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Original Article

The Role of Dynamic (99m) Tc Pertechnetate Scintigraphy in Early Detection and Differentiation of Hyperthyroidism

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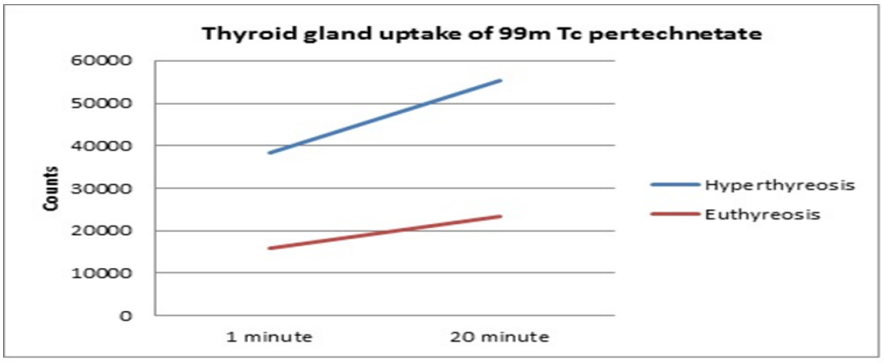
ABSTRACT

Thyrotoxicosis is hypermetabolic states that is not always associated with hyperfunction of thyroid gland and can present a problem in diagnostic differentiation. We have tried to prove that performing thyroid scintigraphy with (99m) Tc pertechnetate immediately after the first minute of intravenous injection enables the differentiation of Morbus Basedow and Plummer's disease from other diseases of thyroid gland. A total of 120 patients were included in this prospective study, 50 of them diagnosed with hyperthyroidism, while the other 70 showed no signs of hyperthyroidism. Dynamic scintigraphy lasting 20 minutes was performed in all patients. Static images of thyroid gland were taken immediately after the 1st and the 20th minute of the study. The dynamic study showed that thyroid blood flow index in patients with hyperthyroidism was approximately the same as that of patients without hyperthyroidism. The uptake capacity of (99m) Tc pertechnetate at the end of the first minute was 6 times higher for thyroid of patients with Basedow's disease and Plummer's disease compared to the other patients ($p<0.05$). The sensitivity and negative predictive value of scintigraphy in identifying Basedow and Plummer disease immediately after the first minute of the study were 100%, while the specificity and positive predictive value were 98.57% and 98.04%, respectively. The results of our study have shown that in cases of hyperthyroidism, it is sufficient to perform only scintigraphic images of thyroid gland immediately after the 1st minute of intravenous application of (99m) Tc pertechnetate.

GRAPHICAL ABSTRACT



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Introduction

Hyperthyroidism is one of the most common disorders of thyroid gland which is characterized by increased thyroid hormone synthesis and secretion from thyroid gland. Prevalence of hyperthyroidism is 0.8% in Europe [1], and 1.3% in the USA [2]. In contrast to hyperthyroidism, thyrotoxicosis refers to the clinical syndrome of excess circulating thyroid hormones, irrespective of the source [3]. The most cases of hyperthyroidism are characterized by increased secretion of free fractions of thyroid hormones into the blood (FT3 and FT4) and the suppression of thyroid stimulating hormone (TSH) secretion. The most common causes of hyperthyroidism are Morbus Graves-Basedow MGB), multinodular toxic goiter (MTG), and Plummer disease (toxic thyroid adenoma). Less common causes of hyperthyroidism are: drug-induced thyroiditis, hyperemesis gravidarum, postpartum thyroiditis, and subacute granulomatous thyroiditis (De Querwin). Rare causes of hyperthyroidism are considered to be factitious hyperthyroidism, metastatic follicular cancer of thyroid, goiter ovary, trophoblastic tumor, and TSH- secreting pituitary adenoma [4]. Graves Basedow (GB) disease is regarded as an autoimmune disease which is caused by autoantibodies against the thyroid-stimulating hormone (TSH) receptor. Toxic adenoma (TA) and toxic multinodular goiter (TMG) are both caused by a somatic activating gain-of-function mutation [5]. Graves-Basedow disease, in more than 80% of the cases is occurred in people with an adequate iodine intake (150 mg/d in adults), while the toxic multinodular goiter usually occurs in people with iodine deficiency [5]. The clinical presentation of hyperthyroidism and thyrotoxicosis is approximately the same and mostly is accompanied by anxiety, tachycardia, or atrial arrhythmia, increased perspiration, heat intolerance, hyperactivity, palpitations, rapid weight loss, nervousness, diarrhea, warm, moist, smooth skin, hand tremor, muscle weakness, and reduction in menstrual flow or oligo menorrhea [6]. The most reliable screening measure of thyroid function is the thyroid-stimulating hormone (TSH) level. Ultrasonography and computed tomography (CT) have proven to be very successful methods in identifying thyroid nodules, while thyroid scintigraphy with iodine 123 (J-123), iodine 131 (J-131), and (99m) Tc-pertechnetate is used to determine the functional state of thyroid gland and nodes in thyroid gland [7].

