

67-Ga CITRATE AND 75-Se METHIONINE IN THE DIFFERENTIAL DIAGNOSIS OF THYROID NODULES

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Povzetek: Avtorji so scintigrafirali 71 bolnikov z obolenjem ščitnice s pomočjo 75-Se metionina in 67-Ga citrata, da bi ugotovili vrednost teh radiofarmakov v preoperativni diagnostiki malignih tumorjev. Ugotovili so, da je tolmačenje konvencionalnih scintigrafskih slik težko in nezanesljivo. Izdelali so računalniško metodo, ki je omogočila izražanje radioaktivnosti tkiv vratu v odnosu na »telesnega ozadja« in omogočila iztiskavanje »kvantitativne slike«. S to metodo so prikazali, da se oba radiofarmaka kopičita v različnih normalnih in patoloških strukturah vratu, pri čemer se razmerje do »telesnega ozadja« giblje med 1,5—2,5. Izjemo predstavljajo anaplastični karcinom, maligni limfomi in thyreoiditis Hashimoto, kjer so našli vrednosti do 5,2. Med uspešno terapijo in po njej je bilo ugotovljeno zniževanje vrednosti za 67-Ga, s čimer je podana možnost zasledovanja uspešnosti zdravljenja.

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Solitary thyroid nodules which fail to concentrate radioiodine or radiopertech-
netate (cool and cold nodules) occur frequently and represent, histologically, a variety of conditions including malignancy. Early and adequate surgery is likely to »cure« patients with well differentiated adenocarcinomas, whereas for anaplastic tumors radiation seems to be the preferable treatment (1). Benign adenomas and regressive changes may not need immediate treatment.

In this study, scintillation scanning with 67-Ga citrate and 75-Se methionine has been tried in order to examine its ability to improve the preoperative differentiation of thyroid nodules.

Material and methods. — To the first group of 35 patients with thyroid nodules 2 mC of 67-Ga citrate and/or 0.25 mC of 75-Se methionine were administered i. v. If both radiopharmaceuticals were

tried on the same patient, the latter was given after a two-weeks delay in order to decrease the background radioactivity within the neck. The images of the neck were made two days later by means of a rectilinear color-dot scintiscanner or an Anger camera.

In the first group of 35 patients, the relative concentration of the radiopharmaceuticals within the nodules was visually scored as higher (+), same (+/—) or lower (—), than that within the normal thyroid tissue.

Since the overall target/non-target ratios were low in most cases, the scoring of images was soon found to be uncertain. Further, the precise topographic correlation of conventional thyroid images with the 67-Ga and/or 75-Se was difficult and errors due to subjective interpretation could not be avoided. In order to improve the reproducibility of

this interpretation, a computer assisted technique was devised for a better assessment of the quantity and topography of the radionuclide concentration within the normal and pathological neck tissue.

A second group of 36 patients was given orally about 1 mC of 99 m-Tc pertechnetate as the second tracer, about 30 minutes before the scintigraphy with either of the two radiopharmaceuticals. A dual-analyser digitalised scintiscanner was used for this study. The spectrometers were set at appropriate photopeaks for either radionuclide. Parallel to the colour-dot imaging, counts from the two analysers were collected by a CAMAC type data acquisition system and punched into the paper tape.

The tapes were processed off-line by a 6000 series CDC digital computer. After the formation of the two matrices within the computer core memory, the background counts for each matrix were assessed by averaging the activity of two adjacent scanning lines with the lowest mean values. Then the »background« counts were subtracted and the remaining data smoothed. The images of the two radionuclide distributions were produced on a fast lineprinter using alphanumeric symbols corresponding to 10 isocount levels. Blanks and overprints were employed to increase the legibility of the image.

The apparent target/bcg ratios of 75-Se and that of 67-Ga within the neck structures were visualised by an additional »quantitative« image of the count/background ratio, the printing levels being arbitrarily preset at a »maximum« of 3 times the background value. The highest count/background ratio and its coordinates were printed out also numerically.

In order to facilitate the topographic correlation, the contours of the functioning thyroid, represented by a half-maximum isocount line of the 99 m-Tc matrix established separately, were brought

into the processed 75-Se or 67-Ga matrix by using a particular symbol.

In two cases of autonomous or toxic adenomas the diagnosis was supported only by clinical, laboratory and scintigraphic finding. The rest of the patients were operated. Surgical specimens were topographically oriented and histologically examined. The findings were topographically correlated with scintigrams.

Results. — Results of altogether 148 observations in 71 patient are summarised in Tables 1 and 2. They show on the whole that in various neck structures the concentration of both radiopharmaceuticals employed is roughly comparable.

Apparent differences between the uptake of 67-Ga and 75-Se methionine for papillary and follicular carcinomas shown in tab. 1. are probably due to unavoidably subjective interpretation of conventional images and were not confirmed by computer processed records.

