not on delayed images. Rapid washout was not related to current or previous therapy but appeared to be intrinsic to the tumors.

A theoretical advantage of [^{123}I]MIBG is the feasibility of high-quality SPECT images. Iodine-131-MIBG tomography has been reported (*23*) but, due to high photon energies and difficulties with collimation, spatial resolution and camera

TABLE 2
Planar Imaging: Lesion Visualization at 24 and 48 Hours (48 Studies)

Number of lesions detected at 24 and 48 hr	Studies		Additional Lesions
	No.	%	
24 hr = 48 hr	27	56.4	—
24 hr > 48 hr	14	29.0	25
24 hr < 48 hr	7	14.6	15

TABLE 3
Lesion Visualization with Iodine-123-MIBG: Comparison of SPECT and Planar Results

	Primary/Residual	Bone	Soft tissue (Liver, LN)
SPECT	11	245	26
Planar 24 hr	10	217	14
Planar 48 hr	9	224	15
Planar 24 + 48 hr	11	226	17

LN = lymph nodes.

sensitivity, its images are inferior to those using ^{123}I. Larger administered activities of [^{123}I]MIBG with acceptable radiation dosimetry allow SPECT with reasonable acquisition time, which is especially relevant in studying children. Use of a multihead gamma camera further shortens the imaging time. SPECT offers advantages inherent to tomography: three-dimensional reconstruction in the transaxial, coronal and sagittal planes; the separation of foci of abnormal uptake; and better delineation and localization of lesions to distinguish small tumors from other physiological or pathological uptake. There are only a few conflicting studies in the literature of [^{123}I]MIBG combined with SPECT (*16,20,24*). A previous study of SPECT by Rufini et al. (*20*) studied a selected series after surgery or during follow-up to identify small residual or recurrent tumors. More lesions were detected by SPECT than by planar scan (*20*). SPECT was performed at 24 hr because low count rates at 48 hr precluded high-quality SPECT. However, at 48 hr planar studies had excellent quality and low background.

Gelfand et al. (*24*) compared 35 SPECT and planar [^{123}I]MIBG studies in 25 children with neural crest tumors and found no significant increase in the number of lesions detected by SPECT, although an improvement in certainty of interpretation was documented (*24*). We found a significantly greater number of lesions with SPECT than with planar imaging. SPECT was thus potentially valuable for a more accurate depiction of extent of disease in 32.5% of abnormal studies. A complete depiction of disease extent is important in planning and monitoring therapies. It is possible that more accurate depiction may alter staging, detect critical lesions or otherwise affect management in a small number of cases. The 48-hr delayed images may demonstrate additional lesions due to clearance of background (15 additional lesions in 7 studies).

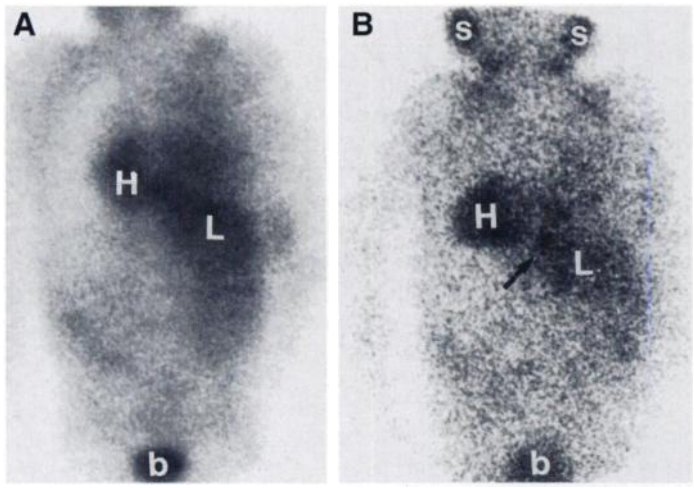

FIGURE 2. Planar posterior 24-hr scan demonstrates no definite abnormalities (A), while the 48-hr scan shows a focal area of uptake in the right lower thoracic paraspinal region (arrow) (B). s = salivary glands, H = heart, L = liver, b = bladder.

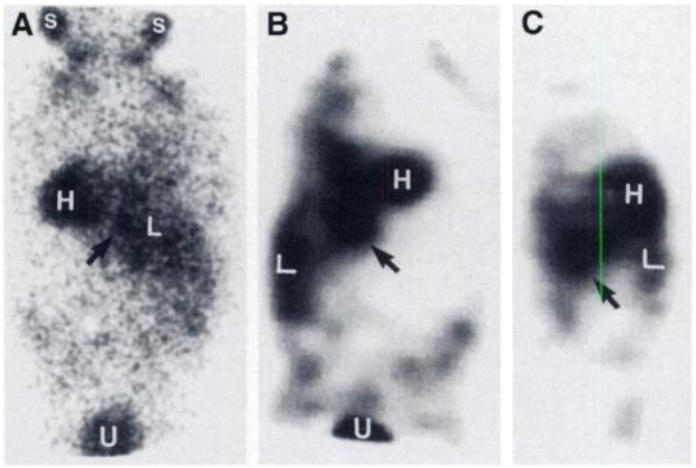

FIGURE 3. Same patient shown in Figure 2. (A) 48-hr posterior planar image, (B) posterior coronal 24-hr SPECT and (C) saggital 24-hr SPECT clearly depict right lower paraspinal lesion in three dimensions (arrows). s = salivary glands, H = heart, L = liver, U = bladder.