In cases of thyrotoxicosis with hyperthyroidism (GB disease, TMG, and TA), high activity of radioactive iodine uptake in thyroid gland is observed, while in cases of thyrotoxicosis without hyperthyroidism (generally in the cases of thyroiditis), when thyrotoxicosis is caused by a release of preformed thyroid hormones into the circulation, the uptake activity of radioactive iodine in thyroid gland is low [8]. Scintigraphy of thyroid gland with (99m) Tc pertechnetate has been shown to be an efficacious method in distinguishing hyperthyroidism from thyrotoxicosis due to the properties that Pertechnetate ions TcO_4^- behave similarly to iodide ions and are actively transported in thyroid gland by the sodium iodide symporter of thyroid follicular cells [9]. Pertechnetate is trapped in thyroid cells, but it is not incorporated in thyroid. In addition to thyroid gland, [99m Tc] TcO_4^- is concentrated in salivary glands, choroid plexus, and stomach. The pertechnetate excretion is mainly conducted by glomerular filtration via the kidneys [9]. Under normal conditions, the maximum distribution of (99m) Tc pertechnetate in thyroid gland is achieved precisely within 15-20 minutes after intravenous administration of (99m) Tc pertechnetate [10-12]. For this reason, the standard nuclear medicine protocols recommend that scintigraphic images of thyroid gland should be performed 15-20 minutes after the intravenous administration of (99m) Tc pertechnetate. Thyrotoxicosis is characterized with a hyper-metabolism of the whole body, including even the acceleration of blood circulation throughout the body. As a result of the acceleration of blood flow in thyroid gland, we have hypothesized that the uptake of (99m) Tc Pertechnetate in thyroid gland may occur faster in patients with hyperthyroidism than in patients without hyperthyroidism. Through this study, we intended to showcase if the thyroid gland in hyperthyroidism accumulates (99m) Tc

pertechnetate faster and with an increased capacity, compared to the thyroid gland without hyperthyroidism.

Martials and Methods

A total of 120 patients were included in this prospective study, 50 of them were identified with hyperthyroidism and 70 of them were without hyperthyroidism. Patients were diagnosed based on the clinical examination, laboratory findings, and ultrasound examination of thyroid gland. The study was done during the period January- August 2022, at the Department of Nuclear Medicine at the University Clinical Center of Kosovo.

A dynamic scintigraphy of thyroid gland was performed at patients in the supine position with neck extended at the moment of intravenous injection of 4 mCi $99mTcO_4$ as a bolus. A dual-head gamma camera (Simmens-Ecam type, manufactured in 2007) with a low-energy all-purpose parallel collimator, positioned approximately 16 cm anteriorly to the thyroid gland, was used for capturing images. Dynamic images of thyroid gland during the first minute were performed in 30 sequences in duration of 2 seconds, while other dynamic images up to the 20^{th} minute were performed in 19 sequences in duration of 60 seconds. Static images of thyroid gland were taken at the end of the 1^{st} minute and the 20^{th} minutes of the study in duration of 3 minutes and were used as comparison points between hyperthyroidism patients and patients without hyperthyroidism. Thyroid images were recorded in a 64×64 matrix, using a magnification factor of 1.3 [10].

The determination of dynamic thyroid activity in the form of activity curves was processed through encircling the region of interest over the entire thyroid gland, as well as a different region of interest on the side of the thyroid gland, to determine its background activity.