Both agents were taken up by normal thyroid gland about twice as much as by the surrounding normal tissue. The mean values of the gland uptake seemed to depend slightly on the hormonal activity but the ranges in normal, suppressed and hyperactive thyroid tissue obtained by quantitative scanning largely overlap. Regressive changes within nodular goiter concentrated neither of the two agents.

Acute purulent inflammation showed a moderate content of both radionuclides.

Chronic thyroiditis showed a large variety of uptake values of either agents, the highest ones were obtained in Hashimoto disease while in the fibroplastic inflammation the values found were approaching the body background.

Both agents were markedly concentrated in anaplastic carcinomas and in malignant lymphomas, but the values obtained in papillary, follicular and medullary carcinoma were virtually undistinguishable from the normal thyroid tissue.

Discussion and conclusions. — Difficulties in the correct preoperative differen-

Table 1
Conventional imaging of 75-Se methionine and/or 67-Ga citrate uptake;
61 observations in 35 patients

	No. of observ.	75-Se methionine			No. of observ.	67-Ga citrate		
		—	+/-	+		—	+/-	+
Adenomas	5	—	—	5	6	4	2	—
Toxic adenomas	2	—	—	2	2	2	—	—
Nodular goiter with regression changes	14	4	10	—	15	14	1	—
Papillary and follicular carcinoma	6	—	3	3	4	3	1	—
Anaplastic carcinoma and malignant lymphoma	2	—	—	2	3	—	—	3
Purulent inflammation	1	—	—	1	1	—	—	1
Total No. of observations	30				31			

The uptake of radionuclides within lesion was visually scored as higher (+), same (+/-), or lower (—) than that within thyroid tissue.

Table 2
Computer-assisted imaging of 67-Ga citrate and/or 75-Se methionine uptake;
87 observations in 36 patients

	No. of observ.	Uptake of 67-Ga citrate		No. of observ.	Uptake of 75-Se methionine	
		mean	range		mean	range
Normal thyroid	7	2.2	1.5—2.5	9	1.9	1.2—2.3
Suppressed thyroid	2	1.7	1.7	2	1.45	1.3—1.6
Toxic adenomas	2	1.75	1.7—1.8	3	2.0	1.6—2.3
Manubrium sterni	15	1.7	1.5—2.1			
Nodular goiter with regression changes	12	1.5	1.0—1.8	8	1.6	1.2—2.2
Papillary and follicular carcinoma	5	1.8	1.2—2.3	6	1.95	1.2—2.2
Medullary carcinoma	1	2.0	2.0			
Anaplastic carcinoma and malignant lymphoma	6	3.2	1.2+—4.9			
Thyroiditis Hasimoto and focal thyroiditis with lymphocytic infiltration	5	2.8	1.3+—5.2	2	4.5	2.1—6.9
Lymphadenitis tbc	1	2.0	2.0			
Purulent inflammation	1	2.2	2.2	1	2.3	2.3
Total No. of observations	56			31		

+ after treatment

Results are given in values of structure/body background ratio as read out of the quantitative images. Three patients were reexamined with 67-Ga citrate after treatment.

tiation of cold thyroid nodules led several authors to investigate possibilities offered by positive scintillation scanning using various »tumor-seeking« radiopharmaceuticals. It has been shown that

131-Cs citrate concentration reflects to some extent the »cell density« and can tell thyroid cysts from solid nodules (2). 75-Se methionine, widely used to indicate sites with increased protein synthesis,

has been investigated for this purpose but results were not unanimous. While some authors (3) were able to identify all malignant thyroid tumors unless they had a diameter smaller than 2 cm, the others (4) failed to demonstrate neoplasia in two out of five cases.

Radiogallium has been introduced recently (5) and its usefulness is shown in cases of fast growing malignant tumors.

The present study has been initiated in order to assess the relative value of both ^{75}Se methionine and ^{67}Ga citrate in identifying malignant tumors of the thyroid before the operation and thus to improve the possibility of a correct planning of the extent of surgery before the operation, particularly since the histological differentiation of highly differentiated carcinomas and adenomas in frozen sections is often impossible (6).

First difficulties met with in this study were the technical ones. In most cases scanning images were of a poor quality because of the inherently low target/non target concentration ratio and large statistical fluctuation of the counts. Also the topographic correlation of scanning image and physical findings was uncertain. Therefore the $^{99\text{m}}\text{Tc}$ pertechnetate was introduced as the simultaneous label of the functioning gland and a computer-assisted method was worked out in order to quantitate the uptake of either radiopharmaceutical within a given structure.