Not all these were in the camera's field of view (three bone lesions in two studies), but those that were could be demonstrated by both techniques. Use of 24-hr SPECT would shorten the study to 1 day, an important consideration with children. In our work and that of Gelfand et al. (*24*), the three-dimensional projection images were helpful to clearly delineate normal bowel activity. SPECT increased sensitivity, but this was achieved with some loss of specificity; in four patients (11 studies) SPECT was equivocally positive in the liver. Thus, when using SPECT, subtle inhomogeneities of tracer distribution in the liver must be interpreted with caution and correlated with clinical and other diagnostic imaging data (*25*).

CONCLUSION

The most useful study with [^{123}I]MIBG remains the planar 24-hr scan. Delayed 48-hr scans may occasionally depict a greater number of lesions but may also miss lesions having a rapid washout of tracer. SPECT significantly increases the number of lesions detected and allows better anatomic localization of neuroblastoma deposits and delineation of normal bowel activity. However, liver images must be interpreted with caution to avoid false-positive studies. It should be noted that SPECT cannot replace 24-hr planar imaging, as it does not fully screen the whole-body. SPECT may, however, substitute for 48-hr delayed imaging.

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Fluorine-18-FDG and Iodine-131-Iodide Uptake in Thyroid Cancer

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We conducted a prospective study to define the sensitivity of ^{131}I scintigraphy and ^{18}FDG PET whole-body scanning in the detection of thyroid cancer and metastases. **Methods:** Forty-one patients with differentiated thyroid carcinoma who underwent thyroidectomy and ^{131}I elimination of the remaining thyroid were studied by ^{18}FDG whole-body PET in 52 examinations and by ^{131}I whole-body scanning. **Results:** Combined ^{18}FDG and ^{131}I imaging resulted in a senstivity of about 95%, with alternating uptake of ^{131}I and ^{18}FDG in the metastases: ^{131}I trapping metastases with no ^{18}FDG uptake and ^{18}FDG trapping metastases with no ^{131}I uptake. Five uptake types were differentiated. Alternating uptake was found in about 90% of the patients, which was nearly identical to the sensitivity of the combined ^{131}I/^{18}FDG investigation. In six patients with increasing human thyroglobulin levels, we found that ^{18}FDG whole-body PET localized positive neck metastases of papillary thyroid carcinomas that were histologically confirmed after extirpation. **Conclusion:** Combination ^{18}FDG and ^{131}I whole-body imaging protocol enables detection of local recurrence or metastases on whole-body scans that are often not shown by other imaging methods. Biochemical grading of thyroid cancer may also be possible with this method: Tumors with remaining functional differentiation for hormone synthesis and iodine uptake have low glucose metabolism in more than 95%; tumors without this functional differentiation of ^{131}I uptake show high glucose metabolism. Fluorine-18-FDG uptake seems to be an indicator of poor functional differentiation, and possibly higher malignancy, in thyroid cancer.

Key Words: fluorine-18-FDG PET; thyroid carcinoma; iodine-131

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Human thyroglobulin (hTg) determination for the detection of local tumor recurrence and metastases and ^{131}I whole-body scanning are well-established methods in the follow-up of patients with thyroid carcinoma (*1*). Other imaging procedures such as radiography, ultrasound, CT and MR offer additional control methods during follow-up. Newer scintigraphic examinations with ^{201}Tl-chloride, ^{99m}Tc-sestamibi and ^{111}In-octreotide, the latter for diagnosing C-cell carcinoma, have not been completely evaluated clinically (*2*).

After ^{131}I elimination of remaining thyroid tissue, increasing hTg levels need to be evaluated. In conventional diagnostic procedures, hTg-producing tissue cannot always be localized. With 2-[^{18}F]-fluorodeoxyglucose (^{18}FDG), it is possible to detect malignant tumors with a sensitivity of 80%–90% (*3*). However, a few published studies report absence of ^{18}FDG uptake in thyroid carcinoma (*4–6*).

This prospective study was designed to define the sensitivity of thyroid cancer and metastases detection with ^{18}FDG whole-body PET in combination with ^{131}I whole-body scanning.

MATERIALS AND METHODS

Forty-one patients with differentiated thyroid carcinoma after thyroidectomy and ^{131}I elimination of the remaining thyroid underwent follow-up ^{18}FDG whole-body PET studies from December 1993 to August 1995. Twelve patients had papillary carcinoma, 23 had follicular carcinoma and 6 had Hürthle-cell carcinoma. Three additional patients with C-cell carcinoma, all MEN II, and with elevated calcitonin levels had no uptake of ^{18}FDG and were not reported in this study. All patients underwent ^{131}I whole-body gamma camera imaging, neck and abdominal US, CT and hTg level determination. All patients gave informed consent for participation in the study.

The ^{18}FDG whole-body PET results were systematically compared with the results from the methods mentioned above, especially with ^{131}I whole-body scans. All examinations were performed not more than 4 wk before or after the PET study.

The ^{18}FDG studies were performed on a scanner with whole-body and high-sensitivity modes. The field of view (FOV) was 15 cm; 5–7 FOV = 75–105-cm body scan. The patients fasted 18 hr prior to the

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