Statistical data

Statistical data were analyzed using IBM SPSS Version 25 (IBM Corp., Armonk, N.Y.). The patient characteristics data were summarized using descriptive statistics. Sub-group analyses were performed, separating the patient population into single or multiple drain cohorts. Fisher's exact testing was used to assess categorical variables. A paired sample Student's t- test was implemented to examine the outcome data between two groups. Statistical significance was defined as P-value <0.05.

The sensitivity determination and reliability of scintigraphy in the early identification of hyperthyroidism has been achieved through the use of sensitivity test, specificity, positive predictive value, and negative predictive value using the relevant formulas (Table 1) [13]:

Sensitivity: A/(A+C) × 100, Specificity: D/(D+B) × 100, Positive Predictive Value: A/(A+B) × 100, and Negative Predictive Value: D/(D+C) × 100.

Table 1. Formula for determination of sensitivity and specificity

	Disease (number)	Non-disease (number)	Total (number)
Positive (number)	A True positive	B (False positive)	$T_{Test\ positive}$
Negative (number)	C (false negative)	D (True negative	$T_{Test\ negaitive}$
	$T_{Disease}$	$T_{Nondisease}$	Total

Results and Discussion

A total of 120 patients, 22 males and 98 females were included as participants in the study. The mean age of all patients was 47.13 years old (the minimum 18 years old and the maximum 75 years old). The difference of the average age between two genders was considered insignificant (p>0.05). In the group of patients initially diagnosed with hyperthyroidism, 32 patients (64%) with Graves-Basedow disease, 9 patients (18%) with Plummer's disease and 9

patients (18%) with multinodular toxic goitre were included. The group of patients without hyperthyroid function included 25 patients with Hashimoto's thyroiditis (35.71%), 12 patients with subacute thyroiditis (17.14%), 11 patients with diffuse goiter (15.71), and 22 patients with nodular goiter (31.42%). The difference of the average age between patients group with hyperthyroidism and group of patients without hyperthyroidism was not significant ($p>0.05$) (Table 2).

During the dynamic study, we observed that the blood flow and (99m) Tc pertechnetate uptake in thyroid gland of patients with hyperthyroidism was approximately the same with the patients without hyperthyroidism. However, the uptake of (99m) Tc pertechnetate at the conclusion of the 1st minute of the study for patients with hyperthyroidism (approximately 600 counts) was 6 folded higher than for the patients without hyperthyroidism (approximately 100 counts), ($p<0.05$) (Figures 1 and 2).

In the scintigraphic images taken in 3 minutes, performed immediately after the first minute of the study, the thyroid gland of patients with hyperthyroidism (Basedow and Plummer disease) was visualized very clearly with a high capacity of collected counts (approximately 38459.45 counts). In patients without hyperthyroidism, thyroid gland was visualized as much fainter and with a significantly lower number of collected counts (approximately 15975 counts), ($p<0.05$) (Figure 3).

Even in static images of thyroid gland that was taken 20 minutes after pertechnetate (99m) Tc administration, thyroid gland of patients with hyperthyroidism (Basedow and Plummer disease) appeared much clearer and with a higher count collection capacity (about 55370, 36 counts) than in patients without hyperthyroidism (approximately, 23449.45 counts) (Table 3 and Figure 4). The accumulative capacity of (99m) Tc pertechnetate in thyroid gland of the patients with hyperthyroidism (Basedow and Plummer disease) was significantly higher than the capacity of patients without hyperthyroidism ($p<0.05$).

Table 2: Distribution of the patients included in the study

General data	No.	%	Average age	Confidence Intervals 0.95	0.99	P-value
Male	22	18.33	52.9091	± 5.82	± 7.92	
Female	98	81.67	45.79	± 3.32	± 4.38	
Total	120	100.0	47.13	± 7.40	± 9.78	0.112667
Hyperthyreosis	50	41.66	41.23	± 5.62	± 7.56	
Graves-Basedow	32	26.66	35.85	± 5.28	± 7.54	
Plummer Disease	9	7.5	40.37	± 4.88	± 6.91	
Multinodular toxic goiter	9	7.5	63.00	± 4.91	± 7.12	
Other thyroid disease	70	49.34	48.66	± 3.99	± 5.28	0.4872
Hashimoto Thyroiditis	25	20.83	42.44	± 5.28	± 7.36	
Subacute Thyroiditis	12	10	50.75	± 7.64	± 8.68	
Diffuse goiter	11	9.16	48.22	± 3.51	± 5.36	
Nodular goiter	22	18.33	49.57	± 2.09	± 4.21	
Total	120	100	47.13	± 7.40	± 9.78	

The difference of the average age in males and females were found nonsignificant (p> 0.05).