Results of the quantitative scanning demonstrated that both radiopharmaceuticals show a similar concentration pattern in a variety of thyroid conditions. Both are concentrated slightly in normal thyroid tissue. Similarly to earlier observations of other authors (7) the uptake of selenomethionine by the gland seemed to parallel slightly its hormonal activity. We believe, however, that the suppression of the gland is not likely to increase the diagnostic ability of the examination.

Slightly increased concentration has been found also in acute inflammation, but a marked uptake was demonstrated in chronic thyroiditis. The focal thyroiditis with lymphocytic infiltration showed a locally increased uptake of radiogallium but the highest values (above 5.0) for both agents were found in two developed cases of diffuse chronic inflammation with lymphocytic infiltration (Hashimoto). When the inflammation subsided after treatment, the uptake values of radiogallium were found to be lower (2.0—4.0). In a case in which histology showed that Hashimoto disease seemed to evolve into chronic fibroplastic thyroiditis, the fibrotic areas showed greatly decreased values (1.3).

In neoplastic conditions of the thyroid, the uptake values depended seemingly on the degree of the cell differentiation.

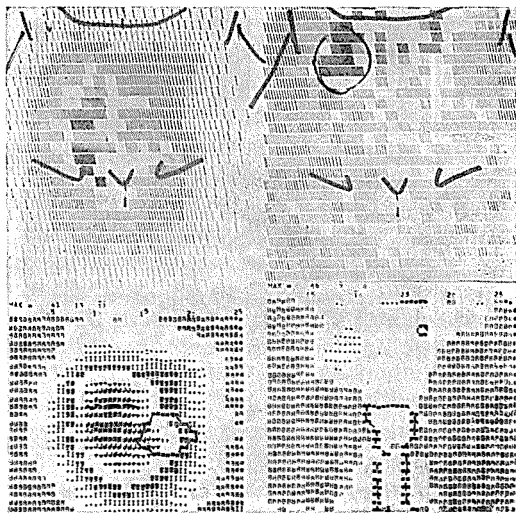


Fig. 1. Conventional (top) and computer-processed quantitative (bottom) images with ^{67}Ga citrate of a case of reticulosarcoma of the thyroid before (left) and after (right) irradiation. Maximum tumor/body background ratios were 3.7 before and 1.5 after treatment. Thyroid contours obtained from $^{99\text{m}}\text{Tc}$ matrix are enhanced for better visualisation.

The highest values for radiogallium (4.9) were obtained in anaplastic carcinomas but conventional scanning performed earlier showed also a remarkable concentration of selenomethionine in these tumors. In a case of reticulosarcoma the radiogallium showed the value of 3.7 but after a successful irradiation this concentration declined to 1.5.

Papillary and follicular carcinomas concentrated roughly the same amount of either agent as the normal gland. We were able to identify such malignant growth scintigraphically in a few cases when the primary or metastatic tumor was well outside of the gland but in a case of metastatic papillary carcinoma there were no detectable amounts of radiogallium in a large lateral neck lump. Two cases with marked histological dedifferentiation showed the highest values in this sub-group.

In conclusion, we believe that the diagnostic power of both radiopharmaceuticals is moderate. Highly differentiated carcinomas can not be distinguished from adenomas. Nodules representing regressive changes can be identified by this method, but the same can be achieved easily by thermography (8). The scintillation scanning with 67-Ga or 75-Se methionine, however, invariably demonstrated fast growing anaplastic carcinomas and malignant lymphomas, which is a great help in planning of the treatment. Chronic thyroiditis of Hashimoto type could perhaps give rise to some diagnostic doubt but the patient's history and other clinical findings can help to establish a correct diagnosis.

From practical point of view 67-Ga citrate has a definite advantage over 75-Se methionine. Its markedly shorter physical half-life (78 hours vs. 121 days) enables the use of larger amounts of radioactivity which improves the statistic quality of the image and also enables subsequent diagnostic procedures with other radio-

nuclides which eventually might be needed for the patient.

For this reason we have abandoned the use of 75-Se methionine for this purpose but have retained 67-Ga citrate in the clinical practice for cases in which this examination could facilitate the differentiation of cold thyroid nodules.

Altogether 71 patients with thyroid nodules were investigated with 75-Se methionine and/or 67-Ga citrate in conjunction with scintillation scanning in order to assess the value of these agents for the preoperative diagnosis of malignancy. It was found that conventional images are equivocal and difficult to interpret. Therefore a computer method was devised by means of which the uptake of various neck structures was expressed in terms of »body background« count rate producing an image of apparent target/non-target ratios. By means of this method it was demonstrated that both agents concentrate in a variety of normal and pathological neck structures, the range of ratios being roughly 1,5—2,5 excepting anaplastic carcinomas, malignant lymphoma and Hashimoto thyroiditis, where the values up to 5,2 were reached. During and after successful therapy the high values for 67-Ga were found decreased which enables assessment of the response to the treatment.

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