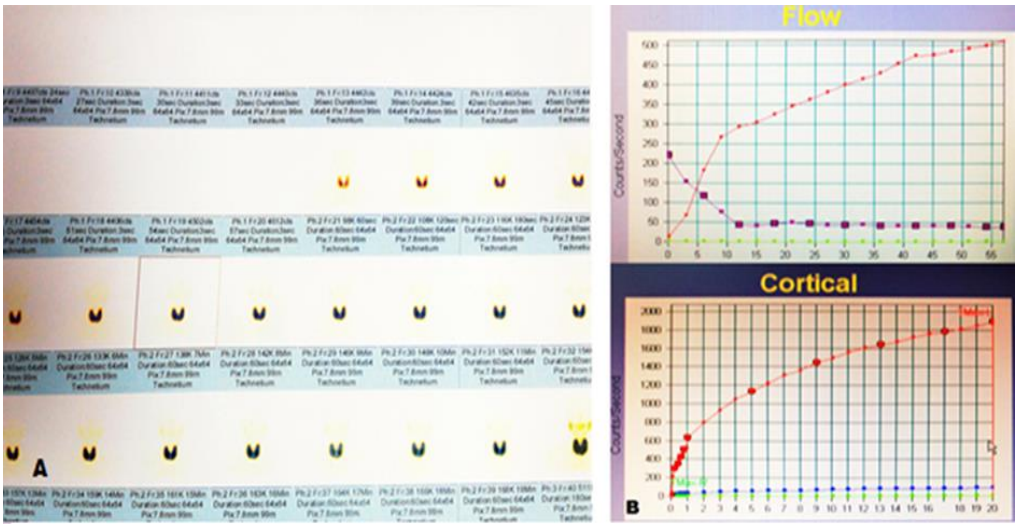

Figure 1. Dynamic scintigraphy of thyroid gland show blood perfusion and thyroid uptake of (99m) Tc pertehchnetate (A) and graphic presentation (B) in one patient with hyperthyroidism

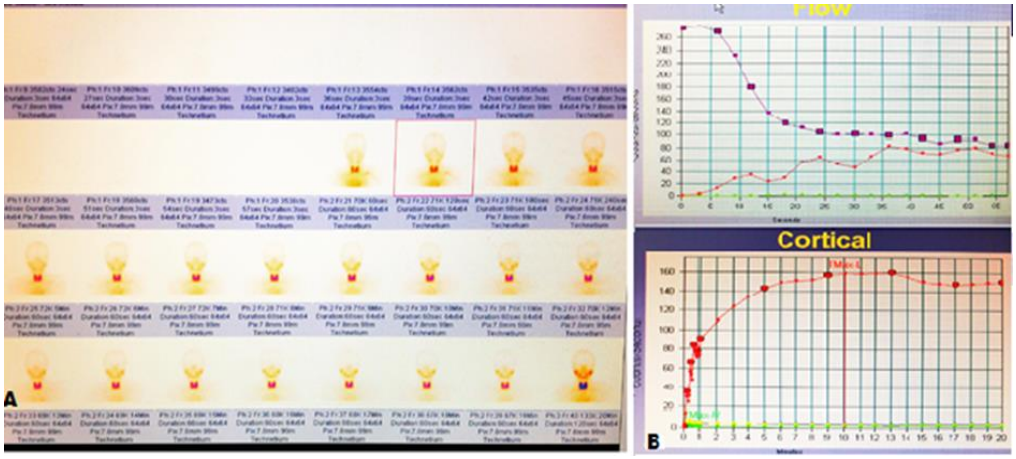

Figure 2: Dynamic scintigraphy of thyroid gland show blood perfusion and thyroid uptake of (99m) Tc pertehchnetate (A) and graphic presentation (B) in one patient without hyperthyroidism

Figure 3: Thyroid uptake (99m) Tc pertechnetate after the 1st minute and 20 minutes after administration: For the patient with hyperthyroidism (a and b) and for the patient without hyperthyroidism (c and d)

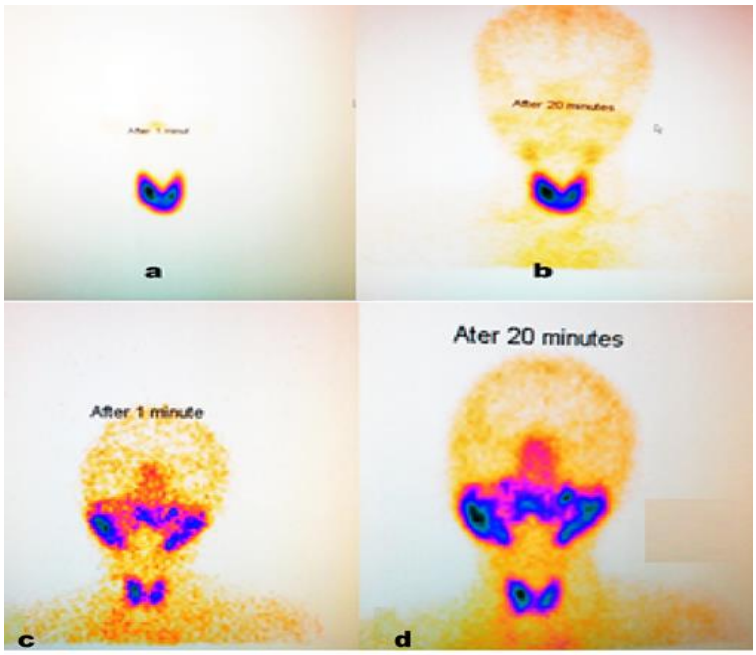

Table 3: The uptake capacity of (99m) Tc pertechnetate by thyroid gland immediately after the 1st and the 20th minute after intravenous administration

Patients diagnosis	Number	Thyroid uptake immediately after 1 min. (Counts)	Thyroid uptake immediately after 20 min.(Counts)	P-Value
Hyperthyroidism	50	Mean:38459.45±19927.187 Minimum:20128 Maximum:129987	Mean:55370.36±22783 Minimum:34563 Maximum:160365	<0.05
Other thyroid disease	70	Mean:15975±5928.97 Minimum:4214 Maximum:56987	Mean:23449.45±9713.5 Minimum:7289 Maximum:90587	<0.05
Total	120	Mean:25343± 17544.26 Minimum:4214 Maximum:129987	Mean:36691±22893.45 Minimum:7298 Maximum:160365	>0.05
P Value		<0.05	<0.05	

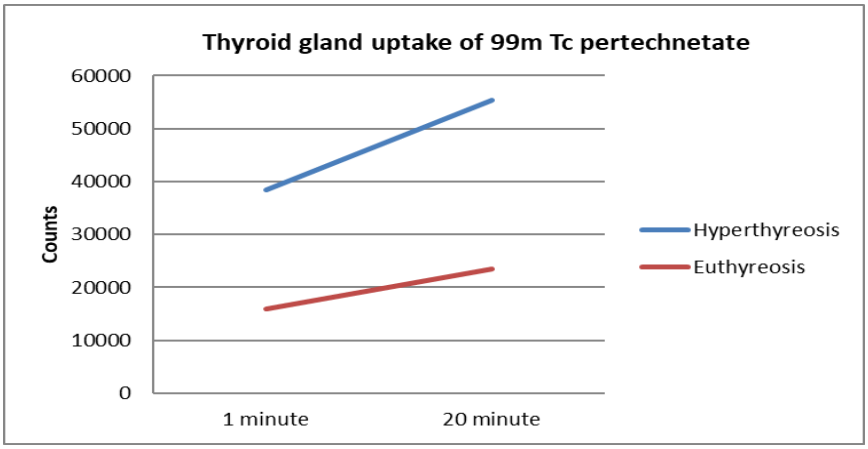

Figure 4: The uptake capacity of (99m) Tc pertechnetate by thyroid gland immediately after the first and the twentieth minute throughout the observation (the diagram was drawn in Microsoft Excel and represents the mean number of counts recorded in thyroid scan immediately after the first minute of dosing and in thyroid scan taken at 20 minutes after dosing)

Rapid and clear visualization of thyroid gland immediately after the first minute of the examination is observed in patients with hyperthyroidism, whereas only in a single case on the group of patients without hyperthyroidism (diagnosed as postpartum thyroiditis). From the obtained the data, it was observed that the sensitivity and negative predictive value of scintigraphy in the hyperthyroidism identification immediately after the first minute of the observation were 100%, while the specificity value and positive predictive value were 98.57% and 98.04%, respectively (Table 4). Scintigraphy of thyroid gland with (99m)Tc pertechnetate is considered as a very important method for distinguishing the hyperthyroidism disease from normal states of thyroid function as well as from other diseases of thyroid gland such as: infectious disease(acute thyroiditis and subacute thyroiditis), autoimmune disease (Hashimoto thyroiditis, postpartum thyroiditis, and painless thyroiditis), and inflammatory disease (Riedel thyroiditis and Radiation-induced thyroiditis). In addition, through scintigraphy with (99m) Tc pertechnetate, nodular functional changes can be distinguished from hypo-functional and non-functional ones, as well as normal and ectopic positioning of thyroid gland.

Table 4: Sensitivity and specificity of early thyroid scintigraphy on hyperthyroidism identification

Uptake of (99m) Tc pertechnetate in the thyroid gland immediately after the 1st minute of iv application of the	Hyperthyroidism (number)	Without hyperthyroidism	Total (number)

dose		(number)	
High thyroid uptake	50	1	51
Low thyroid uptake	0	69	69
Total number	50	70	120

Normally, 99m Tc-O_4 in the thyroid gland is obtained at the maximum capacity at 15-20 minutes after intravenous injection, upon which the clearest image of thyroid gland is obtained. In addition to the thyroid gland, (99m) Tc pertechnetate is commonly seen in the salivary glands and in the network capillary of the neck tissue [14]. In cases of hyperthyroidism, especially in cases with Graves Basedow, thyroid gland on scintigraphy appears diffusely enlarged, with homogeneous distribution, and very marked accumulation of the radiotracer, in most cases with the presentation of pyramidal lobe and almost total visualization suppression of the salivary glands [15]. In cases of toxic multinodular goiter, the thyroid appears enlarged with functional and non-functional nodules, the activity of which is above normal, while in the case of toxic adenoma, we have the appearance of a dominant hyperfunctional nodule with suppression of the contralateral lobe [16, 17]. In all cases with hyperthyroidism, the thyroid gland was presented as enlarged, with a significant increase in the uptake of (99m) Tc pertechnetate, compared to the cases of patients without hyperthyroidism. In cases of subacute thyroiditis, visualization of thyroid gland was almost absent, despite the high values of thyroid hormones in the blood. This occurred as a result of reduced uptake of Tc pertechnetate by thyroid gland cells involved in inflammation [18, 19].

Similar to the data reported by Hamid Javadi et al. (10), this study observed that the dynamic flux of (99 m) Tc pertechnetate in thyroid gland in the first 60 seconds of the study was almost the same in both cases of hyperthyroidism and cases without hyperthyroidism. However, in the scintigraphic images performed immediately after the first minute of the study, we observed that the uptake of (99m) Tc pertechnetate in the thyroid gland of patients with hyperthyroidism was significantly higher compared to the cases of patients without hyperthyroidism ($p<0.05$). We noticed that in the cases of hyperthyroidism, there was no significant difference between the scintigraphic images taken immediately after the 1st and the 20th minute of the study, because in both cases, the thyroid gland appears very clearly and with significant accumulation of (99m) Tc pertechnetate. In the cases without hyperthyroidism, such as Hashimoto's thyroiditis, subacute thyroiditis, or euthyroid goiter, visualization of thyroid gland at the first minute of the study is very weak or absent. Therefore, it represents a strong diagnostic signal that we are not dealing with hyperthyroidism. Our data reveals that the scintigraphy sensitivity in the hyperthyroidism identification immediately after the first minute of the study was 100%, while the value of specificity was 98.57%.

Conclusion

The results of this study have shown that in cases of hyperthyroidism (Basedow's and Plummer's disease), it is sufficient to perform only scintigraphic images of the thyroid gland immediately after the 1st minute of intravenous application of (99m) Tc pertechnetate, since the quality of scintigraphic images and the visualization of hyperactive thyroid gland is almost the same as the images taken after 20 minutes.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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